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Review

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

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A B S T R A C T

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.

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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

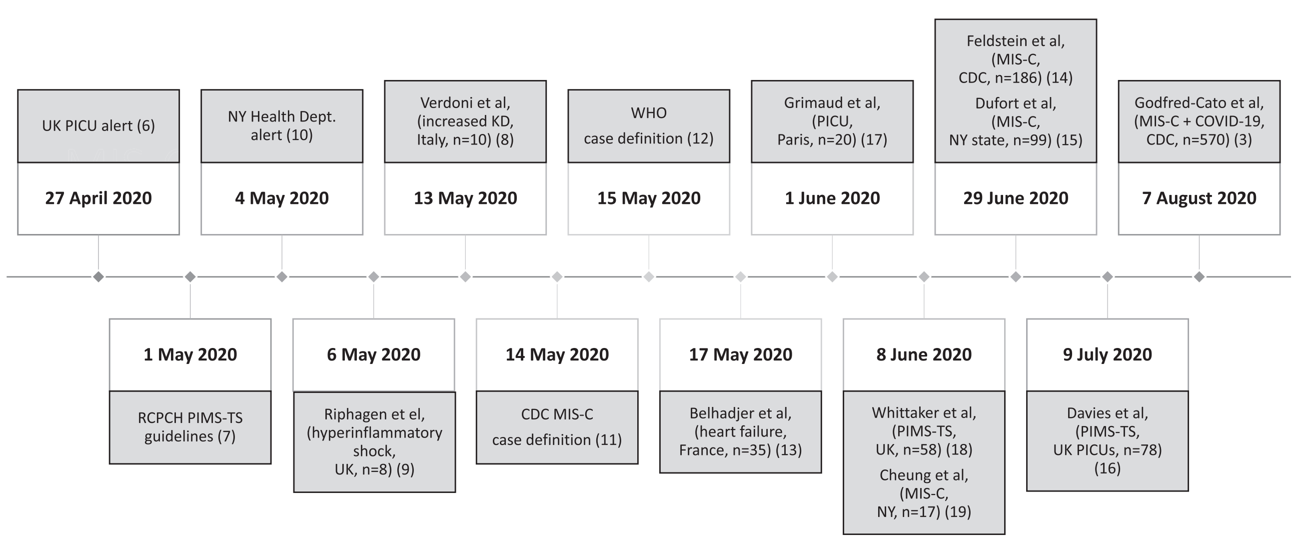

Fig. 1. Timeline of initial recognition and description of MIS-C.Abbreviations: UK, United Kingdom; PICU, pediatric intensive care unit; RCPCH, Royal College of Paediatricians and Child Health; PIMS-TS, pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2; NY, New York; Dept., department; KD, Kawasaki Disease; CDC, Centers for Disease Control and Prevention; MIS-C, multisystem inflammatory syndrome in children; WHO, World Health Organization.

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

were published detailing the clinical presentations, laboratory findings and diagnostic results of patients with the emerging 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 dysreg-

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 (average/median)	3.3–12.5* (8.3)	0–20	8–14 (11)	1–16 (10)
older age	15.5% age 15–20	26% age 13–20	0	0
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.

ulation 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 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 cell 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 cell in end-organs [29,47,48].

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

Cohort Location #Patients	**Feldstein (14)** **USA** **186**	**Dufort (15)** **New York** **99**	**Davies (16)** **UK** **78**	**Belhadjer (13)** **France** **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)

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 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.

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

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.

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.

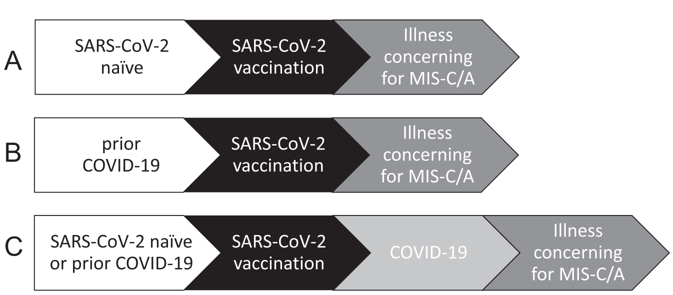

Fig. 2. Potential post-vaccination scenarios.**A**. Persons naïve to SARS-CoV-2 infection may be vaccinated against SARS-CoV-2 and then develop an illness for which they are evaluated for MIS-C/A.**B**. Persons who have had COVID-19 may subsequently be vaccinated to SARS-CoV-2 and then develop an illness for which they are evaluated for MIS-C/A.**C**. Persons 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.

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 $\geq$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.

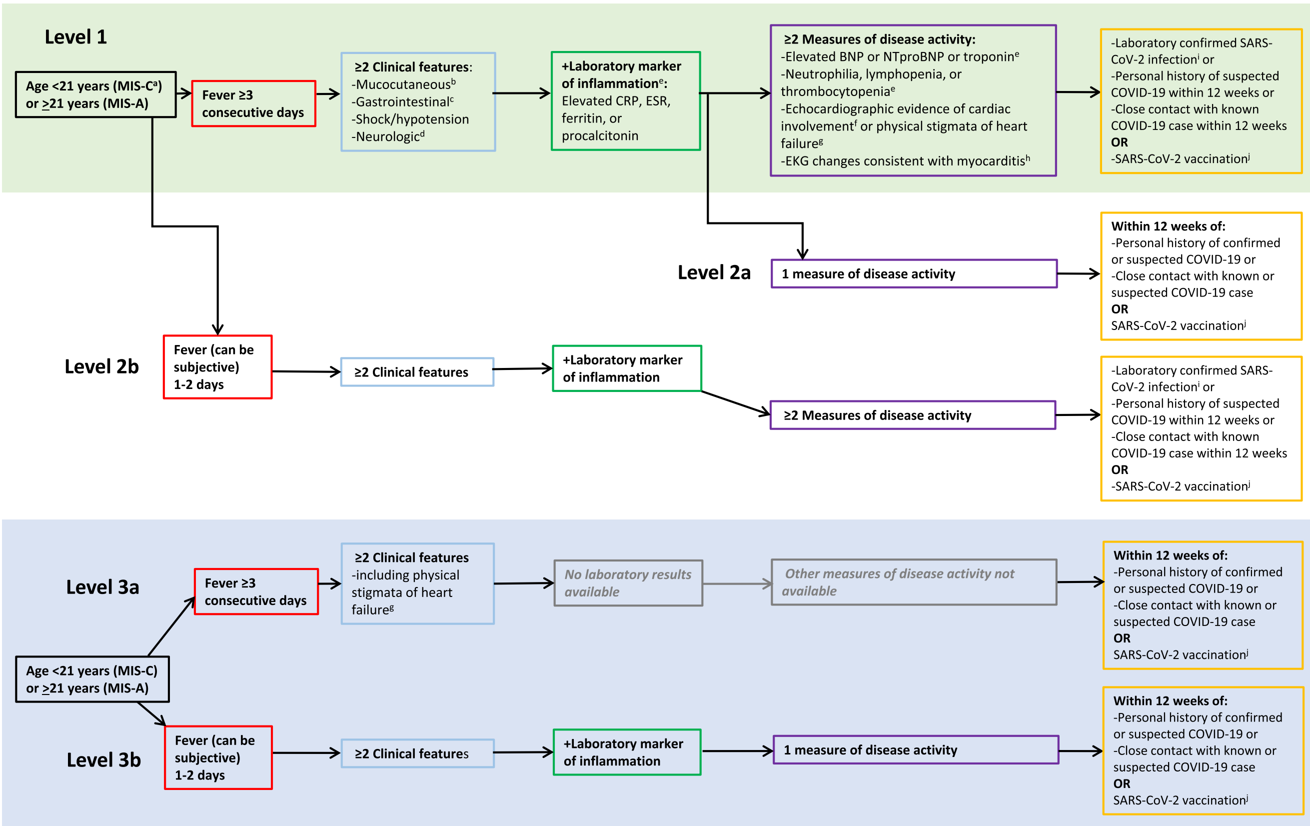

Fig. 3. Algorithm for utilization of the case definition for MIS-C/A.Note: Minimal to mild respiratory symptoms may be present and does not exclude a case of MIS-C/A, however a case must be excluded if there is concern for COVID-19-related pulmonary disease. One of the critical components of the case definition is that it is only applied when there is no clear alternative diagnosis for the reported event.Footnotes: [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] rash, erythema or cracking of the lips/mouth/pharynx, bilateral nonexudative conjunctivitis, erythema or edema of the hands or feet. [c] abdominal pain, vomiting, diarrhea. [d] altered mental status, headache, weakness, paresthesias, lethargy. [e] laboratory values are defined as low or high based on local laboratory norms. [f] echocardiographic signs: dysfunction, wall motion abnormality, coronary abnormality (dilation, aneurysm, echobrightness, lack of distal tapering), valvular regurgitation, pericardial effusion, evidence of abnormal left ventricular strain. [g] physical stigmata of heart failure: gallop (IF diagnosed by expert) *or* rales, lower extremity edema, jugular venous distension, hepatosplenomegaly. [h] 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. [i] laboratory evidence of SARS-CoV-2 infection: serologic evidence of SARS-CoV-2 infection OR SARS-CoV-2 antigen positivity OR SARS-CoV-2 nucleic acid amplification positivity. [j] if a known or suspected COVID-19 infection has not occurred within the preceding 12 weeks.

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]

Table 4 (*continued*)

Level 1 of Diagnostic Certainty – Definitive Case

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
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* $\geq$ 21 years (MIS-A)
AND
Fever $\geq$ 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 2a 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.

Footnotes:
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, evidence of abnormal left ventricular strain.

[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.

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.

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.

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Appendix A. Supplementary material

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

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