Myocarditis and Pericarditis: Case Definition and Guidelines for Data Collection, Analysis, and Presentation of Immunization Safety Data

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Myocarditis and/or pericarditis (also known as myopericarditis) are inflammatory diseases involving the myocardium (with non-ischemic myocyte necrosis) and/or pericardial sac. Myocarditis/pericarditis (MPC) may present with variable clinical signs, symptoms, etiologies and outcomes to include 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, now including the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) with non-infectious, drug/vaccine associated hypersensitivity and/or autoimmune causes less well defined and with potentially different inflammatory mechanisms and treatment responses (6,7). However, in the developing world, rheumatic carditis, parasitic and bacterial causes still contribute to the burden of disease (1,2,8).

Potential cardiac adverse events following immunization (AEFI) encompass a larger scope of diagnoses such as triggering or exacerbating ischemic cardiac events (ICE), 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 to background unvaccinated incidence. In the context of AEFI, the only literature supporting a possible causal association of MPC with a vaccine were isolated 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. Clinical diagnostic criteria for other cardiac diseases have been extensively addressed in the medical literature and specialty organization guidelines.

Currently, there is no uniformly accepted global case definition for myocarditis and/or pericarditis as an adverse event following immunization. In the context of vaccine related events evaluation, 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. The challenges for vaccine safety surveillance questions raised by possible subclinical presentations with delayed diagnosis of complications are not addressed by acute case definitions that depend on acute onset of clinical symptoms.

Existing Case Definitions

The only experience with a published vaccine safety surveillance case definition for MPC was in relation to the launch of a biodefense Smallpox Vaccine Immunization Program (started in 2003) published by the U. S. Centers for Disease Control and Prevention (CDC) (14,15). Table 1 outlines these national consensus guidelines with adjudication criteria for classification as possible, probable or confirmed acute myocarditis or pericarditis with temporal association to the smallpox vaccination (day 4-30) (15). These definitions have been used globally in connection with the Military Health System clinical vaccine safety surveillance since 2002 with over 2.6 million immunizations to classify case clusters and estimate passive surveillance incidence as well as in prospective studies and civilian surveillance (5,16,17). A public health review of ischemic cardiac events surveillance post-smallpox vaccine was published by the CDC in 2008 (18).
Table 1: Myocarditis case definition for surveillance of adverse events after smallpox vaccination in the United States, 2003\textsuperscript{16}

<table>
<thead>
<tr>
<th>Evidence for Level of Certainty</th>
<th>Signs &amp; Symptoms</th>
<th>Testing</th>
<th>Imaging Studies\textsuperscript{2}</th>
<th>Histopathology</th>
</tr>
</thead>
</table>
| Suspected Myocarditis           | Dyspnea, palpitations, and/or chest pain of probable cardiac origin, in the absence of any other likely cause of symptoms | **Cardiac enzymes:** Normal or not performed\textsuperscript{*}  
**ECG findings:** New, beyond normal variant\textsuperscript{7} | Evidence of diffuse or focal depressed left ventricular function of indeterminate age | Not performed or normal |
| Probable Myocarditis            | Same as Suspect   | **Cardiac enzymes:** Elevated cTnT, cTnI or CK-MB\textsuperscript{*}  
**ECG findings:** New, beyond normal variant\textsuperscript{7} | Evidence of focal or depressed left ventricular function that is documented new onset or increased severity\textsuperscript{‡}; myocardial inflammation | Not performed or normal |
| Confirmed Myocarditis           | Same as Probable  | **Cardiac enzymes and ECG findings:** Not performed, normal or abnormal\textsuperscript{7} | 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\textsuperscript{7} | Not performed, normal, or abnormalities not described below | Not performed or normal |
| Probable Pericarditis           | Same as Suspect 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\textsuperscript{*} | Not performed, normal, or abnormal | Evidence of pericardial inflammation |

\textbf{FOOTNOTES:}  
\textsuperscript{*}**Cardiac enzymes:** Cardiac-specific troponin I (cTnI) or T (cTnT) preferred but includes creatine kinase-myocardial band (CK-MB).  
\textsuperscript{†}**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.  
\textsuperscript{2}**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.  
\textsuperscript{‡}**ECG findings:** Electrocardiogram findings not previously documented or resolving. [Adapted (15): https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5221a2.htm#box.]
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Hypersensitivity MPC as a drug/vaccine induced cardiac adverse event has been a long term concern in the context of post-licensure safety surveillance as well as pre-licensure safety data submission for licensure. Other cardiac adverse events such as dilated cardiomyopathy also were defined in the smallpox vaccine CDC definitions for adverse events after smallpox vaccination in 2006 (8). In addition, multiple think tanks have been initiated to attempt to develop and improve the definition and adjudication of post-vaccination cardiovascular events (5,6). We created the current case definitions for myocarditis and pericarditis as AEFI building from team experience and lessons learnt. Consideration of other etiologies and causal relationship must be established and is outside the purview of this document.

Methods for the Development of the Case Definition and Guidelines for Data Collection, Analysis, and Presentation of Myocarditis or Pericarditis as AEFI

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 guidelines published by Kohl et al. (19). Members had pertinent experience in clinical, academic, public health, vaccinology, epidemiology, and pharmacovigilance approaches. Decision-making for the case definition and guidelines was based on a comprehensive literature review. To achieve consensus for this document, the Working Group considered past experiences with case definitions to include considerations important to experienced adjudicators.

Clinicians involved in the adjudication and case evaluations over time provided feedback as to the deficiencies of the 2003 definitions particularly in view of the evolving understanding for measuring and interpreting cardiac injury and the low frequency of cardiac biopsies, often clinically unavailable in diverse settings and less indicated given the precision of cardiac magnetic resonance imaging (CMR) over time. 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 diagnostic coding systems do not offer a code for myopericarditis.

Prevalence and Background rates of Myocarditis/Pericarditis

The prevalence of myocarditis and pericarditis is poorly understood because many cases resolve without detection, have overlap features making a diagnosis of myopericarditis more accurate, and access to diagnostic tools may be limited. (1,2). The incidence of myocarditis, as ascertained by the International Classification of Diseases, 9th Revision diagnoses, was 22 per 100,000 people or approximately 1.5 million cases in the 2013 world population (with prevalence estimated at 9.1 per 100,000) (8). However, this number varies greatly by country, setting, and 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 initial epidemiologic 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 prospective 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 or EKG), etc.) and a relative risk compared to a cohort of influenza vaccinees of 4.0 (95% confidence interval 1.7-9.3) (5). These data were consistent with FDA submitted clinical trial safety data reflected in the current package insert for ACAM2000® (20). The possibility of subclinical myocarditis in military prospective study was supported by some of the data (5). In the U.S. civilian population using stimulated passive surveillance, post smallpox vaccination myocarditis prevalence rate in 2003 was estimated at 5.5 per 100,000 population (21). More recently, development of MPC after COVID-19 m-RNA vaccination occurred in multiple reports with unclear frequency. The CDC reported the highest risk in males 12-29 years with 40.6 cases per million second doses of mRNA COVID-19 vaccines. Females of the same age experience 4.2 per million second doses. Fewer reports occur in older individuals.
Etiology and Risk Factors of Myocarditis and Pericarditis

Pericarditis and myocarditis share similar etiologies and risk factors, which include infectious, non-infectious and idiopathic (Table 2). In the majority of cases, myocarditis/pericarditis is classified as idiopathic. Viral infection is the most common infectious cause of myocarditis/pericarditis in developed countries. Now SARS-CoV-2 also has become one of the viral causes of myocarditis/pericarditis in both developed and developing countries (22). Most bacterial causes, with the exception of diphtheria (Golpour et al, 2021), are less common with tuberculosis being the major cause in developing countries. Non-infectious causes include immune-mediated diseases, systemic inflammatory diseases, systemic diseases, hypersensitivity to drugs, vaccines, and toxins (23). [17]

Table 2. Etiologies of myocarditis 1,2 and pericarditis 22-24

<table>
<thead>
<tr>
<th>Infectious causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Viruses: Coxsackievirus, adenoviruses, herpes viruses, echovirus, Epstein-Barr virus, cytomegalovirus,</td>
</tr>
<tr>
<td>influenza virus, hepatitis C virus, parvovirus B19, Rubella, Dengue, HIV, SARS-CoV-2</td>
</tr>
<tr>
<td>● Bacterial: Mycobacterium tuberculosis, Streptococci, Staphylococci, Haemophilus influenzae, Borellia</td>
</tr>
<tr>
<td>burgdorferi, Legionella, Mycoplasma</td>
</tr>
<tr>
<td>● Fungal: Histoplasma, Aspergillus, Blastomyces, Coccidiodomyces</td>
</tr>
<tr>
<td>● Parasites: Toxoplasma, Amebae, Chagas disease</td>
</tr>
<tr>
<td>Non-infectious causes</td>
</tr>
<tr>
<td>● Systemic inflammatory diseases: Lupus, rheumatoid arthritis, scleroderma, Sjogren, mixed connective</td>
</tr>
<tr>
<td>tissue disease</td>
</tr>
<tr>
<td>● Other inflammatory conditions: Granulomatosis, inflammatory bowel disease</td>
</tr>
<tr>
<td>● Metastatic cancers: Especially lung cancer, breast cancer, melanoma</td>
</tr>
<tr>
<td>● Primary cardiac tumors: Rhabdomyosarcoma</td>
</tr>
<tr>
<td>● Metabolic: Hypothyroidism, Renal failure/uremia</td>
</tr>
<tr>
<td>● Post-radiation to the chest cavity</td>
</tr>
<tr>
<td>● Trauma to the chest cavity</td>
</tr>
<tr>
<td>● Drugs (cardiotoxic effects or hypersensitivity reactions): procainamide, isoniazid, hydralazine, alcohol,</td>
</tr>
<tr>
<td>anthracycline, heavy metals</td>
</tr>
<tr>
<td>● Post-radiation to the chest cavity</td>
</tr>
<tr>
<td>● Immunizations (hypersensitivity reactions): Smallpox, Diphtheria-tetanusacellular pertussis (DTaP),</td>
</tr>
<tr>
<td>diphtheria, tetanus, polio, and Sars-CoV-2 vaccines, influenza and vaccine combinations.</td>
</tr>
<tr>
<td>Ref:1,2,3</td>
</tr>
</tbody>
</table>

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. (25,26).

In the setting of 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). (27). In patients with self-controlled immune responses, the infection is cleared and the inflammatory process downregulates (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 (25,27).

An alternative possibility for pathophysiology of 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 and is defined as inflammation, usually with lymphocytic and eosinophilic infiltration, of the myocardium. This is often linked to drug reactions but has also been seen with
autoimmune diseases and environmental factors (13,28). Studies after smallpox vaccination have demonstrated mixed eosinophilic-lymphocytic myocarditis and myocyte necrosis in patients presenting with symptoms of myocarditis (28).

**Diagnosis of Myocarditis and Pericarditis**

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 new onset 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. One must consider myocarditis and pericarditis in the differential diagnosis of acute onset chest or abdominal pain, difficulty breathing, 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. (30). If cardiac enzymes are positive, then the case classification is myocarditis with potential features of pericarditis.

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

<table>
<thead>
<tr>
<th>Symptoms (New onset, acute)</th>
<th>Myocarditis</th>
<th>Pericarditis</th>
<th>Both, Overlap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain, pressure, tightness</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Positional changes in chest pain</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Dyspnea, after exercise or at rest</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Fatigue, malaise</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Palpitations</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Syncope or near-syncope</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Peripheral edema (rare)</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Fever</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Fatigue</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

**Infant < 6 months of age**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Myocarditis</th>
<th>Pericarditis</th>
<th>Both, Overlap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor feeding</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Vomiting</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Irritability</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Lethargy</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

**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 outlined in **Table 4**.

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

<table>
<thead>
<tr>
<th>Markers of myonecrosis</th>
<th>Creatine Kinase (CK-MB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troponin I or T</td>
<td></td>
</tr>
<tr>
<td><strong>Less Specific</strong></td>
<td></td>
</tr>
<tr>
<td>Lactate dehydrogenase (LDH)</td>
<td></td>
</tr>
<tr>
<td>Alanine transaminase (ALT)</td>
<td></td>
</tr>
<tr>
<td>Aspartate transaminase (AST)</td>
<td></td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Inflammatory Markers</th>
<th>White blood cell count – leukocytosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C-reactive Protein</td>
</tr>
<tr>
<td></td>
<td>D-dimer</td>
</tr>
<tr>
<td></td>
<td>Erythrocyte sedimentation rate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Biomarkers</th>
<th>Interleukin -10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Auto-antibodies:</td>
</tr>
<tr>
<td></td>
<td>ANA</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid factor</td>
</tr>
<tr>
<td></td>
<td>Anti-topoisomerase</td>
</tr>
<tr>
<td></td>
<td>Anti-myosin</td>
</tr>
<tr>
<td></td>
<td>Anti-beta-adrenergic receptor</td>
</tr>
</tbody>
</table>

Cardiac Specific Diagnostic Tests

Electrocardiogram (ECG)

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

Imaging Diagnosis

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 (35). 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 when compared to cardiomyopathy (36). Transient increase in interventricular septum and left ventricular wall thickness can be seen in the early stages of myocarditis, even before significant contractility decline (37). 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 (38). Pericardial effusion, intra-cavity thrombus, and wall aneurysms can easily be detected by echocardiography. Transesophageal echocardiography is the gold standard for echo 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 which 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 correlate well with the presence of myocardial edema demonstrated on cardiac MRI (39,40).

Cardiac Magnetic Resonance (CMR)

CMR has become a very effective, non-invasive tool in the evaluation of myocarditis. The International Consensus Group on CMR Diagnosis of Myocarditis, founded in 2006, has developed recommendations on the use of CMR for myocarditis, and came up with protocol standards, terminology of reporting, and diagnostic criteria (Table 5) (41). In 2009, Lake Louise CMR criteria for diagnosis of myocarditis included the presence of two out of three changes: tissue edema, early enhancement, and late enhancement resulting in a sensitivity of 72.5% and specificity of 96.2% (42,43). 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 indicates tissue edema, increase T2 relaxation times. In addition, T1-weighted images demonstrating early Gadolinium enhancement indicating 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 (41).

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 (44,45). Although neither specific nor sensitive for myocarditis, evaluation of myocarditis necessitates functional assessment which correlates with severity and prognosis. Functional derangements/ depressed ejection fraction in myocarditis may include global dysfunction, regional wall dysfunction or measurable functional derangement.

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

<table>
<thead>
<tr>
<th>Pericarditis</th>
<th>Myocarditis</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG</td>
<td>Sinus tachycardia, ST elevation, T wave inversion (common) QT prolongation, QRS deviation (less common) Conduction issues: AV block, bundle branch block, intraventricular conduction delay (46,47) Tachyarrhythmias: SVT, atrial fibrillation, PVCs, VT, VF (5,48)</td>
<td>Low cost Non-invasive Safe Available in all centers/countries</td>
<td>Findings are usually non-specific</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>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</td>
<td>Low/medium cost Non-invasive Safe/ Generally no contraindications Available in most centers/countries Reasonable sensitivity in severe disease</td>
<td>Findings may not be specific Low sensitivity in mild disease Needs some level of experience/ special equipment</td>
</tr>
<tr>
<td>CMR</td>
<td>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</td>
<td>More sensitive than echo Criteria well established Reasonable safety</td>
<td>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 income countries Needs high level of experience/ special equipment</td>
</tr>
<tr>
<td>Histopathologic diagnosis (through biopsy)</td>
<td>Evidence of inflammation of the pericardium can be diagnostic, analysis of pericardial tissue and fluid inflammatory infiltrate within the myocardium Evidence of myocyte necrosis.</td>
<td>Highly specific when positive Provides evidence towards etiology (i.e. PCR for viral myocarditis, specific inflammatory cells such as eosinophilic infiltrate</td>
<td>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</td>
</tr>
</tbody>
</table>
For many years, the diagnosis of myocarditis relied primarily on histopathological features attained by tissue sampling. This may be done with autopsy specimen examination, or through obtaining an endomyocardial biopsy (EMB). EMB has been considered by many cardiologists as the gold standard for diagnosis. EMB is done using a biotome inserted into the right ventricle via a major venous access and obtaining 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 (49), has been the primary diagnostic tool for myocarditis over the past three decades. It requires an inflammatory infiltrate and associated myocyte necrosis or damage in the absence of ischemic characteristics. The criteria allowed 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 (50). Polymerase chain reaction to detect viral genomes has also been helpful to determine the etiology in case of post-viral myocarditis (51,52). Obviously, the demonstration of these findings requires that the biopsy be representative of the inflamed myocardium. It has been shown that the more the tissue is obtained, the more the sensitivity of the histopathological diagnosis becomes. The sensitivity reached 79% when an average of 17 tissue samples per patient were analyzed (53).

The lack of homogeneous inflammatory process leads to the low sensitivity and those with patchy involvement will have high rates of false negative biopsies. To increase the sensitivity of histopathological diagnosis, CMR guidance for biopsy site (54) and intracardiac electrocardiogram assessment at biopsy site (55,56) have been utilized.

Despite being of good value for diagnosis of inflammation as well as its etiology, EMB has significant limitations, (57), see table 5. Therefore, and with emergence of other non-invasive technologies that provide important diagnostic abilities, biopsies have fallen out of favor by many clinicians in practice.

### Myocarditis/Pericarditis after COVID-19

Even though 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) (58). Of 62 deceased patients, 30% have shown acute myocardial injury and 20% have shown acute heart failure in a cohort of 671 severely ill hospitalized COVID-19 patients (59). Surprisingly, a small number of hospitalized COVID-19 patients developed CVD without any manifestations of the respiratory system disease (60). In addition, mortality has been found to be very high in COVID-19 patients with cardiovascular complications than those without them (60% vs. 9%) (61). 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 and it was generally described as myocardial injury characterized by an increase in troponin levels. [1] Some of the proposed mechanisms of troponin release in COVID-19 patients include myocardial injury induced directly by the SARS-CoV-2 virus, systemic hyperinflammatory response, hypoxemia, downregulation of angiotensin-converting enzyme 2, systemic endothelialitis, and type 1 and type 2 myocardial infarction. [66, 67]

Most of the COVID-19 patients with myocarditis were in the fifth decade of their life with both the genders equally affected (62). The predominant complaints on presentation were dyspnea followed by coughing, fever, and chest pain (63). There is a lack of a precise morphological and functional characterization of the heart in these patients. ECG revealed ST-segment elevation in majority of the cases and inverted T waves in some cases (62,63). In many cases, 2D-echocardiogram revealed decreased left ventricular ejection fraction, and cardiomegaly or increased wall thickness were also observed (62,63). CMR revealed late gadolinium enhancement in all these patients, and myocardial edema.
was seen in some patients (64). Viral particles in myocardium were found in only one of the two cases in which endomyocardial biopsy was done (65).

In myocarditis due to SARS-CoV-2, the mechanisms of myocardial injury are not well established, but they likely involve an increase in cardiac stress due to respiratory failure as well as hypoxemia, acute coronary syndrome (ACS), indirect lesion from the systemic inflammatory response, direct myocardial infection, and other factors (66,67).

Rare case reports of pericarditis in COVID-19 patients and pericardial involvement as an extra-pulmonary manifestation of COVID-19 exist (68,69). One report demonstrated a patient presenting with isolated pericarditis with no other COVID-19 symptoms or signs (70). These cases demonstrated pericardial effusion and cardiac tamponade requiring therapeutic pericardiocentesis. Pericardial fluid analysis had shown mainly exudative fluid with high polymorphonuclear cells, proteins and LDH, with bloody exudative fluid in two patients (71). The exact mechanism is unclear though it is plausible that SARS-CoV-2 elicits an inflammatory response similar to other viruses that cause pericarditis.

Cases of stress cardiomyopathy (takotsubo syndrome) have been found to be increased due to COVID-19 even though 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 (67). 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.

Myocarditis and pericarditis post COVID-19 vaccines is a focus of interest for current vaccine safety surveillance efforts in the United States and globally (https://www.webmd.com/vaccines/covid-19-vaccine/news/20210524/cdc-post-covid-vaccine-heart-inflammation) with increasing numbers of cases being seen after mRNA vaccination particularly in males 15-30 years old.

**Guidelines for data collection, analysis and presentation**
The 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.

**Periodic review**
Similar to all Brighton Collaboration case definitions and guidelines, review of the definition with its guidelines is planned on a regular basis or as needed.
CASE DEFINITIONS:

The purpose of these case definitions is to be able to ascertain cases of myocarditis and pericarditis. The case definition of myocarditis has 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.

Considerations relevant to both Myocarditis and Pericarditis:

The purpose of the case definition is to be able to ascertain a case of myocarditis or pericarditis in the context of safety assessments after immunization. It is not the purpose of the case definition to assess severity or causality. It is important to remember that myocarditis and pericarditis are a spectrum of illnesses and frequently occur in combination. If symptoms of both exist, each case definition should be evaluated independently and reported with a level of certainty for each diagnosis (may not be the same LOC for each diagnosis).

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 diagnostic, and may depend on variables like clinical status, time to treatment, and other clinical parameters.

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., immunizations). Therefore, to avoid selection bias, a restrictive time interval from immunization to onset of myocarditis or pericarditis should not be an integral part of the case definition. Instead, where feasible, details of this interval should be assessed and reported as described in the data collection guidelines.

Further, myocarditis and pericarditis often occur outside the controlled setting of a clinical trial or hospital. In some settings it may be impossible to obtain a clear timeline of the event, particularly in disadvantaged settings. In order to avoid selecting against such cases, the Brighton Collaboration case definition avoids setting arbitrary time frames. However, 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 of viral illness or insult. As such, either event occurring within these respective time frames after immunization is more likely to represent a vaccine induced event due to the appropriate temporal association.

CASE DEFINITION: Myocarditis

Rationale for selected decisions about the case definition of myocarditis as an adverse event following immunization

It is important to note that the grading of definition levels is entirely about diagnostic certainty, not clinical severity of an event. Thus, a clinically very severe event may appropriately be classified as Level 2 or 3 rather than Level 1. Additional detailed information about the severity of the event should always be recorded, as specified by the data collection guidelines.

The term myocarditis

Myocarditis refers to 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 frequently inflammation of one leads to or includes inflammation of the other. The evaluation for, and diagnosis of, myocarditis/pericarditis is similar independent of the individual disease processes.

Related terms of myocarditis

Alternative terminology for myocarditis includes inflammatory cardiomyopathy, cardiac inflammation, myocardial inflammation, idiopathic myocarditis, and viral myocarditis. The continuum of myocarditis and pericarditis may be referred to as myopericarditis or perimyocarditis when inflammation of both the myocardium and pericardium are involved.
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 Appendix B, with an algorithm shown in Figure 1. There are 2 ways to reach LOC 1, a definitive diagnosis, including when myocardial edema is present on EMB or autopsy or with elevated cardiac enzymes and imaging studies suggestive of myocarditis with edema on CMR with/without delayed enhancement or an echocardiogram with abnormal function, segmental dyskinesis, abnormal strain, or echo-brightness. A probable case, LOC 2, requires symptoms and at least one abnormal test including ECG, echocardiogram, or elevated cardiac biomarker. A possible case, LOC 3, relies on clinical findings and abnormal inflammatory markers or an ECG without characteristic findings of myocarditis.

The symptoms that must be present vary by age of the individual. Infants have more systemic symptoms including irritability, vomiting and poor feeding. Older individuals including children and adults, may present with cardiac symptoms including dyspnea after exercise, at rest or lying down, diaphoresis, palpitations, acute chest pain/pressure, or sudden death or with non-specific symptoms including fatigue, abdominal pain, dizziness/syncope, edema, or cough.

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

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

One of the greatest challenges to the diagnosis of myocarditis is the lack of specific symptoms. Instead, there may be no symptoms or only vague non-specific general symptoms. Occasionally the symptoms can be confused with other cardiac problems such as a myocardial infarction.

Use of physical examination findings

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

Rationale for histopathology as definitive diagnosis

Histopathology has long been considered the gold standard for diagnosis of myocarditis. 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 may be directed by prior CMR, if available, to increase the likelihood of obtaining a sample from an affected area of myocardium. (83).

Rationale for imaging findings

The Working Group looked at standardized recommendations for imaging findings in myocarditis. CMR criteria as described above (Table 5) include tissue and functional evaluation. Echocardiogram is more commonly available throughout the world. Important echocardiographic findings are described above and include primarily functional and shape evaluation. Finally, as ECG is available essentially worldwide we considered it as a diagnostic test though the findings are less specific for myocarditis and may be seen in other cardiac entities. Common findings are described above and shown in Table 5.

Rationale for coronary artery disease (CAD) exclusion in adults

Other etiologies of myocardial inflammation should not be included in this definition. CAD and myocardial infarction can cause myocardial inflammation, not necessarily secondary to a primary viral, bacterial or inflammatory process and thus would not be considered in this definition.

Rationale for laboratory findings

Cardiac enzymes

Elevated cardiac enzymes, including troponin I/T and CKMB, indicate myocardial damage. In the setting of other findings associated with myocarditis, elevated troponin assists in the definitive diagnosis of myocarditis.
Other supporting laboratory tests
Other markers of inflammation, including C-reactive protein, erythrocyte sedimentation rate, and D-dimer, can provide evidence of inflammation and with appropriate supporting symptoms may lead to a possible case of myocarditis.

Table 6 – Myocarditis Case Definition and Levels of Diagnostic Certainty

<table>
<thead>
<tr>
<th>Level of Certainty 1 (Definitive Case)</th>
<th>Histopathologic examination of myocardial tissue (autopsy or endomyocardial biopsy) showed myocardial inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>Elevated myocardial biomarkers (at least 1 of the findings below)</td>
</tr>
<tr>
<td></td>
<td>Troponin T</td>
</tr>
<tr>
<td></td>
<td>Troponin I</td>
</tr>
<tr>
<td></td>
<td>AND</td>
</tr>
<tr>
<td></td>
<td>Abnormal Imaging study (at least 1 of the findings below)</td>
</tr>
<tr>
<td></td>
<td>Abnormal Cardiac Magnetic Resonance Study (at least 1 of the findings below)</td>
</tr>
<tr>
<td></td>
<td>Edema on T2 weighted study, typically patchy in nature</td>
</tr>
<tr>
<td></td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>Abnormal Echocardiogram (at least 1 of the findings below)</td>
</tr>
<tr>
<td></td>
<td>New focal or diffuse left or right ventricular function abnormalities (eg. decreased ejection fraction)</td>
</tr>
<tr>
<td></td>
<td>Segmental wall motion abnormalities</td>
</tr>
<tr>
<td></td>
<td>Global systolic or diastolic function depression/abnormality</td>
</tr>
<tr>
<td></td>
<td>Ventricular dilation</td>
</tr>
<tr>
<td></td>
<td>Wall thickness change</td>
</tr>
<tr>
<td></td>
<td>Intracavitary thrombi</td>
</tr>
</tbody>
</table>
## Level of Certainty 2 (Probable Case)

<table>
<thead>
<tr>
<th>Clinical Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Symptoms (at least 1 finding below)</td>
</tr>
<tr>
<td>Acute chest pain or pressure</td>
</tr>
<tr>
<td>Palpitations</td>
</tr>
<tr>
<td>Dyspnea after exercise, at rest, or lying down</td>
</tr>
<tr>
<td>Diaphoresis</td>
</tr>
<tr>
<td>Sudden Death</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>Non-Specific Symptoms (at least 2 findings below)</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Dizziness/Syncope</td>
</tr>
<tr>
<td>Edema</td>
</tr>
<tr>
<td>Cough</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>Infants and young Children(at least 2 findings below)</td>
</tr>
<tr>
<td>Irritability</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Poor feeding</td>
</tr>
<tr>
<td>Tachypnea</td>
</tr>
<tr>
<td>Lethargy</td>
</tr>
</tbody>
</table>

**AND**

<table>
<thead>
<tr>
<th>Testing supporting diagnosis (Biomarkers, ECHO, and ECG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated myocardial biomarkers (at least 1 of the findings below)</td>
</tr>
<tr>
<td>Troponin T</td>
</tr>
<tr>
<td>Troponin I</td>
</tr>
<tr>
<td>CK Myocardial Band</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>Echocardiogram (ECHO)</td>
</tr>
<tr>
<td>New focal or diffuse left or right ventricular function abnormalities (e.g., decreased ejection fraction)</td>
</tr>
<tr>
<td>Segmental wall motion abnormalities</td>
</tr>
<tr>
<td>Global systolic or diastolic function depression/abnormality</td>
</tr>
<tr>
<td>Ventricular dilation</td>
</tr>
<tr>
<td>Wall thickness change</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>Electrocardiogram (EKG) abnormalities that are new and/or normalize on recovery(at least 1 of the findings below)</td>
</tr>
<tr>
<td>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)</td>
</tr>
</tbody>
</table>
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

**Cardiac Symptoms** (at least 1 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 2 findings below)
- Fatigue
- Abdominal pain
- Dizziness/Syncope
- Edema
- Cough

**OR**

**Infants and young Children** (at least 2 findings below)
- Irritability
- Vomiting
- Poor feeding
- Tachypnea
- Lethargy

**AND**

**Testing supporting diagnosis (Biomarkers and ECG)**

**Elevated biomarkers supporting evidence of inflammation (at least 1 of the findings below)**
- Elevated CRP
- Elevated ESR
- Elevated D-dimer

**OR**

**Electrocardiogram (EKG) 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

CASE DEFINITION: Pericarditis

Rationale for selected decisions about the case definition of pericarditis as an adverse event following immunization

The term pericarditis
Pericarditis is inflammation of the pericardium with the associated symptoms without an ischemic cause.

Related terms of pericarditis
Alternative terminology for pericarditis includes inflammatory pericarditis, pericardial inflammation, idiopathic pericarditis, viral pericarditis, and inflamed pericardial sac. In the continuum of myocarditis and pericarditis, when both the myocardium and pericardium are inflamed it is referred to as myopericarditis or perimyocarditis.

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 Appendix C with an algorithm shown in Figure 2. Level of certainty 1, a definitive diagnosis, is obtained when edema or an inflammatory infiltrate on a pericardial biopsy or at autopsy is present. Additionally, abnormal testing in at least 2/3 testing areas including abnormal fluid collection or pericardial inflammation determined by imaging, characteristic ECG changes or characteristic physical examination findings for pericarditis can meet LOC 1. A probable case, LOC 2, requires symptoms and physical examination findings or imaging suggestive of abnormal fluid collection or abnormal findings on ECG. A possible case, LOC3, requires symptoms, and either non-specific ECG changes or an enlarged heart on chest X-ray.

Rationale for individual criteria or decision made related to the case definition
Factors important for the diagnosis of pericarditis include clinical, laboratory, imaging and pathology findings.

Selection of clinical symptoms for the case definition of myocarditis (clinical presentation)
One of the greatest challenges to the diagnosis of pericarditis is the lack of specific symptoms. Instead, there may be no symptoms or vague generalized symptoms. Occasionally the symptoms can be confused with other cardiac problems such as a myocardial infarction and myocarditis.

Prioritization of symptoms for pericarditis
Symptoms vary by individual’s 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 including cough, weakness, shoulder/upper back pain, GI symptoms (nausea, vomiting, diarrhea), cyanosis, low grade intermittent fever, altered mental status, edema, or fatigue.

Prioritization of physical findings for pericarditis
Physical examination findings provide helpful information for the diagnosis of pericarditis. Even though the physical examination findings of pericarditis may overlap with those of other cardiac entities including cardiomyopathy and heart failure, some are more specific to pericarditis. The physical examination findings include a 3 part pericardial friction rub, distant heart sounds, pulsus paradoxus, hypotension, and venous distension. Additionally, pericarditis is frequently accompanied by examination findings of the underlying cause of pericarditis such as bacterial or viral etiologies.

Clinical symptom relevance for each level
Symptoms must be present to consider pericarditis. However, with confirmative testing, the symptoms present are not specifically necessary to confirm the diagnosis of pericarditis. With decreasing degree of certainty in the confirmative testing, reliance on more specific and common symptoms for pericarditis becomes important to increase the pre-test probability and likelihood of appropriate diagnosis for the lower levels of certainty. Additionally, physical examination findings specific for diagnosis of pericarditis are included for lower levels of certainty.

Rationale for histopathology as definitive diagnosis
Evaluation for areas of local inflammation in pericardium can definitively diagnose pericarditis and, frequently, the cause of pericarditis with appropriate tissue testing.

**Rationale for imaging findings**

Standardized recommendations for imaging findings in pericarditis are available. CMR criteria for diagnosis of pericarditis includes thickening on black blood imaging (84), acute or subacute pericardial edema/inflammation, enhancement on LGE (94–100% sensitive) (85). Echocardiogram is more commonly available throughout the world. Common findings in pericarditis include pericardial effusion. ECG is available essentially worldwide and thus necessary to include as a diagnostic test for pericarditis. Four stages of ECG changes have been described during acute pericarditis (86). These stages involve diffuse, upwardly concave ST-segment elevation, T-wave inversion, and PR-segment depression (87,88).

**Rationale for CAD exclusion in adults**

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

**Table 7. Pericarditis Case Definition and Levels of Diagnostic Certainty**

<table>
<thead>
<tr>
<th>Level of Certainty 1 (Definitive Case)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Histopathologic examination of myocardial tissue (autopsy or pericardial biopsy) showed pericardial inflammation</td>
<td>OR</td>
</tr>
<tr>
<td>Abnormal testing need at least 2/3 of the following:</td>
<td></td>
</tr>
<tr>
<td>Evidence of abnormal fluid collection or pericardial inflammation by imaging (Echo, MR, cMR, CT)</td>
<td>OR</td>
</tr>
<tr>
<td>Electrocardiogram (EKG) Abnormalities that are new and/or normalize on recovery (must have all findings)</td>
<td></td>
</tr>
<tr>
<td>Diffuse concave-upward ST-segment elevation</td>
<td></td>
</tr>
<tr>
<td>ST-segment depression in aVR</td>
<td></td>
</tr>
<tr>
<td>PR-depression throughout the leads without reciprocal ST-segment changes</td>
<td>OR</td>
</tr>
<tr>
<td>Physical examination finding: at least 1 finding</td>
<td></td>
</tr>
<tr>
<td>Pericardial friction rub</td>
<td></td>
</tr>
<tr>
<td>Distant heart sounds (infants and children)</td>
<td></td>
</tr>
<tr>
<td>Pulsus paradoxus</td>
<td></td>
</tr>
<tr>
<td>Level of Certainty 2 (Probable Case)</td>
<td></td>
</tr>
<tr>
<td>------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>Cardiac Symptoms (at least 1 finding below)</td>
<td></td>
</tr>
<tr>
<td>Acute chest pain or pressure</td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td></td>
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<tr>
<td>Dyspnea after exercise, at rest, or lying down</td>
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<tr>
<td>Diaphoresis</td>
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<tr>
<td>Sudden Death</td>
<td></td>
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<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>Infants and young Children (at least 2 findings below)</td>
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</tr>
<tr>
<td>Irritability</td>
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<tr>
<td>Vomiting</td>
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<td>Poor feeding</td>
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<tr>
<td>Tachypnea</td>
<td></td>
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<tr>
<td>Lethargy</td>
<td></td>
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<tr>
<td>AND</td>
<td></td>
</tr>
<tr>
<td>Physical examination findings: (at least 1 finding)</td>
<td></td>
</tr>
<tr>
<td>Pericardial friction rub</td>
<td></td>
</tr>
<tr>
<td>Pulsus paradoxus</td>
<td></td>
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<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>Evidence of abnormal fluid collection or pericardial inflammation by imaging (ECHO, MR, cMR, CT)</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>Electrocardiogram (EKG) abnormalities that are new and/or normalize on recovery (at least 1 finding below)</td>
<td></td>
</tr>
<tr>
<td>Diffuse concave-upward ST-segment elevation</td>
<td></td>
</tr>
<tr>
<td>ST-segment depression in aVR</td>
<td></td>
</tr>
<tr>
<td>PR-depression throughout the leads without reciprocal ST-segment changes</td>
<td></td>
</tr>
<tr>
<td>AND</td>
<td></td>
</tr>
<tr>
<td>No alternative diagnosis for symptoms (MI, PE, mediastinitis, etc.)</td>
<td></td>
</tr>
</tbody>
</table>
### Level of Certainty 3 (Possible Case)

#### Clinical Symptoms

**Cardiac Symptoms (at least 1 finding below)**
- New onset cardiac chest pain or pressure
- Palpitations
- Dyspnea after exercise, at rest, or lying down

**Non-Specific Symptoms (at least 2 findings below)**
- Cough
- Weakness
- Gastrointestinal – nausea, vomiting, diarrhea
- Shoulder/upper back pain
- Cyanosis
- Low grade intermittent fever
- Altered mental status
- Edema
- Fatigue

#### Infants and young Children (at least 2 findings below)

- Irritability
- Vomiting
- Poor feeding
- Tachypnea
- Lethargy

**AND**

#### Abnormal testing supporting diagnosis

- Abnormal chest radiograph showing enlarged heart

**OR**

- Electrocardiogram (EKG) abnormalities that are new and/or normalize on recovery

**AND**

- No alternative diagnosis for symptoms (MI, PE, mediastinitis, etc.)
References:


Cardiovascular Injury CEPI-Brighton Working Group Draft Contributions
S. Kristen Tejtel – 28 MAR 2021


Cardiovascular Injury CEPI-Brighton Working Group Draft Contributions
S. Kristen Sexson Tejel – 28 MAR 2021


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Appendices
Appendix A

GUIDELINES FOR DATA COLLECTION, ANALYSIS AND PRESENTATION OF MYOCARDITIS AND PERICARDITIS

It was the consensus of the Brighton Collaboration Myocarditis and Pericarditis Working Group to recommend the following guidelines to enable meaningful and standardized collection, analysis, and presentation of information about myocarditis and pericarditis. However, implementation of all guidelines might not be possible in all settings. The availability of information may vary depending upon resources, geographical region, and whether the source of information is a prospective clinical trial, a post-marketing surveillance or epidemiological study, or an individual report of myocarditis and pericarditis. Also, as explained in more detail in the overview paper in this volume, these guidelines have been developed by this Working Group for guidance only, and are not to be considered a mandatory requirement for data collection, analysis, or presentation.

1.1. Data collection

These guidelines represent a desirable standard for the collection of data on availability following immunization to allow for comparability of data and are recommended as an addition to data collected for the specific study question and setting. The guidelines are not intended to guide the primary reporting of myocarditis and pericarditis to a surveillance system or study monitor. Investigators developing a data collection tool based on these data collection guidelines also need to refer to the criteria in the case definition, which are not repeated in these guidelines.

Guidelines 1-43 below have been developed to address data elements for the collection of adverse event information as specified in general drug safety guidelines by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and the form for reporting of drug adverse events by the Council for International Organizations of Medical Sciences (CIOMS). These data elements include an identifiable reporter and patient, one or more prior immunizations, and a detailed description of the adverse event, in this case, of myocarditis or pericarditis following immunization. The additional guidelines have been developed as guidance for the collection of additional information to allow for a more comprehensive understanding of myocarditis or pericarditis following immunization.

1.1.1. Source of information/reporter

For all cases and/or all study participants, as appropriate, the following information should be recorded:

1) Date of report.

2) Name and contact information of person reporting and/or diagnosing the myocarditis or pericarditis as specified by country-specific data protection law.

3) Name and contact information of the investigator responsible for the subject, as applicable.

4) Relation to the patient (e.g., immunizer [clinician, nurse], family member [indicate relationship], other).

1.1.2. Vaccinee/Control

1.1.2.1. Demographics

For all cases and/or all study participants, as appropriate, the following information should be recorded:

5) Case/study participant identifiers (e.g. first name initial followed by last name initial) or code (or in accordance with country-specific data protection laws).

6) Date of birth, age, and sex.

7) For infants: Gestational age and birth weight.

1.1.2.2. Clinical and immunization history

For all cases and/or all study participants, as appropriate, the following information should be recorded:
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8) Past medical history, including hospitalizations, underlying diseases/disorders, pre-immunization signs and symptoms including identification of indicators for, or the absence of, a history of allergy to vaccines, vaccine components or medications; food allergy; allergic rhinitis; eczema; asthma.

9) Any medication history (other than treatment for the event described) prior to, during, and after immunization including prescription and non-prescription medication as well as medication or treatment with long half-life or long term effect. (e.g. immunoglobulins, blood transfusion and immunosuppressants).

10) Immunization history (i.e. previous immunizations and any adverse event following immunization (AEFI)), in particular occurrence of myocarditis or pericarditis after a previous immunization.

1.1.3. Details of the immunization
For all cases and/or all study participants, as appropriate, the following information should be recorded:

11) Date and time of immunization(s).

12) Description of vaccine(s) (name of vaccine, manufacturer, lot number, dose (e.g. 0.25mL, 0.5 mL, etc) and number of dose if part of a series of immunizations against the same disease).

13) The anatomical sites (including left or right side) of all immunizations (e.g. vaccine A in proximal left lateral thigh, vaccine B in left deltoid).

14) Route and method of administration (e.g. intramuscular, intradermal, subcutaneous, and needle-free (including type and size), other injection devices).

15) Needle length and gauge.

1.1.4. The adverse event
16) For all cases at any level of diagnostic certainty and for reported events with insufficient evidence, the criteria fulfilled to meet the case definition should be recorded.

Specifically document:

17) Clinical description of signs and symptoms of myocarditis or pericarditis, and if there was medical confirmation of the event (i.e. patient seen by physician).

18) Date/time of onset\(^2\), first observation\(^3\), end of episode\(^4\), and final outcome\(^6\).

19) Concurrent signs, symptoms, and diseases.

20) Measurement/testing
   - Values and units of routinely measured parameters (e.g. temperature, blood pressure, cardiac enzymes, ECG values, etc) – in particular those indicating the severity of the event;
   - Method of measurement (e.g. type of thermometer, oral or other route, duration of measurement, etc.);
   - Results of laboratory examinations, surgical and/or pathological findings and diagnoses if present.

21) Treatment given for myocarditis or pericarditis, especially the following:
   - **Myocarditis** - Supportive treatment (ECMO, pacing), prednisone, IVIG
   - **Pericarditis** – Pericardiocentesis, Aspirin, Colchicine, Prednisone

22) Outcome\(^6\) at last observation.

23) Objective clinical evidence supporting classification of the event as “serious” \(^7\).

24) Exposures other than the immunization 24 hours before and after immunization (e.g. other treatments or procedures, environmental) considered potentially relevant to the reported event.
1.1.5. Miscellaneous/ General

25) The duration of surveillance for myocarditis or pericarditis should be predefined based on
   - Biologic characteristics of the vaccine e.g. live attenuated versus inactivated or other type of vaccines;
   - Biologic characteristics of the vaccine-targeted disease;
   - Biologic characteristics of myocarditis or pericarditis including patterns identified in previous trials (e.g. early-phase trials); and
   - Biologic characteristics of the vaccinee (e.g. nutrition, underlying disease, immunodepressing illness, etc).

26) The duration of follow-up reported during the surveillance period should be predefined likewise. It should aim to continue to resolution of the event.

27) Methods of data collection should be consistent within and between study groups, if applicable.

28) Follow-up of cases should attempt to verify and complete the information collected as outlined in data collection guidelines 1 to 24.

29) Investigators of patients with myocarditis or pericarditis should provide guidance to reporters to optimize the quality and completeness of information provided.

30) Reports of myocarditis or pericarditis should be collected throughout the study period regardless of the time elapsed between immunization and the adverse event. If this is not feasible due to the study design, the study periods during which safety data are being collected should be clearly defined.

1.2. Data analysis

The following guidelines represent a desirable standard for analysis of data on myocarditis or pericarditis to allow for comparability of data and are recommended as an addition to data analyzed for the specific study question and setting.

31) Reported events should be classified in one of the following five categories including the three levels of diagnostic certainty. Events that meet the case definition should be classified according to the levels of diagnostic certainty as specified in the case definition. Events that do not meet the case definition should be classified in the additional categories for analysis.

**Event classification in 5 categories**

- **Event meets case definition**
  - 1) Level 1: Criteria as specified in the myocarditis or pericarditis case definition
  - 2) Level 2: Criteria as specified in the myocarditis or pericarditis case definition
  - 3) Level 3: Criteria as specified in the myocarditis or pericarditis case definition

- **Event does not meet case definition**
  - 4) Reported myocarditis or pericarditis with insufficient evidence to meet the case definition
  - 5) Not a case of myocarditis or pericarditis

32) The interval between immunization and reported myocarditis or pericarditis could be defined as the date/time of immunization to the date/time of onset of the first symptoms and/or signs consistent with the definition. If few cases are reported, the concrete time course could be analyzed for each; for a large number of cases, data can be analyzed in the following increments:

<table>
<thead>
<tr>
<th>Subjects with myocarditis or pericarditis by Interval to Presentation</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interval*&lt; 7 days after immunization</td>
<td></td>
</tr>
<tr>
<td>8 - &lt; 42 days after immunization</td>
<td></td>
</tr>
</tbody>
</table>
The duration of a possible myocarditis or pericarditis could be analyzed as the interval between the date/time of onset¹ of the first symptoms and/or signs consistent with the definition and the end of episode² and/or final outcome³. Whatever start and ending are used, they should be used consistently within and across study groups.

If more than one measurement of a particular criterion is taken and recorded, the value corresponding to the greatest magnitude of the adverse experience could be used as the basis for analysis. Analysis may also include other characteristics like qualitative patterns of criteria defining the event.

The distribution of data (as numerator and denominator data) could be analyzed in predefined increments (e.g. measured values, times), where applicable. Increments specified above should be used. When only a small number of cases is presented, the respective values or time course can be presented individually.

Data on myocarditis or pericarditis obtained from subjects receiving a vaccine should be compared with those obtained from an appropriately selected and documented control group(s) to assess background rates of hypersensitivity in non-exposed populations, and should be analyzed by study arm and dose where possible, e.g. in prospective clinical trials.

1.3. Data presentation
These guidelines represent a desirable standard for the presentation and publication of data on myocarditis or pericarditis following immunization to allow for comparability of data and are recommended as an addition to data presented for the specific study question and setting. Additionally, it is recommended to refer to existing general guidelines for the presentation and publication of randomized controlled trials, systematic reviews, and meta-analyses of observational studies in epidemiology (e.g. statements of Consolidated Standards of Reporting Trials (CONSORT), of Improving the quality of reports of meta-analyses of randomized controlled trials (QUORUM), and of Meta-analysis Of Observational Studies in Epidemiology (MOOSE), respectively).

All reported events of myocarditis or pericarditis should be presented according to the categories listed in guideline 31 (verify numbers).

Data on possible myocarditis or pericarditis events should be presented in accordance with data collection guidelines 1-24 (verify numbers) and data analysis guidelines 31-36 (verify numbers).

Terms to describe myocarditis or pericarditis such as “mild”, “moderate”, “severe” or “significant” are highly subjective, prone to wide interpretation, and should be avoided, unless clearly defined.

Data should be presented with numerator and denominator (n/N) (and not only in percentages), if available.

Although immunization safety surveillance systems denominator data are usually not readily available, attempts should be made to identify approximate denominators. The source of the denominator data should be reported and calculations of estimates be described (e.g. manufacturer data like total doses distributed, reporting through Ministry of Health, coverage/population based data, etc.).

The incidence of cases in the study population should be presented and clearly identified as such in the text.

If the distribution of data is skewed, median and range are usually the more appropriate statistical descriptors than a mean. However, the mean and standard deviation should also be provided.

Any publication of data on myocarditis or pericarditis should include a detailed description of the methods used for data collection and analysis as possible. It is essential to specify:
  ● The study design;
  ● The method, frequency and duration of monitoring for myocarditis or pericarditis;
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- The trial profile, indicating participant flow during a study including drop-outs and withdrawals to indicate the size and nature of the respective groups under investigation;
- The type of surveillance (e.g. passive or active surveillance);
- The characteristics of the surveillance system (e.g. population served, mode of report solicitation);
- The search strategy in surveillance databases;
- Comparison group(s), if used for analysis;
- The instrument of data collection (e.g. standardized questionnaire, diary card, report form);
- Whether the day of immunization was considered “day one” or “day zero” in the analysis;
- Whether the date of onset and/or the date of first observation and/or the date of diagnosis was used for analysis; and
- Use of this case definition for myocarditis or pericarditis, in the abstract or methods section of a publication.

Notes for guidelines

1If the reporting center is different from the vaccinating center, appropriate and timely communication of the adverse event should occur.
2The date and/or time of onset is defined as the time post immunization, when the first sign or symptom indicative for myocarditis or pericarditis occurred. This may only be possible to determine in retrospect.
3The date and/or time of first observation of the first sign or symptom indicative for myocarditis or pericarditis can be used if date/time of onset is not known.
4The date of diagnosis of an episode is the day post immunization when the event met the case definition at any level.
5The end of an episode is defined as the time the event no longer meets the case definition at the lowest level of the definition.
6E.g. recovery to pre-immunization health status, spontaneous resolution, therapeutic intervention, persistence of the event, sequelae, death.
7An AEFI is defined as serious by international standards if it meets one or more of the following criteria: 1) it results in death, 2) is life-threatening, 3) it requires inpatient hospitalization or results in prolongation of existing hospitalization, 4) results in persistent or significant disability/incapacity, 5) is a congenital anomaly/birth defect, 6) is a medically important event or reaction.
8To determine the appropriate category, the user should first establish, whether a reported event meets the criteria for the lowest applicable level of diagnostic certainty, e.g. Level three. If the lowest applicable level of diagnostic certainty of the definition is met, and there is evidence that the criteria of the next higher level of diagnostic certainty are met, the event should be classified in the next category. This approach should be continued until the highest level of diagnostic certainty for a given event could be determined. Major criteria can be used to satisfy the requirement of minor criteria. If the lowest level of the case definition is not met, it should be ruled out that any of the higher levels of diagnostic certainty are met and the event should be classified in additional categories four or five.
9If the evidence available for an event is insufficient because information is missing, such an event should be categorized as “Reported myocarditis or pericarditis with insufficient evidence to meet the case definition”.
10An event does not meet the case definition if investigation reveals a negative finding of a necessary criterion (necessary condition) for diagnosis. Such an event should be rejected and classified as “Not a case of myocarditis or pericarditis”.
11Use of this document should preferably be referenced by referring to the respective link on the Brighton Collaboration website (https://brightoncollaboration.us/).
APPENDIX B
MYOCARDITIS BRIGHTON CASE DEFINITION AND LEVELS OF DIAGNOSTIC CERTAINTY

Definitions Related to Acute Symptoms

Cardiac symptoms:
- Acute chest pain or pressure
- Palpitations
- Dyspnea after exertion, at rest, or lying down
- Diaphoresis
- Sudden death

Non-specific symptoms:
- Fatigue
- Abdominal pain
- Dizziness / syncope
- Edema
- Cough

Definitions Related to Acute Symptoms
Chest pain: Pressure, tightness, soreness, pain, or a squeezing or aching sensation in the chest or arms that may spread to the neck, jaw, throat, back or to the shoulders and arms. May present as throat or jaw or arm/shoulder pain alone. Pain can be described like a heavy weight or pressure on the chest or pinching/burning. Positional changes in chest pain: May or may not worsen with different positions or movement.

Dyspnea: Shortness of breath at rest and/or with exercise.

Gastrointestinal: Nausea, indigestion, heartburn, or abdominal/stomach pain.

Diaphoresis: Cold sweats usually without fever.

Fatigue or Exhaustion: Often with marked change in exercise tolerance.

Pallitations: Irregular heartbeat, skipping beats.

Syncope, Near-Syncope: Lightheadedness or sudden dizziness or fainting.

Cough: Usually persistent (“won’t quit”) dry cough without sputum production

Leg and feet swelling: Acute/rapid onset rarely associated with fulminant myocarditis.

Sudden Death: Cardiogenic shock is clinical diagnosis rather than a symptom.

ELECTROCARDIOGRAM (ECG/EKCG) Abnormalities

ST-segment or T wave (elevation or inversion): Note that in younger healthy populations early repolarization as a normal variant is frequently normal but it can be abnormal if it returns to normal rhythm or if there are time evolving changes (Courtesy of Dr. Atwood, Cardiology, Walter Reed National Military Medical Center).

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: To detect frequent atrial or ventricular ectopy.

ECHOCARDIOGRAM Abnormalities

Ventricular Function Abnormalities (Right or Left): Segmental wall motion abnormalities, global systolic or diastolic function depression/abnormality, ventricular dilation, wall thickness changes, pericardial effusion, and intracavitary thrombi.

Ejection Fraction (EF): Low <50%; Low Normal = 50-55%; Normal = >55% [Note: confirmed abnormality if it normalizes after recovery or was documented previously as higher] INCLUDE: Bedside or portable ultrasound documenting EF.

CMR Abnormalities: Edema (T2-weighted), typically patchy in nature and/or late gadolinium enhancement (T1-weighted) with an increased enhancement ratio between myocardial and skeletal muscle typically involving at least one non-ischemic regional distribution with recovery (myocyte injury).
APPENDIX C: PERICARDITIS CASE DEFINITION AND LEVELS OF DIAGNOSTIC CERTAINTY

Definitions Related to Acute Symptoms

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Leg and feet swelling: Acute/rapid onset rarely associated with fulminant myocarditis

Sudden Death: Cardiogenic shock is clinical diagnosis rather than a symptom

ELECTROCARDIOGRAPH (ECG/EKG) Findings

ST-segment or T wave (elevation or inversion): Note that in younger healthy populations early repolarization as a normal variant is frequently normal but it can be abnormal if it returns to normal rhythm or if there are time evolving changes. (Courtesy of Dr. Atwood, Cardiology, Walter Reed National Military Medical Center).

Echocardiogram Abnormalities

Presence of a pericardial effusion: Fluid collection in the pericardial sac surrounding the heart

INCLUDE: Bedside or portable ultrasound documenting presence or absence of fluid