Myocarditis and pericarditis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data

S. Kristen **Sexson Tejtel**[a]*, Flor M. **Munoz**[b], Iyad **Al-Ammouri**[c], Fabio **Savorgnan**[d], Rama K. **Guggilla**[e], Najwa **Khuri-Bulos**[f], Lee **Phillips**[g], Renata J. M. **Engler**[h].

[a] Department of Pediatrics, Cardiology Section, Baylor College of Medicine, Houston, TX, USA

[b] Departments of Pediatrics, Section of Infectious Diseases, and Molecular Virology and Microbiology, Baylor College of Medicine, Houston, TX, USA

[c] Pediatric Cardiology, the University of Jordan. Amman, Jordan

[d] Department of Pediatrics, Section of Pediatric Critical Care Medicine, Baylor College of Medicine, Houston, TX, USA

[e] Department of Population Medicine and Lifestyle Diseases Prevention, Faculty of Medicine with the Division of Dentistry and Division of Medical Education in English, Medical University of Bialystok, Poland

[f] Pediatric Infectious Diseases, Vaccines, the University of Jordan, Amman, Jordan

[g] Pharmaco-epidemiology, cardiovascular drug safety, USA

[h] Allergy-Immunology-Immunizations, Department of Medicine, Walter Reed National Military Medical Center, Uniformed Services University of the Health Sciences, and Immunization Healthcare Division, Defense Health Agency, Bethesda, MD, USA

*Corresponding author: S. Kristen Sexson Tejtel, MD, PhD, MPH, Tel: +1 832-826-5600. Department of Pediatrics, Division of Cardiology, Baylor College of Medicine and Texas Children's Hospital, 6651 Main Street, Suite E 1920, Houston, TX 77030 USA

E-mail: sxsexson@texaschildrens.org

bc-coordinator@taskforce.org

[1]Brighton Collaboration homepage: https://brightoncollaboration.us/

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1. Introduction

Myocarditis and/or pericarditis (also known as myopericarditis) are inflammatory diseases involving the myocardium (with non-ischemic myocyte necrosis) and/or the pericardial sac. Myocarditis/pericarditis (MPC) may present with variable clinical signs, symptoms, etiologies and outcomes, including acute heart failure, sudden death, and chronic dilated cardiomyopathy [1, 2]. Possible undiagnosed and/or subclinical acute myocarditis, with undefined potential for delayed manifestations, presents further challenges for diagnosing an acute disease and may go undetected in the setting of infection as well as adverse drug/vaccine reactions [3-5].

The most common causes of MPC are viral, including the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) with non-infectious, drug/vaccine associated hypersensitivity and/or autoimmune causes being less well defined and with potentially different inflammatory mechanisms and treatment responses [6, 7]. However, in low- and middle-income countries, rheumatic carditis, and parasitic and bacterial infections still contribute to the burden of disease [1, 2, 8]. Potential cardiac adverse events following immunization (AEFIs) encompass a larger scope of diagnoses such as triggering or exacerbating ischemic cardiac events, cardiomyopathy with potential heart failure, arrhythmias and sudden death. The current published experience does not support a potential causal association with vaccines based on epidemiologic evidence of relative risk increases compared with background unvaccinated incidence. The only evidence supporting a possible causal association of MPC with a vaccine comes from case reports [9-11]. However, it is noteworthy that the reintroduction of live attenuated smallpox vaccine was the first time that cardiac adverse events (limited to MPC) became a focus of safety surveillance and produced evidence of epidemiologic increased relative risk [12, 13]. Addressing cardiac adverse events beyond MPC is beyond the scope of this paper.

Currently, there is no uniformly accepted global case definition for myocarditis and/or pericarditis as an AEFI. There is a need for a discriminating case definition of MPC that can be applied globally with ongoing considerations of how to define causality related to vaccines versus other causes. Possible subclinical presentations with delayed diagnosis of complications are not addressed by acute case definitions that depend on the acute onset of clinical symptoms, and are challenging for vaccine safety surveillance.

2. Existing Case Definitions

The U. S. Centers for Disease Control and Prevention (CDC) published the only vaccine safety surveillance case definition for MPC for the launch of the Smallpox Vaccine Immunization Program, a biodefence project, started in 2003 [14, 15]. **Table 1** outlines these national consensus guidelines with adjudication criteria for classification as suspected, probable or confirmed acute myocarditis or pericarditis with temporal association to

the smallpox vaccination (day 4-30) [15]. These definitions have been used by the Military Health System clinical vaccine safety surveillance since 2002, with over 2.6 million immunizations, to classify case clusters and to estimate passive surveillance incidence as well as in prospective studies and civilian surveillance [5, 16, 17]. A public health review of post-smallpox vaccine ischemic cardiac event surveillance was published by the CDC in 2008 [18].

Hypersensitivity MPC as a drug/vaccine induced cardiac adverse event has long been a concern for post-licensure safety surveillance, as well as safety data submission for licensure. Other cardiac adverse events, such as dilated cardiomyopathy, were also defined in the CDC definitions for adverse events after smallpox vaccination in 2006 [15]. In addition, several groups have attempted to develop and improve the definition and adjudication of post-vaccination cardiovascular events [5, 6]. We developed the current case definitions for myocarditis and pericarditis as an AEFI building on experience and lessons learnt, as well as a comprehensive literature review. Considerations of other etiologies and causal relationships are outside the scope of this document.

3. Methods for the development of case definitions and guidelines for data collection, analysis, and presentation of myocarditis or pericarditis as AEFIs

Following the process described on the Brighton Collaboration website, the Brighton Collaboration Myocarditis/Pericarditis Working Group was formed in September 2020 with the task of developing the MPC case definitions in compliance with published guidelines [19]. The group members had pertinent experience in clinical, public health, vaccinology, epidemiology, and pharmacovigilance. The case definitions and guidelines were based on a comprehensive literature review. To achieve consensus for this document, the working group members also used their experiences with case definitions to make the definitions and guidelines practical for experienced adjudicators.

Since the publication of the definitions in **Table 1** in 2003, clinicians involved in adjudication and case evaluations have identified deficiencies, particularly in view of the evolving knowledge about the measurement and interpretation of cardiac injury and the low frequency of cardiac biopsies, which are often unavailable and are generally replaced by non-invasive cardiac magnetic resonance imaging (CMR) today. It was noted that the clinical continuum of myocarditis-pericarditis made separate criteria challenging to adjudicate as distinct (reflecting myopericarditis rather than myocarditis/pericarditis) but the International Classification of Diseases (ICD), Tenth Revision (ICD-10) diagnostic coding system does not include a code for myopericarditis.

4. Myocarditis and pericarditis

4.1 Prevalence and background rates

The prevalence of myocarditis and pericarditis is probably underestimated because many cases resolve without detection and access to diagnostic tools can be limited [1, 2]. They have overlapping features making a diagnosis of myopericarditis more accurate. The incidence of myocarditis, using ICD-9 codes, was 22 per 100,000 people or approximately 1.5 million cases in the 2013 world population (with prevalence estimated at 9.1 per 100,00) [8]. However, there is great variation by country, setting, age group, and gender, with confounders related to the availability and quality of surveillance, as well as limitations to establishing a diagnosis of cardiac injury. There are no data regarding the incidence of post-vaccine/drug associated MPC with the literature largely limited to case reports except for smallpox vaccine (live attenuated vaccinia). The initially reported incidence of post-smallpox vaccine MPC was approximately 1 in 10,000 primarily naïve vaccinees (67 cases meeting the CDC case definition out of 540,824) [12, 13]. The incidence of MPC post-smallpox vaccine was 4.6 per 1000 based on pre- and post-vaccine clinical screening (symptoms, cardiac enzyme changes, electrocardiogram (ECG), etc.) with a relative risk of 4.0 (95% confidence interval (CI) 1.7-9.3), compared with a cohort of influenza vaccinees, [5]. These data are consistent with FDA submitted clinical trial safety data reflected in the current package insert for ACAM2000® [20]. Post-smallpox vaccination myocarditis prevalence rate in 2003 in the U.S. civilian population was estimated to be 5.5 per 100,000 population, based on active and passive surveillance data [21]. More recently, several publications have reported the association of MPC following COVID-19 m-RNA vaccination [22, 23]. The CDC reported the highest risk in males 12-29 years with 40.6 cases per million second dose of a mRNA COVID-19 vaccine [23]. The incidence in females of the same age was 4.2 cases per million second dose. Fewer reports occur in older individuals. The United States Military Health System reported 23 young male (median age 25) MPC cases within 4 days following a m-RNA COVID-19 vaccine ([23]. The majority occurred after the second dose and those that occurred after the first dose were in those with prior infection. The rate within the timeframe of case ascertainment was higher than expected among male military members after a second dose [23]. In Israel, a nationwide study of the BNT162b2 mRNA Covid-19 vaccine reported a myocarditis incidence of 2.7 events per 100,000 persons (95% CI, 1.0-4.6), which was substantially lower than that in those with SARS-CoV-2 disease (11.0 events per 100,000 persons, 95% CI, 5.6-15.8) [22].

4.2 Etiology and risk factors

Pericarditis and myocarditis share similar etiologies and risk factors, and these include infectious, non-infectious and idiopathic factors (**Table 2**) [1, 2, 6, 24-27]. In most cases, MPC is classified as idiopathic. Viral

infections, including SARS-CoV-2 infections, are the most common infectious cause of myocarditis/pericarditis globally. Non-infectious causes include immune-mediated diseases, systemic inflammatory diseases, systemic diseases, hypersensitivity to drugs, vaccines, and toxins [28].

4.3 Pathophysiology

Inflammatory injury to the myocardium and/or pericardial sac causes varying degrees of injury with more severe injury potentially leading to heart failure, arrhythmias, pericardial tamponade, cardiac arrest and/or sudden death [25, 29]. In viral myocarditis, there are three phases related to initial damage to myocardial tissues from inflammatory response (innate immunity) followed by an autoimmune reaction due to cross-reactivity between myocardial specific epitopes and viral structures (peptide similarities) generating an enhanced humoral and cellular response (a pathogenic mechanism known as molecular mimicry) [30]. In patients with self-controlled immune responses, the infection is cleared and the inflammatory process is downregulated, thus avoiding further tissue injury. Patients with an exaggerated immune response or ongoing autoimmune inflammation suffer damage to the myocardium due to persistent inflammation and may progress to fulminant myocarditis. In phase 3, patients completely recover or develop chronic dilated cardiomyopathy [25, 30].

An alternative pathophysiology mechanism for post-vaccination myocarditis and pericarditis may be hypersensitivity myocarditis resulting from an inflammatory response to the vaccine. Hypersensitivity myocarditis is an uncommon subclassification of inflammatory myocarditis which is defined as inflammation of the myocardium, usually with lymphocytic and eosinophilic infiltration. However, eosinophilia is not required for diagnosis. This is often linked to drug reactions but has also been seen with autoimmune diseases and environmental factors [13, 31]. In patients presenting with symptoms of myocarditis following smallpox vaccination mixed eosinophilic-lymphocytic myocarditis and myocyte necrosis has been reported [31].

4.4 Diagnosis

The clinical diagnosis of myocarditis and pericarditis is challenging as these entities can have a broad spectrum of clinical manifestations with significant overlap in symptoms. Acute chest pain or chest pain variants (abdominal, shoulder, back), dyspnea at rest and/or with exercise, and palpitations have been the classic presenting symptoms with positional worsening associated more with pericarditis than myocarditis. **Table 3** outlines the array of symptoms seen with MPC as well as varying features in infants and children. Myocarditis and pericarditis should be considered in the differential diagnosis of acute onset chest or abdominal pain, breathing difficulties, and fever of unknown origin. While the symptoms of pericarditis have considerable overlap with myocarditis, classic positional changes (better when leaning forward, worse when reclining) are

more frequent in pericarditis but often are in a mixed presentation of both myocarditis and pericarditis [32]. If cardiac enzyme tests are positive, then the case classification is myocarditis with potential features of pericarditis.

4.5 Laboratory diagnosis

Laboratory data supporting the diagnosis of MPC includes measures of myocardial injury (particularly cardiac troponin I and T), evidence of systemic inflammation, as well as other biomarkers associated with myocardial inflammation as summarized in **Table 4**.

4.5.1 Cardiac specific diagnostic tests

Most patients with myocarditis have abnormal electrocardiograms (ECG) as summarized in **Table 5**. Abnormalities may be transient or persistent. Nonspecific changes may be significant if the ECG reverts to normal after recovery.

4.5.2 Imaging diagnosis

4.5.2.1 Echocardiography

Echocardiography is useful for both anatomical and functional assessment. Findings consistent with myocarditis and pericarditis are shown in **Table 5**. Global or regional left ventricular wall dysfunction is the most common finding in patients with myocarditis, particularly those with congestive heart failure [33]. Increased left ventricular sphericity, as measured by the ratio of mid-cavity dimension to the long axis dimension, is a common finding during the early stages of myocarditis [34]. Transient increase in interventricular septum and left ventricular wall thickness can be seen in the early stages of myocarditis, even before significant contractility decline [35]. In addition, right ventricular dysfunction, measured by the degree of the descent of the right ventricular base, has been shown to correlate with poor outcome [36]. Pericardial effusion, intra-cavity thrombus, and wall aneurysms can easily be detected by echocardiography. Transesophageal echocardiography is the gold standard in those with limited transthoracic views where function, thrombus, aneurysms, etc. are not easily visualized.

The more recent two-dimensional speckle tracking echocardiography allows measurement of systolic myocardial deformation [37, 38]. This may provide additional diagnostic and prognostic information in patients with myocarditis, where lower circumferential and longitudinal strain and strain rates are associated with early inflammation, even without significant functional derangement, and these correlate well with the presence of myocardial edema observed on CMR (39,40).

4.5.2.2 Cardiac magnetic resonance

CMR has become a very effective, non-invasive tool for myocarditis diagnosis. The International Consensus Group on CMR Diagnosis of Myocarditis has developed recommendations on the use of CMR for myocarditis diagnosis (**Table 5**) [5, 39-42]. In 2009, Lake Louise CMR criteria for diagnosis of myocarditis included the presence of two of three changes: tissue edema, early enhancement, and late enhancement, resulting in a sensitivity of 72.5% and specificity of 96.2%. The 2018 revision that incorporated functional assessment including relaxation times, had a sensitivity of > 85% [43-45].

The revised CMR criteria for myocarditis diagnosis largely depend on myocardial tissue characterization. Global or regional edema can be evaluated using T2-weighted images where high signal intensity and increased relaxation times indicate tissue edema. In addition, T1-weighted images demonstrating early Gadolinium enhancement indicate increased myocardial hyperemia due to vasodilation associated with tissue inflammation and increased myocardial relaxation time. Subepicardial, septal, or transmural (non-ischemia) late gadolinium enhancement indicates focal or diffuse irreversible tissue necrosis and fibrosis [39, 45].

CMR also has great value in both morphological and functional assessment of the heart. Morphological assessment can detect the presence of pericarditis, pericardial effusion, and myocardial thickening which have been associated with early stages of myocarditis and are seen in pericarditis [46, 47]. Evaluation of myocarditis necessitates functional assessment, which correlates with severity and prognosis, but this is not specific or sensitive. Functional abnormalities in myocarditis may include global dysfunction with depressed ejection fraction or regional wall motion abnormalities.

4.5.3 Histopathologic diagnosis

For many years, the diagnosis of myocarditis relied primarily on histopathological features requiring tissue sampling, obtained either with autopsy or endomyocardial biopsy (EMB). EMB has been considered by many cardiologists as the gold standard for diagnosis. EMB is done using a bioptome inserted into the right ventricle via a major venous access to obtain tissue bites (usually 5-6) from the myocardium, typically from the right ventricular aspect of the interventricular septum.

The Dallas Criteria, initially proposed in 1986, has been the primary diagnostic tool for myocarditis over the past three decades [48]. It requires an inflammatory infiltrate and associated myocyte necrosis or damage in the absence of ischemic characteristics. The criteria allow for the diagnosis of borderline cases where inflammatory infiltrate is detected without evidence of myocyte necrosis. Additional immunohistochemistry to identify specific inflammatory cells, as seen in lymphocytic, granulomatous, or giant cell myocarditis can be helpful to determine the etiology and prognosis of disease. The presence of eosinophilic and mixed lymphohistiocytic

infiltrate, with predominance of T-lymphocytes along natural planes of myocardial tissue is suggestive of hypersensitivity myocarditis [49]. Polymerase chain reaction (PCR) to detect viral genomes has also been helpful to determine the etiology in post-viral myocarditis [50, 51]. Obviously, the biopsy sample should be representative of the inflamed myocardium in order to obtain these findings. It has been shown that the sensitivity of the histopathological diagnosis increases with increasing amounts of tissue obtained, and a sensitivity of 79% was reported with average of 17 tissue samples per patient [52]. The non-homogeneous inflammatory process results in low sensitivity and high rates of false negative biopsies will be obtained for those with patchy or regional areas of involvement. CMR guidance for biopsy site (54) and intracardiac electrocardiogram assessment at biopsy site (55,56) have been reported to increase the sensitivity of histopathologic diagnosis [53-55].

Although EMB is useful for diagnosis of inflammation as well as its etiology, it has significant limitations as shown in **Table 5.** Biopsies are less frequently performed in children as many practicing clinicians prefer non-invasive diagnostic tools that are also useful [56].

4.6 Myocarditis and pericarditis associated with coronavirus disease

Although coronavirus disease (COVID-19) is primarily a disease of the respiratory system, it also affects the cardiovascular system, especially in more severe cases, with up to 30% of hospitalized COVID-19 patients manifesting cardiovascular disease (CVD) [57]. In a cohort of 671 patients hospitalized with severe COVID-19, 30% of the 62 patients who died had acute myocardial injury and 20% had acute heart failure [58]. A small number of hospitalized COVID-19 patients have been reported to develop CVD without pulmonary disease [59]. In addition, mortality has been found to be higher in COVID-19 patients with cardiovascular complications than in those without (60% vs. 9%) [60]. COVID-19 can cause cardiovascular injury in the form of electrical aberrance (arrhythmias) and mechanical dysfunction (pericardial and myocardial injury).

There are a few case reports of myocarditis in COVID-19 patients in which it is generally described as myocardial injury characterized by an increase in troponin levels [60]. Some of the proposed mechanisms of troponin release in COVID-19 patients include myocardial injury induced directly by the SARS-CoV-2 virus, systemic inflammatory response, hypoxemia, downregulation of angiotensin-converting enzyme 2, systemic endothelialitis, and type 1 and 2 myocardial infarction [61, 62].

In one meta-analysis of nine case reports and two retrospective cohorts, most COVID-19 patients with myocarditis were over 50 years old with both the genders equally affected [63]. The most common presenting symptoms were dyspnea, cough, fever, and chest pain, but the morphological and functional characterization of

myocarditis in these patients were not described. ECG revealed non-specific ST-segment elevation and inverted T waves [63, 64]. 2D-echocardiogram revealed decreased left ventricular ejection fraction, and cardiomegaly or increased wall thickness. In a case series of 10 patients, CMR revealed late gadolinium enhancement in all patients, and myocardial edema was seen in some patients [65]. A systematic review of 316 cardiac autopsies for fatal COVID-19 found that nearly 50% had detectable SARS-CoV-2 within the myocardium but only 1.5% had evidence of inflammatory myocarditis [66].

The mechanisms for myocardial injury in myocarditis due to SARS-CoV-2 are not well understood, but it is likely to involve an increase in cardiac stress due to respiratory failure as well as hypoxemia, acute coronary syndrome, indirect lesions from the systemic inflammatory response, direct myocardial infection, and other factors [61, 62].

Pericarditis has been reported in four case reports of COVID-19 patients [67-70]. Three of these patients had cardiac tamponade due to pericardial effusion [67-69]. One of these case reports described a patient presenting with isolated pericarditis with none of the classic COVID-19 symptoms or signs [69]. Although the exact mechanism is unclear it is plausible that SARS-CoV-2 elicits an inflammatory response similar to that observed with other viruses that cause pericarditis.

In children with COVID-19 infection, there have been several reports of myocardial injury in what is known as multisystem inflammatory syndrome in children (MIS-C) [71-74]. The manifestations include hypotension, myocardial dysfunction with increased inflammatory markers, cardiac enzymes and B-type natriuretic peptide This usually occurs several weeks after the infection and tends to resolve completely in most children following treatment with intravenous immunoglobulins or steroids.[72, 73]. Myocardial inflammation and edema without late enhancement indicating the absence of tissue necrosis has been observed with CMR [71]. While some similarities between myocardial involvement in MIS-C and viral myocarditis due to COVID-19 in adults have been reported, children with COVID-19 infection generally have an excellent prognosis, and do not develop acute coronary syndrome that commonly seen in adults [74].

There is a higher incidence of stress cardiomyopathy (takotsubo syndrome) in patients with COVID-19 [62]. The mechanism is unclear, but the presence of microvascular dysfunction, cytokine storm, sympathetic increase, emotional stress, and the respiratory infections can contribute to stress cardiomyopathy [62]. Patients with COVID-19 associated myocarditis have many other factors contributing to the pathophysiology of cardiac injury, therefore, the typical course of myocarditis may vary with COVID-19.

5. Guidelines for data collection, analysis and presentation

The Brighton Collaboration case definition is accompanied by guidelines including data collection, analysis and presentation. (Appendix A). Both the case definition and guidelines were developed to improve data comparability and are not intended to guide or establish criteria for management of ill infants, children, or adults.

5.1 Periodic review

As for all Brighton Collaboration case definitions and guidelines, it is planned to review the definition with its guidelines on a regular basis or as needed.

5.2 Case definitions

The purpose of these case definitions is to enable cases of myocarditis and pericarditis to be ascertained in the context of safety assessments after immunization. It is not the purpose of the case definition to assess severity or causality. The definitions have been formulated with three levels of certainty (LOC) for broad applicability in various settings. The Level 1 definition is highly specific for the identification of a case of myocarditis and pericarditis. As maximum specificity normally implies a loss of sensitivity, two additional diagnostic levels have been included in the definition, offering a stepwise increase of sensitivity from Level 1 down to Level 3, while retaining an acceptable level of specificity at all levels. In this way it is hoped that all possible cases of myocarditis and pericarditis can be captured. The grading of definition levels is for the diagnostic certainty, not for the clinical severity of an event. Thus, a very severe clinical event may be classified as Level 2 or 3 and not necessarily Level 1. Additional detailed information about the severity of the event should always be recorded, as specified in the data collection guidelines.

Myocarditis and pericarditis are a spectrum of illnesses and frequently occur in combination. If symptoms of both exist, they should be evaluated against both case definitions independently and reported with a LOC for each diagnosis, which may not be the same for each diagnosis.

6. Considerations relevant to both myocarditis and pericarditis

6.1 Influence of treatment on fulfilment of case definition

The Working Group decided against using ‘treatment’ or ‘treatment response’ towards fulfillment of the myocarditis or pericarditis case definitions. A treatment response or its failure is not in itself a diagnostic, and may depend on variables like clinical status, time to treatment, and other clinical parameters.

6.2 Timing post-immunization

We postulate that a definition designed to be a suitable tool for testing causal relationships requires ascertainment of the outcome independent from the exposure, e.g., immunization. Therefore, to avoid selection bias, a restrictive time interval from immunization to onset of myocarditis or pericarditis symptoms is not an

integral part of the Brighton Collaboration case definition. In addition, since myocarditis and pericarditis often occur outside the controlled setting of a clinical trial or hospital, it may be impossible to obtain a reliable timeline for the event. Instead, the details of this interval should be assessed, when feasible, and reported as described in the data collection guidelines. Most cases of myocarditis occur within 2 to 6 weeks of viral illness or insult and most cases of pericarditis within 1 to 6 weeks. Hence, events occurring within these delays after immunization are more likely to be vaccine-induced because of the appropriate temporal association. Post-mortem evaluation resulting in documentation of myocarditis must be considered as a potential case.

7. Myocarditis case definition

7.1 Myocarditis

Myocarditis is an inflammation of the myocardium with associated symptoms and *without* an ischemic cause. Given the proximity of the pericardium and the myocardium, myocarditis and pericarditis occur in a continuum and inflammation of one frequently results in or includes inflammation of the other. The evaluation and diagnosis of myocarditis and pericarditis are similar, independent of the individual disease processes. Alternative terms for myocarditis include inflammatory cardiomyopathy, cardiac inflammation, myocardial inflammation, idiopathic myocarditis, and viral myocarditis. Myopericarditis or perimyocarditis is the term used when both the myocardium and pericardium are inflamed.

7.2 Formulating a case definition that reflects diagnostic certainty

The Working Group determined an order of symptoms and testing indicating diagnostic certainty for the diagnosis of myocarditis as shown in **Table 6** and the algorithm in **Appendix B**. The LOC 1 classification can be reached either by histopathologic demonstration of myocardial inflammation or by a combination of elevated myocardial biomarkers with an abnormal imaging study (either CMR or echocardiography). Given the relative specificity of these diagnostic modalities the Working Group did not include symptomatology as part of LOC1 since it was assumed that decisions to test for elevated myocardial biomarkers, CMR or echocardiography would be driven by symptoms of myocarditis.

A probable case, LOC 2, requires the presence of clinical symptoms and at least one abnormal CMR, ECG, echocardiogram, or elevated cardiac biomarker test result. A possible case, LOC 3, requires the presence of clinical symptoms and abnormal inflammatory markers or an ECG without the characteristic findings of myocarditis. The symptoms that must be present are dependent on the age of the individual. For infants these are more systemic symptoms such as irritability, vomiting and poor feeding. Whereas older individuals, including children and adults, can present with cardiac symptoms, such as dyspnea after exercise, at rest or lying down,

diaphoresis, palpitations, acute chest pain or pressure, sudden death or with non-specific symptoms including fatigue, abdominal pain, dizziness or syncope, edema, or cough.

7.3 Rationale for individual criteria or decision made about the case definition

Based on our literature review, the important factors for the diagnosis of myocarditis include clinical, laboratory, imaging and pathology findings.

7.3.1 Selection of clinical symptoms for the case definition of myocarditis (clinical presentation)

One of the greatest challenges in the diagnosis of myocarditis is the lack of specific symptoms. Patients may have no symptoms or only vague non-specific general symptoms, and the symptoms may be confused with other cardiac problems such as a myocardial infarction.

7.3.2 Use of physical examination findings

Physical examination findings alone do not provide sufficient information to diagnose myocarditis, as they overlap with many other cardiac diseases including cardiomyopathy and heart failure. Additionally, myocarditis is frequently accompanied by findings of the underlying cause, such as bacterial or viral infections. Given the broad symptomatology that may be present, more specific findings are necessary.

7.3.3 Rationale for histopathology as definitive diagnosis

Histopathology has been considered the gold standard for diagnosis of myocarditis for a long time. Local inflammation of myocardium can definitively diagnose myocarditis and, frequently, the cause of myocarditis can be determined with appropriate tissue testing. Biopsies should be obtained from more than one area of the heart and can be guided by CMR, if available, to increase the likelihood of obtaining a sample from an affected area of myocardium [75].

7.3.4 Rationale for imaging findings

The Working Group looked at standardized recommendations for imaging findings in myocarditis. CMR criteria include tissue and functional evaluation (Table 5). Since CMR is not 100% specific for myocarditis, laboratory findings are also required for LOC 1 classification. CMR findings with symptoms is sufficient for LOC 2 classification. Echocardiography is more frequently available than CMR in many settings. Important echocardiographic findings, primarily functional and shape evaluations, are described in Table 5. Finally, as ECG is available essentially worldwide, we considered it as a diagnostic test although the findings are less specific for myocarditis and may be seen in other cardiac diseases. Common findings are summarized in Table 5.

7.3.5 Rationale for exclusion of obstructive coronary artery disease in adults

Other etiologies of myocardial inflammation should not be included in this definition. Obstructive coronary artery disease (CAD) and myocardial infarction can cause myocardial inflammation, not necessarily secondary to a primary viral, bacterial or inflammatory process and thus will not be considered in this definition.

7.3.6 Rationale for laboratory findings

7.3.6.1 Cardiac enzymes

Elevated cardiac enzymes, including troponin I and T and creatine kinase-myocardial band, indicate myocardial damage. In the presence of other findings associated with myocarditis, elevated troponin contributes to a classification of a definitive diagnosis of myocarditis.

7.3.6.2 Other supporting laboratory tests

Other markers of inflammation, including C-reactive protein, erythrocyte sedimentation rate, and D-dimer, can provide evidence of inflammation and in the presence of appropriate supporting symptoms could lead to classification as a possible case of myocarditis.

8. Pericarditis case definition

8.1 Pericarditis

Pericarditis is an inflammation of the pericardium with the associated symptoms without an ischemic cause. Alternative terms for pericarditis include inflammatory pericarditis, pericardial inflammation, idiopathic pericarditis, viral pericarditis, and inflamed pericardial sac. Myopericarditis or perimyocarditis is the term used when both the myocardium and pericardium are inflamed.

8.2 Formulating a case definition that reflects diagnostic certainty

The case definition of pericarditis has been formulated with three levels of certainty for broad applicability in various settings. The Working Group determined an order of symptoms and testing that indicates diagnostic certainty of pericarditis as shown in Table 7 and the algorithm in Appendix C. A LOC 1 classification can be reached either by observation of edema or inflammatory infiltrate on a pericardial biopsy or at autopsy, or at least two abnormal results (abnormal fluid collection or pericardial inflammation determined by imaging, characteristic ECG changes or characteristic physical examination findings for pericarditis). A LOC 2 (probable case) diagnosis requires clinical symptoms and physical examination findings or imaging suggestive of abnormal fluid collection or abnormal findings on ECG. A LOC3 (possible case) diagnosis requires either non-specific ECG changes or an enlarged heart on chest X-ray.

8.3 Rationale for individual criteria or decision made related to the case definition

Based on our literature review, clinical, laboratory, imaging and pathology findings are important for the diagnosis of pericarditis.

8.3.1 Selection of clinical symptoms for the case definition of pericarditis (clinical presentation)

One of the greatest challenges to the diagnosis of pericarditis is the lack of specific symptoms. Patients often present with no symptoms or vague generalized symptoms. Occasionally the symptoms can lead to an incorrect diagnosis of another cardiac problem such as a myocardial infarction and myocarditis.

8.3.2 Prioritization of symptoms for pericarditis

Symptoms for pericarditis vary by age. Infants present with more systemic symptoms, including irritability, vomiting, sweating, and poor feeding. Older individuals, including children and adults, present with cardiac symptoms, including dyspnea after exercise, at rest, or lying down, diaphoresis, palpitations, acute chest pain or pressure, or sudden death and non-specific symptoms such as cough, weakness, shoulder or upper back pain, gastrointestinal symptoms (nausea, vomiting, diarrhea), cyanosis, low-grade intermittent fever, altered mental status, edema, or fatigue.

8.3.3 Prioritization of physical findings for pericarditis

Some physical examination findings of pericarditis can be similar to those for other cardiac diseases, including cardiomyopathy and heart failure, but some are specific to pericarditis and can provide helpful information for the diagnosis. The physical examination findings include a 3-part pericardial friction rub, distant heart sounds, pulsus paradoxus, hypotension, and venous distension. Additionally, underlying cause of pericarditis such as bacterial or viral etiologies can be frequently found.

8.3.4 Relevance of clinical symptom for each level of certainty

Symptoms must be present to consider pericarditis but if test results confirm the diagnosis of pericarditis, the symptoms present are not essential. As the degree of certainty for the confirmative test results decreases, the specific and common symptoms for pericarditis become more important to ensure an appropriate diagnosis. Additionally, specific physical examination findings for pericarditis are included in lower levels of diagnostic certainty.

8.3.5 Rationale for histopathology as definitive diagnosis

Histopathologic results from examination for areas of local inflammation in the pericardium can result in a LOC 1 diagnose (definitive pericarditis) and can, frequently, be used to identify the cause of pericarditis with appropriate tissue testing.

8.3.6 Rationale for imaging and electrocardiogram findings

Standardized recommendations for imaging findings in pericarditis are available. CMR criteria for diagnosis of pericarditis includes thickening on black blood imaging [76], acute or subacute pericardial edema or inflammation, enhancement on late gadolinium enhancement MRI (94–100% sensitive) [77]. Echocardiogram is more commonly available throughout the world. Common findings in pericarditis with echocardiography include pericardial effusion. Since electrocardiography is essentially available worldwide it is necessary to include as a diagnostic test for pericarditis. ECG changes described for acute pericarditis include low voltage QRS, diffuse, upwardly concave ST-segment elevation, T-wave inversion, and PR-segment depression, [78].

8.3.7 Rationale for exclusion of obstructive coronary artery disease in adults

Other etiologies of pericardial inflammation should not be included in this definition. Coronary artery disease and myocardial infarction can cause myocardial inflammation which is not secondary to a primary viral, bacterial or inflammatory process and thus should not be considered in this definition.

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Table 1: Myocarditis case definition for surveillance of adverse events after smallpox vaccination in the United States, 2003

Evidence for level of certainty	Signs & symptoms	Testing	Imaging studies[c]	Histopathology
Suspected myocarditis	Dyspnea, palpitations, and/or chest pain of probable cardiac origin, in the absence of any other likely cause of symptoms	Cardiac enzymes[a]: Normal or not performed ECG findings[b]: New, beyond normal variant	Evidence of diffuse or focal depressed left ventricular function of indeterminate age	Not performed or normal
Probable myocarditis	Same as suspected	Cardiac enzymes[a]: Elevated cTnT, cTnI or CK-MB* ECG findings[b]: New, beyond normal variant	Evidence of focal or depressed left ventricular function that is documented new onset or increased severity‡; myocardial inflammation	Not performed or normal
Confirmed myocarditis	Same as suspected	Cardiac enzymes[a] and ECG findings[b]: Not performed, normal or abnormal	Not performed, normal, or abnormal	Evidence of myocardial inflammatory infiltrate with necrosis/myocyte damage
Suspected pericarditis	Typical chest pain (i.e., pain made worse by lying down and relieved by sitting up and/or leaning forward) in the absence of other likely causes	Not performed, normal, or with preexisting or new abnormalities not described below[a]	Not performed, normal, or abnormalities not described below	Not performed or normal
Probable pericarditis	Same as suspected and/or pericardial friction rub	Diffuse ST-segment elevations or PR depressions without reciprocal ST depressions	Presence of an abnormal collection of pericardial fluid (e.g., anterior & posterior effusion or a large posterior effusion alone	Not performed or normal
Confirmed pericarditis	Same as probable	Not performed, normal or abnormal[a]	Not performed, normal, or abnormal	Evidence of pericardial inflammation

[a]**Cardiac enzymes:** cardiac-specific troponin I (cTnI) or T (cTnT) preferred but includes creatine kinase-myocardial band (CK-MB). [b]**ECG findings**: Electrocardiogram findings (beyond normal variants) not previously documented to include ST-segment or T-wave abnormalities; paroxysmal or sustained atrial or ventricular arrhythmias; atrial ventricular nodal conduction delays or intraventricular conduction defects; continuous ambulatory electrocardiographic monitoring that detects frequent atrial or ventricular ectopy. [c]**Imaging studies**: Include echocardiograms and radionuclide ventriculography using cardiac MRI with gadolinium or gallium-67; in absence of a previous study, findings of depressed left ventricular function are considered of new onset if, on follow-up studies, these findings improve or worsen. Adapted from [5].

Table 2. Etiologies of myocarditis and pericarditis [1, 2, 6, 24-28]

Infectious causes

- Viruses: coxsackievirus, adenoviruses, herpes viruses, echovirus, Epstein-Barr virus, cytomegalovirus, influenza virus, hepatitis C virus, parvovirus B19, rubella, dengue, HIV, SARS-CoV-2
- Bacterial: Mycobacterium tuberculosis, Streptococci, Staphylococci, Hemophilus influenzae, Borrelia burgdorferi, Legionella, Mycoplasma
- Fungal: Histoplasma, Aspergillus, Blastomyces, Coccidioidomycosis
- Parasites: Toxoplasma, Amebae, Chagas disease

Non-infectious causes

- Systemic inflammatory diseases: lupus, rheumatoid arthritis, scleroderma, Sjogren's syndrome, mixed connective tissue disease
- Other inflammatory conditions: granulomatosis, inflammatory bowel disease
- Metastatic cancers: especially lung cancer, breast cancer, melanoma
- Primary cardiac tumors: rhabdomyosarcoma
- Metabolic: hypothyroidism, renal failure/uremia
- Post-radiation to the chest cavity
- Trauma to the chest cavity
- Drugs (cardiotoxic effects or hypersensitivity reactions): procainamide, isoniazid, hydralazine, alcohol, anthracycline, heavy metals
- Post-radiation to the chest cavity
- Immunizations (hypersensitivity reactions): smallpox, diphtheria-tetanus-acellular pertussis (DTaP), diphtheria, tetanus, polio, and SARS-CoV-2 vaccines, influenza and vaccine combinations

650 **Table 3: Clinical symptoms associated with myocarditis and/or pericarditis**

Symptoms (acute)	Myocarditis	Pericarditis
Chest pain, pressure, tightness	X	X
Positional changes in chest pain	X	X
Dyspnea, after exercise or at rest	X	
Fatigue, malaise	X	X
Palpitations	X	
Syncope or near-syncope	X	
Peripheral edema (rare)	X	
Nausea and vomiting		X
Abdominal pain	X	X
Fever	X	X
Infant < 6 months of age		
Poor feeding	X	X
Vomiting	X	X
Tachypnea	X	
Irritability	X	X
Lethargy	X	X

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653 **Table 4: Laboratory abnormalities associated with pericarditis and myocarditis**

Myonecrosis markers	Creatine kinase (CK-MB) Troponin I or T **Less Specific** Lactate dehydrogenase (LDH) Alanine transaminase (ALT) Aspartate transaminase (AST)
Inflammatory markers	White blood cell count – leukocytosis C-reactive protein D-dimer Erythrocyte sedimentation rate
Other Biomarkers	Interleukin -10 Auto-antibodies: Anti-nuclear antibodies Rheumatoid factors Anti-topoisomerase antibodies Anti-myosin antibodies Anti-beta-adrenergic receptor antibodies

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Table 5: Common diagnostic test findings in pericarditis and myocarditis with advantages and limitations

	Pericarditis	Myocarditis	Advantages	Limitations
Electrocardiography	Tachycardia, diffuse ST elevation, PR depression, low voltage ECG (common)	Sinus tachycardia, ST elevation, T wave inversion (common) QT prolongation, QRS deviation (less common) Conduction issues: AV block, bundle branch block, intraventricular conduction delay [40, 41] Tachyarrhythmias: SVT, atrial fibrillation, PVCs, VT, VF [5, 42]	Low cost Non-invasive Safe Available in all centers/countries	Findings are usually non-specific
Echocardiography	Effusion, pericardial thickening, hemodynamic effect of fluid accumulation	Global or regional left ventricular dysfunction Early ventricular wall thickening, increased left ventricular sphericity Decreased longitudinal and circumferential strain and strain rates on tissue Doppler	Low/medium cost Non-invasive Safe, usually no contraindications Available in most centers/countries Reasonable sensitivity for severe disease	Findings may not be specific Low sensitivity in mild disease Needs some level of experience/ special equipment
Cardiac magnetic resonance	Pericardial thickening, pericardial inflammation, late gadolinium enhancement Pericardial effusion	Myocardial edema, increased wall thickness Early gadolinium enhancement indicating tissue hyperemia Late gadolinium enhancement indicating fibrosis Global or regional left ventricular dysfunction Increased relaxation time	More sensitive than echo Criteria well established Reasonable safe	High cost May need anesthesia in some patients Needs IV gadolinium, limitation in renal and heart failure Cannot determine etiology of inflammation Not available in small centers / low-middle-income countries Needs high level of experience / special equipment
Histopathologic diagnosis (through biopsy)	Evidence of inflammation of the pericardium can be diagnostic, analysis of pericardial tissue and fluid may provide evidence on etiologies	Inflammatory infiltrate within the myocardium Evidence of myocyte necrosis.	Highly specific when positive Provides evidence towards etiology (i.e., PCR for viral myocarditis, specific inflammatory cells such as eosinophilic infiltrate in hypersensitivity myocarditis	Low sensitivity depending on amount of tissue obtained and the nature of inflammation (patchy vs diffuse) Invasive Needs high level of expertise in obtaining and processing samples Reported risks include cardiac perforation, bleeding, arrhythmias, anesthesia and radiation risks

AV: atrioventricular; ECG: electrocardiogram; IV: intravenous; PCR: polymerase chain reaction; PVC: premature ventricular contraction; SVT: supraventricular tachycardia: VF: ventricular fibrillation; VT: ventricular tachycardia

660 **Table 6 – 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**

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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

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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

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Table 7. 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**

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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.)

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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.)

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