Safety Platform for Emergency vACcines

SO2- D2.5.2.2 - AESI Case Definition Companion Guide for 2nd Tier AESI

Myocarditis and Pericarditis

Dear user, we would appreciate your feedback for this guide through the following form:

Companion guide evaluation form

Work Package: WP2 Standards and tools

V1.0 – [13 May 2022]

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Nature: Report | Diss. level: Public

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DOCUMENT INFORMATION

Master Service Agreement				Service order	SO2
Project acronym	SPEAC	Full project title	Safety Platform for Emergency Vaccines		
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Deliverable number	SO2 D2.5.2.2	Title	Transform Tier 2 AESI Tools
Work package number	WP2	Title	Standards and tools

Delivery date	15-Apr-2022	Changes on due date ☑	Actual date	13-May-2022
Status	Draft ☐ Final ☑	Old due date:	Version	1.0
Nature	Report ☑ Toolbox ☐ List ☐ Template ☐ Guidance ☐ Handbook ☐ Questionnaire ☐			
Dissemination Level	Public ☑ Confidential ☐			

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Description of the deliverable	This deliverable collates into a single document the SPEAC Myocarditis and Pericarditis resources (Risk factors, background rates, ICD9/10-CM, MedDRA, SNOMEDCT_US, MeSH codes), tools (data abstraction & interpretation form, tabular summary of key case definition criteria and algorithm for level of certainty determination, pictorial level of certainty algorithm) and guidance (real time investigation, data collection, analysis and presentation). This guide can be used by stakeholders to assess the occurrence of Myocarditis and Pericarditis in several settings including as an adverse event following immunization.
Key words	Myocarditis and Pericarditis, Brighton case definition, risk factors, background rates, ICD-9-CM, ICD-10-CM, MedDRA, SNOMEDCT_US, MeSH, case definition level of certainty.

DOCUMENT HISTORY

NAME OF DOCUMENT	DATE	VERSION	CONTRIBUTOR(S)	DESCRIPTION
SO2-D2.5.2.2 Transform Tier 2 AESI Tools	05-Mar-2022	V0.1	Barbara Law Marta Rojo Villaescusa	First draft
SO2-D2.5.2.2 Transform Tier 2 AESI Tools	15-Mar-2022	V0.1	Steve Black Wan-Ting Huang Miriam Sturkenboom	Review
SO2-D2.5.2.2 Transform Tier 2 AESI Tools	10-Apr-2022	V1.0	Bob Chen	Final review and approval
SO2-D2.5.2.2 Transform Tier 2 AESI Tools	13-May-2022	V1.0	Miriam Sturkenboom Barbara Law	Final review and consolidation

DEFINITIONS & ACRONYMS

AEFI	Adverse Event Following Immunization
AESI	Adverse Events of Special Interest
ANCA	Anti-Neutrophil Cytoplasmic Antibody
BC	Brighton Collaboration
CAD	Coronary Artery Disease
CD	Case Definition
CDCP	Centers for Disease Control and Prevention
CEPI	Coalition for Epidemic Preparedness and Innovation
CI	Confidence Interval
CK-MB	Creatine Kinase – Myocardial Band
cMRI	Cardiac Magnetic Resonance Imaging
CMV	Cytomegalovirus
CT	Computed Tomography
CUI	Concept Unique Identifier
EBV	Epstein Barr Virus
ECG	Electrocardiogram
ECHO	Echocardiogram
ER	Emergency Room
HBV	Hepatitis B Virus
HF	Heart Failure
HHV	Human Herpes Virus
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HSV	Herpes Simplex Virus
IC	Information Component (Bayesian measure of disproportionality)
ICD-9-CM	International Classification of Diseases-9th Revision-Clinical Modification
ICD-10-CM	International Classification of Diseases-10th Revision-Clinical Modification
ICI	Immune Checkpoint Inhibitor
ICU	Intensive Care Unit
IPV	Inactivated Polio Vaccine
IRR	Incidence Rate Ratio
LMIC	Lower- or Middle-Income Country
LOC	Level of Certainty
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MMR	Measles Mumps Rubella vaccine
MRI	Magnetic Resonance Imaging
OPV	Oral Polio Vaccine
PAC	Premature Atrial Contraction
PCR	Polymerase Chain Reaction
PVC	Premature Ventricular Contraction
ROR	Reporting Odds Ratio
RSV	Respiratory Syncytial Virus
SD	Standard Deviation

SPEAC	Safety Platform for Emergency Vaccines
TB	Tuberculosis
Tdap	Tetanus diphtheria acellular pertussis vaccine (formulated for ≥7-year-olds)
UMLS	Unified Medical Language System
VAERS	Vaccine Adverse Event Reporting System
VZV	Varicella Zoster Virus

1. Background

CEPI has contracted with the Brighton Collaboration (BC), through the Task Force for Global Health, to harmonize the safety assessment of CEPI-funded vaccines via its Safety Platform for Emergency vACcines (SPEAC) Project.

A key aspect of this harmonization has been creation of lists of priority potential adverse events of special interest (AESI) that are relevant to vaccines targeting CEPI target diseases.

SPEAC Work Package 2 is creating resources and tools for the AESI including:

1. Tabular summaries of risk factors and background rates for each AESI.
2. Guidance on AESI real time investigation, data collection, analysis and presentation.
3. Spreadsheet summaries of ICD9/10 and MedDRA codes for each AESI.
4. Tools to facilitate capturing the specific clinical data needed to meet AESI case definitions across a variety of settings applicable to clinical trials, epidemiologic studies and individual case causality assessment. These include:
    a. Data abstraction and interpretation forms to facilitate capturing data from medical charts and applying it to determine a given AESI case definition level of certainty.
    b. Tabular checklists are a stand-alone tool useful for summarizing key clinical data needed to determine the level of diagnostic certainty for a given case definition.
    c. Tabular logic and pictorial decision tree algorithms, also stand-alone tools, to facilitate correct application of key clinical data to determine the level of diagnostic certainty for each AESI.
    d. Glossary of terms relevant to each AESI.

All tools and resources noted above are compiled together into a companion guide for each Brighton AESI case definition. That is the purpose of this deliverable, which focuses on Myocarditis and Pericarditis.

2. Objective of this deliverable

To collate SPEAC & BC tools, resources and guidance that have been developed for Myocarditis and Pericarditis.

3. Methods

The methods for developing each of the tools included in this guide were detailed in previously completed SPEAC deliverables as follows:

- Myocarditis and Pericarditis risk factors and background rates: SO1-D2.4 Tier 1 AESI: Risk Factors and Background Rates
- Myocarditis and Pericarditis Case definition key caveats for diagnosis, data analysis and presentation: SO1-D2.7 Guidance for CEPI Developers
- Myocarditis and Pericarditis Diagnostic Codes: SO2-D2.3 Tier 1 AESI: ICD-9/10-CM and MedDRA Codes
- Myocarditis and Pericarditis Tabular checklist and Level of Certainty algorithms: SO2-D2.5.1.1-Tools for Tier 1 AESI Data Collection and Interpretation

The methods are briefly described in Appendix 6 of this Guide along with links to source documents which have more detailed methodology. A new feature of this and future Companion Guides is that a systematic search was done for risk factors and background rates. The methods section in Appendix 6 has been amended to include the new approach and specific search strategy used. Additionally, SNOMEDCT_US and MeSH terms have been added to the Codes appendix 3.

Another change introduced for this, and subsequent case definition companion guides, is to combine the tools from three separate appendices (5. Data abstraction and interpretation form, 6. Tabular algorithm and 7. Pictorial algorithm for assessing case definition level of certainty) into a single appendix 5.

4. Results

4.1 Systematic Search for Background incidence and Risk Factors

A total of 5067 articles were retrieved of which 4829 were screened out for the following reason: 64 duplicates, 1 commentary, 1416 focused on treatment, diagnosis or prevention and 3348 non-contributory to risk factors or general population background incidence.

Of 238 articles screened in for full text review there were 85 with potential to provide data on background incidence. Further screening eliminated 60 publications that either didn't provide incidence data or were for sub-populations such as athletes or groups with underlying co-morbidity. Only 4 articles provided original source data.[46, 68, 70, 74]. Of the remaining articles, 21 provided links to original source data in 40 publications, all of which were used, including: 3 for myocarditis[2, 47,48], 1 for pericarditis[22], 9 for arrhythmia[50-58], 12 for acute MI[59-67, 69, 71, 72], 2 for sudden cardiac death[63, 73], 4 for cardiomyopathy[75-78] and 10 for heart failure[79-88]. The European ACCESS study[49] was published after the searches were done, and data were added to the tables for myocarditis, pericarditis, arrhythmia, cardiomyopathy, and heart failure. (See appendix 2, Tables 1 – 6).

Among the 238 screened in articles were 33 on myocarditis/pericarditis that were all reviewed in full for relevant risk factors. Of 9 that had already been chosen for background incidence only 2 contributed to risk factors[2,3] (see Appendix 1). Of the remaining 24 articles, 11 contributed to the evidence on risk factors[4, 5, 7-11, 21, 23-25], and 2 to considerations for real time investigation[92, 96] (Appendix 4). The remaining 11 did not contribute anything further.

Finally, the screened in articles included 131 that focused on cardiac injuries other than myocarditis/pericarditis (79 cardiac arrest, 19 cardiomyopathies, 17 heart failure and 16 arrhythmia) but did not contribute to background rates.

4.2 Literature Search for myocarditis and pericarditis temporally associated with vaccination

A total of 131 articles on post-COVID-19 vaccine myocarditis/pericarditis were found,100 were excluded because they were case series (30), case reports (41), commentary (15), limited to pathogenesis (5), guidelines (2) or off topic (7: 1 focused on myocarditis with COVID-19 infection; 2 on background rates prior to COVID vaccine; 1 on risk-benefit of COVID-19 vaccination; 2 on AESIs other than myocarditis – sensory neural hearing loss and autoimmune hemolytic anemia; 1 on drug associations). 12 of 14 epidemiologic studies were included: 1 self-controlled case series[20], 5 descriptive datalink studies[26-29, 31] (summarized in Appendix 1, Table 6, A&B), 2 cohort studies[32, 33] (summarized in Appendix 1, Table 7, A&B) and 4 pharmacovigilance studies[35-38] (summarized in Appendix 1, Table 8). The two excluded epidemiologic studies included a US Vaccine Safety Datalink rapid cycle analysis for AESIs following COVID-19 vaccine (myocarditis was just one of several outcomes and no signal was observed) and a descriptive pharmacovigilance study that did not provide risk estimates. The remaining 17 articles were reviews of reported cases of myocarditis/pericarditis following immunization: 7 were included[36-42] (summarized in Appendix 1, Table 9). The remaining 10 reviews were excluded because they added no new cases to the included studies, had no original data or were off-topic (focus on risk-benefit). Two additional epidemiologic studies[30, 34] were found via hand search

of the citations in included articles, or via daily pre-print updates; the first paper[30] provides info on additional ICD search codes that should be included for case finding of myopericarditis in databases.

The search yielded 42 articles for myocarditis associated with vaccines other than COVID-19 including 22 for Vaccinia and 20 for other vaccines. The two articles included for Vaccinia were a prospective study of myocarditis following smallpox vaccination of American military[11] (summarized in Appendix 1, Table 1) and a related study that provided background incidence data in the same population.[12]. The remaining 20 were excluded because they were: less robust study conducted earlier in the same setting (1); descriptive with no risk analysis (5); cost-benefit (1); summaries of ACIP reviews (2); or case reports (11). Of 20 articles retrieved for non-Vaccinia vaccines 3 were included: a 2-case series where endomyocardial biopsies were done[14]; a VAERS disproportionate reporting analysis[16]; and a third which compared myopericarditis to viral or idiopathic acute pericarditis.[94] Vaccines were not discussed in the article but it was included because of its relevance for recommendations on real time investigation (discussed in Appendix 4). The remaining 17 articles were excluded because they were: limited to pathogenesis (2); case reports or series (9); or off topic (6: 2 sudden death, 1 ADEM, 1 wild type influenza infection and 2 COVID-19: a news article and a case report). Reference search of included articles yielded two additional studies, 1 a risk estimates study of Vaccinia myocarditis in civilian adults[13] and the other a US Vaccine Safety Data link study of myocarditis in adults following live viral vaccines.[15]

All outputs are provided in separate appendices as shown below:

1. Myocarditis and Pericarditis Risk Factors
2. Myocarditis, Pericarditis and related cardiac injury Background Rates
3. Myocarditis, Pericarditis and related cardiac injury Diagnostic Codes: ICD-9CM, ICD-10CM, MedDRA, SNOMEDCT_US, MeSH
4. Myocarditis and Pericarditis Case Definition key caveats for diagnosis, data analysis and presentation
5. Myocarditis and Pericarditis Data Abstraction and Interpretation Forms with Algorithms for Assessing Level of Certainty
6. Summary of methods. Also provides links, as appropriate, to the original deliverable documents with more detailed methodology.

5. Recommendations & discussion

This guide brings together many resources and tools related to the AESI of Myocarditis and Pericarditis, including risk factors, background rates, guidance for real time investigation, ICD-9/10-CM and MedDRA codes for data entry or database searching and provides tools for collecting and interpreting clinical data to apply the Brighton Myocarditis and Pericarditis case definition and determine the level of diagnostic certainty.

The choice of tabular or pictorial algorithm is up to the user in terms of what is best suited to the situation and the assessor. SPEAC recommends that the tools be used in order to assign level of certainty for all identified AEFI with features of Myocarditis and Pericarditis. The tools can also support studies of background incidence and controlled studies to test for a vaccine-AESI association. This standard, harmonized approach will facilitate signal detection and assessment as well as the capacity to combine data across trials for meta-analyses.

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APPENDIX 1.

Myocarditis and Pericarditis Risk Factors, Etiologies and Summary of Evidence Regarding the Safety Signal Linking COVID-19 Vaccination to Myocarditis and Pericarditis

1.1. Myocarditis and Pericarditis Risk Factors, Etiologies and Evidence relating to the safety signal linking COVID-19 vaccination to myocarditis and pericarditis.

TABLE 1. MYOCARDITIS RISK FACTORS.

Age	• Children: two peaks in incidence by age: 0-4 and 15-18 year olds [2]
Gender	• Male:Female Incidence Rate Ratio higher for 6-10 years (2.46; 95% CI: 1.03-5.89) & 11-15 years (3.89; 2.68-5.67); no difference for 0-5 yrs[2] • Myocarditis more prevalent in males: 82% of cases[3]
Behavioral	• Competitive athletes: aftermath of myocarditis (e.g., non-ischemic myocardial scar) number 3 cause of Sudden Cardiac Death[4,5]
Geography	• Geographic differences primarily related to differences in myocarditis etiology[3,4,6,7] (see Table 2 below)
Comorbidity	• Myocarditis may occur as part of the clinical spectrum of many systemic diseases.[1,3,4,] (See Table 3 below)
Infection	• Viral infections are among the most frequent causes of myocarditis: estimated to be 28% of all cases based on a 2020 systematic review.[8] Coxsackievirus B3 & A, Influenza A&B, CMV, Adenovirus and Parvovirus B19 are implicated most frequently but the full list of pathogens is long. [3,4,6-8]. Bacteria, Fungi, Parasites and Protozoa each contribute to <1% of cases[8] but prevalence varies geographically. (See Tables 3 and 4 below)
Medication / Toxins	• Infrequent (<1%) cause of myocarditis[8] ; many drugs implicated via direct toxicity or hypersensitivity.[2,4,9,10] (see Table 3) • Myocarditis has been linked to Immune Checkpoint Inhibitors (ICIs): anticancer monoclonal antibodies that work by enhancing T-cell mediated immune response against tumor cells. A variety of cardiac injuries have been observed: myocarditis in 0.09-2.4%, pericarditis in <1-2%, pericardial effusion in 2%, cardiac arrhythmia in 4%, MI in <1-2% and heart failure in 0.4% of those on ICI therapy.[10]
Vaccine	Vaccinia (smallpox) vaccine: • Prospective observational cohort study[11] of 1081 US military personnel identified 4 myocarditis & 1 pericarditis within 30 days of vaccination for an incidence of 463 (95% CI 150-1079)/100,000. This rate was 214 (95% CI 65-558) times higher than that observed in a 2002 background rate study of 1,390,352 military personal, that identified 30 cases for an incidence of 2.2 (95% CI 1.9-2.3)/100,000 [12]. In the prospective study the interval from vaccination to disease onset was more than 5 days for all cases, but no details were provided. An earlier study focused on myocarditis, pericarditis and dilated cardiomyopathy among US civilians given smallpox immunization in 2003.[13] Among 37,901 vaccinated, 21 cases of myocarditis or pericarditis were identified that met the case definition for an incidence of 55/100,000. Median time to onset: 11 days (range 2-42). Mild illness in all; no deaths. No long-term impact (e.g. dilated cardiomyopathy). Vaccines other than smallpox or COVID-19: • 2 myocardial biopsy-confirmed cases of eosinophilic myocarditis reported[14]: 12-year-old girl 1 day after 2nd dose of HBV (Engerix® , GSK) and a 14-year-old boy 13 days after Meningococcal conjugate C vaccine (NeisVac®; Pfizer). Notable given the confirmatory cardiac biopsy but do not prove causality; In the 2nd case there was also Group A streptococcal pharyngitis treated with penicillin, 4 weeks prior.

- A California Kaiser Permanent vaccine safety data link study found no increased risk of myocarditis and pericarditis after adult immunization with live viral vaccines other than smallpox (MMR, VZV, OPV, YF).[15] Cases were found using ICD9 codes (422.0, 422.90, 422.91, 422.99 and 420) and all ascertained cases were reviewed by a cardiology doctor and nurse to classify cases as definite, probable or possible based on the US CDCP criteria. A self-controlled risk interval of 42 days following vaccination was used. The study followed 416,629 people who received doses as follows: MMR 297,000; VZV 87,295; YF 76,606; OPV 35,291. A total of 120 pericarditis cases were found of which only 54 could be validated; the cases were evenly distributed by age and 69% were male; comorbidities: 30% had hypertension; 20% hyperlipidemia. There were 32 cases of myocarditis found, of which 18 were validated; 67% were 18-29 years old and 79% were male. Only 1 case of pericarditis occurred in the 42-day risk interval: 36 days post YF vaccine given concomitantly with Td and meningococcal vaccine and 32 days post additional vaccines (IPV, Hepatitis A, influenza). The remaining 71 validated cases all occurred ≥43 days post vaccination. The incidence after vaccine was 0.24/100,000 with an incident reporting rate of 0.57 (0.07-4.51).
- VAERS data from 2011 to 2015 was used to analyze reporting rates for myocarditis, myopericarditis and pericarditis following vaccination.[16] A disproportionality signal was defined as a Reporting Odds Ratio (ROR) with a lower bound >1. Among individuals aged < 18 years, there were only 8 myocarditis and 7 pericarditis reports implicating vaccines targeting: HPV (6 cases), meningococcus (5), hepatitis A (4) and influenza (4). The only signal was for Meningococcal vaccine with ROR (95% CI) for: Myocarditis 5.52 (1.01-30.17); Myopericarditis 3.55 (1.23-10.24). Among individuals aged ≥18 years there were a total of 184 reports, 149 of which implicated Smallpox vaccine which was designated a control for the analysis. The other 35 reports (12 myocarditis, 20 pericarditis and 3 myopericarditis), implicated vaccines targeting: influenza (16 cases), TDaPTdap (7) and others not enumerated. Observed signals included: Typhoid vaccine - Myocarditis 11.11 (7.01-17.62); Pericarditis 1088 (6.38-18.56); Myopericarditis 11.13 (7.73-16.03); Japanese encephalitis vaccine – Myocarditis 13.84 (4.35-44.03); Myopericarditis 8.54 (2.7-27.01); and Anthrax vaccine – Myopericarditis 25.5 (18.8-34.5). Smallpox vaccine RORs were: Myocarditis 73.53 (41.87-129.14); Pericarditis 59.06 (36.45-95.67); Myopericarditis 71.88 (49.25-104.89). In both age groups several cases (9 myocarditis, 21 pericarditis) failed to meet diagnostic guidelines set out by the European Society of Cardiology.[17,18] Further, causality, based on the WHO algorithm[19], was judged to be 'undetermined' for 45 of 50 reports. Of relevance to what has been observed following COVID-19 vaccines, the mean time to onset following vaccination was long: 48 days in <18 years; 26 days in ≥18 years.

COVID-19 vaccines: See tables 5 (datalink studies), 6 (non-datalink cohort studies), 7 (pharmacovigilance data) and 8 (Reviews of published case series and case reports) below for the spectrum of evidence on myocarditis and pericarditis temporally associated with COVID-19 vaccines. To date there has just been a single hypothesis testing study[20] to examine a possible causal association, as summarized below:

- A UK Self Controlled Case Series study was done to look for association between Pfizer (16,993,389 1st doses and 11,972,733 2nd doses), Moderna (1,006,191 1st doses and 368,791 2nd doses) and ChAdOx1 (20,615,911 1sts doses and 32,095,748 2nd doses) vaccines and myocarditis, pericarditis and arrhythmias using a risk interval of 28 days. Analyses were done separately for dose 1 and dose 2 as well as for occurrence of a positive COVID-19 test as a secondary exposure. The study ascertained 1615 myocarditis, 1574 pericarditis and 14 myopericarditis cases. For the 1-28 days post-vaccination period there was an increased risk of myocarditis as follows (data expressed as Incidence Rate Ratio (IRR), 95% confidence interval; and number of extra cases (95% confidence interval) per million vaccinated:

	○ **Dose 1:** ▪ Pfizer: 1.31; 1.03, 1.66; 1(0-2) extra case / million vaccinated ▪ Moderna: 2.97; 1.3, 6.58; 6 (2-8) extra cases/million vaccinated ▪ ChAdOx1: 1.29; 1.05, 1.58; 2 (0,-3) extra cases/million vaccinated ○ **Dose 2:** ▪ Moderna: 9.84; 2.69, 36.03; 10 (7-11) extra cases/million vaccinated ○ **Test positive for SARS-CoV-2**: 40 (38-41) extra cases/million infected

TABLE 2. PERICARDITIS RISK FACTORS. * Relative % cases (95% CI) from a 2007 systematic review of acute pericarditis (1978-2005); 23 eligible studies with ≥50 subjects.21 Table 5 lists specific etiologies by Comorbidity, Infection, Trauma, Iatrogenic & Others not clearly fitting into a category.

Gender	More frequent in males(M) than females(F) but less than in myocarditis. Finnish incidence study found: age-adjusted likelihood ratio of 1.85 (95% CI 1.65-2.06) for M versus F (p<0.0001); males also significantly younger: mean ± SD: M - 45.9±18.3 years; F - 56.2±17.3 years (p<0.0001). No sex difference in rates for ≥66 years.[22]
Geography	Tuberculosis is the most common cause of pericarditis in LMICs but otherwise is rare.[22,23]
Comorbidity	• Malignancy: *26.6% (CI 19.7, 31.4)** • Metabolic disease: *8.2% (CI 3.3-13.1)** • Connective tissue disease, vasculitis: *4.1% (2.3, 5.8)** • Diseases of contiguous structures *2.1% (0.9, 3.2)** • Individuals with a prior episode of acute pericarditis at risk for recurrence. [7]
Infection	*9.4% (CI 6.4, 12.3)**
Trauma	*1.1% (CI 0.3-1.9%)**
Iatrogenic	*16.3% (10.2-22.4)**
Other	*6.4% (4.0, 8.7)**

TABLE 3. Myocarditis and pericarditis etiologies that are more prevalent in one or more global regions [3,4,6,7,23]

Region	Subcategory	Specific etiologies found more commonly in the region
Africa	Infection	Viral: HIV; Bacterial: Shigella sp; Mycobacterial: TB – especially for pericarditis[23]
Australia/Oceana	Infection	Viral: Outbreaks of Coxsackie B3, Enterovirus 61 and 71
Asia	Infection Insect bite	Viral: Coxsackie B, Hepatitis C, Chikungunya Bacterial: Diphtheria, typhoid fever Scorpion
Europe	Infection	Viral: Parvovirus B19
North America	Infection	Viral: Tick borne diseases: Northeast US - Borrelia burgdorferi, Babesia sp, Anaplasma sp Fungal: Southwest US – Coccidioides immitis; St Lawrence & Mississippi river systems: Blastomyces dermatidis
Latin and South America	Infection	Viral: Measles, Dengue, HIV; Bacterial: Diptheria, Meningococcus; Fungal: North Mexico – Coccidioides immitis Protozoal: Trypanasoma cruzii (Chagas disease)

TABLE 4. Myocarditis Etiologies [2-4,6-10] Boldface type indicates the more common infectious etiologies. While not exhaustive, this is meant to portray the breadth of what has been reported, although some may be very rare. Many drugs have been implicated but it would be impossible to list all. The drug section of the table is organized by class of medication, and some examples listed for each. When assessing myocarditis as an AESI, it will be important to gather information on recent & concurrent medications and to seek up to date information on association with myocarditis.

Category	Subcategory	Specific Etiologies
Infection	**Viral**	**Adenovirus (especially children**), Chikungunya, **CMV,** Dengue, Enteroviruses, Coxsackievirus (especially **B3 & A),** echovirus, polio, Enterovirus 71), Hepatitis B / C, Herpesviruses (HHV, HSV, VZV, EBV), HIV, **Influenza A + B,** Measles, Mumps, Parainfluenza, **Parvovirus B1**, Rhinovirus, RSV, Rubella, SARS-CoV-2
	Bacterial	*Brucella sp, Chlamydia pneumonia/psittaci,* **Diphtheria** (LMIC), *Francisella tularensis, Gonococcus sp, H. influenzae, Klebsiella sp, Legionella sp, Meningococcus sp, M. tuberculosis, Mycoplasma pneumonia, Pneumococcus sp, Salmonella typhi/paratyphi, Shigella sp, Spirochetes: Borrelia burgdorferi(Lyme Disease), Leptospira sp, T pallidum, Borrelia recurrentis, Staphylococcus sp, Streptococcus sp, Vibrio cholerae*
	Rickettsia	*Coxiella burnetti* (Q fever), *Rickettsia rickettsia* (Rocky Mountain Spotted Fever), *Rickettsia prowazekii*
	Fungi	Actinomyes Aspergillis, Blastomyceses, Candida, Coccidioides, Cryptococcus, Histoplasma, Mucor, Nocardia, Sporothrix
	Parasites	Ascaris, Cysticercosis, *Echinococcus granulosus,* Trichinosis, Schistosomiasis, Visceral larva migrans, *Wucheria bancrofti*
	Protozoa	*E histolytica,* Leishmania, *P. falciparum, N. fowleri, Toxoplasma gondii,* **Trypanasomomiasis (Chagas disease)**
Toxicity / Hypersensitivity	**Drugs**	**Allergy and asthma medications** (pyribenzamine, aminophylline, theophylline); **Anti-arrhythmics** (procainamide, quinidine, mexiletine); **Antibacterials, antifungals & antivirals** (penicillin, ampicillin, azithromycin, cephalosporins, tetracyclines, INH, tetracycline, sulfonamides, chloramphenicol, streptomycin, trimethoprim amphotericin B, dapsone, zidovudine); **Anti-diabetic** (chlorpropamide); **Anti-hypertensives** (reserpine, triamterene); **Anti-inflammatory** (indomethacin, diclofenac, colchicine, allopurinol, phenylbutazone); **Antimigraine** (methylsergide); **Antineoplastic** (anthracyclines, cyclophosphamide, doxorubicin, 5-FU, Immune checkpoint inhibitors, tyrosine kinase inhibitors, trastuzumab, TNF-antagonists); **Anti-seizure** (phenytoin); **Cardiac medications** (digoxin, dobutamine, catecholamines); **Diuretics** (thiazide, hydrochlorothiazide, furosemide, spironolactone); **Local anaesthetic** (lidocaine); **Psychiatric drugs** (tricyclic antidepressants, benzodiazepines, clozapine [*NOTE: up to 15% of cases may have a delayed onset, as long as 2 years after starting the drug*[9]], lithium, methyldopa); **Recreational/illicit drugs** (metamphetamine, cocaine)
	Other	**Alcohol; Bites** (scorpion, bee/wasp, black widow spider, snakes); **Radiation; Heavy metal** (Copper, lead, arsenical, iron)
Metabolic		Hemochromatosis, Pheochromocytoma, Thiamine deficiency (Beriberi), Thyrotoxicosis
Autoimmunity		ANCA vasculitis, Celiac disease, Churg-Strauss syndrome, Dermatomyositis & Polymyositis, Diabetes Mellitus (Type 1), Inflammatory bowel disease, Kawasaki disease, Mixed connective tissue disease, Myasthenia gravis, Rheumatoid Arthritis, Sarcoidosis, Systemic lupus erythematosus, Scleroderma, Sjogren's syndrome, Wegener's granulomatosis

Cancer		Primary Cardiac: Rhabdomyosarcoma; Metastatic spread (e.g. from lung or breast cancer, melanoma)

TABLE 5. Pericarditis Etiologies[7,22-25]

Category	Subcategory	Components
Infection	**Viral**	Adenovirus, Enteroviruses (coxsackie A & B), Hepatitis A, B, C, Herpesviruses (CMV, EBV, HSV, VZV), HIV, Influenza A & B, Lymphogranuloma venereum, Mumps, Parvovirus B19
	Bacterial	*Chlamydia psittaci, Coxiella burnetii, Francisella tularensis,H. influenzae sp, Leptospira sp, Listeria monocytogenes,* Meningococcus, *M. tuberculosis, Mycoplasma pneumoniae,* Salmonella, Spirochetes, Staphylococcus, Streptococcus
	Fungal	Actinomyces, Histoplasmosis
	Parasitic	Echinococcosis, Toxoplasmosis
Non-infectious	**Neoplastic**	**Primary** (mesothelioma, sarcoma, fibroma, lipoma); **Metastatic/ direct extension** (carcinoma, sarcoma, lymphoma, leukaemia, carcinoid)
	Metabolic / endocrine	Gout, Hypothyroidism, Myxedema, Pancreatitis, Renal failure (acute or chronic), Renal dialysis, Scurvy
	Vasculitis / Connective tissue disease *Note: pericarditis prevalence 20-60% in* ***bold-face*** *entities* [25]	Ankylosing spondylitis, Behcet's syndrome, **Churg-Strauss syndrome,** Dermatomyositis, Familial Mediterranean fever, Giant cell arteritis, Inflammatory bowel disease, Kawasaki's disease, Microscopic polyangiitis, **Mixed connective tissue disease**, Polyarteritis, Polymyositis, Reiter's syndrome, Relapsing polychondritis, Rheumatic fever, **Rheumatoid arthritis including adult-onset Still's disease,** Sarcoidosis, **Scleroderma**, Serum sickness, Sjogren's syndrome, **Systemic Lupus Erythematosus**, Takayasu arteritis, Temporal arteritis, Thrombotic thrombocytopenic purpura, Wegener's granulomatosis
	Trauma	**Direct pericardial perforation** (penetrating chest injury; in association with esophageal or gastric perforation); **Direct cardiac injury:** (e.g. cardiac surgery, post-catheterisation procedure such as pacemaker insertion); **Indirect cardiac injury:** (e.g. radiation, non-penetrating chest injury)
	Diseases of contiguous structures	**Myocardial infarction (MI):** acute MI, post-MI or Post-pericardiotomy syndromes; **Aneurysm:** ventricular; dissecting aortic**; Pleural and pulmonary disease:** pneumonia, pulmonary embolism, pleuritis; Bile fistula; Diaphragmatic hernia
	Hypersensitivity	Drug reactions, serum sickness, allergic granulomatosis, giant urticaria
	Other	Congenital anemias (e.g. Thalassemia), Fat embolism, Pericardial fat necrosis,

TABLE 6. Vaccine Safety Datalink Epidemiologic Studies of Myocarditis and Pericarditis following COVID-19 vaccination.

Abbreviations use in Tables: **Vaccination status**: V=vaccinated; NV=not vaccinated; **COVID-19 status**: Pos=infected; Neg=uninfected; **Outcomes:** M=myocarditis; MP=myopericarditis; P=Pericarditis; **Health care related**: e-HR = electronic health record; MRec=Medical record; OPD=outpatient visit; ER=emergency room visit; Hsp=Hospitalization; **Other**: CD=Case Definition; CDC classification: C=confirmed; P=probable; S=Suspect; BGR=Background Rate;

6.A Key details of study methods, data sources, population, study period, case ascertainment and adjudication, vaccine and risk period by dose

Author	Country	Method & Data Source(s)	Study Period(s)	Case Finding	Case Validation; CD if used	Vaccine	Risk Period (days)
Mevorach[26]	Israel	Retrospective review Ministry of Health database Age ≥16 years	**Vaccine:**12/20-05/21 **BGR:** 2017-2019	**M:** ICD9 422.0-9; 429.0 (excluded P cases unless associated with M)	Cardiologist review CD: Brighton	Pfizer	Dose 1: 21 Dose 2: 30
Barda[27]	Israel	Case-control, 1:1 match for: V:NV: COVID Pos:Neg Clalit Health Services (52% Israeli popn); Age ≥16 years	**Vaccine:**12/20-05/21 **COVID+:03**/20-05/21	Multiple AESIs; ICD9 codes: **M:** 422*,429.0*, 398.0*, 391.2* **P:** 420* and e-HR free text	No case validation beyond codes	Pfizer	Dose 1: 42 Dose 2: 21
Witberg[28]	Israel	Retrospective cohort Clalit Health Services	12/21-05/21	**M:** ICD9 422, 429.0, 398.0, 391.2	Independent review by 2 cardiologists **CD:** US CDCP -C, P&S cases	Pfizer	Dose 1: 21 Dose 2: 21
Simone[29]	USA	Kaiser Permanente Southern California; ≥18 years	12/20-07/21	**M:** MD reports + Hsp discharge diagnoses	Independent review ≥2 cardiologists	Pfizer Moderna	Dose 1: 10 Dose 2: 10
Sharff [30] **Preprint**	USA	Retrospective cohort Kaiser Permanente Northwest (KPNW) US VSD; 12-39 years	12/20-09/21	**Text search:** KPNW telehealth, OPD, urgent care, ER, Hospital **ICD10 codes: M:** I40*, B33.22 & **P:** I30*, B33.23 in KPNW ER/Hsp, unaffiliated Hsp claims	Independent review by 2 MDs **CD:** US CDCP-C&P cases	Pfizer Moderna	Dose 2: 30

6.B Study results (see table legend above for abbreviations)

Author	Vaccine doses	M cases	Standardized Incidence Ratio (Observed / Expected cases)	Incidence Rate Ratio	Incidence Rate Difference/100,000 persons
Mevorach[26] ***Definite or probable myocarditis post dose 2: 1/26,000 M 1/218,000 F***	1: 5,442,696 2: 5,125,635	304	**Ages** / **Dose 1** / **Dose 2** 16-19: M: 1.62(0.32-4.72) / 13.6 (9.30-19.20) F: 0 / 6.74 (0.76-24.35) 20-24: M: 2.14 (0.69-5.00) / 8.53(5.57-12.50) F: 2.37 (0.03-13.20) / 10.76(3.93-23.43) 25-29: M: 1.39 (0.28-4.05) / 6.96 (4.25-10.75) F: 0 / 2.54 (0.03-14.14) ≥30: M: 1.23 (0.5902.26) / 2.90 (1.98-4.09) F: 1.42 (0.29-4.15) / 2.44 (0.98-4.09)	**V (2 doses) vs UV:** **All:** 2.35(1.10-5.02) **16-19 years:** **M:** 8.96(4.50-17.82) **20-24 years:** **M:** 6.13(3.16-11.88) **F:** 7.56(1.47-38.96) **25-29 years:** **M:** 3.58 (1.82-7.01)	**After Dose 2 relative to Dose 1:** **Ages** / **Males** / **Females** All: **3.19 (2.37-4.02)** / 0.39 (0.10-0.68) 16-19: **13.73(8.11-19.46)** / 1.00 (-0.63-2.72) 20-24: **8.95(4.42-13.55)** / 2.16 (0.13-4.24) 25-29: **5.77(2.02-9.58)** / 0 (-0.83-0.89) 30-39: **3.28(1.41-5.18)** / 0.22 (-0.37-0.84) 40-49: 0.50(-0.82–1.84) / 0.24 (-0.61-1.11) ≥50: 0.11(-0.29-0.52) / 0.10 (-0.26-0.46) All: 1.76 (1.33-2.19)
Barda[27]	≥1: 938,812	27	Not reported	**V vs UV:** 3.24 (1.55-12.44) **COVID Pos vs Neg:** 18.28 (3.95-25.12)	**V vs UV:** 2.72 (0.97-4.60) **COVID Pos vs Neg:** 10.96 (5.57-15.80)
Witberg[28]	0: 1,577,741 1: 2,558,421 2: 2,401,605	54	**Incidence/100,000 persons given at least 1 dose:** **Ages** / **Male** / **Female** All: **4.12 (2.99-5.26)** / 0.23 (0-0.49) 16-29 yrs: **10.69 (6.93-14.46)** ≥30 yrs: All: 1.13 (0.66-1.60)	Not reported	Not reported / Not reported
Simone[29]*	2,392,924	90	Incidence/100,000 persons after: 1st dose: 0.08 (0.2-3.3) 2nd dose: 5.9 (3.4-10) 1 case / 172,414 fully vaccinated	Not reported	**Relative to unvaccinated control:** After 1st dose: 0.38 (0.05-1.40) After 2nd dose: **2.7 (1.4-4.8)** **Relative to self control (10days in prior year):** After 1st dose: 1.0 (0.1-13.8) After 2nd dose: **3.3 (1.0-13.7)**
Sharff[30]*	2: 146,785	16	2nd dose: **All:** 9.54 (1.21-16.0) **M:** 19.4 (10.4-33.41)	Not reported	Not reported
Nygaard[31]*	≥1: M133,477 & F 127,857	15	After ≥1 dose of vaccine: M 9.7 & F 1.6 /100,000 After COVID-19 infection: M 35.5 & F 18.7/100,000 Pre-COVID-19 incidence: M 1.2 & F 0.2/100,000	Not reported	Not reported

* Study presented data as per million doses; converted in table to per 100,000 for comparison purposes

TABLE 7. Cohort studies of myocarditis following COVID-19 vaccination

7A. Key details of study methods, data sources, population, study period, case ascertainment and adjudication, vaccine and risk period by dose

Author	Country	Method & Data Source(s)	Study Period(s)	Case Finding	Case Validation; Case Definition, if used	Vaccine	Risk Period (days)
Perez[32]	USA	Retrospective case series; Mayo Clinic Vaccine Registry; all ages	Dec17/20 to May13/21	Myocarditis: ICD10: I40.0, I40.2, I40.8, I40.9, I41, I51.4, B33.22	2 MDs screened medical record	Pfizer Moderna	14
Chua[33]	China	Population Cohort All 12-17 year olds, post-vaccination	Jun14/21 to Sept4/21	Incident reporting system for all suspect Myocarditis & Pericarditis admitted to health authority hospital	Followed standard Diagnostic Protocol Brighton Case Definition	Pfizer	14

7B. Study Results

Author	Vaccine doses	Myocarditis cases	Standardized Incidence Ratio (Observed / Expected cases)	Incidence Rate Difference/100,000 persons
Perez[32]	≥1: 175,471	7	**Incidence rates/100,000 person years** • All Vaccinated: 55.35 (22.25-114) • Vaccinated Males: 109.52 (40.19-238.4) • Vaccinated Females: 13.95 (3.53-77.72) **Background rate (2016-2020)** • All: 13.25 (10.6-16.36) • Males: 16.37 (12.33-21.3) • Females: 9.9 (6.73-14.05)	**For Vaccinated vs Pre-Covid incidence:** • All: 4.18 (1.63-8.98) • Males: 6.69 (2.35-15.52) • Females: 1.41 (0.03-8.45)
Chua[33]	≥1: 305,406	33	**Incidence / 100,000 vaccinated:** • **All:** 18.52 (11.67-29.01) • **1st Dose: All** 3.37 (1.12-9.51) **Male:** 5.57 (2.38-12.53) • **2nd Dose: All** 21.22 (13.78-32.28) **Male:** 37.32 (26.98-51.25) **Background Incidence:** • **All:** 0.11(0.01-20.36) **Male:** 0.21(0.01-10.34)	**Vaccinated versus Background Incidence** All: 18.41 (9.95-26.87) Male: 32.08 (20.91-43.25)

TABLE 8. Published Pharmacovigilance Data for Myocarditis

Lead author	Country	Data Source	Surveillance Type	Case Definition (CD)	Reporting Period	Risk Period	Total reports (met CD)	Analysis	Key Findings
Oster[34]	USA	VAERS	Passive	CDCP Confirmed & Probable	14Dec/20-31Aug/21	7 days	1991 (1626)	Crude reporting rates by vaccine, sex, age group & dose (1st or 2nd)	**Highest reporting rate**: in adolescent and young adult males following the 2nd dose of Pfizer of Moderna
Li[35]	China	VAERS	Passive	Not used	11Dec/20-13Aug/21	Not stated	2116: 703 Moderna; 1335 Pfizer; 78 Janssen	Reporting odds ratio (ROR)	**RORs for all ages and sex:** Moderna: 2.91 (2.21-3.83) Pfizer: 5.37 (4.10-7.04) Janssen: 1.39 (0.99-1.97) Highest ROR for Pfizer in 12-17 yrs; Moderna not being used in this age group at the time
Chouchana[36]	France	Vigibase	Passive	Not used	Start of vaccination to 30Jun/21	Not stated	2277	ROR for M and P separately by age and sex	**Highest RORs for 12-17 yr old males:** Myocarditis: 18.5 (15.6-21.9) relative to older Pericarditis: 12.7 (4.5-35.5 relative to 12-17 yr old females
Foltran[37]	France	Vigibase	Passive	Not used	1Jan/21-14Sept/21	Not stated	242 (191 M, 51P)	ROR, focus on 12-17 year olds	**ROR for Boys vs Girls:** 1st Dose: 10.10 (4.26-29.60) 2nd dose: 10.20 (4.99-25.00) Only M: 14.90 (7.63-33.60) Only P: 4.42 (1.53-15.80)
Kerneis[38]	France	Vigibase	Passive	Not used	1967 through 5Jul/21	Not stated	8664 (1251 after any vaccine; 214 after COVID vaccine)	Calculated IC (observed vs expected disproportionality Bayesian analysis)	**Only COVID vaccines with IC>1 were Pfizer and Moderna**

TABLE 9. Key Reviews of Reported Cases of Myocarditis and Pericarditis following COVID-19.

Abbreviations: Study Type: CR = Case Report; CS = Case Series; Co = Cohort; RCT = Randomized controlled trial
Case diagnosis: M = myocarditis; MP = myopericarditis; P = pericarditis; NS = not stated

Lead author	Search end date	Study Types	Studies Included /Screened	Total Cases •# M/MP •# P	% Male	Median Age (Range) in years	Vaccine				% 2nd Dose	Median days to onset (range)
							Pfizer	Moderna	Astro Zeneca	Janssen		
Fazlollahi[39]	Sept 25	CR/CS	69 / 485	234 • 227M/MP • 7 P	 92.1 71.4	 21 (12-70) 37(21-80)	 169 7	 58 0	 0 0	 0 0	 87.7 42.8	 3 (<1-90) 4 (1-11)
Woo[40]	Sept 10	CR/CS	24 / 63	74 M	94.6	17.6 (14-70)	58	16	0	0	90.5	3 (<1-16)
Ho JSY[41]	July 19	CR/CS/ Coh/RCT	42	381 • 373 M/MP • 8 P	 65.1 42.8	 NS (14-67) NS (21-80)	 87* 6	 71* 	 0 1	 1* 1	NS	99.4% ≤7 days after vaccine
Matta[42]	July 17	CR/CS	25 / 130	69 M	92.7	21 (14-70)	53	16	0	0	88.5	2(0-25)
Sulemankhil[43]	July 4	CR/CS	23 / 38	81 M	87.6	Most <30	NS	NS	NS	1	87.6	NS
Aye[44]	Jun 29	CR/CS	16 / 48	42 M	91	20.5 (11-70)	35	6	0	1	83	3 (2-3)**
Sessa[45]	Dec 2	Deaths with Autopsy	17 / 33	2 M ***	100	32 (22-42)	1	1	0	0	50	10 (5-15)

* *For 214 M/MP cases, specific vaccine not specified.*

** *Interquartile range as opposed to full range*

*** *Study included 38 cases but only 2 were myocarditis.*

APPENDIX 2.

Myocarditis and Pericarditis Background Rates

TABLE 1A. Myocarditis BACKGROUND RATES Study methodology: * National Health Care Register Search; **Hospital based

Country [reference]	Study years	Population (age in years)	Incidence rate per 100,000 person years [95% confidence interval] (total cases)		
			All	Males	Females
GLOBAL					
Global Burden of Disease Study[46]	1990 2013	All ages All ages	22.8 [21.5-24.5] 22.0 [20.5-23.6]		
AMERICAs **NONE FOUND**					
USA[2] **	2007 To 2008	0-4 5-9 10-14 15-18 **All ages** All ages – White All ages – Black All ages – Hispanic All ages– Asian & Pacific Islander & Native American	1 [0.804-1.196] 0.3 [0.104-0.496] 0.3 [0.104-0.496] 1.3 [1.104-1.496] **0.7 [0.622-0.778]** 0.4 [0.322-0.478] 0.5 [0.304-0.696] 0.6 [0.404-0.796] 0.3 [0.104-0.496]	**0.9 [0.704-1.096]**	**0.5 [0.304-0.696]**
	2009-10	0-4 5-9 10-14 15-18 **All ages** All ages – White All ages – Black All ages – Hispanic All ages– Asian & Pacific Islander & Native American	1 [0.804-1.196] 0.4 [0.204-0.596] 0.4 [0.204-0.596] 1.2 [1.004-1.396] **0.8 [0.722-0.878]** 0.5 [0.402-0.598] 1 [0.804-1.196] 0.5 [0.304-0.696] 0.7 [0.504-0.896]	**0.9 [0.704-1.096]**	**0.6 [0.404-0.796]**
	2011-12	0-4 5-9 10-14	0.9 [0.704-1.096] 0.3 [0.104-0.496] 0.5 [0.304-0.696]		

		15-18 **All ages** All ages – White All ages – Black All ages – Hispanic All ages– Asian & Pacific Islander & Native American	1.6 [1.404-1.796] **0.8 [0.722-0.878]** 0.6 [0.404-0.796] 0.9 [0.704-1.096] 0.6 [0.404-0.796] 0.6 [0.502-0.698]	**1.1 [0.904-1.296]**	**0.6 [0.404-0.796]**
	2013-14	0-4 5-9 10-14 15-18 **All ages** All ages – White All ages – Black All ages – Hispanic All ages– Asian & Pacific Islander & Native American	1 [0.804-1.196] 0.3 [0.104-0.496] 0.7 [0.504-0.896] 1.6 [1.404-1.796] **0.8 [0.702-0.898]** 0.7 [0.504-0.896] 1 [0.804-1.196] 0.6 [0.404-1.096] 0.9 [0.704-1.096]	**1.1 [0.904-1.296]**	**0.5 [0.304-0.696]**
	2015-16	0-4 5-9 10-14 15-18 All ages All ages – White All ages – Black All ages – Hispanic All ages– Asian & Pacific Islander & Native American	1.2 [1.004-1.396] 0.3 [0.104-0.496] 0.6 [-0.404-0.796] 1.8 [1.604-1.996] **0.9 [0.802-0.998]** 0.7 [0.504-0.896] 1.1 [0.904-1.296] 0.9 [0.704-1.096] 0.6 [0.404-0.796]	**1.2 [1.004-1.396]**	**0.7 [0.504-0.896]**

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	2007-16	0-4 5-9 10-14 15-18 **All ages** All ages – White All ages – Black All ages – Hispanic All ages– Asian & Pacific Islander & Native American	1 [0.922-1.078] 0.3 [0.261-0.339] 0.5 [0.461-0.539] 1.5 [1.422-1.578] **0.8 [0.761-0.839]** 0.6 [0.561-0.639] 0.9 [0.822-0.978] 0.6 [0.541-0.659] 0.6 [0.561-0.693]	**1 [0.961-1.039]**	**0.6 [0.580-0.620]**
ASIA	**NONE FOUND**				
AUSTRALIA/OCEANIA	**NONE FOUND**				
EUROPE					
Finland[47] *	2004-14	≤15	1.95 [1.69-2.24]	2.92 [2.49-3.42]	0.94 [0.70-1.25]
Switzerland[48] **	2015 2016	18-96	10.0 (4) 63.0 (26)		
Netherlands[49] PHARMO Database Network	2017	**All ages :** 1. Inpatient 2. GP & inpatient	1. 1.31 [1.08-1.57] 2. 15.87 [12.42-19.99]		
Denmark[49] Danish Registries (DCE-AU)	2010	**All ages**	3.66 [3.19-4.20]		
Spain[49] BIFAP	2017	**All ages :** 1. Inpatient 2. GP & inpatient	1. 2.00[1.72-2.30] 2. 2.50[2.05-3.03]		
Spain[49] SIDIAP GP based	2017	**All ages**	0.85[0.62-1.12]		
Spain[49] FISABIO	2017	**All ages**	2.35[1.96-2.80]		
Italy[49] PEDIANET database, GP based	2018	**0-14**	0.68[0.02-3.79]		
Italy[49] ARS database inpt & ER	2017	**All ages**	6.28[5.24-7.47]		
United Kingdom[49]	2017	**All ages**	2.86[2.34-3.47]		
MIDDLE EAST	**NONE FOUND**				

TABLE 1B. Pericarditis background rates. Study methodology: * National Health Care Register Search

Country [reference]	Study years	Population (age in years)	Incidence rate per 100,000 person years [95% confidence interval] (total cases)		
			All	Males	Females
AMERICAs	**NONE FOUND**				
ASIA	**NONE FOUND**				
AUSTRALIA/OCEANIA	**NONE FOUND**				
EUROPE					
Finland[22] *	2000-2009	≥16	3.32 [**3.14–3.50**] (1361)	4.52 [**4.22–4.83**]	2.11[**1.91–2.32**]
Netherlands[49] PHARMO Database Network	2017	**All ages** 1. Inpatient 2. GP and inpatient	1. 4.18[3.77-4.62] 2. 23.59 [19.33-28.51]		
Denmark[49] Danish Registries (DCE-AU) In u&outpt	2010	**All ages**	16.05[15.03-17.13]		
Spain[49] BIFAP	2017	**All ages:** 1. GP based 2. GP& inpatient	1. 16.54 [15.73-17.38] 2. 18.73 [17.45-20.08]		
Spain[49] SIDIAP GP based	2017	**All ages**	18.63[17.53-19.79]		
Spain[49] FISABIO in and outpatient	2017	**All ages**	11.01[10.14-11.94]		
Italy[49] PEDIANET database GP based	2018	**0-14**	3.40 [1.11-7.94]		
Italy[49] ARS database inpt & Emergency room	2017	**All ages**	33.49 [31.03-36.11]		
United Kingdom[49.] CPRD & HES	2017	**All ages**	12.38[11.27-13.58]		
MIDDLE EAST	**NONE Found**				

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TABLE 2. Arrhythmia background rates. All included studies focused on Atrial fibrillation, and some included atrial flutter [50,52,53,55,57]

Country [reference]	Study years	Population (age in years)	Incidence rate per 100,000 person years [95% confidence interval] (total cases)		
			All	Males	Females
AMERICAs					
USA[50]	1989-93	65-69 70-74 75-79 ≥80 **All ages**		1230 (27) 2280 (50) 3480 (46) 5870 (50) 2640 (173)	1090 (41) 910 (26) 2310 (40) 2510 (24) 1410 (131)
USA[51]	1980-2000	<55 55-64 65-74 75-84 ≥85 **All ages**	**340 [330-350] 4618**	62 (364) 434 (354) 1291 (671) 2452 (670) 3966 (306) **453 [435-472] (2365)**	20 (25) 175 (32) 591 (82) 1575 (156) 2792 (133) **259 [248-270] (2253)**
USA[52] Specific counties in NC, MD, plus Pittsburgh PA	1989-2008 White	65-69 70-74 75-79 80-84 85-89		1520[1010-2280] (23) 1920[1560-2360] (89) 2770[2370-3230] (162) 3880[3380-4460] (200) 4930[4170-5830] (136)	670[420-1060] (18) 1260[1030-1540] (93) 1950[1690-2260] (182) 2640[2320-3020] (222) 3470[2970-4060])156)
	1989-2008 Black	65-69 70-74 75-79 80-84 85-89		2000[900-4460] (6) 1230[660-2280] (10) 1480[880-2500] (14) 2600[1660-4070] (19) 2400[1200-4810] (8)	1380[660-2900] (7) 990[590-1680] (14) 1670[1160-2380] (30) 1990[1390-2850] (30) 3090[2090-4570] (25)
USA[53] Massachusetts	1958-67 1968-77 1978-87 1988-97 1998-07	50–89		370 (40) 731 (101) 907 (166) 1432 (266) 1337 (248)	252 (35) 469 (90) 547 (161) 614 (194) 855 (243)

USA[54] *NOTE: publication included age breakdown for all years but only showing most recent period.*	1993 1998 2003 2007	≥ 67	2730 (31266) 2860 (28698) 2820 (28537) 2830 (20451)	3390 (14099) 3530 (12909) 3400 (12744) 3390 (9178)	2320 (17167) 2420 (15789) 2450 (15793) 2470 (11273)
	2007	67-79 70-74 75-79 80-84 85-89 ≥ 90	1290 (1609) 1880 (3721) 2880 (4530) 3830 (4496) 5350 (3634) 6890 (2461)		
ASIA	**NONE FOUND**				
AUSTRALIA/OCEANIA					
Australia[55]	2004-5	**≥35**	200[150-260] (53)	280[200-390] (34)	130[80-200] (19)
EUROPE					
Scotland[56]	2001-2	<45 45-54 55-64 65-74 75-84 > 65 > 75 > 85 **All ages**	4.15(9) 50 (24) 110 (46) 320 (95) 620 (115) 470 (256) 660 (161) 770 (46) **90 (335)**	10 (6) 80 (20) 170 (34) 380 (52) 740 (54) 530 (120) 770 (68) 860 (14) **100 (180)**	2.81(3) 20 (4) 60 (12) 270 (43) 540 (61) 430 (136) 600 (93) 740 (32) **80 (155)**
Netherlands[57]	1990-99	55-59 60-64 65-69 70-74 75-79 80-84 ≥ 85 **All ages**	110 [30-290] (3) 330 [220-470] (27) 550 [420-710] (54) 1150 [950-1400] (100) 1470[1200-1770](101) 2070 [1680-2530] (92) 1820 [1400-2330] (60) **990 [900-1090] (437)**	260 (3) 490 (17) 660 (28) 1240 [920-1640] (45) 1990 [1570-2590] (51) 2550 [1810-3480] (36) 2540 [1560-3920] (18) **1150 [1000-1320] (198)**	(0) 210 [110-370] (10) 470 [310-680] (26) 1010 [830-1410] (55) 1150 [870-1510] (50) 1820 [1410-2380] (56) 1620 [1190]2170] (42) **890 [780-1020] (239)**

Iceland[58] *NOTE: publication included age breakdown for all years but only showing most recent period.*	1991-3 1994-6 1997-9 2000-2 2003-5 2006-8	**All Ages**	220 (640) 230 (748) 240 (808) 230 (839) 220 (872) 230 (998)	260 (378) 290 (452) 270 (449) 270 (477) 260 (506) 260 (552)	180 (262) 180 (296) 210 (359) 200 (362) 180 (366) 210 (446)
	2006-8	20-54 55-64 65-74 75-84 85-99		40 (62) 370 (106) 800 (127) 1550 (162) 3460 (95)	10 (12) 130 (37) 500 (89) 1230 (176) 2440 (132)
Netherlands[49] PHARMO Database Network	2017	**All ages** 1. Inpatient 2. GP based & inpatient	1. 353.91[350.01-357.84] 2. 1497.25[1461.42-1533.74]		
Denmark[49] DCE-AU in & outpatient	2010	**All ages**	650.83 [644.15-657.58]		
Spain[49] BIFAP	2017	**All ages** 1. GP based 2. GP based & inpatient	1. 719.40[713.97724.85] 2. 872.38[863.45-881.38]		
Spain[49] SIDIAP	2017	**All ages** 1. GP based 2. GP based & inpatient	1. 885.49[877.71-893.32] 2. 1345.61[1327.02-1364.40]		
Spain[49] FISABIO in/outpt	2017	**All ages**	1161.45 [1152.16-1170.79]		
Italy[49] PEDIANET database	2018	**0-14**	130.88[113.0-150.76]		
Italy[49] ARS database	2017	**All ages**	1207.50[1192.33-1222.80]		
United Kingdom[49] CPRD & HES	2017	**All ages**	495.71[488.47-503.03]		
MIDDLE EAST	**NONE FOUND**				

TABLE 3. Acute Myocardial Infarction background rates

Country reference (case ascertainment method)	Study years	Population (age in years)	Incidence rate per 100,000 person years [95% confidence interval] (total cases)		
			All	Males	Females
AMERICAs					
USA[59] Minnesota, Olmsted County	1987-2006	**All ages**	186 [150-221] 180 [151-209]		
USA[60] Massachusetts (Framingham Study) NOTE: data shown for last decade only; 3 additional decades (1960-1989) included in publication	1990-99	40–49 50–59 60–69 70–79 80–89		24.71 39.78 55.11 117.36 166.03	3.99 7.53 20.05 45.21 130.00
USA[61] North Carolina	1987-1994	**35-74**		410 410	190 [160-220] 180 [150-210]
USA[62] Massachusetts	1975 1981 1995	**All ages**	244 272 184		
USA[63] Massachusetts	-	35-84		1410	440
USA[64] National Medicare and Medicaid Data	2002	65–74 75–84 ≥85 **Overall**	790 1319 2053 **1131**	**1344**	**981**
	2003	65–74 75–84 ≥85 **Overall**	752 1273 2029 **1093**	**1296**	**948**
	2004	65–74 75–84 ≥85	700 1188 1904		

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		Overall	**961**	**1204**	**890**
	2005	65–74 75–84 ≥85 **Overall**	653 1114 1822 **961**	**1138**	**833**
	2006	65–74 75–84 ≥85 **Overall**	612 1027 1672 **893**	**1055**	**775**
	2007	65–74 75–84 ≥85 **Overall**	585 994 1647 **866**	**1017**	**754**
USA[65] California	1999 2000 2008	**≥30**	274 287 208		
USA[66] Oregon	2011-2012	45-64 ≥65	102 [92-113] 275 [250-300]		
	2014-2015	45-64 ≥65	85 [76-94] 269 [245-292]		
USA[67] New York	2002-3	>18	67 [65-69] (4053)		
USA[68] Oregon	2002-2005	all - Black all - white		175 [101–291] 84 [73–97]	90[48–150] 40 [33–48]
USA[69] National Pregnancy-Related Acute Myocardial Infarction	2000-2	<20 20–24 25–29 30–34 35–39 ≥ 40			1.0[0.5–1.6] (14) 2.3 [0.7–3.9] (70) 4.0 [2.0–6.0] (133) 8.8 [6.2–11.4] (265) 19.0[13.4–24.6](280) 30.2 [17.2–43.2] (97)
ASIA **NONE FOUND**					
AUSTRALIA/OCEANIA					
New Zealand [70]	2016-18	all ages	105.0 (9319)	144.1	67.7

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EUROPE					
UK[71] *NOTE: prospective study with 7735 men aged 40-59 recruited over 3 years (1978-1980) and followed for up to 25 years. Rates shown are for first occurrence of MI.*	0-5 years follow-up	40-44 45-49 50-54 55-59 60-64		194 [97-389] 363 [255-516] 642 [490-840] 783 [612-1003] 1116 [836-1489]	
	10-15 years follow-up	45-49 50-54 55-59 60-64 65-69		222 [116-428] 630 [480-827] 729 [562-945] 1151 [930-1423] 1553 [1195-2018]	
	15-20 years follow-up	55-59 60-64 65-69 70-74 75-79		509 [325-798] 634 [477-844] 911 [706-1176] 1708 [1396-2091] 1725 [1270-2343]	
	20-25 years follow-up	60-64 65-69 70-74 75-79 80-84		508 [320-806] 926 [725-1183] 1228 [973-1550] 1822 [1461-2272] 2141 [1545-2969]	
UK [72] Pregnancy MI	2005-2010	**Not Given**			0.7 [0.5–1.1] (25)
MIDDLE EAST **NONE FOUND**					

TABLE 4. Sudden cardiac death background rates

Country [reference]	Study years	Population (age in years)	Incidence rate per 100,000 person years [95% confidence interval] (total cases)		
			All	Males	Females
AFRICA	NONE	FOUND			
AMERICAs					
US MA[63]		**35-84**		310	110
ASIA					
Japan[73]	1981-1985	30-64 65-74 75-84 40-74 **All ages**	24.1 [4.8 - 43.4] 217.1 [64.9 - 369.3] 541.0 [187.9-894.1] 65.0 [29.9 -100.1] **76.0 [44.8 -107.2] (114)**	**111.7[53.1-170.3] (70)**	**50.6[17.1 -84.1] (44)**
	1986-1990	30-64 65-74 75-84 40-74 **All ages**	19.7 [3.3-36.1] 100.2[1.7 -198.7] 527.2 [210.6-843.8] 40.0 [14.1- 65.9] **57.9 [32.7 -83.1] (101)**	**82.1 [36.0 -128.2] (61)**	**39.5[12.0 - 67.0] (40)**
	1991-1995	30-64 65-74 75-84 40-74 **All ages**	15.7 [1.8 - 29.6] 99.7 [8.6 -190.8 258.5 [67.2 - 449.8] 34.6 [12.2 - 57.0] **39.3 [20.3-58.3] (83)**	**54.4[20.2 -88.6] (49)**	**27.1[6.3 - 47.9] (34)**
	1996-2000	30-64 65-74 75-84 40-74 **All ages**	12.4 [0.7 -24.1] 83.8 [8.9 - 158.7] 204.3 [39.5 -369.1] 28.8 [10.0 - 47.6] **31.6 [15.6-47.6] (76)**	**49.3[18.6-80.0] (50)**	**16.7[2.0-31.4] (26)**
	2001-2005	30-64 65-74 75-84	17.0 [2.5 -31.5] 101.8 [24.1-179.5] 190.8 [51.1- 330.5]		

		40-74 **All ages**	33.4 [13.5 -53.3] **36.8 [19.8 -53.8] (97)**	**57.9[26.2-89.6](67)**	**18.2 [2.5-33.9] (30)**
AUSTRALIA/OCEANIA	**NONE FOUND**				
EUROPE					
Denmark[74]	2000-2006	1-35	2.3 [2.0-2.7]	3.2 [2.6-3.8]	1.5 [1.1-1.9]
	2007-2009	36-49	21.7 [29.2-23.4]	32.1 [29.5-34.9]	11.1 [9.5-12.8]
	2007-2009	1-49	8.6 [8.0-9.2]		
MIDDLE EAST	**NONE FOUND**				

TABLE 5. Cardiomyopathy background rates. All studies involved women during pregnancy or post-partum period, except the European ACCESS project study. All peripartum studies defined peripartum cardiomyopathy as heart failure occurring in the last month of pregnancy or within 5 months after delivery.

Country [reference]	Study years	Population (age in years)	Incidence rate/1000 live births [95% confidence interval] (total cases)		
			All	Males	Females
AMERICAs	**NONE FOUND**				
USA[75] National	2004-2011	15 - 19 20- 29 30 - 39 40 - 54 **All ages**			5.3 (1713) 8.3(14506) 12.7(14683) 36.7(3316) **10.3(34219)**
USA[76] National	2004-2006	15–24 25–34 35 or older **All ages**			0.29[0.22–0.36] 0.41[0.37–0.45] 0.80[0.69–0.90] **0.46[0.42–0.49]**
USA[77] California	1995-2004	**All ages**			**8.53 [7.38 -9.82] (110)**
ASIA					
Singapore[78]	2009-2010	21-42			0.89 (11)
AUSTRALIA/OCEANIA	**NONE FOUND**				
EUROPE					
Spain[49] BIFAP	2017	**All ages** 1. GP based 2. GP based & inpatient	1. 0.24 [0.15-0.36] 2. 1.58 [1.23-2.01]		
Spain[49] SIDIAP	2017	**All ages** 1. GP based 2. GP based & inpatient	1. 0.05 [0.01- 0.15] 2. 3.63 [2.73-4.72]		
Spain[49] FISABIO in/outpt	2017	**All ages**	3.48 [2.99-4.01]		
Italy[49] ARS database inpt&ER	2017	**All ages**	7.12 [6.01-8.38]		
MIDDLE EAST	**NONE FOUND**				

TABLE 6. Heart failure background rates

Country [reference]	Study years	Population (age in years)	Incidence rate per 100,000 person years [95% confidence interval] (total cases)		
			All	Males	Females
AMERICAs					
USA[79] Massachusetts Framingham study	1950–1969	28-62		627 [475–779]	420 [336–504]
	1970–1979			563 [437–689]	311 [249–373]
	1980–1989			536 [448–623]	298 [247–350]
	1990–1999			564 [463–665]	327 [266–388]
USA[80] 4 states (NC, Mississippi, Minn, MD)	1987-2002 Caucasian	45–49		240 (41)	170 (37)
		50–54		561 (101)	310 (66)
		55–59		840 (151)	440 (85)
		60–64		1430 (233)	770 (124)
		All ages		**600 (526)**	**340 (312)**
	1987-2002 African–American	45–49		520 (34)	380 (41)
		50–54		720 (35)	760 (66)
		55–59		1400 (57)	1010 (64)
		60–64		1340 (55)	1740 (92)
		All ages		**910 (181)**	**810 (263)**
	1987-2002	**All**	**570 (1282)**		
USA[81] National Medicare	1994	≥65	3220 (46258)	3680 (19317)	2920 (26941)
	1995		3180 (44962)	3590 (18572)	2910 (26390)
	1996		3140 (43299)	3550 (17926)	2870 (25373)
	1997		3230 (43139)	3670 (18030)	2930 (25109)
	1998		3150 (40900)	3600 (17125)	2850 (23775)
	1999		3000 (38362)	3360 (15820)	2750 (22542)
	2000		3030 (39824)	3430 (16283)	2750 (23541)
	2001		2880 (37867)	3290 (16128)	2600 (21739)
	2002		2890 (39123)	3220 (16459)	2650 (22664)
	2003		2910 (40269)	3290 (17288)	2640 (22981)

USA[82] 6 states (MD, Il, NC, CA, NY, Minn)	2000-2002	45-84	310 (79)		
US [83] National Framingham	1990-1999 2000-2009	≥ 60 ≥ 60	1970[1840-2100] (1367) 1890[1770- 2010](1157)		
Canada[84] National	1997 1999 2001 2003 2005 2007	20-105	454.7 (39869) 450.1 (41380) 422.0 (40795) 358.2 (36480) 334.2 (35701) 306.1 (34545)		
ASIA	**NONE FOUND**				
AUSTRALIA/OCEANIA	**NONE FOUND**				
EUROPE					
Netherlands[85] all living in a Rotterdam suburb	1989-2000	55–59 60–64 65–69 70–74 75–79 80–84 85–89 ≥90 **Overall**	140[50-330] (4) 310[210-440] (27) 540[410-690] (56) 1170[970-1400] (113) 1700[1430-2000] (136) 3010[2580-3500] (166) 4190[3530-4940] (137) 4740[3869-5820] (86) **1440 [1340-1550] (725)**	**1760 [1580-1950]**	**1250 [1130-1380]**
Netherlands[86] Groningen(city)	1997-2010	**28–75**		370 [310-450]	240 [190-310]

Sweden[87] National	**2006**	40–49		60	30
		50–59		240	110
		60–69		700	350
		70–79		1910	1440
		80–89		4340	3520
		≥90		7170	5740
		All ages		**360**	**390**
	2007	40–49		60	30
		50–59		220	120
		60–69		580	340
		70–79		1750	1420
		80–89		4110	3480
		≥90		6260	5290
		All ages		**330**	**370**
	2008	40–49		60	20
		50–59		210	80
		60–69		570	290
		70–79		1680	1200
		80–89		4260	3500
		≥90		6030	4960
		All ages		**330**	**350**
	2009	**40–49**		60	200
		50–59		220	800
		60–69		480	290
		70–79		1490	1200
		80–89		3950	3460
		≥90		5640	5140
		All ages		**300**	**330**
	2010	40–49	40	50	20
		50–59	160	210	100
		60–69	370	520	230
		70–79	1190	1320	1070
		80–89	3370	3820	3100

		≥90 **All ages**	4500 **290**	5150 **290**	4250 **290**
Denmark[88] National	1995	18–34 35-44 45–54 55–64 65–74 >74	4 13 50 200 630 1640		
	2012	18–34 35-44 45–54 55–64 65–74 >74	7 20 64 170 350 1150		
UK[89] National	2002 2014	**≥16**	358 332		
Germany[49]. GePaRD claims data	2017	**All ages**	100.67[91.77-110.19]		
Netherlands[49]. PHARMO Database Network	2017	**All ages** 1. GP based 2. GP based & inpt	1. 143.97[141.49-146.48] 2. 426.13[407.28-445.62]		
Denmark[49]. DCE-AU in & outpatient	2010	**All ages**	276.39[272.06-280.79]		
Spain[49] BIFAP	2017	**All ages** 1. GP based 2. GP based & inpt	1. 231.53[228.47-234.62] 2. 359.59[353.89-365.37]		
Spain[49] SIDIAP	2017	**All ages** 1. GP based 2. GP based & inpt	1. 241.06[237.02-245.14] 2. 491.57[480.43-502.90]		
Spain[49] FISABIO. in and outpatient	2017	**All ages**	510.8[504.75-516.98]		
Italy[49] ARS database. Inpt &ER	2017	**All ages**	725.90[714.20-737.74]		
United Kingdom[49] CPRD&HES GP based	2017	**All ages**	155.80[151.76-159.92]		
MIDDLE EAST **NONE FOUND**					

APPENDIX 3

Myocarditis and Pericarditis Diagnostic Codes: ICD-9/10-CM and MedDRA

3.1 Myocarditis and Pericarditis Diagnostic Codes: ICD-9/10-CM and MedDRA

TABLE 1. Narrow terms for Myocarditis and Pericarditis

UMLS Concept		Diagnostic Coding System Term and Codes				
CUI	Concept Name	Term	MedDRA	ICD9CM	ICD10CM	SNOMEDCT_US
C0027059	Myocarditis	Myocarditis Myocarditis, unspecified Myocarditis NOS Myocarditis NOS Myocardial inflammation	10028606 10028619 10028613	429.0	I51.4	50920009 155380004 195119007 251060004
C0155686	Acute myocarditis	Acute myocarditis Acute myocarditis Acute myocarditis, unspecified [X]Acute myocarditis, unspecified Acute myocarditis NOS	10000932 10000934	422 422.90	I40 I40.9	46701001 155336004 194952006 195569005 194961006
C0729608	Myocarditis due to infectious agent	Infective myocarditis Infectious myocarditis Myocarditis infectious	 10052768 10066857		I40.0	
C0348611	Myocarditis in bacterial diseases classified elsewhere	[X]Myocarditis in bacterial diseases classified elsewhere				195570006
C0348612	Myocarditis in viral diseases classified elsewhere	[X]Myocarditis in viral diseases classified elsewhere				195571005
C0348613	Myocarditis in other infectious and parasitic diseases classified elsewhere	[X]Myocarditis in other infectious and parasitic diseases classified elsewhere				195572003
C0348614	Myocarditis in other diseases classified elsewhere	[X]Myocarditis in other diseases classified elsewhere				195573008
C0027060	Interstitial. Myocarditis	Myocarditis interstitial	10028611			
C0155689	Isolated (Fiedler's) myocarditis	Idiopathic myocarditis Isolated myocarditis	10021234	422.91	 I40.1	

C0155690	Septic myocarditis	Septic myocarditis Myocarditis septic	10040068 10028615	422.92	I40.0	
C0155691	Toxic myocarditis	Toxic myocarditis	10044235	422.93		
C0155692	Other acute myocarditis	Other acute myocarditis Other and unspecified acute myocarditis Other acute myocarditis NOS [X]Other acute myocarditis [X]Other acute myocarditis	10031466 10031516	422.99 422.9	I40.8	194952006 194960007 195568002
C0155679	Acute pericarditis	Acute pericarditis Acute pericarditis Acute pericarditis Acute pericarditis, unspecified Acute pericarditis NOS	10000996 10000998	420 420.90	I30 I30.9	15555002 155333007 194902002 194914005 194920006
C0155680	Other and unspecified acute pericarditis		10031517	420.9		
		Acute idiopathic pericarditis Acute nonspecific idiopathic pericarditis		420.91	 I30.0	
C0265147	Infectious pericarditis	Infective pericarditis Infectious pericarditis Pericarditis infective	 10034490 10062491		I30.1	
C0265150	Non-infectious pericarditis		10034494			
C0031046	Pericarditis	Pericarditis Pericarditis NOS	10034484 10034495			3238004
C0348597	Other forms of acute pericarditis	Other forms of acute pericarditis Other acute pericarditis [X]Other forms of acute pericarditis	 10031469	 420.99	I30.8	 195552008
C0348598	Pericarditis in bacterial diseases classified elsewhere	[X]Pericarditis in bacterial diseases classified elsewhere				195554009
C0348599	Pericarditis in other infectious and parasitic diseases classified elsewhere	[X]Pericarditis in other infectious and parasitic diseases classified elsewhere				195555005
C0348600	Pericarditis in other diseases classified elsewhere	[X]Pericarditis in other diseases classified elsewhere				195556006

C0265122	Disorder of pericardium	Pericardial disorders Disease of pericardium, unspecified Disorder of pericardium Unspecified disease of pericardium Pericardial disease NOS Pericardial disease NOS Pericardial disease	10034468 10045752 10034470 10061338	 423.9 	 I31.9 	 55855009 155341007 266295005
		Myocarditis/pericarditis	10028650			

* ICD9 for 'Other acute pericarditis' includes pneumococcal, purulent, staphylococcal, streptococcal, suppurative, pneumopyopericardium, pyopericardium

TABLE 2. BROAD SEARCH TERMS FOR MYOCARDITIS and PERICARDITIS (related to underlying etiology)

UMLS Concept		Diagnostic Coding System Term and Codes				
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM	SNOMEDCT_US
C0155687	Acute myocarditis in diseases classified elsewhere	Acute myocarditis in diseases classified elsewhere Acute myocarditis in diseases EC Acute myocarditis in diseases EC, NOS	10000933	422.0	I41	 19492007 19491004
Etiologic specific myocarditis:						
C0153106	Coxsackie myocarditis		10011258	074.23	B33.22	
C0152961	Meningococcal myocarditis	Meningococcal myocarditis Myocarditis meningococcal	10027277 10028612	036.43	A39.52	
C0265147 C0155680	Rheumatic myocarditis Acute rheumatic myocarditis		10001058	391.2	I01.2	
C0152961		Chagas disease - acute			B57.0	
		Diphtheritic myocarditis	10028615	032.82	A36.81	
C015557		Scarlet fever with myocarditis		034.1	A38.1	
C0155690		Gonococcal myocarditis			A54.83	
Not mapped to all terminologie		Influenza due to other identified influenza virus with myocarditis Influenza due to unidentified influenza virus with myocarditis		488.09 488.19	J10.82 J11.82	
		Lyme myopericarditis			A69.29	

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s searched independently		Mumps myocarditis			B26.82	
		Rheumatoid arthritis myocarditis			M05.31	
		Sarcoid myocarditis			D86.85	
		Syphilitic myocarditis		093.82	A52.06	
		Toxoplasmosis myocarditis		130.3	B58.81	
		Tuberculous myocarditis		017.9	A18.84	
C0694496	Pericarditis in diseases classified elsewhere				I32	194903007

C0348598	Pericarditis in bacterial diseases classified elsewhere			420.0	!32.0	
Etiologic specific pericarditis:						
C0155680		Acute Rheumatic pericarditis		420.90	I30.1	
C0265150		Dressler's syndrome			I24.1	
Not mapped to all terminologies searched independently		Viral pericarditis – Coxsackie Acute pericarditis – coxsackie			B33.23	194905000
		Gonococcal pericarditis Acute pericarditis - gonococcal			A54.83	194910001
		Meningococcal pericarditis Acute pericarditis – meningococcal			A39.53	194906004
		Acute pericarditis – pneumococcal				194916007
		Acute pericarditis – staphylococcal				194917003
		Acute pericarditis - streptococcal				194918008
		Rheumatoid arthritis pericarditis			M05.31	
		Syphilitic pericarditis Acutte pericarditis – syphilitic			A52.06	194907008
		SLE pericarditis			M32.12	
		Tuberculosis pericarditis Acute pericarditis – tuberculous TB – acute pericarditis			A18.84	194908003 194908003
C0265150	Non-infectious pericarditis		10034494			

TABLE 3. BROAD SEARCH TERMS FOR MYOCARDITIS and PERICARDITIS RELATED TO SYMPTOMATOLOGY AND/OR MANNERS OF PRESENTATION IN BOTH THE SHORT TERM (E.G., ARRHYTHMIAS, HEART FAILURE, ANGINA, ELEVATED CARDIAC ENZYMES, CARDIAC TAMPONADE, PERICARDIAL EFFUSION) AND THE LONG TERM (E.G CARDIOMYOPATHY)

UMLS Concept		Diagnostic Coding System Term and Codes				
CUI	Name	Term	MedDRA	ICD9-CM	ICD10-CM	SNOMEDCT_US
C0494595	Atrioventricular and left bundle-branch block				I44	
C0006384	Bundle Branch Block	Right fascicular block			I45.0	
		Other and unspecified Right Bundle Branch Block			I45.1	
		Bifascicular block			I45.2	
		Trifascicular block)			I45.3	
		Bundle Branch Block NOS	10006581		I45.4	
		Bundle branch Block	10006578	426.2		251122006
		Bundle Branch Block		426.3		6374002
		Bundle Branch Block		426.4		
		Bundle Branch Block		426.5		
		Bundle branch block, unspecified	10006584	426.50		195048003
		Block bundle branch	10005268			
		Heart block bundle branch	10019261			
C0155706	Other bilateral bundle branch block	Other bilateral bundle branch block	10031693	426.53		195050006
C0348624	Other specified heart block	Other specified heart block			I45.5	
		[X]Other specified heart block				195584001
C0043202	Wolff-Parkinson-White Syndrome	Wolff-Parkinson-White Syndrome	10048015		I45.6	155360000
		Wolff-Parkinson-White Syndrome				266304003
		Wolff-Parkinson-White pattern				251115003
		Wolff-Parkinson-White pattern				74390002
		WPW syndrome	10048041			
		Wolff-Parkinson-White syndrome congenital	10049291			
C0348621	Other and unspecified atrioventricular block	Other and unspecified atrioventricular block			I44.3	
		Atrioventricular block, other and unspecified	10003679	426.1		
		[X]Other and unspecified atrioventricular block				195581009

C0348623	[X]Other and unspecified right-bundle-branch block	[X]Other and unspecified right bundle-branch-block				195583007
C0392470	Anomalous Atrioventricular excitation	Anomalous atrioventricular excitation Anomalous atrioventricular excitation Anomalous atrioventricular excitation NOS Anomalous A-V excitation Anomalous A-V excitation	10002611	426.7	I45.6	17869006 195057009 195061003 155360000 266304003
C0264886	Conduction disorder of the heart	Conduction disorders Conduction disorders Conduction disorders Conduction disorder(s), unspecified Conduction disorder NOS Conduction disorders NOS Conduction disorders NOS Defect conduction (NOS) Conduction disorder Cardiac conduction disorders Conduction disorder of the heart	10010279 10010278 10010277 10012117 10010276 10000032	426 426.9	I45.9	155354000 195038000 266302004 195066008 155362008 195068009 44808001
C0003811	Cardiac arrhythmia	Cardiac dysrhythmias Cardiac dysrhythmia, unspecified Cardiac dysrhythmia NOS Cardiac dysrhythmia NOS Cardiac dysrhythmias NOS Cardiac dysrhythmias NOS Cardiac arrhythmia, unspecified Cardiac arrhythmia Cardiac arrhythmia (NOS) Cardiac arrhythmia NOS Cardiac arrhythmias Arrhythmia Arrhythmia Arrhythmia Arrhythmia (NOS)	10007545 10007544 10007518 10007519 10007520 10007521 10003119 10003120	427 427.9	 I49.9	 155369004 195107004 155373001 266307005 698247007 251151005 44808001 53488008

		Arrhythmia cardiac (NOS) Arrhythmia NOS Dysrhythmias	10003123 10003127 10013978			
C0003813	Sinus arrhythmia	Sinus arrhythmia Sinus arrhythmia Arrythmia sinus Arrhythmia sinus	10040739 10003133 10050488			19508002 71792006
C0039239	Sinus tachycardia	Sinus tachycardia Sinus tachycardia Tachycardia sinus	10040752 10043083			11092001 367107008
C0080203	Tachyarrhythmia	Tachyarrhythmia	10049447			6285003
C0039236	Tachycardia, Paroxysmal	Paroxysmal tachycardia Paroxysmal tachycardia, unspecified Paroxysmal tachycardia (NOS) Tachycardia paroxysmal Tachycardia paroxysmal NOS Bouveret-Hoffmann syndrome Essential paroxysmal tachycardia	 10034047 10034045 10043079 10043081 10067520	427.0 427.2	I47 I47.9	12026006 195076006 195079004 195078007 195077002
C0349069	Re-entry ventricular arrhythmia	Re-entry ventricular arrhythmia			I47.0	195105007
C0039240	Supraventricular tachycardia	Supraventricular tachycardia Supraventricular tachycardia Supraventricular tachycardia Supraventricular tachycardia NOS SVT Tachycardia supraventricular	10042604 10042644 10043084		I47.1	155363003 266305002 6456007 195104006
C0030590	Paroxysmal supraventricular tachycardia	Paroxysmal supraventricular tachycardia Paroxysmal tachycardia (supraventricular) Paroxysmal supraventricular tachycardia NOS Paroxysmal sup. tachy. Paroxysmal sup. tachy.	10034044 10034046	427.0		67198005 195074009 155363003 266305002

C0428974	Supraventricular arrhythmia	Supraventricular arrhythmia(s) Supraventricular arrhythmia NOS Arrhythmia supraventricular	10042600 10042599 10003130			72654001
C0042514	Tachycardia, Ventricular	Ventricular tachycardia Ventricular tachyarrhythmia Tachycardia ventricular V.tach Tachycardia – ventric. Tachycardia – ventric.	10047302 10065341 10043085 10046857		I47.2	25569003 6624005 155370003 195075005
C0344428	ECG: ventricular tachycardia	ECG: ventricular tachycardia EKG: ventricular tachycardia				142055005 164895002
C0004238	Atrial fibrillation	Atrial fibrillation Atrial fibrillation Atrial fibrillation Fibrillation atrial Auricular fibrillation AFib AF	10003658 10016566 10003796 10001452 10001434	427.31		155364009 266306001 49436004
C3264374	Unspecified atrial fibrillation	Unspecified atrial fibrillation			I48.91	
C0004239	Atrial Flutter	Atrial flutter Atrial flutter Atrial flutter Flutter atrial	10003662 10016827	427.32		155364009 266306001 5370000
C3264370	Typical atrial flutter	Typical atrial flutter			I48.3	720448006
C3264369	Type 1 atrial flutter	Type 1 atrial flutter			I48.3	
C3264372	Atypical atrial flutter	Atypical atrial flutter			I48.4	
C3264375	Unspecified atrial flutter	Unspecified atrial flutter			I48.92	
C0155709	Atrial fibrillation and flutter	Atrial fibrillation and flutter Atrial fibrillation and flutter Atrial fibrillation and flutter NOS	10003660	427.3	I48	195080001 81216002 195084005

		Atrial flutter/fibrillation Flutter/fib	10003663 10016828			
C3264373	Unspecified atrial fibrillation and atrial flutter				I48.9	
C0235480	Paroxysmal atrial fibrillation	Paroxysmal atrial fibrillation Paroxysmal atrial fibrillation Atrial fibrillation paroxysmal Fibrillation paroxysmal atrial	10034039 10003661 10016570		I48.0	195081002 282825002
C0033036	Atrial Premature Complexes	Atrial premature depolarization Atrial premature complex Atrial premature complex Atrial premature complex Supraventricular premature beats Supraventricular extrasystoles Supraventricular ectopics Supraventricular ectopic beats Extrasystoles supraventricular Extrasystoles atrial SVE Premature beat atrial Premature atrial contraction PAC Ectopic atrial beats Ectopic atrial beats Atrial ectopic	 10042603 10042602 10042601 10015862 10015857 10042643 10036591 10056964 10033350 10050077	 427.61	I49.1	 195094000 251169001 287057009 63593006 155366006 284470004 406461004 73712003 60299007
C0029712	Other premature beats	Other premature beats	10032404	427.69		
C0428908	Sinus Node Dysfunction (disorder)	Coronary sinus rhythm disorder Sinoatrial node dysfunction Sinus node dysfunction Sinoatrial. Node dysfunction NOS	 10040737	 427.81	I49.8	 60423000 195100002
C0264893	Nodal rhythm disorder	Nodal rhythm disorder Nodal arrhythmia Arrhythmia nodal	 10029458 10003125		I49.8	

		Arrhythmia nodal (NOS)	10003126			
C0085612	Ventricular arrhythmia	Arrhythmia ventricular Arrhythmia ventricular (NOS) Ventricular arrhythmia Ventricular arrhythmia NOS	10003131 10003132 10047281 10047282			
C0151636	Premature ventricular contractions	Ventricular premature depolarization Extrasystole ventricular Extrasystoles ventricular Premature VEB's Premature ventricular contractions PVC's VEB's Ventricular contractions premature Ventricular ectopics Ventricular extrasystoles VPC's Ventricular ectopic beats Ventricular ectopic beats Premature ventricular ectopic beats Ventricular premature beats Ventricular premature complex Ventricular premature complex	 10015854 10015864 10036613 10036614 10037582 10047175 10047287 10047288 10047289 10047718 10058291 10058292		I49.3	 155367002 195093006 17738001 195096003 251175005
C0042510	Ventricular fibrillation	Ventricular fibrillation Ventricular fibrillation Ventricular fibrillation paroxysm Ventricular fibrillation paroxysmal VF Fibrillation paroxysmal vent Fibrillation ventricular Paroxymal ventricular fibrillation	10047290 10047292 10047293 10047395 10016571 10016573 10034048	427.41	I49.01	155371004 71908006
C0152173	Ventricular Flutter	Ventricular flutter	10047294	427.42	I49.02	111288001

C0155710	Ventricular fibrillation and flutter	Ventricular fibrillation and flutter Ventricular fibrillation and flutter NOS Ventricular flutter-fibrillation	10047291	427.4	I49.0	195083004 195084005 23265007
C0428981	Junctional premature complex (disorder)	Junctional premature depolarization Premature nodal contraction PNC	 10056965 10035636		I49.2	
C0348626	Other specified cardiac arrhythmias	Other specified cardiac arrhythmias Other specified cardiac dysrhythmias Other specified cardiac dyrhythmias Other specified cardiac dysrhythmia [X]Other specified cardiac arrhythmias	 10032536 10032535	 427.8 427.89	I49.8	 195587008
C0340464	Premature Cardiac Complex	Ectopic beats Premature beats Premature beats, unspecified Premature beats NOS Ectopic heartbeats Heartbeats ectopic Heartbeats premature Extrasystoles Extrasystoles NOS Extrasystoles (NOS)	10014150 10036592 10036593 10014159 10019321 10019324 10015856 10015861 10048512	 427.6 427.60	I49.49 I49.40	
C0348625	Other and unspecified premature depolarization				I49.4	
C0037052	Sick Sinus Syndrome	Sick sinus syndrome Sick sinus syndrome Sick sinus syndrome Syndrome sick sinus	10040639 10042845		I49.5	155373001 266307005 36083008
C0494598	Other cardiac dysrhythmias	Other cardiac arrhythmias			I49	
C0947788	Rate and rhythm disorders NEC	Rate and rhythm disorders NEC	10037908			
C0002962	Angina pectoris	Angina pectoris	10002383	413	I20	

C0741921	Cardiac enzymes increased	Cardiac enzymes increased Cardiac enzymes NOS high Cardiac enzymes NOS increased Heart enzymes elevated	10007548 10007552 10007553 10058166			
C1142294	Troponin T increased	Troponin T increased	10058269			
C1141949	Troponin I increased	Troponin I increased	10058268			
C1141948	Troponin increased	Troponin increased	10058267			
C0031039	Pericardial effusion	Pericardial effusion Effusion, pericardial	10034474 10014311			
C0007177	Cardiac Tamponade	Cardiac tamponade Cardiac tamponade Cardiac tamponade Cardiac tamponade Tamponade cardiac Pericardial. Tamponade	10007610 10043113 10053565	423.3	I31.4	155341007 194975004 266295005 35304003
C0428977	Bradycardia	Bradycardia Bradycardia, unspecified [X]Bradycardia, unspecified [X]Bradycardia, unspecified Bradycardia NOS Heart rate decreased Heart rate low	10006093 10006095 10019301 10019305		R00.1	48867003 207041006 207585002
C0039231	Tachycardia	Tachycardia Tachycardia, unspecified Tachycardia NOS Heart rate fast Heart rate high Heart rate increased Heartbeats increased High pulse rate Pulse fast Pulse increased Pulse rapid	10043071 10043086 10043078 10019302 10019303 10019322 10020081 10037474 10037484	785.0	R00.0	3424008 6285003 86651002

		Pulse rate increased Quick pulse [D]Rapid heart beat	10037490 10037733			 207003004
C0340515	Myocardial dysfunction	Myocardial dysfunction Myocardial depression Myocardial depression	 10069140			233928007
C0018801	Heart failure	Heart failure Heart failure Heart failure, unspecified Heart failures Heart failure (NOS) Heart failure NOS Heart insufficiency Failure heart Insufficiency cardiac Insufficiency cardiac Cardiac failure Cardiac failure (NOS) Cardiac failure NOS Cardiac function failed Cardiac function failure Cardiac insufficiency	10019279 10019285 10019280 10019282 10019290 10016145 10022462 10007554 10007555 10007562 10007568 10007569 10007582	428 428.9	I50 I50.9	155374007 84114007 155377000 266248006 155375008 266308000 195117009
C0018802	Congestive heart failure	Congestive heart failure Congestive heart disease Congestive heart failure, unspecified Cardiac failure congestive Cardiac failure, congestive Congestive cardiac failure Congestive cardiac fail Congestive cardiac fail CCF Congestive heart failure CHF	10010684 10007559 10007564 10010682 10007836 10010684 10008502	 428.0	I50.0 I50.9	 195108009 155375008 266308000 42343007

		Failure heart congestive Heart failure, congestive	10016146 10019284			
C0264719	Acute congestive heart failure					10633002 195109001
C0685095	Biventricular congestive heart failure	Biventricular heart failure Biventricular failure Biventricular congestive heart failure			I50.82	 195108009 92506005
C0023212	Left-sided heart failure	Left ventricular failure Left ventricular failures LVF Left heart failure Failure left heart Failure heart left Cardiac failure left Left cardiac failure Left ventricular insufficiency Pulmonary edema cardiac cause Pulmonary edema cardiac cause	10024119 10024120 10025163 10024106 10016151 10016147 10007561 10024102 10060948 10037376 10037425	428.1	I50.1	195113008 85232009
C1306063	Acute left ventricular failure	Acute left ventricular failure Acute edema of lung with heart disease	10063081			195114002 85232009
C0155582	Congestive rheumatic heart failure	Rheumatic heart failure Rheumatic heart failure (congestive) Congestive rheumatic heart failure	10039062	398.91	I09.81	 82523003
C2039715	Systolic (congestive) heart failure	Systolic (congestive) heart failure		428.2	I50.2	
C1135191	Heart failure, Systolic	Systolic heart failure Systolic heart failure, unspecified Unspecified systolic (congestive) heart failure	10074631	428.2 428.20	 I50.20	417996009
C2732748	Acute systolic heart failure	Acute systolic heart failure	10077979	428.21	I50.21	443254009
C2733492	Acute on chronic systolic heart failure	Acute on chronic systolic heart failure Acute on chronic systolic (Congestive) heart failure		428.23	 I50.23	443253003

C2183328	Diastolic (congestive) heart failure	Diastolic (congestive) heart failure			I50.3	
C1135196	Heart Failure, Diastolic	Diastolic heart failure Diastolic heart failure, unspecified Unspecified diastolic (congestive) heart failure	10069211	428.3 428.30	 I50.30	418304008
C2732951	Acute diastolic heart failure	Acute diastolic heart failure	10080288	428.31	I50.31	443343001
C2732749	Acute on chronic diastolic heart failure	Acute on chronic diastolic heart failure Acute on chronic diastolic (congestive) heart failure		428.33	 I50.33	443344007
C2882272	Combined systolic(congestive) and diastolic (congestive) heart failure	Combined systolic and diastolic (congestive) heart failure			I50.4	
C2882273	Unspecified combined systolic (congestive) and diastolic (congestive) heart failure				I50.40	
	Unspecified combined systolic (congestive) and diastolic (congestive) heart failure	Combined systolic and diastolic heart failure Combined systolic and diastolic heart failure, unspecified		428.4 428.40		
C0235527	Heart Failure, Right-Sided	Right heart failure Failure right heart Cardiac failure right	10039152 10016163 10007563		I50.81	128404006
C2939447	Right ventricular failure	Right ventricular failure NOS Right ventricular failure Right ventricular failures RVF Right ventricular insufficiency Right heart failure Right heart failure Right heart failure RHF – Right heart failure	 10039163 10039164 10039340 10060947		I50.810	 367363000 155375008 195108009 266308000 233925005
C0685095	Heart failure, Biventricular Heart failure, High output Heart failure, unspecified			 428.9	I50.82 I50.83 I50.9	

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C0481377	Decompensated cardiac failure	Decompensated heart failure	10066159			
C0340515	Myocardial dysfunction	Myocardial depression	10069140			
C1959583	Myocardial failure	Myocardial failure				84114007
C0878544	Cardiomyopathies	Cardiomyopathy Cardiomyopathy, unspecified Myocardial disease Cardiomyopathies Cardiomyopathy NOS Myocardiodystrophy	10007636 10007635 10007640 10072122	425 425.4	I42 I42.9 I51.5 I42.8	
C0007193	Cardiomyopathy, Dilated	Dilated cardiomyopathy Congestive (dilated) cardiomyopathy Congestive cardiomyopathy COCM Congestive (dilated) cardiomyopathy	10056419 10010681 10056370 10009836		I42.0	
C0033141	Cardiomyopathies, primary	Cardiomyopathy primary Cardiomyopathy primary NOS Idiopathic cardiomegaly	10061029 10007641 10052650			
C0340419	Other primary cardiomyopathies		10032416	425.4		
C0348617	Other cardiomyopathies				I42.8	
C0264787	Non-obstructive cardiomyopathy		10049813			
C0694499	Cardiomyopathy in diseases classified elsewhere				I43	

TABLE 4. MESH terms linked to UMLS Concepts

UMLS Concept		MESH	
CUI	Name	MESH code	MESH term
C0027059	Myocarditis	D009205	Myocarditides
C0031046	Pericarditis	D010493	Pericarditis
C0007177	Cardiac Tamponade	D002305	Cardiac Tamponade
C0003811	Cardiac Arrhythmia	D001145	Arrhythmia
C0340464	Premature Cardiac Complex	D005117	Beat, Premature
C0033036	Atrial Premature Complexes	D018880	Atrial Beat, Premature
C0037052	Sick Sinus Syndrome	D012804	Sick Sinus Node Syndrome
C0151636	Premature ventricular contractions	D018879	Ectopic Beats, Ventricular
C0152173	Ventricular Flutter	D054141	Ventricular Flutter
C0042510	Ventricular Fibrillation	D014693	Fibrillations, Ventricular
C0878544	Cardiomyopathies	D009202	Cardiomyopathies
C0033141	Cardiomyopathies, Primary	D009202	Cardiomyopathies, Primary
C0007193	Cardiomyopathy, Dilated	D002311	Cardiomyopathies, Dilated
C0031039	Pericardial effusion	D010490	Effusion, Pericardial

APPENDIX 4

Myocarditis and Pericarditis Case Definition

Key Caveats for Diagnosis, Data Analysis and Presentation

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4. Myocarditis and Pericarditis Case Definition[1] Key Caveats for Diagnosis, Data Analysis and Presentation

4.1 Key elements of Case Definition (CD) [1]

- There are **3 levels of certainty** for both myocarditis and pericarditis: 1 (Definite case), 2 (Probable case) and 3 (Possible case). No level can be met with clinical signs and symptoms alone, so appropriate investigation in real time, when possible, is essential. (see Tables 4.1 and 4.2). There is a great deal of clinical overlap between myocarditis and pericarditis, and it is not uncommon to have a combination (myopericarditis). That said, the case definition for each is unique and cases should be assessed against both. If both are satisfied at the same level of certainty, the case should be classified as myopericarditis (e.g. myopericarditis level 2). If both are satisfied at different levels of certainty, classify them separately (e.g. myocarditis level 1, pericarditis level 2).

- The **presenting clinical features** of myocarditis and pericarditis can be subtle and non-specific, so a high level of suspicion is needed. (see Table 4.3) On the other hand, myocarditis can present in a variety of ways overlapping with other cardiac illness including: acute MI like syndrome (coronary arteries will be normal); new onset atrial or ventricular arrhythmias or complete heart block; fulminant heart failure; and sudden cardiac death.[90] Among 99 cases of myocarditis identified over a 20 year period in young healthy Finnish military recruits, 98 presented with acute chest pain and ECG changes of acute MI and 1 presented with sudden unexpected death.[91] Finally the first clinical appearance of myocarditis can be dilated cardiomyopathy, months to years later.[8] The overlap in clinical presentation was the rationale for providing background rates for all the mentioned cardiac injuries (arrhythmia, acute MI, sudden cardiac death, cardiomyopathy, heart failure entities in appendix 2 (Tables 2-6) and ICD and MedDRA codes in appendix 3 (Table 3).

- The **differential diagnosis** for each must be considered, especially for levels 2 and 3, where there must be no alternative diagnosis to explain the illness. This is particularly important if the target population has a high prevalence of cardiac, pulmonary or vascular comorbidities. (See Table 4.4)

- **Considerations for using administrative data:** There are specific ICD codes for myocarditis, and pericarditis but not myopericarditis. Appendix 3 of this guide provides narrow and broad terms for case ascertainment using administrative health data. A 2013 systematic review searched for validated methods for capturing myopericarditis using administrative or claims data.[92] Of 9 included studies, only one provided evidence of validation. In that instance 5 cases of acute myocarditis or pericarditis were identified using ICD9 codes but none could be validated as true cases.[93] This underlines the importance of expert adjudication with cardiology experts when possible. The tools in appendix 5 provide data collection forms that specifically address what information is needed to meet each case definition and guides for assessing the level of certainty. Also of note, when using ICD10 codes, most studies use I40.* (acute myocarditis), but it is also important to use the less specific I54.1 as well (Myocarditis, unspecified) as shown recently by Sharff et al[30] using Kaiser Permanente Southern California data where 3 of 17 identified cases of myocarditis were missed when I54.1 wasn't included.

- **Considerations for case finding when doing prospective surveillance:** Lessons learned first with smallpox vaccine, and more recently with COVID-19 mRNA vaccines have underscored differences between myocarditis following viral infection versus that following vaccination. Woo et al[41] contrasted the clinical course of 42 cases of COVID-19 disease associated myocarditis versus 74 cases that followed COVID-19 vaccination. All but 1 post-vaccine case were admitted to hospital

but there were significant differences in the hospital course. For COVID disease versus COVID vaccine cases there were, respectively: 0% and 35.6% managed conservatively; 36.8% and 16.2% admitted to ICU; 21.6% and 1.4% needing inotropic support; 44.7% and 5.4% suffering complications; 17.6% and 0% fatal outcome. Further, focusing on hospital admissions may not find all cases following vaccination. A prospective study of smallpox vaccination among healthy military, identified 5 cases of myocarditis but 3 would have been missed had they not been assessed as part of routine follow-up.[11] It is important to diagnose and follow cases of myocarditis following vaccination because it is not yet known whether or not there could be long term consequences such as dilated cardiomyopathy or sudden cardiac death as seen with post-viral and other causes of myocarditis.

- **Factors that are not part of either case definition:** Brighton case definitions are designed for use in epidemiologic settings and are not intended to guide management or assign causality. Accordingly, neither response to treatment nor defined risk intervals from vaccination to illness onset are included as criteria in the case definitions. The Brighton case definitions are a key first step in causality assessment but are not designed to assign causality. They also support determination of background incidence as well as case incidence among non-exposed controls.

4.2 **Duration of Surveillance[1]:**

This period should be pre-defined based on biologic characteristics of the:

- Vaccine and vaccine platform
- Vaccine targeted disease
- Vaccinee (e.g. age, pregnancy, underlying disease, immunosuppression).

Similarly, the duration of follow-up for individual cases should be predefined, and at a minimum should continue until the resolution of the event. Myocarditis presents a particular concern for long term evolution to cardiomyopathy. This can take years which would not be feasible for most studies. Still, for cases with demonstrated abnormalities of cardiac function (e.g. diminished left ventricular ejection fraction), follow-up should be scheduled to determine whether abnormalities persist over time or resolve.

4.3 Recommendations for real time assessment[1]: Levels of certainty for both myocarditis and pericarditis depend on several specific cardiac investigations as outlined in the table below:

Table 1. Brighton case definition[1] diagnostic criteria for myocarditis and pericarditis:

Diagnostic Criteria	Myocarditis	Pericarditis	Level of Certainty[1] (for specific details of requirements see algorithm in appendix 5)
Endomyocardial biopsy	✓	✓	• Meets level 1 if myocardial/pericardial inflammation (by biopsy or autopsy sample).
Cardiac MRI (cMRI)	✓		• Meets level 1 if also elevated Troponin(s) • Supports* level 2 in absence of elevated Troponin(s)
Echocardiography	✓	✓	**Myocarditis:** • Meets level 1 if also elevated Troponin(s) • Supports* level 2 in absence of elevated Troponin(s) **Pericarditis:** • Supports* level 1 and 2 if abnormal pericardial fluid collection demonstrated
ECG	✓	✓	Both entities: • Supports* level 2: if ≥1 characteristic finding that is new or normalizes on recovery • Supports* level 3: ≥1 non-specific abnormality that is new or normalizes on recovery
Elevated myocardial biomarker	✓		• Supports* level 1: elevated Troponin I or T • Supports* level 2: elevated Troponin I or T or CK myocardial band
Elevated inflammation biomarker	✓		• Supports* level 3: ≥1 of elevated ESR, D-dimer, CRP or high-sensitivity CRP
Chest MRI/CT		✓	• Supports* level 2: if abnormal pericardial fluid collection demonstrated
Chest X-ray		✓	• Supports* level 3: if enlarged heart seen

* 'Supports' indicates that other criteria must be satisfied to reach a given level. See appendix 5 algorithms for specific details.

Table 2. Sensitivity and Specificity of Modalities for real-time investigation of myocarditis[94]

Diagnostic modality	Sensitivity (%)	Specificity (%)
ECG	47%	Unknown
Troponin	34%	89%
CK-MB	6%	100%
Antibodies to virus or myosin	25-32%	49%
Myocardial biopsy (Dallas criteria)	35-50%	78-89%
Myocardial biopsy (PCR)	38%	90-100%
Cardiac MRI	84-100%	90-100%
Indium-111 antimyosin antibody scan	66%	71%
Gallium 67 scan	87%	86%

Table 3.
A. Clinical presentation of myocarditis4, 7, 90,91,95,96

	Adults	Children	Infants
Dyspnea at rest, on exertion or on lying down	✓	✓	
Chest pain	✓	✓	
Cold sweats (diaphoresis)	✓	✓	
Mimic heart attack[91]	✓		
New onset arrhythmias	✓	✓ *Tachycardia in absence of fever or dehydration should raise suspicion[95]*	
Heart failure	✓	✓ *Myocarditis one of most common causes of new onset heart failure[7, 95]*	
Sudden death	✓ *Myocarditis is an important cause of sudden death in young adults & adolescents, especially high performance athletes[7, 95, 96]*		✓ *Myocarditis found in 16-20% of SIDS autopsies[7]*

Non-cardiac	Fatigue, abdominal pain, cough, edema, dizziness or syncope	Fever, myalgia, coryza anorexia, vomiting or seizure	Irritability, vomiting, poor feeding, tachypnea or lethargy

B. Clinical presentation suggestive of pericarditis[7, 24, 90]

Shown below are features that specifically suggest pericarditis and that are not necessarily associated with age. There is a lot of overlap between myocarditis and pericarditis and any of the features mentioned in Table 4.3.A could be present in pericarditis especially if myocarditis is also present.

Symptom or sign	Features that suggest pericarditis
Chest pain	• May be sharp or stabbing in nature and can be pleuritic (worse when breathing in) • May be positional: relieved by sitting up & leaning forward; worse when lying down • May radiate to or be referred to left shoulder
Signs associated with pericardial effusion:	• Pericardial friction rub • Pulsus paradoxus • Distant or muffled heart sounds (most relevant to young children/infants)
Non-cardiac	Cough, edema, cyanosis, weakness, fatigue, shoulder and/or upper back pain, nausea, vomiting, diarrhea, altered mental status, low grade intermittent fever.

Additional considerations for children: The large majority (80% or more) of pediatric patients with myocarditis are not diagnosed when they first present to medical care. Non-specific prodromal symptoms are common in children including diarrhea or vomiting, poor feeding, fever, myalgias, fatigue and lethargy: from 36-48% of cases.[7] Both case definitions acknowledge this, with non-specific symptoms considered acceptable clinical criteria for young infants and children (irritability, vomiting, poor feeding, tachypnea, lethargy).

Table 4. Possible differential diagnoses of myocarditis and pericarditis: this is not meant to provide an exhaustive list but rather some of the more common alternatives that should be considered, and how they might be determined.

Alternate diagnoses	Myocarditis	Pericarditis	Distinguish with:

Coronary artery disease (CAD) syndromes (acute chest pain, ECG with ST-segment elevation, blood markers of myocardial injury)[91]	✓		• Cardiology consultation if feasible
			• Diagnostic modalities to assess coronary arteries[1, 94]
			  ○ Coronary angiography
			  ○ Stress echocardiogram
			  ○ Nuclear stress perfusion scan (especially if risk of CAD is low)

			○ Multi-Detector Computed Tomography (MDCT) has up to 99% negative predictive value for significant coronary artery stenosis[97]
Valvular heart disease or cardiomyopathy	✓		• Echocardiogram, an important part of the workup for myocarditis, can help distinguish these
Heart failure	✓	✓	• Echocardiogram helps rule out other causes of HF
Pulmonary embolus		✓	• CT pulmonary angiography +/- venography[98] • Ventilation Perfusion (V/Q) scan if renal failure, hypersensitivity to contrast medium or pregnancy)

4.4 Data Collection Guidelines: the following should be documented[1]:

1. Clinical description of signs & symptoms and whether there was medical health professional confirmation
2. Date and time of: illness onset, first observation, definitive diagnosis, end of episode
3. Final outcome of illness or outcome at last observation (including spontaneous resolution or response to therapeutic intervention; return to baseline health prior to illness onset or event persistence, sequelae or fatality)
4. Concurrent signs, symptoms, and diseases
5. Test measurement(s):
   5.1. Values and units of routinely measured parameters (e.g. temperature, blood pressure, cardiac and inflammatory biomarkers; ECGs)
   5.2. Results of laboratory/imaging investigations, surgical and/or pathological findings
6. Treatment given for:
   6.1. Myocarditis: supportive therapy (ECMO, cardiac pacing), prednisone, IVIG
   6.2. Pericarditis: pericardiocentesis, aspirin, colchicine, prednisone
7. Objective clinical evidence supporting classification of the event as 'serious'
8. Exposures, other than the immunization, 24 hours before and after immunization considered potentially relevant to the reported event (e.g. other treatments or procedures, environmental)

Most of the above go beyond the criteria needed to meet the case definition of myocarditis and pericarditis, which are the focus of the data abstraction forms in Appendix 5. Accordingly separate forms will be required to capture the data outlined in the bullets.

4.5 Data Analysis Guidelines[1]

All reported myocarditis and pericarditis should be classified in one of five categories (see algorithms in appendix 5):

- Levels 1, 2 or 3 of the case definitions for myocarditis and pericarditis
- Level 4: reported myocarditis or pericarditis with insufficient evidence to meet the case definition
- Level 5: not a case of myocarditis or pericarditis

The interval between immunization and reported myocarditis or pericarditis can be defined as date/time of immunization to the date/time of onset of first symptoms or signs consistent with the case definition. If only a few cases are reported, the actual time course should be presented for each. If a large number of cases are reported or found as part of a study, data can be analyzed as the number %) of cases occurring in intervals of: <7 days, 8-<42 days and >42 days after immunization. These are just suggestions and it is noted that in the setting of COVID-19 vaccination, intervals of 10, 21 and 30 days have been used. Key is to specify the period used.

The duration of illness can be analyzed as the interval from the date/time of onset of the first symptoms and/or signs consistent with the definition to the end of the episode (defined as the time when the event no longer meets the lowest level of the case definition (level 3) or the final outcome (see 4.4.3 above). Whichever is used should be used consistently within and across study groups.

If more than one measurement of a particular criterion (e.g. cardiac troponin) is taken, the highest measured value could be the basis for analysis.

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

APPENDIX 5

Myocarditis and Pericarditis Data Abstraction and Interpretation Forms

With Algorithms for Assessing Level of Certainty

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This appendix provides tools that can be used to gather data pertinent to myocarditis and/or pericarditis and use the data to assess the level of certainty for each based on the published Brighton case definition.[1] These tools can be used in a variety of settings including: medical chart review to validate myocarditis / pericarditis cases; summarize known case information from an AEFI report and guide what supplemental information would be needed to assign a level of certainty; guide data collection and case investigation during a clinical vaccine trial or as part of active surveillance.
Six tables and two figures are included in this appendix:

- **Table 5.1** lists all Brighton case definition[1] criteria for myocarditis and pericarditis and identifies likely sources of information for each.
- **Table 5.2** is the main data abstraction form that can be used to record data pertinent to both myocarditis and pericarditis.
- **Table 5.3** provides a guide for assigning a '**Y**es', '**N**o' or '**U**nknown' status to each criterion based on data entered into table 2.
- **Table 5.4** is a brief summary of the final value for each criterion.
- **Table 5.5** A and B provide the formulae used to assign level of certainty for myocarditis and pericarditis, respectively, based on criterion values.
- **Figures 5.1 and 5.2** show a pictorial algorithm for determining level of certainty for myocarditis and pericarditis respectively.

Brief instructions are provided with each table.

TABLE 1. MYOCARDITIS and PERICARDITIS KEY CASE DEFINITION CRITERIA, LIKELY AND ACTUAL SOURCES OF INFORMATION

Criterion	Criterion category	Likely sources of information	Actual sources of information
A	Symptoms of myocarditis	Emergency report, admitting history/exam, consultation reports, ICU admission, discharge summary	
B	Physical exam findings of pericarditis		
C	Markers of Inflammation	• Laboratory investigations including blood tests, cardiac biomarkers • Cardiac examinations including electrocardiogram (ECG), echocardiography and cardiac Magnetic Resonance (cMR) • Radiologic investigations including MRI or CT of chest, chest-X-ray	`
D	Cardiac biomarkers		
E	ECG abnormalities		
F	Echocardiogram abnormalities		
G	Cardiac MRI abnormalities		
H	Chest MRI or chest CT abnormalities		
I	Chest X-Ray abnormality		
J	Endomyocardial biopsy	Histopathology report of cardiac biopsy; Autopsy report	
X	Alternate diagnoses	Discharge diagnosis, Discharge summary, consultant reports, laboratory investigations, follow-up visits to specialty clinics, readmission to hospital	

TABLE 2. MYOCARDITIS and PERICARDITIS DATA ABSTRACTION FORM: **Record specific information, to the extent possible, for all rows in the table below. The red font identifies specific criteria related to the myocarditis and/or pericarditis case definitions.**

1. Date of illness onset			
2. Hospital admission?			
3. Admitting diagnosis:			
4. Discharge diagnosis:			
5. Criterion A1: Cardiac symptoms	☐ 1. Acute chest pain or pressure ☐ 2. Palpitations ☐ 3. Dyspnea at rest, with exercise or lying down	☐ 4. Diaphoresis ☐ 5. Sudden death ☐ 6. None of the above	☐ 7. Unknown if any of 1-5 present or absent
6. Criterion A-2: Non-specific symptoms: Adults & older children	☐ 1. Dizziness or syncope ☐ 2. Abdominal pain ☐ 3. Fatigue ☐ 4. Edema ☐ 5. Cough ☐ 6. Nausea, vomiting +/or diarrhoea	☐ 7. Shoulder or upper back pain ☐ 8. Weakness ☐ 9. Cyanosis ☐ 10. Altered mental status ☐ 11. Low grade intermittent fever (≥38.0°C) ☐ 12. None of the above	☐ 13. Unknown if any of 1-11 present or absent
7. Criterion A-3: Non-specific symptoms: Infants & young children	☐ 1. Poor feeding ☐ 2. Vomiting ☐ 3. Lethargy	☐ 4. Tachypnea ☐ 5. Irritability ☐ 6. None of the above	☐ 7. Unknown if any of 1-5 present or absent
8. Criterion B: Physical exam features	☐ 1. Pericardial friction rub ☐ 2. Pulsus paradoxus	☐ 3. Distant heart sounds (infants & children) ☐ 4. None of the above	☐ 5. Unknown if any of 1-3 present or absent
9. Criterion C: Inflammatory Markers Were there any biomarkers supporting evidence of inflammation? (check all that apply)	☐ 0. None tested, or tested but no results or unknown if tested ☐ 1. ESR elevated (highest measured value: _____) ☐ 2. CRP elevated (highest measured value: _____) ☐ 3. High sensitivity (hs) CRP elevated (highest measured value: _____) ☐ 4. D-dimer elevated (highest measured value: _____) ☐ 5. None of the above (choose this option if whichever ones were tested, were within normal range)		

10. Criteria D1+D2: Cardiac biomarkers Were any myocardial biomarkers measured and if so were they elevated or normal? (check all that apply)	☐ 0. None tested, or tested but no results or unknown if tested ☐ 1. D1.1. Troponin T elevated (highest measured value: _____) ☐ 2. D1.2 Troponin I elevated (highest measured value: _____) ☐ 3. D2 Creatine Kinase Myocardial Band (CK-MB) elevated (highest measured value:_____) ☐ 4. Normal Troponin ☐ 5. Normal CK-MB
11. Criterion E: Electrocardiogram (ECG) abnormalities ECG results relevant to myocarditis and/or pericarditis. Read carefully and check all that apply based on available ECG reports done during the illness AV = atrioventricular	☐ 0. ECG not done, or done but no results available or unknown if done ☐ 1. 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) ☐ 2. AV nodal conduction delays or intraventricular conduction defects (AV block (grade I-III), new bundle branch block) ☐ 3. Continuous ambulatory ECG monitoring that detects frequent atrial or ventricular ectopy ☐ 4. ST-segment or T-wave abnormalities (elevation or inversion) ☐ 5. Newly reduced r-wave height, low voltage, or abnormal q waves ☐ 6. Premature atrial and premature ventricular contractions (PACs, PVCs) ☐ 7. Diffuse concave-upward ST-segment elevation ☐ 8. ST-segment depression in aVR (ECG electrode lead placed on R arm) ☐ 9. PR-depression throughout the leads without reciprocal ST-segment changes ☐ 10.Nonspecific abnormalities other than those listed above (describe: ☐ 11. No abnormalities seen on ECG
12. Criterion F: Echocardiogram (ECHO) abnormalities Echocardiogram results relevant to myocarditis and/or pericarditis. Read carefully and check all that apply based on available echo reports.	☐ 0. ECHO not done, or done but no results or unknown if done ☐ 1. New focal or diffuse left or right ventricular function abnormalities (e.g. decreased ejection fraction) ☐ 2. Segmental wall motion abnormalities ☐ 3. Global systolic or diastolic function depression/abnormality ☐ 4. Ventricular dilation ☐ 5. Wall thickness change ☐ 6. Evidence of abnormal fluid collection or pericardial inflammation ☐ 7. No abnormalities seen on ECHO

13. Criterion G: Cardiac Magnetic Resonance (cMR) abnormalities CMR results relevant to myocarditis and/or pericarditis. Read carefully and check all that apply based on available cMR reports.	☐ 0. cMR not done, or done but no results or unknown if done ☐ 1. Edema on T2 weighted study, typically patchy in nature ☐ 2. 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) ☐ 3. Evidence of abnormal fluid collection or pericardial inflammation ☐ 4. No abnormalities seen ☐ 5. Other abnormality. Describe:	
14. Criterion H: Chest MRI and/or CT abnormalities NOTE: one or the other of chest MRI and CT may have been done.	☐ 0. Chest MRI and CT not done, or unknown if done, or no results available ☐ 1. Chest MRI or CT showed evidence of abnormal pericardial fluid collection or pericardial inflammation ☐ 2. Chest MRI and CT normal (choose this if only 1 test done but normal)	☐ 3. Chest MRI and/or CT had abnormalities other than above. Describe:
15. Criterion I: Chest X-Ray (CXR) abnormalities	☐ 0. CXR not done, or unknown if done, or no results available ☐ 1. CXR abnormal showing enlarged heart ☐ 2. CXR normal ☐ 3. CXR had abnormalities other than enlarged heart. Describe	
16. Criterion J: Cardiac tissue examination Histopathologic exam of cardiac tissues (autopsy or endomyocardial biopsy (check all that apply)	☐ 0. Not done, unknown if done or no results ☐ 1. Myocardial inflammation* ☐ 2. Pericardial inflammation* ☐ 3. No inflammation seen * Describe the abnormalities seen:	

17. Criterion X: Alternate diagnosis for cardiac findings. Alternate diagnosis/diagnoses for the cardiac findings exclude myocarditis or pericarditis as a diagnosis. The case definition doesn't require that investigation(s) be done for these entities, but any that are documented should be noted here. If there is a history of prior events it would also be good to capture but would need discussion with a physician to determine if it is an exclusión to myocarditis and/or pericarditis. (Check all that apply)	☐ 1. No alternate diagnosis identified ☐ 2. Systemic inflammatory disease. Specify: _____ ☐ 3. Cardiac tumour (rhabdomyosarcoma) ☐ 4. Metastatic acáncer. Specify:_____ ☐ 5. Metabolic disorder (e.g. hypothyroidism, renal failure, uremia) Specify:_____ ☐ 6. Cardiotoxic drug / other toxins. Specify:_____ ☐ 7. Chest cavity radiation ☐ 8. Myocardial infarction ☐ 9. Pulmonary embolism ☐ 10. Mediastinitis ☐ 11. Other: Describe below

TABLE 3. INTERPRETATION FORM FOR MYOCARDITIS and PERICARDITIS CRITERION VALUES: **Based on clinical data entered into Table 2, assign a value to each criterion using the rules in the Criterion Options columns.** **** These criteria are relevant only to the pericarditis case definition***

CRITERIA		CRITERION OPTIONS			Criterion Value
		Criterion = YES (Y) IF:	Criterion = NO (N) IF:	Criterion = UNKNOWN (U) IF:	
A-1: Cardiac Symptoms		__≥1 of A-1: (1,2,3,4 or 5)	__ A-1 = 6	__ A-1 - 7	A-1 = Y N U
A-2: Non-specific symptoms: *Relevant to Adult/older child*		__≥2 of A-2: (1,2,3,4 or 5)	__< 2 of A-2(1,2,3,4 or 5) OR A2 = 12	__ A-2 = 13	A-2 = Y N U
A-3: Non-specific symptoms: *Relevant to Infant/young child*		__≥2 of A-3: (1,2,3,4 or 5)	__< 2 of A-3(1,2,3,4 or 5) OR A3 = 6	__ A-3 = 7	A-3 = Y N U
A-4*: Combination of A-1 & A-2		__≥1 of A-1(1-3) & ≥2 of A-2(3-11)	__A-1 = None of (1,2 or 3) OR A-2 = <2 of (3-11) OR A-2 = 12	__A-1 = 7 or A-2 = 13	A-4 = Y N U
B: Physical exam features	B-1*	__For B-1: ≥1 of B (1, 2 or 3)	__B = 4	__ B = 5	B-1 = Y N U
	B-2*	__For B-2: ≥1 of B: (1 +/or 2)	__B = 4	__ B = 5	B-2 = Y N U
C-Inflammatory markers		__C = 1,2,3 or 4	__ C = 5	__ C = 0	C = Y N U
D-Cardiac biomarkers	D-1	__D = 1 +/or 2	__D = 4	__ D = 0	D-1 = Y N U
	D-2	__D = 3	__ D = 5	__ D = 0	D-2 = Y N U
E-ECG (Electrocardiogram)	E-1	__E = 1 +/or 2 +/or 3	__E = 11	__E = 0	E-1 = Y N U
	E-2	__ E = 4 +/or 5 +/or 6	__E = 11	__E = 0	E-2 = Y N U
	E-3*	__E = all 3 of (7 + 8 + 9)	__E = 11	__E = 0	E-3 = Y N U
	E-4*	__E = 1-2 of (7 or 8 or 9)	__E = 11	__E = 0	E-4 = Y N U
	E-5*	__E = 10	__E = 11	__E = 0	E-5 = Y N U
F-Echocardiogram	F-1	__F = ≥1 of:(1,2 3,4or5)	__F = 7	__F = 0	F-1 = Y N U
	F-2*	__F = 6	__F = 7	__F = 0	F-2 = Y N U
G-cMR (Cardiac Magnetic Resonance imaging)	G-1	__G = 1 +/or 2	__G = 4	__G = 0	G-1 = Y N U
	G-2*	__G = 3	__G = 4	__G = 0	G-2 = Y N U
H-Chest MRI/CT	H*	__H = 1	__H = 2	__H = 0	H = Y N U
I-Chest-X-Ray	I*	__I = 1	__I = 2	__I = 0	I = Y N U
J-Endomyocardial Biopsy *(heart tissues microscopy)*	J-1	__J = 1	__J = 3	__J = 0	J-1 = Y N U
	J-2*	__J = 2	__J = 3	__J = 0	J-2 = Y N U

X-Alternative diagnosis	X	__ Any of X (1-11) checked	__No alternative diagnosis	Not Applicable	X = Y N

TABLE 4. SUMMARY OF MYOCARDITIS and PERICARDITIS CRITERION VALUES Record the final value for each Criterion from Table 3.

Criterion colour coding: Relevant to both myocarditis & pericarditis | Relevant to myocarditis only | Relevant to pericarditis only

Criterion	A-1	A-2	A-3	A-4	B-1	B-2	C	D-1	D-2	E-1	E-2	E-3	E-4	E-5	F-1	F-2	G-1	G-2	H	I	J-1	J-2	X
Final Value																							

TABLE 5. A&B. TABULAR ALGORITHM TO DETERMINE MYOCARDITIS and PERICARDITIS LEVEL OF CERTAINTY (LOC)BASED ON CRITERION VALUES

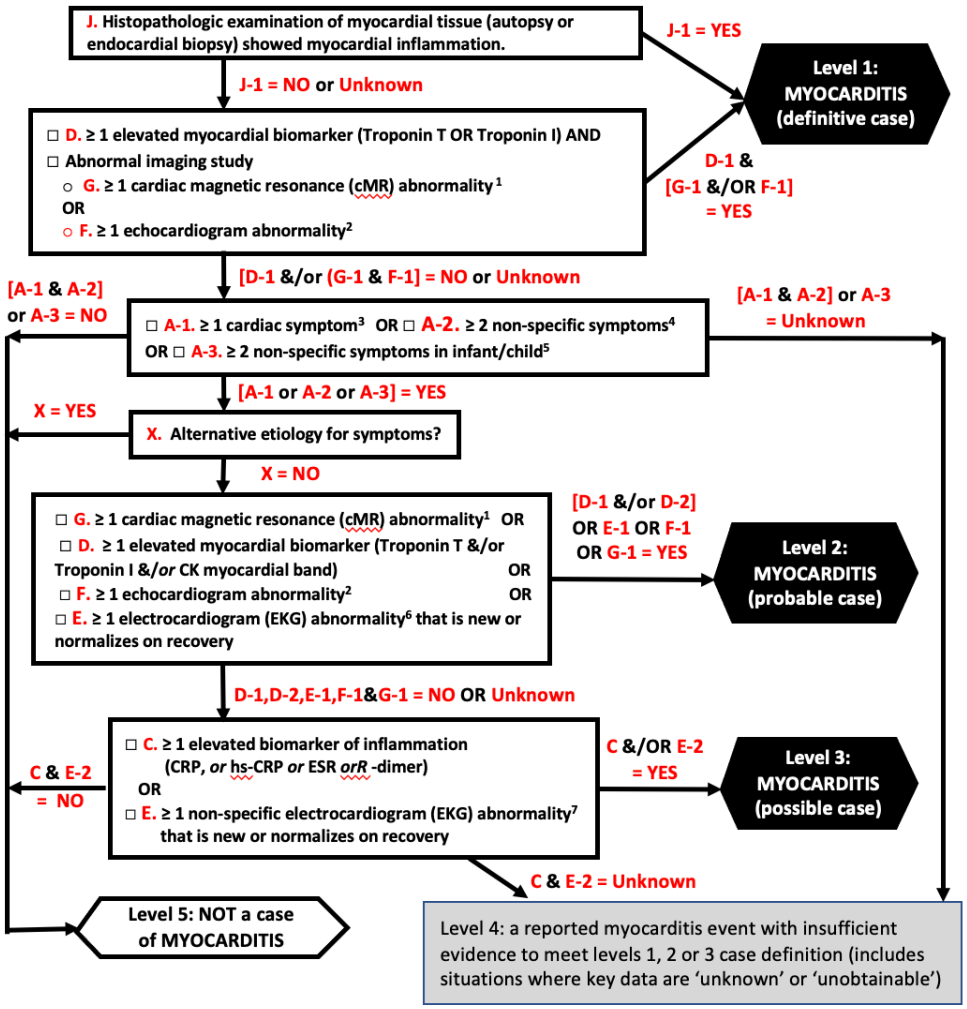
Use the final values of all criteria recorded in Table 4 to determine LOC based on the formulae below. The highest row in the table where all criteria are met will be the LOC. Assess myocarditis and pericarditis separately. If both present and the same LOC, then classify as a case of myopericarditis. If different levels of certainty record and classify each separately. E.g. Level 2 myocarditis and level 3 pericarditis.

Level of Certainty	A. MYOCARDITIS
Level 1 : 2 possibilities (1.1 OR 1.2)	1.1 J-1 = YES
	1.2 [D-1 = YES) AND (F-1 OR G-1 = YES)]
Level 2	[A-1 OR A-2 OR A-3 = YES] AND [(D1 +/or D2 = YES) OR (E-1 = YES) OR (F-1 = YES) OR (G-1 = YES)] AND [X = NO]
Level 3	[A-1 OR A-2 OR A-3 = YES] AND [(C = YES) OR (E-2 = YES)] AND [X = NO]
Level 4	Reported as a case of myocarditis but fails to meet any level of certainty
Level 5	X = YES *(NOTE : this exclusion applies only to levels 2 and 3)*

Level of Certainty	B. PERICARDITIS
Level 1 : 2 possibilities (1.1 OR 1.2)	1.1 J-2 = YES
	1.2 ≥2 of : [(B-1 = YES) OR (E-3 = YES) OR (F-2 or G-2 or H = YES)]
Level 2	[A-1 or A-3 = YES] AND [(B2 = YES) OR (E-4 = YES) OR (F-2 or G-2 or H = YES)] AND [X = NO]
Level 3	[A-3 or A-4 = YES] AND [(E-5 = YES) or (I = YES)] AND [X = NO]

Level 4	Reported as a case of pericarditis but fails to meet any level of certainty
Level 5	X = YES *(NOTE : this exclusion applies only to levels 2 and 3)*

FIGURE 1. Pictorial algorithm for determining Myocarditis level of certainty.



CRP: c-reactive protein ; ESR: erythrocyte sedimentation rate; hs-CRP: high sensitivity CRP

[1] **G-1. cMR abnormalities:**
- Edema on T2 weighted study, typically patchy
- Late gadolinium enhancement on T1 weighted images with an increased enhacement ratio between myocardial and skeletal muscle typically involving ≥1 non-ischemic regional distribution with recovery (myocyte injury)

[2] **F-1. Echocardiogram abnormalities:**
- 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/abnormality
- Ventricular dilation
- Wall thickness change

[3] **A-1. Cardiac symptoms:**
- Acute chest pain or pressure
- Palpitations
- Dyspnea after exercise, at rest, or lying down
- Diaphoresis
- Sudden death

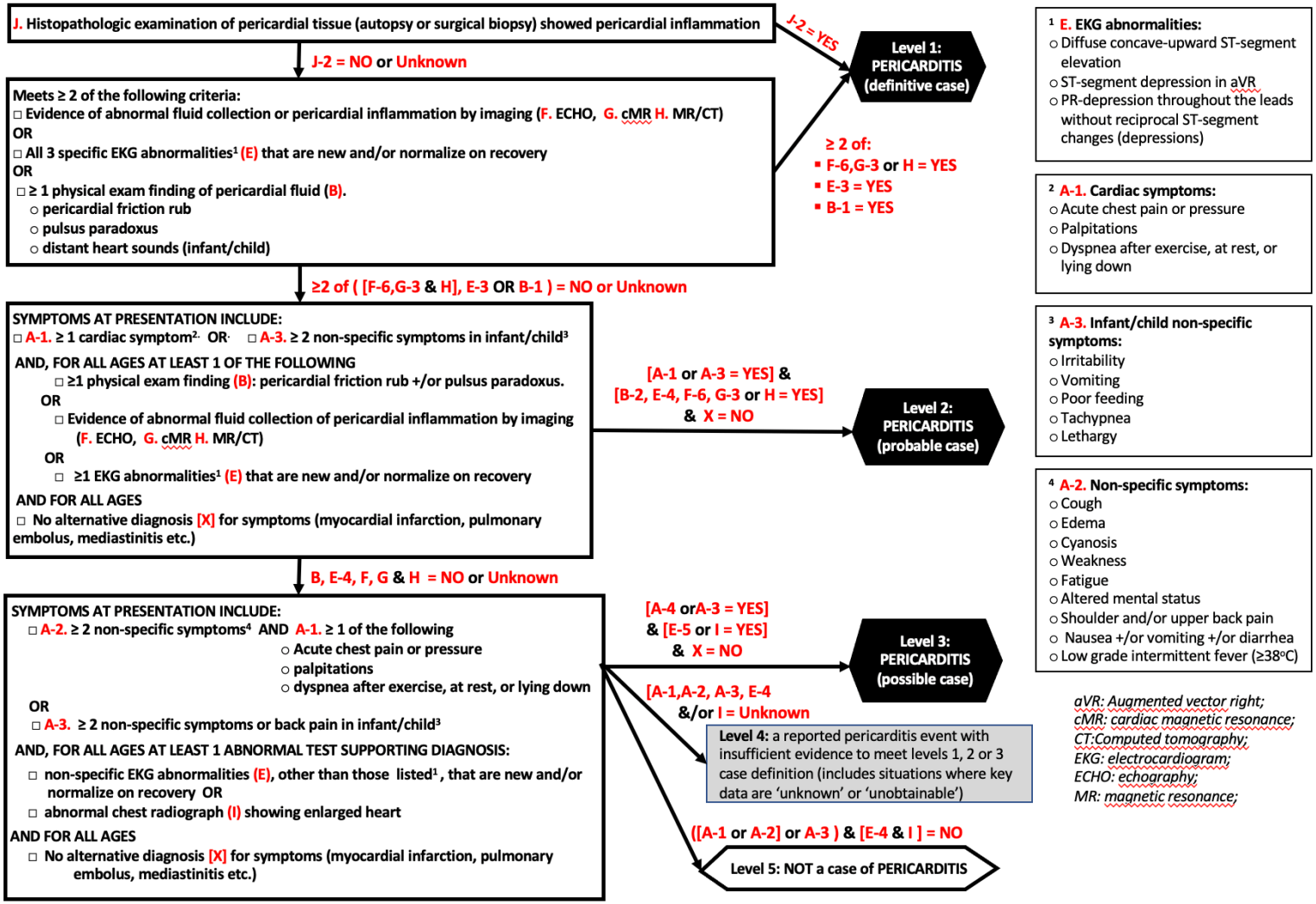
[4] **A-2. Non-specific symptoms:**
- Fatigue
- Abdominal pain
- Dizziness or syncope
- Edema
- Cough

[5] **A-3. Infant/child non-specific symptoms:**
- Irritability
- Vomiting
- Poor feeding
- Tachypnea
- Lethargy

[7] **E-2 Non-specific EKG abnormalities:**
- ST-segment or T-wave abnormalities (elevation or inversion
- Premature atrial and ventricular contractions
- Newly reduced r-wave height, low voltage or abnormal q waves

6 **E-1. EKG abnormalities:**
- 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

FIGURE 2. Pictorial algorithm for determining Pericarditis level of certainty.



APPENDIX 6.

Methodology: Brief Summary

THIS PROJECT HAS BEEN FUNDED IN WHOLE BY CEPI.

6.1. Myocarditis and Pericarditis Risk Factors

A risk factor is “an exposure, behavior, or attribute that, if present and active, clearly alters the occurrence of a particular disease compared with an otherwise similar group of people who lack the risk factor”. According to James Last dictionary of epidemiology version 4, a risk factor is an aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that, on the basis of epidemiologic evidence, is known to be associated with health-related condition(s) considered important to prevent. The term risk factor is rather loosely used, with any of the following meanings:

1. An attribute or exposure that is associated with an increased probability of a specified outcome, such as the occurrence of a disease. Not necessarily a causal factor. A RISK MARKER.
2. An attribute or exposure that increases the probability of occurrence of disease or another specified outcome. A DETERMINANT.
3. A determinant that can be modified by intervention, thereby reducing the probability of occurrence of disease or other specified outcomes. To avoid confusion, it may be referred to as a modifiable risk factor.

Risk factors can include infection, medication, diet, surgical or medical procedure, environmental location, stress, toxins, trauma and vaccine. Attribute includes genetic makeup, age, gender, ethnicity, social status, occupation. Behavior includes smoking, drinking, other substance abuse, sexual practices, level of physical activity. A standard tabular format, as shown in the appendices was used to summarize the key known risk factors for each AESI. Risk factors are only included if there is evidence for an association with the AESI.

The published Brighton Case definition[1] for Myocarditis and Pericarditis was reviewed for evidence related to associated risk factors. In addition, a systematic search was conducted to identify evidence for risk factors using the same search strategy shown for background incidence in section 6.2 below. The same expert (BL) screened all retrieved articles and set aside and reviewed all that pertained to the epidemiology of myocarditis and pericarditis. Additional articles were retrieved by a hand search of the article citations.

6.2. Myocarditis and Pericarditis Background Incidence

A systematic literature search to estimate the incidence of acute Myocarditis and Pericarditis as well as entities which could be the presenting features (Cardiac arrest, Arrhythmia, Heart failure) or long term outcome without apparent clinical disease (Cardiomyopathy) in the population was conducted on May 8, 2021 using the following search strategy:

"Myocarditis"[Mesh:noexp] OR "myocarditis"[ti] OR "myopericarditis"[ti] OR "Pericarditis"[Mesh:noexp] OR "pericarditis"[ti] OR "myocardial infarction"[ti] OR "cardiac arrest"[ti] OR "Acute Coronary Syndrome"[Mesh:noexp] OR "acute coronary syndrome"[ti] OR "acute coronary syndromes"[ti] OR "ST Elevation Myocardial Infarction"[Mesh:noexp] OR "STEMI"[ti] OR "Death, Sudden, Cardiac"[Mesh:noexp] OR "sudden cardiac

death"[ti] OR "asystole"[ti] OR "Arrhythmias, Cardiac"[Mesh:noexp] OR "arrhythmia"[ti] OR "arrhythmias"[ti] OR "dysrhythmia"[ti] OR "dysrhythmias"[ti] OR "arrhythmic"[ti] OR "Heart Failure"[Mesh:noexp] OR "heart failure"[ti]) ("cardiomyopathy"[ti] OR "Cardiomyopathies"[Mesh:noexp] OR "cardiomyopathies"[ti] OR "Takotsubo"[ti] OR "Tako-Tsubo"[ti]

AND ("Incidence"[Mesh:noexp] OR "incidence"[tiab])

AND English[lang]

AND ("2000/01/01"[PDAT] : "3000/12/31"[PDAT])

AND ("Observational Study"[Publication Type] OR "Review"[Publication Type] OR "Systematic Review"[Publication Type] OR "Meta-Analysis"[Publication Type])

NOT ("animals"[Mesh:noexp] NOT "humans"[Mesh:noexp])

NOT ("Coronavirus"[Mesh:noexp] OR "coronavirus"[ti] OR "nCoV"[ti] OR "COVID"[ti] OR "SARS-CoV-2"[ti])

NOT ("therapy"[ti] OR "therapies"[ti] OR "therapeutic"[ti] OR "treatment"[ti] OR "treatments"[ti] OR "drug"[ti] OR "drugs"[ti] OR "trial"[ti] OR "trials"[ti] OR "prevention"[ti] OR "prevent"[ti] OR "prevents"[ti] OR "surgery"[ti] OR "procedure"[ti] OR "procedures"[ti])

Articles had to meet the following criteria:

1. Original research/meta-analysis
2. Population-based study (selecting the entire population or using probability-based sampling methods)
3. Reported an incidence estimate (or raw numbers that allowed the calculation of an estimate).

If multiple articles reported data from the same study population, the most comprehensive data were used. When studies reported on different data collection years or subgroups (sex, age), efforts to include all nonoverlapping data were made. Age, sex, study location, sources of ascertainment, and definitions/diagnostic criteria for each searched clinical entity (myocarditis, pericarditis, cardiac arrest, arrhythmia, heart failure, cardiomyopathy) were extracted. For each clinical entity, incidence estimates, raw numbers, and confidence intervals (CIs) (when provided) were recorded along with any stratified results by age, sex, or year of data collection.

Articles were screened by a single medical reviewer (BL). Screened in articles were reviewed and relevant data abstracted for inclusion in the background rate table (MRV) when novel articles were found from systematic reviews, these were included. The spreadsheet with all extracted background incidence data and Forest plots by WHO world region, is available on the Brighton Collaboration website.

A PubMed search for articles focused on myocarditis or pericarditis following vaccination was conducted on December 29, 2021.
A single reviewer (BL) screened the articles first on title and abstract to identify case reports, case series, reviews, descriptive and research studies focused on humans. Editorials, letters to the editor, other commentaries, erratum, guidelines and articles focused only on management or therapy were excluded. A full text review was conducted for all screened in articles. Articles were judged to be contributory or non-contributory for the purpose of the Companion guide which was to identify vaccine as a risk factor for myocarditis or pericarditis and to describe up to date information related to the myopericarditis safety signal associated with COVID-19 vaccines. Hypothesis-testing studies as well as descriptive datalink or other epidemiologic studies that provided risk analyses (Incidence Rate, Incidence Reporting Ratio, Incidence Rate Difference) or disproportionality analyses (Reporting Odds Ratio, Information Component) or that systematically reviewed published case reports and case series or that provided endomyocardial histopathology were considered contributory. Additional relevant articles were found by a hand search of the included article reference list.

6.3. Myocarditis and Pericarditis Case Definition key caveats for diagnosis, data analysis and presentation [1]

The published Brighton case definition for Myocarditis and Pericarditis was reviewed and key aspects identified with particular relevance to real time assessment of Myocarditis and/or Pericarditis in the context of a clinical trial where it occurs as an AEFI. In addition, the guideline section of the published Myocarditis and Pericarditis case definition was reviewed, and key recommendations identified for data collection, analysis and presentation. Finally relevant articles retrieved as part of the risk factor and background rate search, that addressed key aspects of presentation, investigation and differential diagnosis were used to supplement the information in the published case definition.
For a more detailed description of methodology see SO1-D2.7 Guidance for CEPI Developers which is available in the CEPI Developers' Toolbox.

6.4. Myocarditis and Pericarditis ICD-9/10-CM and MedDRA Codes[99-103]

An initial set of codes were retrieved through the Codemapper tool that was developed in the IMI-ADVANCE project. Subsequently they were reviewed and classified into narrow or broad codes by the authors.

CodeMapper[99] builds upon information from the Metathesaurus of the Unified Medical Language System (UMLS). The Metathesaurus is a compendium of many medical vocabularies, which have been integrated by assigning equivalent codes and terms from different source vocabularies to the same concepts. Each concept in the UMLS is identified by a CUI. A CUI is a Concept Unique Identifier for a Metathesaurus concept to which

strings with the same meaning are linked. The Metathesaurus contains more than one million concepts connected to codes from 201 vocabularies. Each concept is assigned to one or more of 127 semantic types, which define broad conceptual categories like Disease or syndrome, Finding, or Substance.[100] Codemapper was built on the version 2016AA of the UMLS. The automatic concept identification of CodeMapper is based on lexical information from the Metathesaurus. The lexical information of a concept consists of terms that can be used in free text to refer to that concept. We compiled a dictionary for the concepts in the semantic groups Anatomy, Chemicals & Drugs, Disorders, Genes & Molecular Sequences, Living Beings, Phenomena, Physiology, and Procedures of non-suppressible, English terms from several vocabularies including ICD-9 CM, ICD-10 CM, and MedDRA.[101, 102] A text-indexing engine Peregrine uses this dictionary to identify medical concepts in the case definition.[103] Of note, while SPEAC focused on ICD-9/10-CM and MedDRA codes, the CodeMapper concepts shown in the table can be used to search for codes in other systems including SNOMED-CT, MeSH, ICPC-2 and Read-CTv3.

CodeMapper has three screens.

1. The first displays the free text entered by the user – in this case the Brighton case definition. Medical concepts are automatically identified in the text and highlighted inline.
2. The second displays the mapping as a table with one row for each medical concept, and one column for each targeted vocabulary. Each cell contains the names of the codes that are used to represent the medical concept of the row in the targeted vocabulary of the column. The codes are displayed when the names are hovered over with the mouse. Several user operations are available for revising the mapping. The user can remove concepts from the mapping, search and add concepts, or retrieve more general and more specific concepts. The retrieved concepts are shown in a list and can be selected by the user for inclusion in the mapping. The user can also add or remove vocabularies that should be targeted by the mapping. After every operation, the codes are automatically updated and displayed in the table.
3. The third shows a list of all operations that have been made, for later traceability of the mapping process. When the user saves the mapping, he has to provide a summary of the modifications, which is incorporated into the mapping history. The user can download the mapping as a spreadsheet file to incorporate the codes into extraction queries. The spreadsheet file comprises the original free-text case definition, the concepts of the mapping, the codes for the targeted vocabulary, and the full history of the mapping process.

Codemapping was conducted by MS. The output of the Codemapper concepts was reviewed by a medical expert (BL) familiar with the Myocarditis and pericarditis Brighton case definitions. Included concepts were those considered relevant for background incidence rate determination as well as to study hypotheses related to Myocarditis and/or Pericarditis as a vaccine-product related reaction. For myocarditis and pericarditis, 3 separate groups of terms were assigned to different tables. First a table of narrow terms for both myocarditis and pericarditis. Secondly, a broader group of terms that focused on the underlying etiologies that can cause myocarditis and/or pericarditis. Finally, a third broad group of terms that captured the potential

presenting complaints for myocarditis and/or pericarditis including those relevant to acute presentation (arrhythmias, heart failure, chest pain, cardiac tamponade and pericardial effusion) and a longer-term presentation given that some cases are clinically silent but may lead to cardiomyopathy.

For a more detailed description of methodology see SO2-D2.3 Tier 1 AESI: ICD-9/10-CM and MedDRA Codes which is available in the CEPI Developers' Toolbox.

6.5. Data Collection and Summary Forms with Tabular and Pictorial Algorithms for Level of Certainty Determination [1]

The Brighton Collaboration published case definitions for Myocarditis and Pericarditis [1] were thoroughly and repeatedly reviewed by one individual (*B. Law*) to identify all clinical, laboratory and other criteria (e.g., temporal course of disease) used to define each case definition level of certainty. A data collection form was created to capture all data needed to reach a level of certainty. The form has been simplified to enable users to check off, for each listed criterion, clinical and lab-based information relevant to myocarditis and pericarditis. Alphabet labels (A, B, C, D, E, F, G, H, I and X [label reserved for exclusionary criteria]) were assigned to each criterion category. For some criteria, it was necessary to have multiple alphanumeric codes to distinguish the final criterion value (e.g., A is the clinical symptom category; A-1 is for cardiac specific clinical symptoms; A-2 for non-specific symptoms in adults and older children and A-3 for non-specific symptoms in infants and young children).

Two separate tables were created to supplement the data collection form: the first to facilitate assigning values (YES, NO, or Unknown) based on the available data as entered into the data collection form and the second to briefly summarize the final values assigned to each criterion.

Finally separate myocarditis and pericarditis level of certainty tables were created, with a row for each level of certainty (Levels: 1-definite case; 2-probable case; 3-possible case; 4-reported case but doesn't meet any level of certainty; and 5-Not a case, based an absence of critical criteria and/or presence of an exclusionary criterion), each of which contain formulae to guide choosing the correct level of certainty based on final criterion values.

In addition to the tabular, formula-based algorithms, pictorial decision tree algorithms were developed to lead to the various levels of certainty depending on the presence, absence, or uncertainty regarding each criterion.

The data collection forms, tables and formula-based as well as pictorial algorithms were reviewed by a second medical expert (Wan-Ting Huang) as a quality check and to ensure there was agreement on the application of the criteria in the published case definition.