Safety Platform for Emergency vACcines

AESI Case Definition Companion Guide

Multisystem Inflammatory Syndrome In Children and Adults (MIS-C/A)

V1.0 – [19 October 2022]

Authors: Barbara Law

Nature: Report | Diss. level: Public

In case you have used this or any other Brighton Collaboration case definition companion guide, please take 3 minutes to respond to this survey, it will help us to improve our tools.

TABLE OF CONTENTS

DOCUMENT INFORMATION

Main Author(s)	Barbara Law	E-mail: barbara.law@cepi.net
WP Leader	Barbara Law	E-mail: barbara.law@cepi.net

SPEAC Project Lead	Robert Chen	E-mail: robert.chen@cepi.net
Scientific Coordinator	Miriam Sturkenboom	E-mail: miriam.sturkenboom@cepi.net

Description of the deliverable	This deliverable collates into a single document the SPEAC MIS-C/A resources (ICD9/10-CM, MedDRA and SNOMEDCT 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 MIS-C/A in several settings including as an adverse event following immunization.
Key words	MIS-C/A, MIS-C, MIS-A, Brighton case definition, ICD-9-CM, ICD-10-CM, MedDRA, SNOMEDCT, case definition level of certainty algorithms.

THIS PROJECT HAS BEEN FUNDED IN WHOLE BY CEPI.

DOCUMENT HISTORY

NAME OF DOCUMENT	DATE	VERSION	CONTRIBUTOR(S)	DESCRIPTION
SO2 D2.5.2.2 MIS-C/A Companion Guide	19 Oct 2022	1.0	Barbara Law	

DEFINITIONS & ACRONYMS

AEFI	Adverse Event Following Immunization
AESI	Adverse Events of Special Interest
BC	Brighton Collaboration
BNP	Brain natriuretic protein
CD	Case Definition
CEPI	Coalition for Epidemic Preparedness and Innovation
COVID-19	Coronavirus disease 2019
CRP	C reactive protein
CUI	Concept Unique Identifier
EKG	Electrocardiogram
ECHO	Echocardiogram
ECMO	Extracorporeal membrane oxygenation
ESR	Erythrocyte sedimentation rate
HLH	Hemophagocytic lymphohistiocytosis
ICD-9-CM	International Classification of Diseases-9th Revision-Clinical Modification
ICD-10-CM	International Classification of Diseases-10th Revision-Clinical Modification
ICU	Intensive care unit
KD	Kawasaki disease
KS	Kawasaki syndrome
LMIC	Low- or Middle-Income Country
LOC	Level of Certainty
MAS	Macrophage Activation Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MIS-A	Multisystem Inflammatory Syndrome in Adults (age ≥21 years)
MIS-C	Multisystem Inflammatory Syndrome in Children (age <21 years)
NT-proBNP	N terminal pro-brain natriuretic protein
PCR	Polymerase Chain Reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus - 2
SD	Standard Deviation
SIRS	Systemic inflammatory response syndrome
SPEAC	Safety Platform for Emergency Vaccines
TEN	Toxic Epidermal Necrolysis
UMLS	Unified Medical Language System

INTRODUCTION

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 that 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 anaphylaxis and the neurologic 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 Multisystem inflammatory syndrome in Children (MIS-C) and Adults (MIS-A).

2. Objective of this deliverable

To collate SPEAC & BC tools and resources that have been developed for MIS-C/A.

3. Methods

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

- MIS-C/A Diagnostic Codes: SO2-D2.3 Tier 1 AESI: ICD-9/10-CM and MedDRA Codes
- MIS-C/A Case definition key caveats for diagnosis, data analysis and presentation: SO1-D2.7 Guidance for CEPI Developers
- MIS-C/A Tabular checklist and Level of Certainty algorithms: SO2-D2.5.1.1-Tools for Tier 1 AESI Data Collection and Interpretation

The methods for each of the above are briefly described in Appendix 4 of this Guide along with links to source documents which have more detailed methodology.

A different approach to that used for other AESI companion guides for background incidence and risk factors was used for MIS-C/A which was first described in association with COVID-19 disease. As such it appears to be a new entity, albeit with overlap with other hyperinflammatory syndromes, especially Kawasaki Disease. Thus, the recently published Brighton Collaboration case definition [1] served as the primary resource for frequency of the event and known risk factors.

4. Results

Incidence and Risk Factors

As a new entity, first described in association with COVID-19 disease due to SARS-CoV-2 infection (COVID-19), background incidence in the population could not be determined. Possibly, as knowledge of the pathophysiology of MIS-C/A increases, it may be recognized that a similar syndrome may occur and studies on incidence may be forthcoming. Thus, the recently published case definition[1] served as the main source for frequency and risk factors for MIS-C/A. Further, given the lack of data for both, instead of separate appendices, what is known is summarized below.

The working group noted an estimated prevalence of MIS-C of 2/100,000 children in communities experiencing wide-spread COVID-19 infections.[7] This estimate was based on experience in New York State from March 1 through May 10, 2020. Per 100,000 individuals aged <21 years, the estimated incidence of laboratory confirmed SARS-CoV-2 infection was 322 and of MIS-C was 2. At present, data are simply insufficient to provide an estimate of the frequency of MIS-C or MIS-A following COVID-19.

Similarly, COVID-19 is the only established risk factor for MIS-C/A. Cases following immunization have been reported but vaccine has not been established as a known risk factor. As evidence accumulates, the guide will be updated but for now it is impossible to provide meaningful data on incidence or risk factors beyond COVID-19 itself.

All outputs are provided in separate appendices as shown below:

1. MIS-C/A Diagnostic Codes: ICD-10-CM, MedDRA, SNOMEDCT
2. MIS-C/A case definition key caveats for diagnosis, data analysis and presentation plus recommendations for real time investigation.
3. MIS-C/A data abstraction and interpretation forms with algorithms for assessing level of certainty.
4. 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 MIS-C/A including ICD-9/10-CM, MedDRA and SNOMEDCT codes for data entry or database searching; guidance for real time investigation; and tools for collecting and interpreting clinical data to apply the Brighton MIS-C/A 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 to assign level of certainty for all identified AEFI with features of MIS-C/A. This standard, harmonized approach will facilitate signal detection and assessment, epidemiologic studies

of background incidence, hypothesis testing for causality and capacity to combine data across trials for meta-analyses.

6. References

1. Vogel TP, Top KA, Karatzios C et al. Multisystem inflammatory syndrome in children and adults (MIS-C/A): Case definition & guidelines for data collection, analysis and presentation of immunization safety data. Vaccine 2021; 39:3037-3049. https://doi.org/10.1016/j.vaccine.2021.01.054

2. Becker BFH, Avillach P, Romio S, van Mulligen EM, Weibel D, Sturkenboom MCJM, Kors J. CodeMapper: Semi-automatic coding of case definitions. A contribution from the ADVANCE project. Pharmacoepidemiology and Drug Safety, 2017 (8) 26: 998-1005. Doi:10.1002/pds.4245

3. McCray AT, Burgun A, Bodenreider O. Aggregating UMLS semantic types for reducing conceptual complexity. Studies Health Technology Information, 2001 84(Pt 1): 216-20. PMID: 11604736; PMCID: PMC4300099.

4. Rogers F. Medical subject headings. Bull Med Libr Assoc, 1963. 51(1): 114-6. PMID: 13982385; PMCID: PMC197951.

5. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). Drug Safety, 1999. 0(2):109-17. Doi: 10.2165/00002018-199920020-00002.

6. Schuemie MJ, Jelier R, Kors JA. Peregrine: Lightweight gene name normalization by dictionary lookup. In: Proc of the Second Biocreative Challenge Evaluation Workshop., 2007. 131–133.

7. Dufort EM, Koumans EH, Chow EJ et al. Multisystem inflammatory syndrome in children in New York State. NEJM 2020; 383:347-358.

APPENDIX 1

MIS-C/A Diagnostic Codes: ICD-9/10-CM, MedDRA and SNOMEDCT

4.1 MIS-C/A Diagnostic Codes: ICD-9/10-CM and MedDRA

TABLE 1. NARROW TERMS FOR MIS-C/A

UMLS Concept	Diagnostic Coding System Term and Codes					
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM	SNOMEDCT
C5391534	Multisystem inflammatory syndrome in children with COVID-19 infection	Multisystem inflammatory syndrome in children	10084767			895448002
C5439527	Multisystem inflammatory syndrome in adults	Multisystem inflammatory syndrome in adults MIS-A	10085850 10085855		M35.81	1119306006

TABLE 2. BROAD TERMS FOR MIS-C/A

UMLS Concept	Diagnostic Coding System Term and Codes					
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM	SNOMEDCT
C5439525	Post-acute COVID-19*	Post-acute COVID-19				119303003
C5203670	COVID-19	COVID-19	100839006		U07.1	840539006
C0026691	Mucocutaneous lymph node syndrome	Mucocutaneous lymph node syndrome (Kawasaki) Acute febrile mucocutaneous lymph node syndrome Acute febrile mucocutaneous lymph node syndrome NOS Kawasaki's disease Kawasaki's disease	10028083 10000747 10023320	 446.1	M30.3	 75053002 195349001 155444003 195348009
C0242966	Systemic inflammatory response syndrome	Systemic inflammatory response syndrome (SIRS) Systemic inflammatory response syndrome (SIRS) NOS Systemic inflammatory response syndrome, unspecified Sepsis syndrome SIRS	10051379 10053879 10062357	995.9 995.90 995.90	R65.10	2381490007 238150007
C3697422	Non-infectious systemic inflammatory response syndrome					700049004
C0024291	Lymphohistiocytosis, Hemophagocytic	Haemophagocytic lymphohistiocytosis	10071580 10071583		D76.1	190958003 234437005
	Macrophage activation syndrome					
C0600327	Toxic shock syndrome	Toxic shock syndrome	10044248	040.82	A48.3	18504008

		Toxic shock syndrome NOS Syndrome toxic shock	10044249 10042852			
C2711695	Systemic inflammatory response syndrome due to infectious process with acute organ dysfunction					441596002
C1719671	Systemic inflammatory response syndrome due to infectious process without acute organ dysfunction*			995.91		
C3874339	Systemic inflammatory response syndrome without acute organ dysfunction*					4364100011910

** These terms don't fit with the MIS case definition which requires acute organ dysfunction. That said, they are included in the table since it is possible the coding may have been inaccurate.*

APPENDIX 2

MIS-C/A Key Caveats for Real Time Investigation and Case Definition Working Group Guidance for Data Analysis and Presentation

2. MIS-C/A Case Definition[1] Key Caveats for Diagnosis, Data Analysis and Presentation

2.1 Key elements of Case Definition (CD)

- The same case definition applies to both children and adults. Designate as MIS-C if age <21 years; MIS-A if age ≥21 years

- There are 3 levels of certainty. The working group formulated the case definition to enable inclusion of cases with incomplete documentation of fever. Specifically, the less specific Levels 2 and 3 each have two subdivisions:
    a. if ≥3 days of measured fever (Temp ≥38.0°C)
    b. if 1-2 days of subjective or measured fever (Temp ≥38.0°C)

- All 3 levels require involvement of 2 or more body systems (mucocutaneous, gastrointestinal, neurologic, or shock/hypotension). These 4 were chosen because they diminish the likelihood of crossover with Kawasaki disease. Mucocutaneous features are present in both MIS and Kawasaki, however, in the case definition they contribute a single required clinical system and at least 1 more is required (gastrointestinal, neurologic, shock/hypotension) which occurs less frequently in Kawasaki Disease.
    - For Level 3a only, which does not require laboratory measures of inflammation or disease activity, an additional cardiac clinical feature is included – 'physical stigmata of heart failure'.

- To meet any level of the case definition there must have been a prior COVID-19 infection, exposure to a contact with COVID-19 or a COVID-19 vaccination. An interval of 12 weeks prior to MIS onset was set for the COVID infection or exposure. An interval was not specified for time to onset following vaccination.

- While there are no specified exclusionary criteria in the MIS case definition, the WG emphasized that the case definition should only be applied when there is no clear alternative diagnosis for the event. Entities such as Kawasaki Disease / Shock, Hemophagocytic lymphohistiocytosis (HLH), Macrophage Activation Syndrome (MAS) and Toxic Shock Syndrome (TSS) should be considered as possible alternative diagnoses. Also, severe COVID-19 disease could be misconstrued as MIS and the case definition should not be applied if there are severe respiratory symptoms.

2.2 Surveillance for MIS cases

- The WG noted, at the time of their review, that all true MIS-C/A cases require hospitalization, and most are admitted to intensive care. Inotropic or vasoactive medications were needed by one to two thirds of patients. So active surveillance for such cases needs to be conducted in a hospital setting and retrospective studies should use hospital record data. Appendix 3 of this Guide provides data abstraction forms focused on the criteria needed to meet the case definition and algorithms for determining level of certainty.
- The WG did not recommend a specific duration of surveillance for possible cases following immunization. They did note, based on a large volume of data for MIS-C that the timeline would likely be similar to what is seen after natural infection, namely 4-6 weeks. There were too few adult data, but a period 12 weeks was adopted by the CDCP for their case definition and the WG used that for both MIS-C and MIS-A in their case definition. Thus 12 weeks post immunization would be a reasonable period for active surveillance.

2.3 Recommendations for real time assessment

- Several clinical criteria were specified for different systems. Only one manifestation required per system but expected that in most cases there would be several including:
    - Mucocutaneous changes:
        - Rash
        - Erythema or cracking of the lips, mouth or pharynx
        - Bilateral nonexudative conjunctivitis
        - Erythema or edema of the hands and feet
    - Gastrointestinal manifestations:
        - Abdominal pain
        - Vomiting
        - Diarrhea
    - Neurologic manifestations:
        - Altered mental status
        - Headache
        - Weakness
        - Paresthesias
        - Lethargy
    - Shock / hypotension

- Several laboratory investigations are included in the case definition criteria. In most cases multiple tests are noted and there need only be one included to meet a criterion.
    - Laboratory evidence of inflammation: elevated ESR or CRP or ferritin or procalcitonin.
    - Laboratory evidence of hematologic disease activity: neutrophilia or lymphopenia or thrombocytopenia. No absolute values were specified and the WG recommended that the range of normal for the testing lab be used to identify upper or lower limits.
    - Laboratory evidence of cardiac injury: elevated BNP or NTproBNP or troponin
    - Echocardiographic evidence of cardiac involvement: ≥1 of the following findings:
        - Dysfunction
        - Wall motion abnormality
        - Coronary abnormality (could be dilation, aneurysm, echobrightness or lack of distal tapering)
        - Valvular regurgitation
        - Pericardial effusion
        - Evidence of abnormal left ventricular strain
    - EKG changes consistent with myocarditis or myo-pericarditis: ≥1 of the following findings:
        - Abnormal ST segments
        - Arrhythmia
        - Pathologic Q waves
        - AV conduction delay
        - PR segment depression
        - Low voltage QRS
    - Laboratory evidence of personal SARS-CoV-2 infection: ≥1 of the following:
        - Serology
        - Antigen positivity
        - Nucleic acid amplification positivity

3 Data Collection Guidelines

- Seek a history of occurrence of any inflammatory syndromes, similar to MIS, after previous immunization(s)
- Treatment is not part of the case definition but is an important element to document, in particular: corticosteroids, IVIG, antiviral medications, aspirin or other anti-platelet agent(s), anti-coagulation therapy or anti-cytokine biologic immunomodulators. For all, should specify dosing and duration.

4 Data Analysis Guidelines

- There is no requirement in the case definition for specific timing from vaccination to MIS onset. The WG did recommend, however, that cases be classified according to onset interval as shown below. These guidelines do not translate to a recommendation for duration of surveillance (see section 2.2 above) but are meant to ensure comparability between studies where multiple cases are included and time from immunization to onset varies.
    - <12 weeks after immunization
    - 12 weeks to <12 months after immunization
    - 12 months to <24 months after immunization
    - 12 month increments thereafter
- The WG suggested a severity grading system for classifying cases:
    - Mild: able to manage as an outpatient or admitted to hospital but did not require ICU care.
    - Moderate: admitted to ICU
    - Severe: admitted to ICU and required ≥2 of vasoactive/inotropic drugs, ventilation, dialysis or ECMO
    - Death

APPENDIX 3

MIS-C/A Data Abstraction and Interpretation Forms With Algorithms for Assessing Level of Certainty

THIS PROJECT HAS BEEN FUNDED IN WHOLE BY CEPI.

3.1. MIS-C/A Data Abstraction and Interpretation Form for Medical Chart Review

This appendix provides tools that can be used to gather data pertinent to MIS-C/A and to use the data to assess the level of certainty based on the published Brighton case definition.[1] These tools can be used in a variety of settings including: medical chart review to validate MIS-C/A 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; and to guide data collection for epidemiologic studies of background incidence or to assess causality.

While there are separate categories of MIS-C and MIS-A based on age, the same case definition applies to both children and adults.

Five tables and 1 figure are included in this appendix:

- **Table 3.1** lists all Brighton case definition[1] criteria for MIS-C/A and identifies likely sources of information for each.
- **Table 3.2** is the main data abstraction form that can be used to record data pertinent to MIS-C/A
- **Table 3.3** provides a guide for assigning a '**Y**es', '**N**o' or '**U**nknown' status to each case definition criterion based on data entered into Table 3.2.
- **Table 3.4** is a brief summary of the final value for each criterion. As per Table 3.3
- **Table 3.5** provides the formulae used to assign level of certainty for MIS-C/A based on criterion values summarized in Table 3.4.
- **Figure** 3.1 shows a pictorial algorithm for determining level of certainty for MIS-C/A.

Brief instructions are provided with each table.

TABLE 3.1. MIS-C/A KEY CASE DEFINITION CRITERIA, LIKELY AND ACTUAL SOURCES OF INFORMATION

Criterion	Criterion category	Likely sources of information	Actual sources of information
A	Fever	Hospital / ICU admission history & physical examination	
B	SARS-CoV-2 / COVID-19 infection/exposure/vaccination	Serology, antigen or PCR testing History of infection or exposure to infection; or vaccination	
C	Lab markers of inflammation	Laboratory reports	`
D	Clinical features of illness	Hospital / ICU admission history & physical examination	
E	Indicators of disease activity	Hospital / ICU admission history & physical examination, Cardiology consultation, Laboratory reports; EKG / echocardiogram reports	
F	Age	Clinical history, date of birth/date of illness onset	

TABLE 3.2. MIS-C/A 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 MIS-C/A case definition.

1. Date of illness onset	
2. Hospital admission?	
3. Admitting diagnosis:	
4. Discharge diagnosis:	
5. Criterion A **FEVER**	☐ **1.** Fever (measured temperature ≥38.0° C) present for ≥3 consecutive days ☐ **2.** Fever (measured temperature ≥38.0° C or subjective) present for 1-2 consecutive days ☐ **3.** No fever (no measured values ≥38.0° C or no subjective report of fever lasting ≥1 day) ☐ **4.** Unknown if fever present
6. Criterion B **SARS-CoV-2 / COVID-19 INFECTION, EXPOSURE or VACCINATION**	**Check all that apply if any of 1, 2, 3 or 4 are known to be true; if none can be chosen, choose either 5 or 6 which is ever is the most suitable option:** ☐ 1. SARS-CoV-2 infection, of the individual with MIS, was laboratory confirmed by one or more of the following: ○ Serology ○ Antigen positivity ○ Nucleic acid amplification positivity ☐ 2. Personal history of confirmed or strongly suspected COVID-19 infection within prior 12 weeks ☐ 3. Close contact with a person with known or strongly suspected COVID-19 infection within prior 12 weeks ☐ 4. Illness occurred following COVID-19 vaccination ☐ 5. None of 1, 2, 3 or 4 are true. ☐ 6. Unknown if any of 1 or 2 or 3 or 4 are true
7. Criterion C **LABORATORY EVIDENCE OF INFLAMMATION**	**Choose the one best answer:** ☐ 1. Elevation of ≥1 of: CRP or ESR or ferritin or procalcitonin ☐ 2. ≥1 of CRP or ESR or ferritin or procalcitonin tested and found to be within normal range for the testing lab ☐ 3. Unknown if any of CRP or ESR or ferritin or procalcitonin tested, or ≥1 tested but results unknown, or none tested

8. Criterion D **CLINICAL FEATURES**	**Check all that apply if any of 1, 2, 3 or 4 present (circle the features that are present); or if not, choose only 5 or 6 whichever is the most suitable option.** ☐ **1. Mucocutaneous features** (≥1 of rash; erythema or cracking of the lips or mouth or pharynx; bilateral nonexudative conjunctivitis; erythema or edema of the hands and feet) ☐ **2. Gastrointestinal features** (≥1 of: abdominal pain; vomiting; diarrhea) ☐ **3. Neurologic features** (≥1 of: altered mental status; headache; weakness; paresthesia; lethargy) ☐ **4. Shock / hypotension** ☐ **5. None** of the features in 1, 2, 3 or 4 were present ☐ **6. Unknown** if any of the features in 1, 2, 3 or 4 were present

9. Criterion E MEASURE OF DISEASE ACTIVITY	**E-i**	**Abnormal hematologic measurement(s): choose the single most appropriate answer from the options below:** ☐ 1. Neutrophilia (elevated PMN count – above range of normal for testing lab); or lymphopenia (reduced lymphocyte count – below range of normal for testing lab); or thrombocytopenia (platelets < 150 X 10^9/liter) ☐ 2. Hematologic measurement(s) done and was reported as normal or none of the findings listed in 1 were present ☐ 3. Unknown if PMN, lymphocyte or platelet counts tested or none tested, or if tested, results unavailable
	E-ii	**Elevation of cardiac biomarker(s): choose the single most appropriate answer from the options below:** ☐ 1. BNP or NT-proBNP or troponin elevated ☐ 2. Normal results for any measured cardiac biomarker (BNP or NT-proBNP or troponin) ☐ 3. Unknown if any cardiac biomarker(s) measured or none tested or, if measured, results unknown
	E-iii-a	**Echocardiogram results: choose the single most appropriate answer from the options below:** ☐ 1. Echocardiogram done and showed ≥1 of: dysfunction, wall motion abnormality; coronary abnormality (dilation or aneurysm or echo brightness or lack of distal tapering); valvular regurgitation; pericardial effusion; evidence of abnormal left ventricular strain) ☐ 2. Echocardiogram done and was reported as normal or none of the abnormalities listed in 1 were present ☐ 3. Echocardiogram not done, or unknown if done, or done but results are unavailable
	E-iii-b	**Presence of physical stigmata of heart failure: choose the single most appropriate answer from the options below:** ☐ 1. ≥1 of the following was present: gallop rhythm diagnosed by expert; pulmonary rales heard by stethoscope; lower extremity edema; jugular venous distention; hepatosplenomegaly. ☐ 2. Physical examination for features of heart failure done by an expert and none of the features listed in 1 were present. ☐ 3. Unknown if any of the features listed in 1 above were present or unknown if physical examination was done by an expert to look for features of heart failure
	E-iv	**ECG results: choose the single most appropriate answer from the options below:** ☐ 1. ECG done and had ≥1 change consistent with myocarditis or myo-pericarditis (abnormal ST segments; arrhythmia; pathologic Q waves; AV conduction delay; PR segment depression; low voltage QRS) ☐ 2. ECG done and was reported as normal or none of the abnormalities listed in 1 were present ☐ E. ECG not done or unknown if done or done but results are unavailable

10.Criterion F AGE	☐ **1.** Age <21 years old ☐ **2.** Age ≥21 years old

TABLE 3.3. INTERPRETATION FORM FOR MIS-C/A CRITERION VALUES: Based on clinical data entered into Table 3.2, assign a value to each criterion using the rules in the Criterion Options columns. NOTE: If Age < 21 years, it is MIS-C; if Age ≥21 years, it is MIS-A

CRITERIA		CRITERION OPTIONS			Criterion Value
		Criterion = YES (Y) IF:	Criterion = NO (N) IF:	Criterion = UNKNOWN (U) IF:	
A. Presence & Duration of Fever	A-1	__A = 1	__A = 2 or 3	__A = 4	A-1 = Y N U
	A-2	__A = 2	__A = 1 or 3	__A = 4	A-2 = Y N U
B. COVID-19 experience		__B = 1, 2, 3 or 4	__B = 5	__B = 6	B = Y N U
C. Laboratory evidence of inflammation		__C = 1	__C = 2	__C = 3	C = Y N U
D. Clinical Features	D-1	__D = ≥2 of (1, 2, 3 or 4)	__D = <2 of (1, 2, 3 or 4) or = 5	__D = 6	D-1 = Y N U
	D-2	__D = 1 of (1, 2, 3 or 4)	__D = 0 or ≥2 of (1, 2, 3 & 4) or = 5	__D = 6	D-2 = Y N U
E. Measures of disease activity	E-1	__≥2 of (E-i, E-ii, E-iii- [a or b] or E-iv) = 1	__ [E-i + E-ii + E-iii-a + E-iii-b + E-iv = 2] OR E-2 = Yes	__E-i + E-ii + E-iii + E-iv = 3	E-1 = Y N U
	E-2	__ 1 of (E-i, E-ii, E-iii [a or b] or E-iv) =1	__E-i + E-ii + E-iii-a + E-iii-b + E-iv = 2 OR E-1 = Yes	__E-i + E-ii + E-iii + E-iv = 3	E-2 = Y N U
	E-3	__E-iii-b = 1	__E-iii-b = 2	__E-iii-b = 3	E-3 = Y N U

TABLE 3.4. SUMMARY OF MIS-C/A CRITERION VALUES Record the final value for each Criterion from Table 3.3. For F see Table 3.2, row 10.

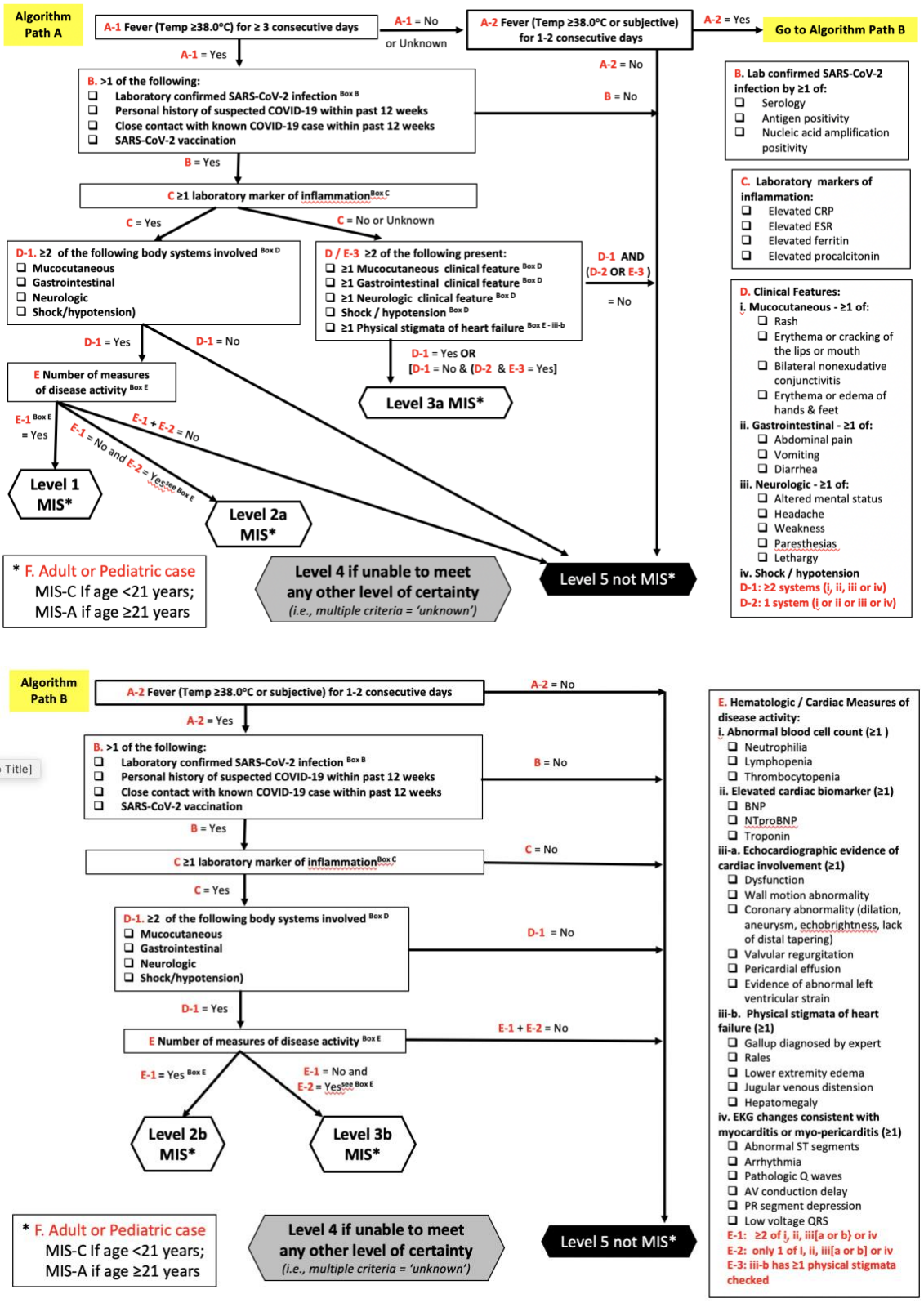
Criterion	A-1	A-2	B	C	D-1	D-2	E-1	E-2	E-3	F For classification of case
Final Value										☐ MIS-C if Age <21 years ☐ MIS-A if Age ≥21 years

TABLE 3.5 TABULAR ALGORITHM TO DETERMINE MIS LEVEL OF CERTAINTY (LOC) BASED ON CRITERION VALUES Use the final values of all criteria recorded in Table 3.4 to determine LOC based on the formulae below. The highest row in the table where **all criteria are met** will be the LOC.

Level of Certainty	NOTE: If Age < 21 years, it is MIS-C; if Age ≥21 years, it is MIS-A
Level 1	A-1 & B & C & D-1 & E-1 = YES
Level 2a	(A-1 & B & C & D-1 & E-2 = YES) AND (E-1 = NO)
Level 2b	(A-2 & B & C & D-1 & E-1 = YES) AND (A-1 = NO)
Level 3a	(A-1 & B & C = Yes) AND (D-1 or [D-2 & E-3] = YES) AND (C & = NO or UNKNOWN)
Level 3b	(A-2 & B & C & D-1 & E-2 = YES) AND (A-1 & E-1 = NO)
Level 4	Unable to meet the case definition at any level of certainty (1, 2a, 2b, 3a, or 3b) or Level 5
Level 5	(A-1 & A-2) OR B OR C OR (D-1 OR (D-2 & E-3) OR (E-1 & E-2) = NO OR an alternative diagnosis has been ascertained

THIS PROJECT HAS BEEN FUNDED IN WHOLE BY CEPI.

FIGURE 3.1 PICTORIAL ALGORITHM FOR DETERMINING MIS-C/A LEVEL OF CERTAINTY.



APPENDIX 4.

Methodology: Brief Summary

4.1. MIS-C/A ICD-9/10-CM and MedDRA Codes [2-6]

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[2] 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.[3] 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.[4,5] A text-indexing engine Peregrine uses this dictionary to identify medical concepts in the case definition.[6] 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 Anaphylaxis Brighton case definitions for all Tier 1 AESI. The concepts identified for

Anaphylaxis were considered relevant for background incidence rate determination as well as to study hypotheses related to Anaphylaxis as a vaccine-product related reaction.

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 and at the Brighton Collaboration website.

4.2. MIS-C/A Case Definition key caveats for diagnosis, data analysis and presentation [1]

The published Brighton case definition for Anaphylaxis was reviewed and key aspects identified with particular relevance to real time assessment of Anaphylaxis in the context of a clinical trial where it occurs as an AEFI. In addition, the guideline section of the published Anaphylaxis case definition was reviewed, and key recommendations identified for data collection, analysis and presentation.

For a more detailed description of methodology see SO1-D2.7 Guidance for CEPI Developers which is available in the CEPI Developers' Toolbox.

4.3. Tabular Checklist and Algorithms for Level of Certainty Determination [1]

The Brighton Collaboration case definition for Anaphylaxis[1] was thoroughly and repeatedly reviewed by the Companion Guide author to identify all clinical, laboratory and other criteria (e.g., temporal course of disease) used to define each and every case definition level of certainty.

The MIS-C/A criteria were displayed in a tabular format to enable recording of all relevant clinical data (based on history, physical examination, laboratory investigation and temporal criteria as relevant to each case definition) needed to meet each criterion.

Algorithms were developed for each level of diagnostic certainty based on the values of each criterion as described in the published case definition.[1] Two types of algorithms were developed for each case definition. For one, formulae based on the logic in the case definition were put into tables with each row representing a level of certainty (Appendix 6). For the second a more visual decision tree algorithm (Appendix 7). was developed.

For a more detailed description of methodology see Tabular checklist and Level of Certainty algorithms: SO2-D2.5.1.1-Tools for Tier 1 AESI Data Collection and Interpretation which is available in the CEPI Developers' Toolbox.