Vaccine xxx (xxxx) xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Multisystem inflammatory syndrome in children and adults (MIS-C/A): Case definition & guidelines for data collection, analysis, and presentation of immunization safety data

Tiphanie P. Vogel [a,b,*], Karina A. Top [c], Christos Karatzios [d], David C. Hilmers [e], Lorena I. Tapia [f], Pamela Moceri [g], Lisa Giovannini-Chami [h], Nicholas Wood [i], Rebecca E. Chandler [j], Nicola P. Klein [k], Elizabeth P. Schlaudecker [l], M. Cecilia Poli [m], Eyal Muscal [a,b], Flor M. Munoz [b,n]

[a] Department of Pediatrics, Section of Rheumatology, Baylor College of Medicine, Houston, TX, USA
[b] Texas Children's Hospital, Houston, TX, USA
[c] Departments of Pediatrics, Division of Infectious Diseases, and Community Health and Epidemiology, Canadian Center for Vaccinology, Dalhousie University, Halifax, NS, Canada
[d] Department of Pediatrics, Division of Infectious Diseases, McGill University Health Centre, Montreal, Canada
[e] Departments of Medicine and Pediatrics, and Center for Space Medicine, Baylor College of Medicine, Houston, TX, USA
[f] Department of Pediatrics, Hospital Roberto del Río and Virology Program, Faculty of Medicine, University of Chile, Santiago, Chile
[g] UR2CA, Department of Cardiology, Centre Hospitalier Universitaire de Nice, Université Côte d'Azur, Nice, France
[h] Department of Pediatric Pulmonology and Allergology, Hôpitaux pédiatriques de Nice CHU- Lenval, Université de Nice Sophia-Antipolis, Nice, France
[i] Department of Child and Adolescent Health, University of Sydney, Sydney, Australia
[j] Uppsala Monitoring Center, Uppsala, Sweden
[k] Kaiser Permanente Vaccine Study Center, Kaiser Permanente Northern California Division of Research, Oakland, CA, USA
[l] Division of Infectious Diseases, Cincinnati Children's Hospital Medical Center and Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA
[m] Departments of Immunology and Rheumatology, Hospital Roberto del Río, Santiago, Chile
[n] Departments of Pediatrics, Section of Infectious Diseases, and Molecular Virology and Microbiology, Baylor College of Medicine, Houston, TX, USA

ARTICLE INFO

Article history:
Available online xxxx

Keywords:
Multisystem inflammatory syndrome
Children
Adults
MIS-C
MIS-A
Adverse event
Immunization
Guidelines
Case definition

ABSTRACT

This is a Brighton Collaboration Case Definition of the term "Multisystem Inflammatory Syndrome in Children and Adults (MIS-C/A)" to be utilized in the evaluation of adverse events following immunization. The case definition was developed by topic experts convened by the Coalition for Epidemic Preparedness Innovations (CEPI) in the context of active development of vaccines for SARS-CoV-2. The format of the Brighton Collaboration was followed, including an exhaustive review of the literature, to develop a consensus definition and defined levels of certainty. The document underwent peer review by the Brighton Collaboration Network and by selected expert external reviewers prior to submission. The comments of the reviewers were taken into consideration and edits incorporated into this final manuscript.

Contents

* Corresponding author at: Baylor College of Medicine, 1102 Bates Street Suite 330, Houston, TX 77030, USA.
E-mail address: bc-coordinator@taskforce.org (T.P. Vogel).

https://doi.org/10.1016/j.vaccine.2021.01.054
0264-410X/

1. Preamble

1.1. Need for developing case definitions and guidelines for data collection, analysis, and presentation for MIS-C/A as an adverse event following immunization

1.1.1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19). Emerging in late 2019, COVID-19 was declared a pandemic in March of 2020, leading to global institution of mitigation strategies to stem the spread of the disease and launching a world-wide effort to unravel the pathogenesis, identify successful therapies and develop a safe and efficacious vaccine.

Children and adolescents are as susceptible to infection with SARS-CoV-2 as adults, but develop symptomatic COVID-19 primary infection at significantly lesser rates and rarely develop severe disease [1,2]. However, it has become clear that a fraction of children develop a life-threatening hyperinflammatory state 4–6 weeks after infection with primary COVID-19 termed Multisystem Inflammatory Syndrome in Children (MIS-C) [3]. A similar condition has also been reported as a rare complication of COVID-19 in adults (MIS-A) [4,5]. It is currently unknown if MIS-C/A might follow immunization against SARS-CoV-2, but a need exists to define this potential entity for monitoring as an adverse event following immunization (AEFI).

MIS-C was first recognized in the United Kingdom in April 2020 (Fig. 1), prompting an alert issued by the Paediatric Intensive Care Society describing a recognized increase in critically ill children presenting with hyperinflammatory shock and evidence of SARS-CoV-2 infection [6]. This was eventually given the name Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS) by the Royal College of Paediatricians and Child Health (RCPCH) [7]. The clinical presentations of these and other patients reported shortly thereafter [8–10], invoked similarities with known disease entities like Kawasaki Disease (KD), toxic shock syndrome (TSS) and macrophage activation syndrome (MAS)/secondary hemophagocytic lymphohistiocytosis (HLH). Subsequent to these initial reports, both the United States Centers for Disease Control and Prevention (CDC) [11] and the World Health Organization (WHO) [12] published case definitions for MIS-C (Table 1). Over the next 4 months, a series of manuscripts were published detailing the clinical presentations, laboratory findings and diagnostic results of patients with the emerging

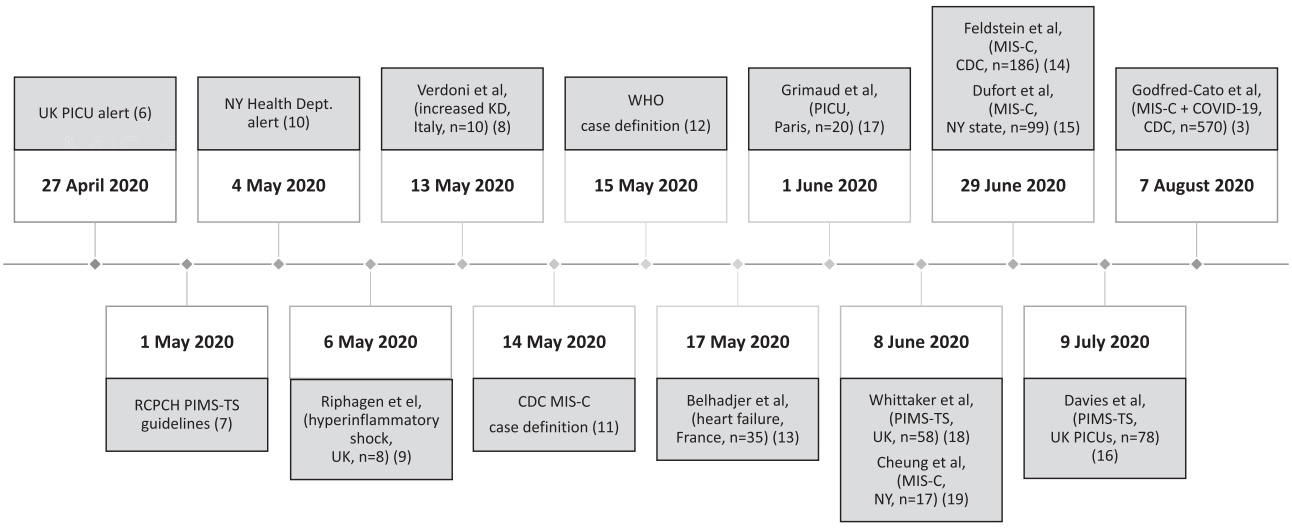

Fig. 1. Timeline of initial recognition and description of MIS-C.

Table 1
Existing Case Definitions of Multisystem Inflammatory Syndromes.

	Pediatric: RCPCH (7)	Pediatric: CDC (11)	Pediatric: WHO (12)	Adult: CDC (4)
Age (years)	"child"	<21	0–19	≥21
Fever	persistent	≥ 1 day	≥ 3 days	no comment
Laboratory Evidence of Inflammation	Y	Y	Y	Y
Hospitalization	N	Y	N	Y
Number of Organ Systems Involved	≥1	≥2	≥2	≥1 extra-pulmonary
Organ Systems Named	shock, cardiac, respiratory, renal, gastrointestinal, neurologic	cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, neurologic	mucocutaneous, hypotension/shock, cardiac, gastrointestinal	hypotension/shock, cardiac, thrombosis/thromboembolism, acute liver injury
Exclusion of Other Causes	Y	Y	Y	Y + exclusion of severe respiratory illness
(+) SARS-CoV-2 RT-PCR/ antigen/serology	N	Y	Y	Y (within 12 weeks)
COVID-19 epidemiologic link allowed in place of viral test	n/a	exposure within 4 weeks	"likely contact"	N

RCPCH, Royal College of Paediatrics and Child Health; CDC, Centers for Disease Control and Prevention; WHO, World Health Organization

disease MIS-C [3,13–20]. The prevalence of MIS-C in communities experiencing wide-spread COVID-19 infections is unclear, but has been estimated at 2/100,000 children [15]. Waves of MIS-C cases appear to follow approximately 4–6 weeks after the peak of adult COVID-19 cases/hospitalizations in a locale [14,15,21]. Subsequently, case reports of MIS-A emerged leading the CDC to spotlight this condition [4], which appears to have clinical overlap with MIS-C but an even less clear prevalence. The CDC used a case definition for MIS-A with 5 criteria [4] (Table 1).

1.1.2. Basic demographic, clinical and diagnostic features of MIS-C/A

Children who develop MIS-C are generally previously healthy individuals. The primary COVID-19 infection in these patients is almost universally mild or asymptomatic. They typically present to medical attention on day 3–5 after developing a persistent fever (Table 2a) associated with gastrointestinal symptoms (pain, vomiting, diarrhea), evidence of mucocutaneous inflammation (rash, conjunctivitis, oromucosal changes), lymphopenia, and high levels of circulating inflammation (Table 2b). A subset of MIS-C patients develops severe disease including hypotension/shock and evidence of cardiac involvement including myocarditis, myocardial dysfunction, and coronary artery changes. Immune modulation has been used with best supportive care to treat MIS-C, leading in most cases to prompt resolution of the inflammation. Fatal cases are rare (2%) [14,15]. Given the emerging nature of this disorder, long term outcomes are unknown, but the overwhelming majority of children appear to return to their pre-morbid baseline with respect to cardiac status [22,23].

From early in the pandemic, it was clear that a subset of adult patients experiences a severe hyperinflammatory response during primary SARS-CoV-2 infection [24]. After MIS-C was recognized, a similar presentation in adult patients, MIS-A, was appreciated as a distinct clinical entity [4,5,25]. MIS-A has been recognized as a severe illness requiring hospitalization in a person aged ≥21 years, with laboratory evidence of current or previous (within 12 weeks) SARS-CoV-2 infection, severe extrapulmonary organ dysfunction (including thrombosis), laboratory evidence of severe inflammation, and absence of severe respiratory disease [4]. Patients with MIS-A have been reported up to age 50 years and, compared to MIS-C, are more likely to have underlying health conditions and experience an identifiable antecedent respiratory illness. MIS-A patients otherwise have remarkably overlapping clinical features with MIS-C, although the severity of cardiac dysfunction, the incidence of thrombosis and the mortality of MIS-A may be higher [4].

1.1.3. Pathophysiology of SARS-CoV-2

Acute COVID-19 can have a severe course characterized by acute respiratory distress syndrome (ARDS) with a local and systemic cytokine storm that may trigger rapid clinical deterioration and multiorgan failure. While both severe primary COVID-19 with ARDS and MIS-C/A are characterized by hyperinflammation and cytokine release, notable pathologic differences have already been noted. What has been reported thus far of the aggressive efforts to fully characterize the human immune response to SARS-CoV-2 infection is summarized below, although there is still much to be learned about this host-pathogen relationship.

1.1.3.1. COVID-19. SARS-CoV-2, a *Betacoronavirus*, is an enveloped single-stranded positive-sense RNA virus [26]. The S (spike) glycoprotein on its surface binds to angiotensin-converting enzyme 2 (ACE2), a highly expressed transmembrane protein located in vascular endothelial cells in the lungs and many other organs [27,28], allowing viral entry and triggering activation of the innate immune response, with a predominant cytokine release and monocyte activation [29].

Recognition by Toll-Like Receptor (TLR) 3 and TLR4 occurs after interaction with viral RNA and oxidized phospholipids induced by the infection [30]. Upon TLR activation, downstream signaling cascades trigger the secretion of type I/III interferons (IFN), important cytokines for an early and accurate antiviral response that can limit SARS-CoV-2 infection [29,31]. In addition to activation of the immune response, several mechanisms to evade innate immune sensing have been described, including inhibition of signal transduction pathways at multiple levels [29]. This may contribute to the lack of a robust IFN I/III response after SARS-CoV-2 infection in severe COVID-19 cases [32]. The importance of innate immunity in controlling SARS-CoV-2 is underscored by the development of severe COVID-19 in patients with genetic or acquired defects in type I IFN signaling [33,34].

Monocytes and natural killer (NK) cells are also activated during the innate response to SARS-CoV-2. Local and peripheral monocytes appear to be responsible for the cytokine storm generated during severe COVID-19 through increased secretion of pro-inflammatory cytokines [35,36]. Specific NK cell activation also results in expansion and increased cytokine-production associated with hyperinflammation [37]. There may also be a role for dysregulation of the renin-angiotensin system in the pathophysiology of COVID-19 [38].

B cells are a critical component of the immune response to SARS-CoV-2, both for antibody production and the development

Table 2a
Clinical Features in Large Cohorts of MIS-C.

Cohort	**Feldstein (14)**	**Dufort (15)**	**Davies (16)**	**Belhadjer (13)**
Location	**USA**	**New York**	**UK**	**France**
#Patients	**186**	**99**	**78**	**35**
Clinical feature				
Age (years)				
Age range	3.3–12.5*	0–20	8–14	1–16
(average/median)	(8.3)		(11)	(10)
older age	15.5%	26%	0	0
	age 15–20	age 13–20		
Fever duration at presentation (days)				
Average/median (range)	6 (5–8*)			~2
Time elapsed from history of COVID-19 infection/exposure (days)	median 25 (range 6–51) in the 7.5% with history of symptoms	median 21 in the 24% with "COVID compatible illness"		contact with virus was > 21 before admission
% reported patients				
Male	62	54	67	51
White, Non-Hispanic	19	19	22	
Overweight	29	29		17
Other (non-obesity) comorbidity	27	17	22	11
Fever	100	100 (+chills)	100	100
Rash	59	60	45	57
Red eyes/conjunctivitis	55	56	29	
Oromucosal changes	42	27		
Hand/foot erythema/swelling	37	9		
Cervical lymphadenopathy	10	6		
Gastrointestinal symptoms	92			83
nausea/vomiting		58	63	
abdominal pain		61	62	
diarrhea		49	64	
Hematologic involvement	76			
thrombosis	2			
Respiratory symptoms	70			
sore throat		16		
congestion		13		43
cough		31		
shortness of breath		19		65
tachypnea		78		
hypoxia		4		94
Cardiac symptoms	80			
chest pain		11		17
tachycardia		97		
Musculoskeletal symptoms	23			
arthralgias	2	4		
myalgias	8	17		
Neurologic symptoms	6			31
headache		29		
altered mental status		2		
Required ICU care	80	80	100	83
intubated				63
poor perfusion/shock		32	87	80
Death	2	2	3	0

*interquartile range.

of memory B cells, and the B cell immune phenotype in severe COVID-19 distinctly differs from both healthy donors and from recovered and moderate COVID-19 patients [39,40]. The S protein and its receptor-binding domain (RBD) are the main target of neutralizing antibodies, which prevent the virus binding to the airway epithelial cells through ACE2 [41].

Neutralizing antibody responses have been found in COVID-19 patients [41], but the relationship between SARS-CoV-2 antibody levels and disease severity remains debated [42–44]. Levels of SARS-CoV-2 S protein RBD IgM and IgG are higher in severe and recovered COVID-19 patients and are proportional to the time since onset of symptoms [44], reflecting a strong SARS-CoV-2 specific humoral response. SARS-CoV-2 IgG and IgM antibodies have been found at lower levels in asymptomatic SARS-CoV-2 positive individuals compared to COVID-19 patients [40]. Whether or not long-lasting protective neutralizing antibody immunity is established following COVID-19 has not yet become clear [40,45].

In COVID-19 patients, B cell plasmablasts were expanded in severe COVID-19 patients as compared to healthy donors and recovered COVID-19 patients [39,43]. Expanded plasmablasts might reflect extra-follicular B cell activation [46], and this maladjusted inflammatory response may be responsible for immune-mediated damage that could amplify tissue injury [43].

Lymphopenia correlates with severity and mortality of SARS-CoV-2 infection; this lymphopenia is a result of decreases in both CD4+ and CD8+ T cells subsets [47]. The etiology of these decreases remains elusive and could be associated with direct viral infection of T cells, as in Middle Eastern Respiratory Syndrome coronavirus (MERS-CoV), or with effects from the inflammatory, milieu or with sequestration of T cells in end-organs [29,47,48].

Despite the low numbers, CD4+ and CD8+ T cell responses are detected in the majority of COVID-19 patients, including those with only mild or asymptomatic infections [49]. T cells are likely fundamental to SARS-CoV-2 infection control, and acute SARS-CoV-2-specific T cells displayed a highly activated cytotoxic

Table 2b
Laboratory Features in Large Cohorts of MIS-C.

Cohort	**Feldstein (14)**	**Dufort (15)**	**Davies (16)**	**Belhadjer (13)**
Location	**USA**	**New York**	**UK**	**France**
#Patients	**186**	**99**	**78**	**35**
Laboratory finding	**% reported patients (or Yes if only ranges available)**			
SARS-CoV-2 PCR/antigen +	56	51	22	40
SARS-CoV-2 antibody +	44	99	94	86
Known COVID-19 contact	30 (of virus negative)	61	10	37
Inflammation				
ESR elevated	77	77		
CRP elevated	91	100	100	100
Fibrinogen elevated	80	86		
Ferritin elevated	61	100	100	
Procalcitonin elevated		92		100 (n = 26)
Cytokines				
IL-6 elevated				100 (n = 13)
Cytopenias				
Leukopenia		0		0
Neutrophilia	68	(no neutropenia)	Yes	97 (n = 34)
Lymphopenia	80	66	Yes	
Anemia	48			
Thrombocytopenia	55	11 (severe)		
Cardiac Biomarkers				
Troponin elevated	50	71	100	100
BNP or NT-proBNP elevated	73	90		100
Coagulation				
Ddimer elevated	67	91	100	100
PTT/PT/INR elevated	77			
Other				
LDH elevated		9		
Hypoalbuminemia	80	48 (<3g/dL)		
AST elevated				
ALT elevated	64			
Cardiac Studies				
EKG abnormality	12			6
Echo with poor function	42	52		100
Coronary dilation	9	9	23	17
Other echo change		32 (effusion)	13 (coronaries echogenic)	9 (effusion)

phenotype [49]. While the induction of T cell immunity is essential for efficient virus control, dysregulated T cell responses may contribute to hyperinflammation in primary COVID-19. Increased frequencies of particular CD4+ T cells capable of substantial *ex vivo* inflammatory cytokine production have been described in critically ill COVID-19 patients [35]. This subset has previously been implicated in inflammatory diseases and in poor outcomes in sepsis [50]. Reduced frequencies of regulatory T cells have also been described in severe COVID-19 cases, which may exacerbate the hyperinflammation [36,47].

Previous studies of MERS-CoV and SARS-CoV-1 have shown potent memory T cell responses that persist for years while antibody responses wane [51,52]. SARS-CoV-2 does elicit memory T cell responses. However, while there is evidence for anti-S antibody as a correlate of protection, the evidence for anamnestic T cell responses in the absence of detectable circulating antibodies is not yet clear, and co-expression of exhaustion markers has been reported on convalescent phase SARS-CoV-2-specific T cells [29]. Nevertheless, recent data in rhesus macaques has shown that SARS-CoV-2 infection generates near-complete protection against rechallenge [53]. There is currently insufficient evidence of reinfection in immunocompetent humans with previously documented COVID-19 to make conclusions.

1.1.3.2. MIS-C. The molecular mechanisms that lead to hyperinflammation in MIS-C are largely unknown at this stage and limited to phenotypic characterizations. No similar studies are yet reported in MIS-A. Recent studies focusing on profiling the immune response during MIS-C have illuminated some potential mechanisms, but the number of patients studied is still small and the immunopathology that leads to this severe inflammatory disorder remains to be discovered.

Immune phenotyping in MIS-C with comparison to severe COVID-19 ARDS and KD has helped generate hypotheses for disease mechanisms; one possibility is an aberrant interferon response leading to hyperinflammation [54]. When cytokine profiles of severe COVID-19 were compared with MIS-C, patients in both groups had high IFN-γ [55]. Interestingly, in these studies the sum of IL-10 and TNF-α levels uniquely identified MIS-C from severe COVID-19 presentations [55]. This marked elevation of IL-10 is distinct from cytokine profiles in KD, characterized by mild elevations of IL-1, IL-2, and IL-6 [56]. While IFN-γ is increased in MIS-C, KD is more characterized by an exacerbated IL-1 pathway response [57–59]. Further, while IL-17A drives KD, it does not seem to be driving inflammation in MIS-C [60].

Most MIS-C patients have positive anti-S IgG and these levels are comparable to adult individuals that survived severe COVID-19, suggesting that MIS-C is associated with a robust immune response [48,61,62]. In line with this observation, and in contrast to severe COVID-19, MIS-C is characterized by lower, and even negative, viral loads at presentation as well as low or absent anti-S IgM, supporting the idea of a post-infectious phenomenon [55,62]. Excellent response to immunomodulation further suggests that MIS-C is driven by post-infectious immune dysregulation rather than directly by the virus.

Interestingly, when comparing anti-S IgG neutralizing activity, MIS-C patients exhibited decreased activity compared to adult patients with COVID-19 ARDS and convalescent plasma donors

but increased compared to other children with COVID-19 [48,61,62]. These findings suggest an abnormal neutralizing activity in the MIS-C pediatric immune response.

The lymphopenia in MIS-C patients has been shown to be due to reduced numbers of CD4+ and CD8+ T lymphocytes and NK cells [60,63]. Immunoprofiling of MIS-C patients revealed marked T cell activation and skewed T cell subsets [48,60,63]. Neutrophils from MIS-C patients showed high expression of activation markers and this was supported by high levels of IL-8 [64]. While T cells appear to be more activated in MIS-C, antigen presenting cells like monocytes, dendritic cells and B cells have lower markers of activation, suggesting a possible deficiency in antigen presentation [64].

Several elements detectable in MIS-C patients suggest an endothelial dysfunction and microangiopathy, including a tendency to higher values of soluble complement components C5b-9 [55]. This finding correlated with higher cytokine levels and a greater frequency of schistocytes and burr cells in blood smears, suggesting that, as in COVID-19 ARDS patients, endothelial dysfunction may contribute to perpetuating inflammation [55].

1.1.4. Differential diagnoses for MIS-C/A

Emerging evidence suggests that MIS-C patients may be separated into distinct clusters by their main features at presentation [3]. One presentation of MIS-C is in adolescents with high disease burden as evidenced by more organ systems involved, almost universally including cardiac and gastrointestinal systems, and with higher incidence of shock, lymphopenia, and elevated cardiac biomarkers indicating myocarditis [3]. Since the first reports of children developing MIS-C, it was evident that others presented with some of the classic symptoms of the well-recognized childhood illness KD [3,8,9,18]. Further, despite KD being ordinarily incredibly rare in adults, patients with MIS-A have also been reported with KD-like features [4].

1.1.4.1. Kawasaki disease. From its first recognition, the similarities between MIS-C and KD (Table 3), especially severe Kawasaki Shock (KS), have been impossible to overlook. The diagnosis of KD is based on clinical findings and laboratory criteria as defined elsewhere [65–66]. Similar to KD and KS, MIS-C/A does not have a specific diagnostic test. Therefore, highlighting the major discerning symptoms between MIS-C and KD/KS can enrich an understanding of the clinical case definition of MIS-C/A.

While gastrointestinal symptoms tend to dominate the presentation of MIS-C patients, abdominal pain, vomiting and diarrhea are uncommon in conventional KD or KS (i.e., those cases that are not associated with SARS-CoV-2) [67]. Other differences between MIS-C and KD have also started to emerge. Patients with MIS-C are older, on average, than KD patients (mean age 8–9 years versus 2–3 years) and more likely to be non-white and non-Asian [3,9,18]. Obesity may be an underlying medical condition predisposing to MIS-C, which has not been noted in KD [3,9,18]. Children presenting with only one day of fever, which can meet the current case definitions for MIS-C, may never meet criteria for complete KD, which requires 5 days of fever. Incomplete forms of KD including minor laboratory criteria further complicate the diagnostic situation [13], but growing evidence suggests that MIS-C also has distinguishing differences in laboratory abnormalities including more highly elevated C reactive protein and other inflammatory markers (ferritin and D-dimer), more anemia, lymphopenia, and thrombocytopenia [3,8,9,13,18].

Conventional KD patients typically have myocardial edema without ischemia and necrosis of cardiomyocytes [13,65]. Therefore, troponin levels in KD are not highly elevated. On the contrary, cardiac involvement of MIS-C frequently leads to elevated troponin levels and elevated brain natriuretic protein (BNP) or N Terminal-pro BNP (NT-proBNP), with high frequencies of cardiac dysfunction [13–15,18,68]. MIS-C patients also frequently have electrocardiogram changes consistent with myocarditis [13,68]. The frequency of KD patients who present with shock is low, around 5% [65], compared to the high frequency of shock, need for respiratory support, and vasoactive/vasopressor medication use in MIS-C, in which upwards of 80% of patients require intensive care [13–15,68]. Cases of MIS-C can include coronary artery dilation, a hallmark of KD, but this appears to be in a minority of cases [3,8,9,14,15,18]. As long-term outcomes are not yet available, it is not clear if MIS-C patients have any risk of long-term coronary sequelae, but most patients with evidence of myocarditis appear to return to baseline by their first outpatient follow-up [22,23].

1.1.4.2. Other differential considerations. The presentation of MIS-C/A also overlaps with other conditions, making recognition of distinguishing demographic, clinical, laboratory and imaging characteristics vital. A wide range of infectious, inflammatory, and allergic/reactive etiologies must be considered. It is critical to distinguish MIS-C/A from alternative diagnoses as the management can vary significantly. A thorough history, physical examination and laboratory investigation accompanied by high clinical suspicion based on exposure history can provide a degree of clinical certainty.

MIS-C/A shares characteristics with mucocutaneous symptom complexes, particularly staphylococcal and streptococcal toxic shock syndrome (TSS) [3,14–16,69,70]. Fever and shock are predominant features of both syndromes. Both staphylococcal and streptococcal TSS can also present with rash, while conjunctivitis is more common in TSS [71]. Abdominal symptoms are predominant features of MIS-C/A, and profuse prodromal diarrhea followed by hypotension is a common presentation of staphylococcal, although less likely streptococcal, TSS. Cardiac dysfunction is a hallmark of MIS-C/A, but not TSS [3,14–16,69,72]. Additional MIS-C/A symptoms of headache and respiratory symptoms are less likely in TSS [3,15,69].

The rash associated with MIS-C/A is "polymorphic." [8] Therefore, other entities presenting with fever, rash and mucocutaneous features must be considered. Fortunately, other staphylococcal and streptococcal syndromes, including Staphylococcal Scalded Skin Syndrome (SSSS), scarlet fever, and other Group A beta-hemolytic streptococcal infections have features which can be distinguishing. SSSS and other staphylococcal exfoliative toxin syndromes can demonstrate the hallmark Nikolsky sign with desquamation during the acute phase. The rash associated with scarlet fever is typically papular erythroderma ("sandpaper rash") with the Pastia sign. While streptococcal infections can demonstrate a strawberry tongue, as can be seen in MIS-C/A and KD, the lips are usually normal, and the oropharynx demonstrates tonsillar exudate and palatal petechiae.

Table 3
Comparison of MIS-C and KD.

	MIS-C (3,14)	KD (65,67)
Age (mean)	8.5 years	3 years
Fever	+++	+++
Rash	++	+++
Conjunctivitis	++	++
Oromucosal change	++	++
Extremity Change	+/-	+
Cervical LAD	+/-	+
Coronary dilation	+	++
Cardiac dysfunction	++	–
GI symptoms	+++	+
Shock/hypotension	++	+/–
Death	2%	0.17%

MIS-C, multisystem inflammatory syndrome in children;
KD, Kawasaki Disease

Many bacterial infections can present with some features of MIS-C/A, ranging from meningitis to cellulitis, but most of these infections are likely to present with involvement of one organ or organ system rather than the multisystem involvement that characterizes MIS-C/A. Severe systemic bacterial infections that present with fever, rash and shock should be considered in the differential, including leptospirosis and rickettsial disease [73]. Therefore, exposures and geographic setting should be considered when evaluating the patient: water sources and exposures to animals, ticks, and mosquitoes should be determined in patients presenting with concern for MIS-C/A to assess risk for these illnesses.

Common viral infections can mimic some features of MIS-C/A, but it is rare to find complete concordance. Fever is a common manifestation of both viral infections and MIS-C/A. Exanthems are frequently observed in enterovirus, adenovirus, parvovirus, and measles, for example, as well as in MIS-C/A. Conjunctival injection can be seen in measles, adenovirus, hantavirus [74] and rubella. Gastrointestinal symptoms, found in the majority of patients with MIS-C/A, are also commonly associated with adenovirus, enterovirus, rotavirus, and Norwalk virus, to name but a few, but the abdominal pain in MIS-C/A can have a severity similar to acute appendicitis [13]. Further, viral infections, like MIS-C/A, can lead to multisystem organ involvement. Of particular note is Epstein-Barr virus (EBV) which may involve the central nervous system, liver, lungs, and heart. EBV and other viruses can also be the inciting factor in such hyperinflammatory states as HLH with hyperinflammation similar to that observed in MIS-C/A [75].

Cardiac dysfunction has been reported in most cases of MIS-C/A [4,13–15,68]. Myocarditis leading to heart failure can be associated with many viruses, including parvovirus, adenovirus, HIV, influenza, echovirus, coxsackieviruses, EBV, and CMV [76]. In these cases, direct viral toxicity to cardiac myocytes is part of the pathologic process but whether this is true in MIS-C/A is not yet known. The cardiac dysfunction associated with MIS-C/A seems more likely to be transient (“stunning”) with return to normal function in a majority of cases [13].

Some of the cutaneous and systemic manifestations of MIS-C/A also overlap diseases such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) [77], and drug reaction with eosinophilia and systemic symptoms (DRESS) [78], also termed drug-induced hypersensitivity syndrome (DIHS). These entities can be caused by a variety of drugs and, less commonly, by infectious agents. Mucocutaneous involvement and fever are common, as they are in MIS-C/A, but the skin involvement is much more prominent in SJS and TEN with Nikolsky’s sign often being present. The multi-organ involvement that defines MIS-C/A, along with shock, can be seen in each, particularly in DRESS. Generally, these entities can be differentiated by a careful history and, if necessary, by skin biopsy [77,78]. Rapid identification is critical in order to remove offending agents while initiating appropriate treatment.

1.1.5. MIS-C/A after vaccination

MIS-C is a new syndrome in children occurring in temporal association with SARS-CoV-2 infection and has not been previously described in association with any vaccine. To date, MIS-A has not been reported in adult participants of SARS-CoV-2 vaccine trials and few children have thus far been included in these trials. MIS-C overlaps with KD and TSS, which have been reported as AEFIs.

A 2017 systematic review by the Brighton Collaboration [79] identified 27 observational studies and case reports of KD following a range of vaccinations, including diphtheria-tetanus-pertussis (DTP)-containing vaccines, *Haemophilus influenzae* type b (Hib) conjugate vaccine, influenza vaccine, hepatitis B vaccine, 4-component meningococcal serogroup B (4CMenB) vaccine, measles-mumps-rubella (MMR)/MMR-varicella vaccines, pneumococcal conjugate vaccine (PCV), rotavirus vaccine (RV), yellow fever vaccine, and Japanese encephalitis vaccine. The review did not find evidence of an increased risk of KD following any of the above immunizations.

Population-based studies have evaluated for associations between KD and PCV vaccines. An early study did not find an association between the 7-valent PCV (PCV7) and KD [80]. A 2013 Vaccine Safety Datalink study noted a non-statistically significant increased risk of KD after the 13-valent PCV (PCV13) when compared with PCV7 (relative risk 1.94, 95% CI 0.79–4.86) [81]. However, more recent studies found no evidence of an association between KD and PCV13 vaccination in the United States [82], and either PCV (7- or 13-valent) or 4CMenB vaccines in the United Kingdom [83]. A study in Singapore similarly reported that PCV13 was not associated with overall KD, although the authors noted a significant association between PCV13 and complete KD following the first dose of PCV13 [84].

Several large epidemiological studies have not found evidence of an association between KD and RV vaccines [85–87]. A recent study in Taiwan noted that risk of KD was higher after the second dose of RV5 and the first dose of RV1, although the authors suggest that further research is needed [88]. Finally, a study among 220,422 children in China assessed cases of KD after vaccination with oral poliovirus vaccine, diphtheria-tetanus-acellular pertussis (DTaP), Hib, and a combined DTaP-inactivated PV (IPV)-Hib polysaccharide conjugated to tetanus (PRP-T) vaccine [89]. There were no cases of KD within 7 days after vaccination and 2 cases during the 30 days following vaccination (incidences of 7.3 per 100,000 person-years after DTaP and 21.9 per 100,000 person-years after DTaP-IPV//PRP-T).

The clinical spectrum of MIS-C/A also includes shock and multiple organ failure without evidence of bacterial infection. Shock and multiple organ failure have been reported rarely in immunocompromised patients who developed vaccine-associated disease following live varicella, herpes zoster, and yellow fever vaccinations [90–93]. There has also been a case reported of shock and multi-organ failure after adjuvanted H1N1 vaccination in a patient with HIV and rheumatoid arthritis, though a causal association with the vaccine was not confirmed [94].

Though MIS-C/A are distinct from both KD and TSS, they are severe inflammatory conditions. Their pathogenesis is not yet understood, but they appear to be a post-infectious manifestation of COVID-19. Therefore, MIS-C and MIS-A are considered AEFIs of special interest with respect to SARS-CoV-2 vaccines.

1.1.6. Existing case definitions of MIS-C/A

The RCPCH, CDC and WHO case definitions for MIS-C have some distinct variations (Table 1) [7,11,12]. The age of the patients, the length of fever and the requirement or not for SARS-CoV-2 positive testing or exposure are the fundamental differences. The CDC definition also requires hospitalization. At this time, the 5 criteria in the preliminary case definition for MIS-A used by the CDC [4] are the only case definition for MIS-A (Table 1).

1.1.7. Need for a case definition of MIS-C/A

Currently there is no uniformly accepted definition of MIS-C and only a preliminary definition for MIS-A. Vaccines for SARS-CoV-2 are under active development with several starting wide distribution, and so it is not yet known if MIS-C/A can or will occur following vaccination for SARS-CoV-2. Thus far, no reports have been made of MIS-C/A following SARS-CoV-2 vaccination. Therefore, there is an opportunity to enhance the case definitions for MIS-C and MIS-A to allow comparability across trials or surveillance systems, facilitate data interpretation and promote scientific understanding of these clinical syndromes.

The original MIS-C case definitions were created shortly after the recognition of this emerging entity when a limited number of

patients had been reported [8,9]. As cases and cohorts have subsequently been published, a better picture of the clinical presentation, laboratory abnormalities, and imaging and other diagnostic findings in MIS-C has materialized [3,8,13–16,18–20], allowing for refinement of the case definition of MIS-C. Although significantly less data exists for MIS-A, there is extensive clinical and laboratory overlap between the two conditions.

Our current understanding of the immunopathology of SARS-CoV-2 and MIS-C is growing but still limited. It is unclear if MIS-C and MIS-A have similar immunopathology. It has not been determined what triggers MIS-C/A following natural SARS-CoV-2 infection. Further, various types of vaccines for SARS-CoV-2 are in development. This makes it difficult to predict the possibility of MIS-C/A following vaccination. Three potential post-vaccination scenarios need to be considered (Fig. 2). First, patients naïve to SARS-CoV-2 infection may be vaccinated against SARS-CoV-2 and then develop an illness for which they are evaluated for MIS-C/A. Second, patients who have had COVID-19 may subsequently be vaccinated to SARS-CoV-2 and then develop an illness for which they are evaluated for MIS-C/A. Finally, patients who have already been vaccinated to SARS-CoV-2 (whether or not they previously had COVID-19) may then become infected/reinfected with SARS-CoV-2 and then develop an illness for which they are evaluated for MIS-C/A. Notably, as children are often asymptomatic of COVID-19 it may not be possible to know if a child has had a former infection with SARS-CoV-2 prior to vaccination. Further, in many locations testing is not readily accessible for all potential cases.

1.2. Methods for the development of the case definition and guidelines for data collection, analysis, and presentation for MIS-C/A as an adverse event following immunization

Following the Brighton Collaboration process (https://brighton-collaboration.us/about/the-brighton-method/), the Brighton Collaboration *MIS-C Working Group* was formed in August 2020 and included members of clinical, academic, public health, and pharmacovigilance backgrounds.

To guide the decision-making for the case definition and guidelines, literature searches were performed using PubMed, including the terms "multisystem inflammatory syndrome in children" and "vaccine". The search resulted in the identification of early cohorts of MIS-C. Several large cohorts were initially reviewed in detail (Tables 2a and 2b) in order to identify clinical features, laboratory results and diagnostic findings of MIS-C and data was continually compared to cohorts that were published during the Working Group activities. The authors also contributed from their personal knowledge of the presentation and evaluation of MIS-C/A cases in clinical practice. The CDC MMWR report of MIS-A was used as the most up to date source of information on this emerging entity.

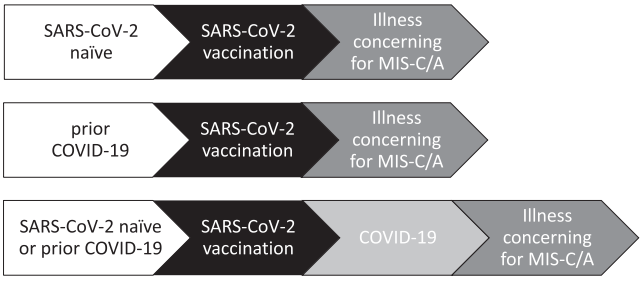

Fig. 2. Potential post-vaccination scenarios.

1.3. Rationale for selected decisions about the case definition of MIS-C/A as an adverse event following immunization

1.3.1. The terms MIS-C and MIS-A

In the literature, MIS-C is also called Pediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS), and multisystem inflammatory syndrome in children and adolescents with COVID-19. No alternative terms have been described for MIS-A. The Working Group created a standardized MIS-C/A case definition that allows for various levels of diagnostic certainty so that it may be applicable in all resource settings. Within the case definition context the three diagnostic levels must not be misunderstood as reflecting different grades of clinical severity.

1.3.2. Term(s) related to MIS-C/A

The Working Group was careful to consider the infectious and inflammatory disorders with overlapping clinical, laboratory and diagnostic findings with MIS-C/A when creating the case definition. This included KD, KS, TSS, MAS and HLH.

1.3.3. Formulating a case definition that reflects diagnostic certainty: weighing specificity versus sensitivity

It needs to be re-emphasized that the grading of definition levels is entirely about diagnostic certainty, not clinical severity of MIS-C/A. Thus, a clinically very severe case may appropriately be classified as Level 2 or 3 rather than Level 1, based on the information available to ascertain a diagnosis. Detailed information about the severity of the event should additionally always be recorded, as specified by the data collection guidelines (Appendix A).

The number of symptoms and/or signs that will be documented for each case may vary considerably. The case definition has been formulated such that the Level 1 definition is highly specific for the condition. As maximum specificity normally implies a loss of sensitivity, two additional diagnostic levels have been included in the definition, offering a stepwise increase of sensitivity from Level 1 down to Level 3, while retaining an acceptable level of specificity at all levels. In this way it is hoped that all possible cases of MIS-C/A can be captured.

1.3.4. Rationale for individual criteria or decisions made related to the case definition

The numerous cases and cohorts of MIS-C patients that have been published subsequent to the creation of the original case definitions have provided a clearer picture of the clinical presentation, laboratory results and other diagnostic findings in MIS-C and allowed for refinement. MIS-A has only recently been recognized and must be distinguished from cases of primary COVID-19-related hyperinflammation [2].

1.3.4.1. Presentation. Patients with febrile multisystem hyperinflammation following SARS-CoV-2 infection, exposure or vaccination may have MIS-C if <21 years of age or MIS-A if ≥21 years. The Working Group focused on features of MIS-C in the development of the case definition given its greater prevalence and larger amount of information available. Due to the limited current reports of MIS-A and the overlapping features with hyperinflammation in adult primary COVID-19 infection, special care to exclude significant pulmonary disease has been included in the case definition. Further, to allow for a uniform case definition for patients of all ages, the longer proposed time frame for onset of MIS-A, 12 weeks post-infection, is used, although MIS-C cases predominantly present 4–6 weeks following SARS-CoV-2 infection/exposure.

1.3.4.2. Clinical findings. The Working Group elected to highlight the mucocutaneous and gastrointestinal findings of MIS-C/A under clinical features along with the tendency for shock/hypotension as these are clearly present in a majority of patients [3,4,8,13–16]. Neurologic findings are included, not because of a high frequency in MIS-C/A, but because they are less likely to be present in MIS-C/A mimics. Including all of the mucocutaneous findings under one clinical category will reduce the likelihood of overlap with a case of KD (see also Section 1.3.7). Cardiac and hematologic involvement are included under laboratory evidence of disease as measurable features and so are not double counted under clinical features (note: in Level 3 a clinical cardiac feature is included when measures of disease activity are unavailable). Renal involvement is not included, as it is not a common or distinguishing finding in MIS-C/A. The Working Group did not include respiratory features in the clinical findings. A fraction of MIS-C patients do present with respiratory features, but they are typically mild [3,14,15]. Importantly, severe respiratory symptoms exclude a diagnosis of MIS-A under the preliminary CDC case definition. Therefore, we did include a comment that having mild respiratory features does not exclude a case of MIS-C/A but that severe respiratory symptoms lead to a case being excluded.

1.3.4.3. Laboratory findings. It is now clear that neutrophilia, lymphopenia and thrombocytopenia are commonly found in MIS-C/A and these features are included as measures of disease activity along with elevations in troponin and BNP/NT-proBNP [3,4,8,13–16]. These measures account for manifestations of the hematologic and cardiac systems. Laboratory evidence of inflammation is indicated by elevations of CRP, ESR, ferritin and procalcitonin. This is not because other markers of inflammation (like D-dimer, IL-6 or LDH) are not elevated in MIS-C/A, but because in the experience of the Working Group, these other features are not isolated findings without elevations of the CRP and/or ESR and/or ferritin and/or procalcitonin. It is becoming more clear that positive serology for SARS-CoV-2 is a finding in the majority of MIS-C/A patients [3,4]. However, the Working Group elected to keep laboratory evidence of SARS-CoV-2 nucleic acid or antigen among the laboratory findings since the exact timing of exposure to SARS-CoV-2 and the development of MIS-C/A is still being investigated and antibody testing is not routine in many locations.

1.3.4.4. Other diagnostic findings. When selecting the echocardiography findings for the case definition of MIS-C/A the Working Group merged a combination of the published MIS-C literature [3,4,8,13–16], highlighting the findings representative of myocarditis, with the findings included when diagnosing a case of incomplete KD [65]. The EKG findings included in the case definition are those associated with myocarditis.

1.3.4.5. Other rationale. The Working Group also felt that incomplete documentation of fever should not exclude a case from consideration for MIS-C/A and so incorporated, at lower levels of certainty, subjective fever as a feature. The Working Group also felt strongly that consideration for MIS-C/A is necessary in all resource settings and this is why the lowest level of certainty definition has features which can be obtained by history and physical examination alone.

1.3.5. Influence of treatment on fulfilment of case definition

The Working Group decided against using "treatment" or "treatment response" towards fulfillment of the MIS-C/A case definition despite the generally prompt response of MIS-C/A patients to immunomodulation. A treatment response or its failure is not in itself diagnostic, and may depend on variables like clinical status, time to treatment, and other clinical parameters.

1.3.6. Timing post immunization

Specific time frames for onset of symptoms of MIS-C/A following immunization are not included. The case definition defines a clinical entity following exposure to SARS-CoV-2. Whether this clinical entity can or will develop following vaccination is unknown, and therefore, a time interval between immunization and the onset of the event cannot be part of the definition. It seems reasonable to predict that vaccine related MIS-C/A, should it exist, would follow a timeline similar to MIS-C/A after natural infection, i.e., presenting within 4–6 weeks after vaccination for MIS-C and up to 12 weeks after vaccination in MIS-A.

A definition designed to be a suitable tool for testing causal relationships requires ascertainment of the outcome (e.g., MIS-C/A) independent from the exposure (e.g., immunization). Therefore, to avoid selection bias, a restrictive time interval from immunization to onset of MIS-C/A should not be an integral part of the case definition. Instead, where feasible, details of this interval should be assessed and reported as described in the data collection guidelines.

Further, MIS-C/A can occur outside the controlled setting of a clinical trial or hospital. In some settings it may be impossible to obtain a clear timeline of the event, particularly in less developed or rural settings. In order to avoid selecting against such cases, the case definition avoids setting arbitrary time frames.

1.3.7. Differentiation from other (similar/associated) disorders

The differential diagnoses for MIS-C/A and comments on distinguishing features are described in detail in Section 1.1.4 and include KD, KS, HLH, TSS and a variety of other entities, particularly ones which cause myocarditis or hyperinflammation [95]. One of the critical components of the case definition is that it is only to be applied when there is no clear alternative diagnosis for the reported event to account for the combination of symptoms, meaning that these other entities would be excluded for a case to meet the case definition. Notably, the case definition has been structured to reduce the overlap of MIS-C and KD in the clinical features. The more common overlapping clinical features between the two, namely rash, oromucosal changes, conjunctivitis, and extremity changes, are included in one clinical feature. To meet the case definition an additional clinical feature of gastrointestinal symptoms, shock/hypotension or neurologic symptoms would need to be present, which are much less common in KD. Finally, the case definition includes the requirement for a personal history or exposure history to SARS-CoV-2 or a vaccine against SARS-CoV-2, making it more likely to define MIS-C/A than other similar disorders.

1.4. Guidelines for data collection, analysis and presentation

The case definition is accompanied by guidelines which are structured according to the steps of conducting a clinical trial, i.e., data collection, analysis and presentation (Appendix A [96–100]). Neither case definition nor guidelines are intended to guide or establish criteria for management of ill infants, children, or adults.

1.5. Periodic review

Similar to all Brighton Collaboration case definitions and guidelines, review of the definition with its guidelines is planned on a regular basis (i.e., every three to five years) or more often if needed.

2. Case definition of MIS-C/A

See Fig. 3 and Table 4.

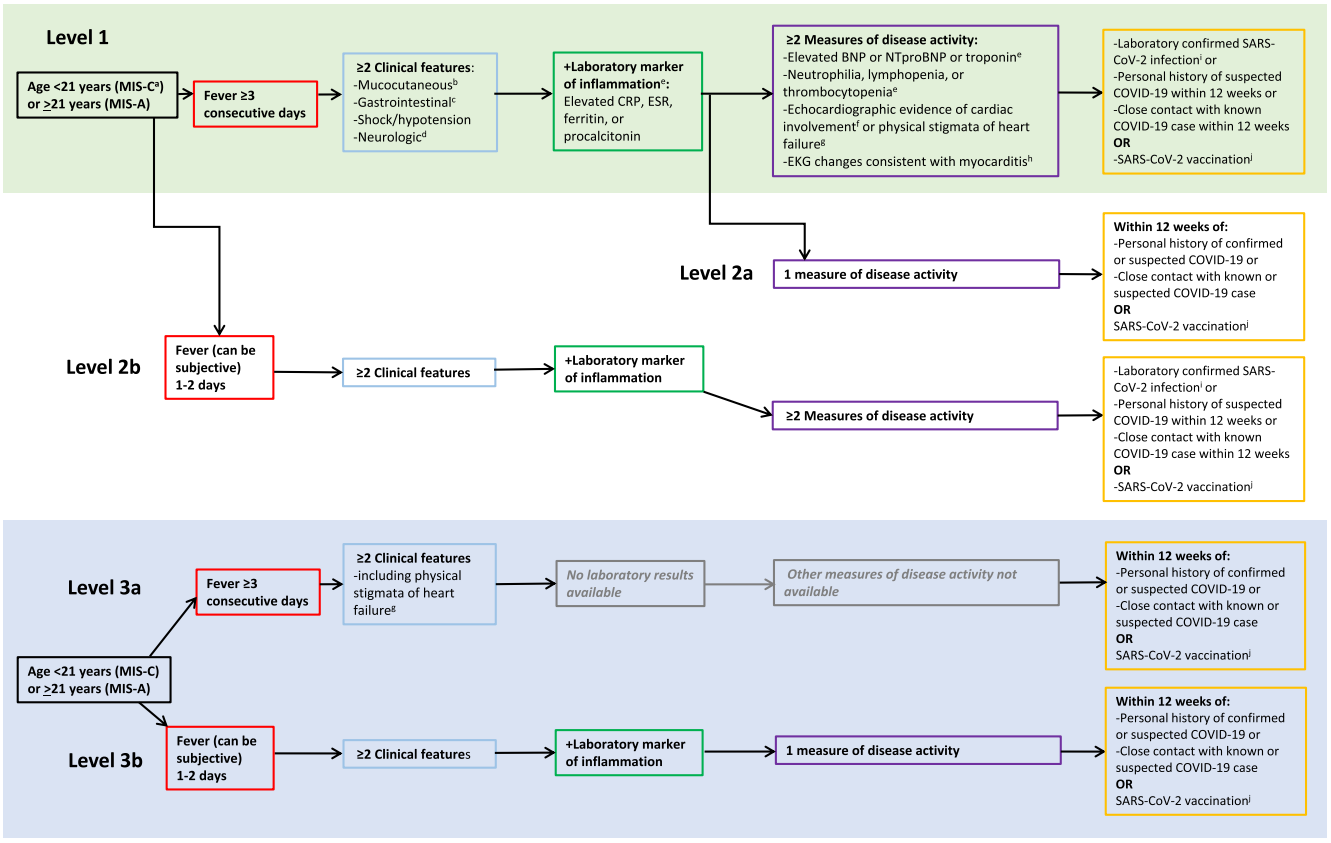

Fig. 3. Algorithm for utilization of the case definition for MIS-C/A.

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

Level 1 of Diagnostic Certainty – Definitive Case
Age < 21 years (MIS-C[a]) *OR* ≥ 21 years (MIS-A) **AND** Fever ≥ 3 consecutive days **AND** 2 or more of the following clinical features: -Mucocutaneous (rash, erythema or cracking of the lips/mouth/pharynx, bilateral nonexudative conjunctivitis, erythema/edema of the hands and feet) -Gastrointestinal (abdominal pain, vomiting, diarrhea) -Shock/hypotension -Neurologic (altered mental status, headache, weakness, paresthesias, lethargy) **AND** Laboratory evidence of inflammation including any of the following: -Elevated CRP, ESR, ferritin, *or* procalcitonin[b] **AND** 2 or more measures of disease activity: -Elevated BNP *or* NT-proBNP *or* troponin[b] -Neutrophilia, lymphopenia, *or* thrombocytopenia[b] -Evidence of cardiac involvement by echocardiography[c] *or* physical stigmata of heart failure[d] -EKG changes consistent with myocarditis or myo-pericarditis[e] **AND** Laboratory confirmed SARS-CoV-2 infection[f] *OR* Personal history of confirmed COVID-19 within 12 weeks *OR* Close contact with known COVID-19 case within 12 weeks *OR* Following SARS-CoV-2 vaccination[g]. **Level 2 of Diagnostic Certainty – Probable Case** **Level 2a** Same criteria as Level 1 except: **1** measure of disease activity **AND** Within 12 weeks of a personal history of known or strongly suspected COVID-19

Table 4 (*continued*)

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

FOOT NOTES:

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

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

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

[c] echocardiographic signs: dysfunction, wall motion abnormality, coronary abnormality (dilation, aneurysm, echobrightness, lack of distal tapering), valvular regurgitation, pericardial effusion

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

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

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

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

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: NP Klein has received research support from Pfizer for COVID-19 vaccine clinical trials and from Pfizer, Merck, GSK, Sanofi Pasteur and Protein Science (now Sanofi Pasteur) for unrelated studies. FM Munoz is a consultant for the Coalition for Epidemic Preparedness Innovations (CEPI) for the development of Brighton Collaboration Case Definitions for the Safety Platform for Emergency vACcines (SPEAC) Project. The following authors have no conflict of interests to disclose: TP Vogel, KA Top, C Karatzios, DC Hilmers, LI Tapia, P Moceri, L Giovannini-Chami, N Wood, R Chandler, EP Schlaudecker, MC Poli, E Muscal. The findings, opinions and assertions contained in the consensus document are those of the individual scientific professional members of the working group. They do not necessarily represent the official positions of each participant's organization (e.g., government, university or corporation). Specifically, the findings and conclusions in the paper are those of the authors and do not necessarily represent the views of their respective institutions.

Acknowledgements

The authors are grateful for the support and helpful comments provided by the Brighton Collaboration and SPEAC Steering Committee (Barbara Law) and reference peer review group, as well as other experts consulted as part of the process, including Drs. Marco Cattalini and Andrea Taddio for sharing unpublished cohort information. The authors are also grateful to Matt Dudley of the

Brighton Collaboration Secretariat for revisions of the final document. We acknowledge the financial support provided by the Coalition for Epidemic Preparedness Innovations (CEPI) for our work under a service order entitled Safety Platform for Emergency vACcines (SPEAC) Project with the Brighton Collaboration, a program of the Task Force for Global Health, Decatur, GA.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.01.054.

References

[1] Mehta NS et al. SARS-CoV-2 (COVID-19): What do we know about children? A systematic review. Clin Infect Dis 2020.
[2] Parri N, Lenge M, Buonsenso D. Children with Covid-19 in pediatric emergency departments in Italy. N Engl J Med 2020;383(2):187–90.
[3] Godfred-Cato S et al. COVID-19-associated multisystem inflammatory syndrome in children - United States, March-July 2020. MMWR Morb Mortal Wkly Rep 2020;69(32):1074–80.
[4] Morris SB et al. Case series of multisystem inflammatory syndrome in adults associated with SARS-CoV-2 infection - United Kingdom and United States, March-August 2020. MMWR Morb Mortal Wkly Rep 2020;69(40):1450–6.
[5] Weatherhead JE et al. Inflammatory syndromes associated with SARS-CoV-2 infection: dysregulation of the immune response across the age spectrum. J Clin Invest 2020;130(12):6194–7.
[6] Paediatric Intensive Care Society. PICS Statement: Increased number of reported cases of novel presentation of multisystem inflammatory disease. 2020 27 April 2020; Available from: https://pccsociety.uk/wp-content/uploads/2020/04/PICS-statement-re-novel-KD-C19-presentation-v2-27042020.pdf.
[7] Royal College of Paediatrics and Child Health. Guidance - Paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS). 2020; Available from: https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19-pims.
[8] Verdoni L et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020;395(10239):1771–8.
[9] Riphagen S et al. Hyperinflammatory shock in children during COVID-19 pandemic. The Lancet 2020;395(10237):1607–8.
[10] New York City Health Department. 2020 Health Alert #13: Pediatric Multi-System Inflammatory Syndrome Potentially Associated with COVID-19. 2020 May 4, 2020; Available from: https://www1.nyc.gov/assets/doh/downloads/pdf/han/alert/2020/covid-19-pediatric-multi-system-inflammatory-syndrome.pdf.
[11] Centers for Disease Control and Prevention. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). 2020 March 27, 2020; Available from: https://emergency.cdc.gov/han/2020/han00432.asp.
[12] World Health Organization. Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19. 2020 May 15, 2020; Available from: https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19.
[13] Belhadjer Z et al. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. Circulation 2020.
[14] Feldstein LR et al. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med 2020;383(4):334–46.
[15] Dufort EM et al. Multisystem inflammatory syndrome in children in New York State. N Engl J Med 2020;383(4):347–58.
[16] Davies P et al. Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: a multicentre observational study. Lancet Child Adolesc Health 2020;4(9):669–77.
[17] Grimaud M et al. Acute myocarditis and multisystem inflammatory emerging disease following SARS-CoV-2 infection in critically ill children. Ann Intensive Care 2020;10(1):69.
[18] Whittaker E et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA 2020;324(3):259–69.
[19] Cheung EW et al. Multisystem inflammatory syndrome related to COVID-19 in previously healthy children and adolescents in New York City. JAMA 2020;324(3):294–6.
[20] Cattalini M et al. Are Kawasaki disease and pediatric multi-inflammatory syndrome two distinct entities? results from a multicenter survey during SARS-CoV-2 epidemic in Italy. SSRN Electronic J 2020.
[21] Belot A et al. SARS-CoV-2-related paediatric inflammatory multisystem syndrome, an epidemiological study, France. Euro Surveill 2020;25(22). 1 March to 17 May 2020.
[22] Jhaveri S et al. Longitudinal echocardiographic assessment of coronary arteries and left ventricular function following multisystem inflammatory syndrome in children. J Pediatr 2020.
[23] Minocha PK, et al. Cardiac findings in pediatric patients with multisystem inflammatory syndrome in children associated with COVID-19. Clin Pediatr (Phila), 2020: p. 9922820961771.
[24] St John AL, Rathore APS. Early insights into immune responses during COVID-19. J Immunol 2020;205(3):555–64.
[25] Most ZM et al. The striking similarities of multisystem inflammatory syndrome in children and a myocarditis-like syndrome in adults: overlapping manifestations of COVID-19. Circulation 2020.
[26] Zhou P et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579(7798):270–3.
[27] Sungnak W et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Nat Med 2020;26(5):681–7.
[28] Walls AC et al. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell 2020;181(2):281–292.e6.
[29] Vabret N et al. Immunology of COVID-19: current state of the science. immunity 2020;52(6):910–41.
[30] Birra D et al. COVID 19: a clue from innate immunity. Immunol Res 2020;68(3):161–8.
[31] Blanco-Melo D et al. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. Cell 2020;181(5):1036–1045.e9.
[32] Hadjadj J et al. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. Science 2020;369(6504):718–24.
[33] Bastard P et al. Auto-antibodies against type I IFNs in patients with life-threatening COVID-19. Science 2020.
[34] Zhang Q et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. Science 2020.
[35] Zhou Y et al. Pathogenic T cells and inflammatory monocytes incite inflammatory storm in severe COVID-19 patients. Natl Sci Rev 2020: nwaa041.
[36] Guo C et al. Single-cell analysis of two severe COVID-19 patients reveals a monocyte-associated and tocilizumab-responding cytokine storm. Nat Commun 2020;11(1):3924.
[37] Maucourant C et al. Natural killer cell immunotypes related to COVID-19 disease severity. Sci Immunol 2020;5(50).
[38] Garvin MR et al. A mechanistic model and therapeutic interventions for COVID-19 involving a RAS-mediated bradykinin storm. Elife 2020;9.
[39] Wilk AJ et al. A single-cell atlas of the peripheral immune response in patients with severe COVID-19. Nat Med 2020;26(7):1070–6.
[40] Long QX et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nat Med 2020;26(8):1200–4.
[41] Liu L et al. Potent neutralizing antibodies against multiple epitopes on SARS-CoV-2 spike. Nature 2020;584(7821):450–6.
[42] Zhang JJ et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy 2020;75(7):1730–41.
[43] Kuri-Cervantes L et al. Comprehensive mapping of immune perturbations associated with severe COVID-19. Sci Immunol 2020;5(49).
[44] Zhao J et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. Clin Infect Dis 2020.
[45] Iyer AS et al. Persistence and decay of human antibody responses to the receptor binding domain of SARS-CoV-2 spike protein in COVID-19 patients. Sci Immunol 2020;5(52).
[46] Woodruff M., et al. Critically ill SARS-CoV-2 patients display lupus-like hallmarks of extrafollicular B cell activation. medRxiv 2020.
[47] Chen G et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest 2020;130(5):2620–9.
[48] Gruber CN et al. Mapping systemic inflammation and antibody responses in multisystem inflammatory syndrome in children (MIS-C). Cell 2020.
[49] Sekine T et al. Robust T cell immunity in convalescent individuals with asymptomatic or mild COVID-19. Cell 2020;183(1):158–168.e14.
[50] Huang H et al. High levels of circulating GM-CSF(+)CD4(+) T cells are predictive of poor outcomes in sepsis patients: a prospective cohort study. Cell Mol Immunol 2019;16(6):602–10.
[51] Ng OW et al. Memory T cell responses targeting the SARS coronavirus persist up to 11 years post-infection. Vaccine 2016;34(17):2008–14.
[52] Tang F et al. Lack of peripheral memory B cell responses in recovered patients with severe acute respiratory syndrome: a six-year follow-up study. J Immunol 2011;186(12):7264–8.
[53] Chandrashekar A et al. SARS-CoV-2 infection protects against rechallenge in rhesus macaques. Science 2020;369(6505):812–7.
[54] Lee PY et al. Immune dysregulation and multisystem inflammatory syndrome in children (MIS-C) in individuals with haploinsufficiency of SOCS1. J Allergy Clin Immunol 2020.
[55] Diorio C et al. Multisystem inflammatory syndrome in children and COVID-19 are distinct presentations of SARS-CoV-2. J Clin Invest 2020.
[56] Yeung RS. Kawasaki disease: update on pathogenesis. Curr Opin Rheumatol 2010;22(5):551–60.
[57] Newburger JW, Takahashi M, Burns JC. Kawasaki disease. J Am Coll Cardiol 2016;67(14):1738–49.

[58] Rowley AH. Multisystem inflammatory syndrome in children and Kawasaki disease: two different illnesses with overlapping clinical features. J Pediatr 2020;224:129–32.
[59] Abe M et al. IL-1-dependent electrophysiological changes and cardiac neural remodeling in a mouse model of Kawasaki disease vasculitis. Clin Exp Immunol 2020;199(3):303–13.
[60] Consiglio CR et al. The immunology of multisystem inflammatory syndrome in children with COVID-19. Cell 2020.
[61] Anderson EM, et al. SARS-CoV-2 antibody responses in children with MIS-C and mild and severe COVID-19. medRxiv, 2020: p. 2020.08.17.20176552.
[62] Weisberg SP, et al. Antibody responses to SARS-CoV2 are distinct in children with MIS-C compared to adults with COVID-19. medRxiv 2020.
[63] Vella L, et al., Deep Immune Profiling of MIS-C demonstrates marked but transient immune activation compared to adult and pediatric COVID-19. medRxiv: the preprint server for health sciences, 2020: p. 2020.09.25.20201863.
[64] Carter MJ et al. Peripheral immunophenotypes in children with multisystem inflammatory syndrome associated with SARS-CoV-2 infection. Nat Med 2020.
[65] McCrindle BW et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation 2017;135(17):e927–99.
[66] Ayusawa M, et al. Revision of diagnostic guidelines for Kawasaki disease (the 5th revised edition). Pediatr Int 2005;47(2): 232–4.
[67] Rowley AH, Shulman ST, Arditi M. Immune pathogenesis of COVID-19–related multisystem inflammatory syndrome in children. J Clin Investig 2020;130(11).
[68] Niaz T et al. Role of a pediatric cardiologist in the COVID-19 pandemic. Pediatr Cardiol 2020.
[69] Moraleda C et al. Multi-inflammatory syndrome in children related to SARS-CoV-2 in Spain. Clin Infect Dis 2020.
[70] Lee PY et al. Distinct clinical and immunological features of SARS-CoV-2-induced multisystem inflammatory syndrome in children. J Clin Invest 2020.
[71] Mucocutaneous symptom complexes. In: Long S, Pickering L, Prober C, (editors.) Principles and Practice of Pediatric Infectious Diseases. Elsevier; 2012.
[72] Jain S et al. Multisystem inflammatory syndrome in children with COVID-19 in Mumbai, India. Indian Pediatr 2020.
[73] Hechemy KE et al. A century of rickettsiology: emerging, reemerging rickettsioses, clinical, epidemiologic, and molecular diagnostic aspects and emerging veterinary rickettsioses: an overview. Ann N Y Acad Sci 2006;1078:1–14.
[74] Duchin JS et al. Hantavirus pulmonary syndrome: a clinical description of 17 patients with a newly recognized disease. The Hantavirus Study Group. N Engl J Med 1994;330(14):949–55.
[75] Marsh RA. Epstein-Barr virus and hemophagocytic lymphohistiocytosis. Front Immunol 2017;8:1902.
[76] Schultz JC et al. Diagnosis and treatment of viral myocarditis. Mayo Clin Proc 2009;84(11):1001–9.
[77] Hsu DY et al. Pediatric Stevens-Johnson syndrome and toxic epidermal necrolysis in the United States. J Am Acad Dermatol 2017;76(5):811–817.e4.
[78] Cacoub P et al. The DRESS syndrome: a literature review. Am J Med 2011;124 (7):588–97.
[79] Phuong LK et al. Kawasaki disease and immunisation: a systematic review. Vaccine 2017;35(14):1770–9.
[80] Center KJ et al. Lack of association of Kawasaki disease after immunization in a cohort of infants followed for multiple autoimmune diagnoses in a large, phase-4 observational database safety study of 7-valent pneumococcal conjugate vaccine: lack of association between Kawasaki disease and seven-valent pneumococcal conjugate vaccine. Pediatr Infect Dis J 2009;28 (5):438–40.
[81] Tseng HF et al. Postlicensure surveillance for pre-specified adverse events following the 13-valent pneumococcal conjugate vaccine in children. Vaccine 2013;31(22):2578–83.
[82] Baker MA et al. Kawasaki disease and 13-valent pneumococcal conjugate vaccination among young children: a self-controlled risk interval and cohort study with null results. PLoS Med 2019;16(7):e1002844.
[83] Stowe J et al. The risk of Kawasaki disease after pneumococcal conjugate & meningococcal B vaccine in England: a self-controlled case-series analysis. Vaccine 2020;38(32):4935–9.
[84] Yung CF et al. Kawasaki Disease following administration of 13-valent pneumococcal conjugate vaccine in young children. Sci Rep 2019;9(1):14705.
[85] Loughlin J et al. Postmarketing evaluation of the short-term safety of the pentavalent rotavirus vaccine. Pediatr Infect Dis J 2012;31(3):292–6.
[86] Layton JB et al. Rotavirus vaccination and short-term risk of adverse events in US infants. Paediatr Perinat Epidemiol 2018;32(5):448–57.
[87] Hoffman V et al. Safety study of live, oral human rotavirus vaccine: a cohort study in United States health insurance plans. Hum Vaccin Immunother 2018;14(7):1782–90.
[88] Huang WT et al. Intussusception and Kawasaki disease after rotavirus vaccination in Taiwanese infants. Vaccine 2020;38(40):6299–303.
[89] Huang K et al. Incidence rates of health outcomes of interest among Chinese children exposed to selected vaccines in Yinzhou Electronic Health Records: a population-based retrospective cohort study. Vaccine 2020;38(18):3422–8.
[90] Gershman MD et al. Viscerotropic disease: case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 2012;30(33):5038–58.
[91] Italiano CM et al. Prolonged varicella viraemia and streptococcal toxic shock syndrome following varicella vaccination of a health care worker. Med J Aust 2009;190(8):451–3.
[92] Costa E et al. Fatal disseminated varicella zoster infection following zoster vaccination in an immunocompromised patient. BMJ Case Rep 2016;2016.
[93] Schrauder A et al. Varicella vaccination in a child with acute lymphoblastic leukaemia. Lancet 2007;369(9568):1232.
[94] De Nardo P et al. Septic shock after seasonal influenza vaccination in an HIV-infected patient during treatment with etanercept for rheumatoid arthritis: a case report. Clin Vaccine Immunol 2013;20(5):761–4.
[95] Henderson LA et al. On the alert for cytokine storm: immunopathology in COVID-19. Arthritis Rheumatol 2020;72(7):1059–63.
[96] Singh J. International conference on harmonization of technical requirements for registration of pharmaceuticals for human use. J Pharmacol Pharmacother 2015;6(3):185–7.
[97] The Council for International Organizations of Medical Sciences. CIOMS I FORM. 2020; Available from: https://cioms.ch/cioms-i-form/.
[98] CONSORT Website. Available from: http://www.consort-statement.org/.
[99] Moher D et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet 1999;354(9193):1896–900.
[100] Stroup DF et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283(15):2008–12.

APPENDIX A

GUIDELINES FOR DATA COLLECTION, ANALYSIS AND PRESENTATION OF MIS-C/A

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

1.1. Data collection

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

The 43 guidelines below have been developed to address data elements for the collection of adverse event information as specified in general drug safety guidelines by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use [96], and the form for reporting of drug adverse events by the Council for International Organizations of Medical Sciences [97]. These data elements include an identifiable reporter and patient, one or more prior immunizations, and a detailed description of the adverse event, in this case, of MIS-C/A following immunization. The additional guidelines have been developed as guidance for the collection of additional information to allow for a more comprehensive understanding of MIS-C/A following immunization.

1.1.1. Source of information/reporter

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

1) Date of report.

2) Name and contact information of person reporting[1] and/or diagnosing MIS-C/A as specified by country-specific data protection law.

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

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

1.1.2. Vaccinee/Control

1.1.2.1. Demographics

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

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

6) Date of birth, age, sex, race and ethnicity.

7) For infants: gestational age and birth weight.

1.1.2.2. Clinical and immunization history

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

8) Past medical history, including hospitalizations, underlying diseases/disorders, pre-immunization signs and symptoms including identification of indicators for, or the absence of, a history of allergy to vaccines, vaccine components or medications; food allergy; allergic rhinitis; eczema; asthma. A prior history of post-infectious inflammatory conditions should be collected.

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

10) Immunization history (i.e., previous immunizations and any AEFI), in particular occurrence of an inflammatory syndrome similar to MIS-C/A (e.g. KD) after a previous immunization.

1.1.3. Details of the immunization

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

11) Date and time of immunization(s).

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

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

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

15) Needle length and gauge.

1.1.4. The adverse event

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

Specifically, document:

17) Clinical description of signs and symptoms of MIS-C/A, and if there was medical confirmation of the event (i.e. patient seen by physician).

18) Date/time of onset[2], first observation[3] and diagnosis[4], end of episode[5] and final outcome[6].

19) Concurrent signs, symptoms, and diseases.

20) Measurement/testing
- Values and units of routinely measured parameters (e.g., temperature, blood pressure, respiratory rate)—in particular those indicating the severity of the event (e.g., respiratory failure, heart failure, shock, etc.);
- Method of measurement (e.g., type of thermometer, oral or other route, duration of measurement, etc.);
- Results of laboratory examinations, surgical and/or pathological findings and diagnoses if present.
- If echocardiography or electrocardiography has been done please include complete reports of all available studies.

21) Treatment given for MIS-C/A, especially corticosteroids, intravenous immunoglobulin, anti-viral medications (e.g., remdesivir), aspirin or other anti-platelet agent, anti-coagulation (e.g., enoxaparin), and/or anti-cytokine biologic immunomodulator. Specify dosing and duration.

22) Outcome[6] at last observation.

23) Objective clinical evidence supporting classification of the event as "serious" [7].

24) Exposures other than the immunization 24 hours before and after immunization (e.g. food, environmental) considered potentially relevant to the reported event.

1.1.5. Miscellaneous/General

25) The duration of surveillance for MIS-C/A should be predefined based on
- Biologic characteristics of the vaccine e.g., live attenuated versus inactivated component vaccines;
- Biologic characteristics of the vaccine-targeted disease;
- Biologic characteristics of MIS-C/A including patterns identified in previous trials (e.g., early-phase trials); and
- Biologic characteristics of the vaccinee (e.g., nutrition, underlying disease like immunocompromising illness).

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

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

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

29) Investigators of patients with MIS-C/A should provide guidance to reporters to optimize the quality and completeness of information provided.

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

1.2. Data analysis

The following guidelines represent a desirable standard for analysis of data on MIS-C/A to allow for comparability of data, and are recommended as an addition to data analyzed for the specific study question and setting.

31) Reported events should be classified in one of the following 5 categories including the 3 levels of diagnostic certainty. Events that meet the case definition should be classified according to the levels of diagnostic certainty as specified in the case definition. Events that do not meet the case definition should be classified in the additional categories for analysis.

Event classification in 5 categories[8]

Event meets case definition
1) Level 1: *Criteria as specified in the MIS-C/A case definition*
2) Level 2: *Criteria as specified in the MIS-C/A case definition*
3) Level 3: *Criteria as specified in the MIS-C/A case definition*

Event does not meet case definition
Additional categories for analysis
4) Reported MIS-C/A with insufficient evidence to meet the case definition[9]
5) Not a case of MIS-C/A

32) The interval between immunization and reported MIS-C/A could be defined as the date/time of immunization to the date/time of onset[2] of the first symptoms and/or signs consistent with the definition. If few cases are reported, the concrete time course could be analyzed for each; for a large number of cases, data can be analyzed in the following increments:

Subjects with MIS-C/A by Interval to Presentation

Interval*	Number (%)
< 12 weeks after immunization	
12 weeks – <12 months after immunization	
12 – < 24 months after immunization	
12 month increments thereafter	
TOTAL	

33) The duration of a possible MIS-C/A case could be analyzed as the interval between the date/time of onset[1] of the first symptoms and/or signs consistent with the definition and the end of episode[5] and/or final outcome[6]. Whatever start and ending are used, they should be used consistently within and across study groups.

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

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

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

1.3. Data presentation

These guidelines represent a desirable standard for the presentation and publication of data on MIS-C/A following immunization to allow for comparability of data, and are recommended as an addition to data presented for the specific study question and setting. Additionally, it is recommended to refer to existing general guidelines for the presentation and publication of randomized controlled trials, systematic reviews, and meta-analyses of observational studies in epidemiology (e.g. statements of Consolidated Standards of Reporting Trials (CONSORT) [98], of Improving the quality of reports of meta-analyses of randomized controlled trials (QUOROM) [99], and of Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [100], respectively).

37) All reported events of MIS-C/A should be presented according to the categories listed in guideline 31.

38) Data on possible MIS-C/A events should be presented in accordance with data collection guidelines 1-24 and data analysis guidelines 31-36.

39) Terms to describe MIS-C/A such as “low-grade”, “mild”, “moderate”, “high”, “severe” or “significant” are highly subjective, prone to wide interpretation, and should be avoided, unless clearly defined.

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

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

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

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

43) Any publication of data on MIS-C/A should include a detailed description of the methods used for data collection and analysis as possible. It is essential to specify:

- The study design;
- The method, frequency and duration of monitoring for MIS-C/A;
- The trial profile, indicating participant flow during a study including dropouts and withdrawals to indicate the size and nature of the respective groups under investigation;
- The type of surveillance (e.g., passive or active surveillance);
- The characteristics of the surveillance system (e.g., population served, mode of report solicitation);
- The search strategy in surveillance databases;
- Comparison group(s), if used for analysis;
- The instrument of data collection (e.g., standardized questionnaire, diary card, report form);
- Whether the day of immunization was considered “day one” or “day zero” in the analysis;
- Whether the date of onset[2] and/or the date of first observation[3] and/or the date of diagnosis[4] was used for analysis; and
- Use of this case definition for MIS-C/A, in the abstract or methods section of a publication[11].

Notes for guidelines

[1]If the reporting center is different from the vaccinating center, appropriate and timely communication of the adverse event should occur.
[2]The date and/or time of onset is defined as the time post immunization, when the first sign or symptom indicative for MIS-C/A occurred. This may only be possible to determine in retrospect.
[3]The date and/or time of first observation of the first sign or symptom indicative for MIS-C/A can be used if date/time of onset is not known.
[4]The date of diagnosis of an episode is the day post immunization when the event met the case definition at any level.
[5]The end of an episode is defined as the time the event no longer meets the case definition at the lowest level of the definition.
[6]e.g. recovery to pre-immunization health status, spontaneous resolution, therapeutic intervention, persistence of the event, sequelae, death.
[7]An AEFI is defined as serious by international standards if it meets one or more of the following criteria: 1) it results in death, 2) is life-threatening, 3) it requires inpatient hospitalization or results in prolongation of existing hospitalization, 4) results in persistent or significant disability/incapacity, 5) is a congenital anomaly/birth defect, 6) is a medically important event or reaction.

> All case series to date indicate that all true cases of MIS-C/A require hospitalization, the majority of patients require admission to the intensive care unit (ICU), between a third to two-thirds need ionotropic or vasoactive medications, and 10-50% are ventilated. Extracorporeal Membrane Oxygenation (ECMO) support and death are rare. Based on this, the following grading system is proposed:
>
> Mild: able to be managed outpatient or admitted, but did not require ICU-level care
> Moderate: admitted to the ICU
> Severe: admitted to the ICU with use of 2 or more of vasoactives/ionotropes, ventilation, dialysis, or ECMO
> Death

[8]To determine the appropriate category, the user should first establish, whether a reported event meets the criteria for the lowest applicable level of diagnostic certainty, e.g., Level 3. If the lowest applicable level of diagnostic certainty of the definition is met, and there is evidence that the criteria of the next higher level of diagnostic certainty are met, the event should be classified in the next category. This approach should be continued until the highest level of diagnostic certainty for a given event could be determined.
[9]If the evidence available for an event is insufficient because information is missing, such an event should be categorized as "Reported MIS-C/A with insufficient evidence to meet the case definition."
[10]An event does not meet the case definition if investigation reveals a negative finding of a necessary criterion (necessary condition) for diagnosis. Such an event should be rejected and classified as "Not a case of MIS-C/A."
[11]Use of this document should preferably be referenced by referring to the respective link on the Brighton Collaboration website (https://brightoncollaboration.us/).