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Supplementary appendix

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Surveillance Investigation of Reported Cases of Multisystem Inflammatory Syndrome in Children (MISC) Aged 12–20 Years in the United States Who Received COVID-19 Vaccine, December 2020 through August 2021

Supplemental Materials Table of Contents

Supplemental Table 1. Vaccine Adverse Event System (VAERS) search terms used to identify potential cases of multisystem inflammatory syndrome in children (MIS-C) after receipt of COVID-19 vaccine

Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms	Multisystem Inflammatory Syndrome in Children SIRS (Systemic Inflammatory Response Syndrome)
Text String Search Terms	"MIS-C" "MISC" "MIS" "Multisystem Inflammatory Syndrome" "Multisystem inflammatory" "Multisystem inflammation" "Multisystem" + "inflammation" "Multisystem" + "inflammatory"

Supplemental Table 2a. Demographic and clinical features of three persons with illness meeting MIS-C clinical and inflammatory criteria except for a positive SARSCoV-2 test— United States, December 2020 through August 2021

		Total, n=3 (%)
Age at Time of Illness Onset (Yrs.)		
	12–15	3 (100)
Sex		
	Male	3 (100)
Race/Ethnicity		
	Hispanic	2 (67)
	White, Non-Hispanic	1 (33)
Inpatient MIS-C Treatment		
	Intravenous immunoglobulin (IVIG)	3 (100)
	Systemic steroids	3 (100)
	Immune modulators	0 (0)
Admitted to intensive care unit		0 (0)
Vasopressors		0 (0)
Invasive mechanical ventilation		0 (0)
Length of hospitalization in days, median (range)		5 (3–9)
Discharged Home		3 (100)

Supplemental Table 2b. SARS-CoV-2 testing and temporal features of three persons with illness meeting MIS-C clinical and inflammatory criteria except for a positive SARS-CoV-2 test— United States, December 2020 through August 2021

Case No.	Laboratory Evidence of SARS-CoV-2 Infection[1]	SARS-CoV-2 Test Results <u>During</u> Evaluation of MIS-C Illness[2]			# Days from Prior Positive NAAT or Antigen Test to MIS-C Illness	# COVID-19 Vaccine Doses Received Before MIS-C Onset	# Days from Vaccine Dose 1 to MIS-C Onset	# Days from Vaccine Dose 2 to MIS-C Onset
		NAAT	Anti-spike Antibody	Anti-nucleocapsid Antibody				
1	No	-	ND	-	NA	2	22	1
2	No	-	ND	-	NA	2	19	0
3	No	-	ND	-	NA	2	61	30

[1]This includes past laboratory evidence of SARS-CoV-2 infection (i.e., history of past positive SARS-CoV-2 NAAT or antigen test) or laboratory evidence of SARS-CoV-2 infection during MIS-C illness (i.e., positive SARS-CoV-2 NAAT, antigen, or anti-nucleocapsid antibody test). Spike antibody assay results are not included in this variable. [2]Cells containing (-) indicate a negative test; ND = Not Done; Tests reported as "not done" were tests reported as not done in the medical notes or not present per our review of available medical records.

Supplemental Table 2c. Clinical phenotypes of three persons with illness meeting MIS-C clinical and inflammatory criteria except for a positive SARS-CoV-2 test— United States, December 2020 through August 2021

Case No.	Clinical Phenotype[1]	Assessment by Brighton MIS-C Criteria, Level	Cardiac					Dermatologic		Gastrointestinal			Hematologic		Neurologic		Pulmonary		Renal
			Shock	↑ Troponin	↑ BNP/ NT-proBNP	Cardiac Dysfunction	CAA	Rash	MC Lesions	↑ Bilirubin	↑ AST/ALT	Diarrhea	↑ Ddimer	↓ Plts	Encephalopathy	Headache	Pulmonary Edema	Cough	AKI
1	D, G, R	Probable, 2b						X	X	X	X	X							X
2	C, D, G, H, N	Definitive, 1		X					X	X	X	X	X	X	X	X			
3	D, G, H, N	Probable, 2a						X			X		X			X			

[1]C=Cardiovascular (elevated troponin, elevated B-type natriuretic peptide (BNP)/ N-terminal pro hormone BNP (NT-proBNP), abnormal echocardiogram, arrhythmia);
D=Dermatologic/mucocutaneous (rash, mucocutaneous lesions); G=Gastrointestinal (elevated bilirubin, elevated liver enzymes, or diarrhea); H=Hematologic (elevated D-dimer, thrombophilia, or thrombocytopenia);
N=Neurologic (headache, meningismus, altered mental status); P=Pulmonary (pneumonia, acute respiratory distress syndrome); R=Renal (acute kidney injury); S=Shock (clinically noted in the medical record)
Abbreviations: CAA=coronary artery aneurysm; AKI= acute kidney injury; ↓ Plts=platelets <150,000/mcl; MC=mucocutaneous

Supplemental Table 3. Clinical features of 26 persons not meeting the CDC multisystem inflammatory syndrome in children (MIS-C) case definition— United States, December 2020 through August 2021

No.[1]	Clinical Phenotype[2]	Reason for Not Meeting MIS-C Definition	Alternative Diagnosis	Laboratory Evidence of SARS-CoV-2 Infection[3]	SARS-CoV-2 Testing Results During Evaluation of Illness[4]		
					NAAT	Anti-spike Antibody	Anti-nucleocapsid Antibody
1	D, G, R	No Positive SARS-CoV-2 Test	NA	No	-	ND	-
2	C, D, G, H, N	No Positive SARS-CoV-2 Test	NA	No	-	ND	-
3	D, G, H, N	No Positive SARS-CoV-2 Test	NA	No	-	ND	-
4	D, G, R, S	Alternative Diagnosis	Hemophagocytic Lymphohistiocytosis	No	-	+	-
5	C, D	Alternative Diagnosis	Sickle Cell Crisis	Yes	-	+	ND
6	C, D, G, H, N	Alternative Diagnosis	Murine Typhus	No	-	+	-
7	D, G, H, N	Alternative Diagnosis	Group A *Streptococcus* mediated disease	No	-	+	ND
8	G, N, P	Alternative Diagnosis	E-cigarette or Vaping-use Associated Lung Injury	No	-	ND	-
9	G, N, P	Alternative Diagnosis	Acute SARS-CoV-2 Infection	Yes	+	ND	ND
10	G, H, P	Alternative Diagnosis	Acute SARS-CoV-2 Infection	Yes	+	ND	ND
11	G, H, P	Alternative Diagnosis	Parainfluenza	No	-	ND	-
12	C, G, H	Alternative Diagnosis	Enterovirus Myopericarditis	Yes	-	+	-
13	C, N	Alternative Diagnosis	Myocarditis	No	-	ND	ND
14	C, G	Alternative Diagnosis	Myocarditis	No	-	+	-
15	C, N	Alternative Diagnosis	Myocarditis	No	-	+	ND
16	C, G	Alternative Diagnosis	Myocarditis	No	-	+	-
17	C, N	Alternative Diagnosis	Myocarditis	Yes	-	ND	+
18	C	Alternative Diagnosis	Myocarditis	No	-	ND	ND
19	C, G	Alternative Diagnosis	Myocarditis	No	-	+	ND
20	C, N	Alternative Diagnosis	Myocarditis	No	-	ND	ND
211	C, D, G, H, P, R, S	Alternative Diagnosis	Idiopathic cardiomyocyte necrosis	No	-	+	-
22	C, D, G, H, N, P, R	No Fever	NA	No	-	ND	ND
23	C, G, N	No Fever	NA	No	-	ND	ND
241	C, G, H, P, R	< 24H of Fever	NA	No	-	+	-
25	G	< 2 Organ System Involvement	NA	No	-	ND	ND
26	C, N	Inflammatory Markers Within Normal Range	NA	No	-	ND	ND

[1]Persons numbered 21 and 24 died during illness. For person 21, medical records including autopsy report were discussed with MIS-C and immunization safety expert clinicians, physician investigators from CDC's Clinical Immunization Safety Assessment (CISA) Project including specialists in infectious diseases and cardiology, and with experts from the CDC Infectious Disease Pathology Branch who had reviewed the case independently; it was concluded that this person did not meet CDC MIS-C case definition and had an alternative diagnosis; cause of death on autopsy was multiorgan failure due to acute heart failure due to idiopathic cardiomyocyte necrosis. Autopsy report was not available for person number 24, but this person had preexisting cardiomyopathy and did not meet MIS-C case definition because the fever criterion was not met.

[2]Clinical phenotypes are described by organ system involved and abbreviated as follows: C=Cardiovascular (elevated troponin, elevated B-type natriuretic peptide (BNP)/ Nterminal pro hormone BNP (NT-proBNP), abnormal echocardiogram, arrhythmia); D=Dermatologic/mucocutaneous (rash, mucocutaneous lesions); G=Gastrointestinal (elevated bilirubin, elevated liver enzymes, or diarrhea); H=Hematologic (elevated D-dimer, thrombophilia, or thrombocytopenia); N=Neurologic (headache, meningismus, altered mental status); P=Pulmonary (pneumonia, acute respiratory distress syndrome); R=Renal (acute kidney injury); S=Shock (clinically noted in the medical record)

[3]This includes past laboratory evidence of SARS-CoV-2 infection (i.e., past positive SARS-CoV-2 NAAT or antigen test) and evidence during MIS-C illness (i.e., positive SARSCoV-2 NAAT, antigen, or anti-nucleocapsid antibody test); Persons numbered 5 and 12 had a positive SARS-CoV-2 NAAT test on 153 and 208 days before illness onset respectively

[4]Cells containing (-) indicate a negative test; person numbered 26 had a negative SARS-CoV-2 viral antigen test during illness. Tests reported as "not done" were tests reported as not done in the medical notes or not present per our review of available medical records.

Abbreviations: ND = Not Done; Tests reported as "not done" were tests reported as not done in the medical notes or not present per our review of available medical records; NA = Not Applicable.

Supplemental Table 4. Clinical phenotypes of 15 persons with multisystem inflammatory syndrome in children (MIS-C) following COVID-19 vaccination with laboratory evidence of SARS-Cov-2 infection— United States, December 2020 through August 2021

Case No.	Clinical Phenotype[1]	Assessment by Brighton MIS-C Criteria, Level[2]	Cardiac					Dermatologic		Gastrointestinal			Hematologic		Neurologic		Pulmonary		Renal
			Shock	↑ Troponin	↑ BNP/NTpro BNP	Cardiac Dysfunction	CAA	Rash	MC Lesions	↑ Bilirubin	↑ AST/ ALT	Diarrhea	↑ Ddimer	↓ Plts	Encephalopathy	Headache	Pulmonary Edema	Cough	AKI
1	C, D, G, H, N, P, R, S	Definitive, 1	X	X	X				X	X		X	X		X		X	X	X
2	C, D, G, N	Definitive, 1		X	X			X				X				X			
3	C, D, G, H, P, R, S	Probable, 2b	X	X	X	X		X	X	X	X	X	X				X		X
4	C, D, G, N	Probable, 2a			X				X			X	X			X			
5	C, G, H	Definitive, 1		X	X	X	X				X		X						
6	C, G, H, R, S	Definitive, 1	X	X	X	X				X				X					X
7	G, H, N	Not a case, 5									X		X			X			
8	C, G, H, N, P	Definitive, 1		X		X				X	X	X		X		X		X	
9	C, D, G, N, P	Definitive, 1					X	X	X		X	X				X		X	
10	C, H, P, S	Not a case, 5	X		X								X					X	
11	C, D, G, H, N, P	Definitive, 1		X				X			X	X	X	X		X		X	
12	C, D, G, H, N, P, S	Definitive, 1	X	X	X	X		X	X			X		X		X	X		
13	C, D, G, H, P, S	Definitive, 1	X	X		X		X		X			X					X	
14	G, H, N	Not a case, 5								X	X			X		X			
15	C, G, H, N, P, R, S	Definitive, 1	X	X	X	X				X	X		X			X	X		X

[1]C=Cardiovascular (elevated troponin, elevated B-type natriuretic peptide (BNP)/ N-terminal pro hormone BNP (NT-proBNP), abnormal echocardiogram, arrhythmia);
D=Dermatologic/mucocutaneous (rash, mucocutaneous lesions); G=Gastrointestinal (elevated bilirubin, elevated liver enzymes, or diarrhea); H=Hematologic (elevated D-dimer, thrombophilia, or thrombocytopenia);
N=Neurologic (headache, meningismus, altered mental status); P=Pulmonary (pneumonia, acute respiratory distress syndrome); R=Renal (acute kidney injury); S=Shock (clinically noted in the medical record)
[2]Three persons were considered not a case per Brighton case definition: two had <2 clinical features and one lacked evidence of disease activity

Abbreviations: CAA=coronary artery aneurysm; AKI= acute kidney injury; ↓ Plts=platelets <150,000/mcl; MC=mucocutaneous

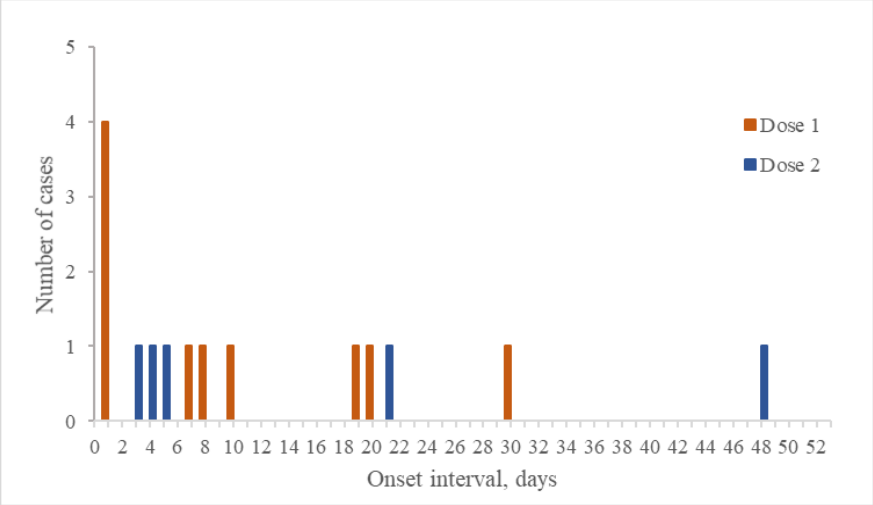
Supplemental Table 5. Clinical phenotypes of six persons with multisystem inflammatory syndrome in children (MIS-C) following COVID-19 vaccination without laboratory evidence of SARS-Cov-2 infection— United States, December 2020 through August 2021

Case No.	Clinical Phenotype[1]	Assessment by Brighton MIS-C Criteria, Level	Cardiac					Dermatologic		Gastrointestinal			Hematologic		Neurologic		Pulmonary		Renal
			Shock	↑ Troponin	↑ BNP/ NT-proBNP	Cardiac Dysfunction	CAA	Rash	MC Lesions	↑ Bilirubin	↑ AST/ALT	Diarrhea	↑ Ddimer	↓ Plts	Encephalopathy	Headache	Pulmonary Edema	Cough	AKI
16	C, H, N, P	Definitive, 1			X								X			X		X	
17	C, D, G, H, P, S	Definitive, 1	X	X				X		X	X		X	X				X	
18	C, D, H	Definitive, 1		X	X			X	X				X						
19	C, D, G, H, N	Definitive, 1		X					X			X	X			X			
20	C, D, G, H, P, R	Definitive, 1	X	X	X	X		X				X	X				X	X	X
21	C, G, N	Probable, 2b		X								X			X	X			

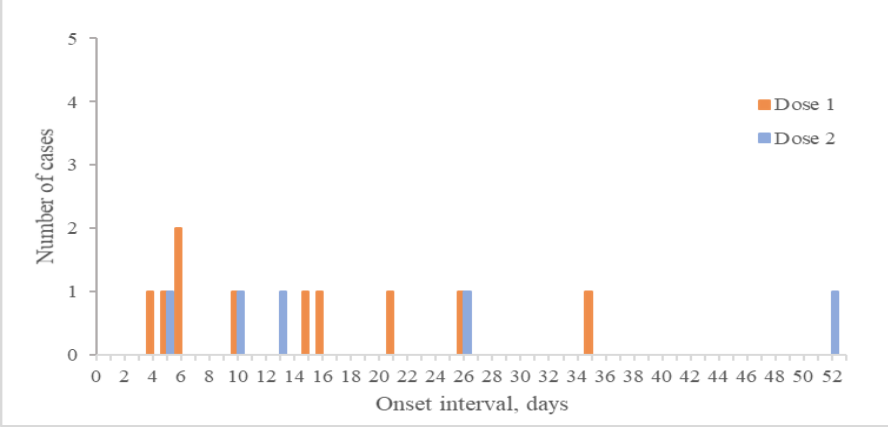
[1]C=Cardiovascular (elevated troponin, elevated B-type natriuretic peptide (BNP)/ N-terminal pro hormone BNP (NT-proBNP), abnormal echocardiogram, arrhythmia);
D=Dermatologic/mucocutaneous (rash, mucocutaneous lesions); G=Gastrointestinal (elevated bilirubin, elevated liver enzymes, or diarrhea); H=Hematologic (elevated D-dimer, thrombophilia, or thrombocytopenia);
N=Neurologic (headache, meningismus, altered mental status); P=Pulmonary (pneumonia, acute respiratory distress syndrome); R=Renal (acute kidney injury); S=Shock (clinically noted in the medical record)
Abbreviations: CAA=coronary artery aneurysm; AKI= acute kidney injury; ↓ Plts=platelets <150,000/mcl; MC=mucocutaneous

Supplemental Figure 1. Number of MIS-C cases with laboratory evidence of SARS-CoV-2 infection, by days from COVID-19 vaccine— United States, December 2020 through August 2021, n=15.

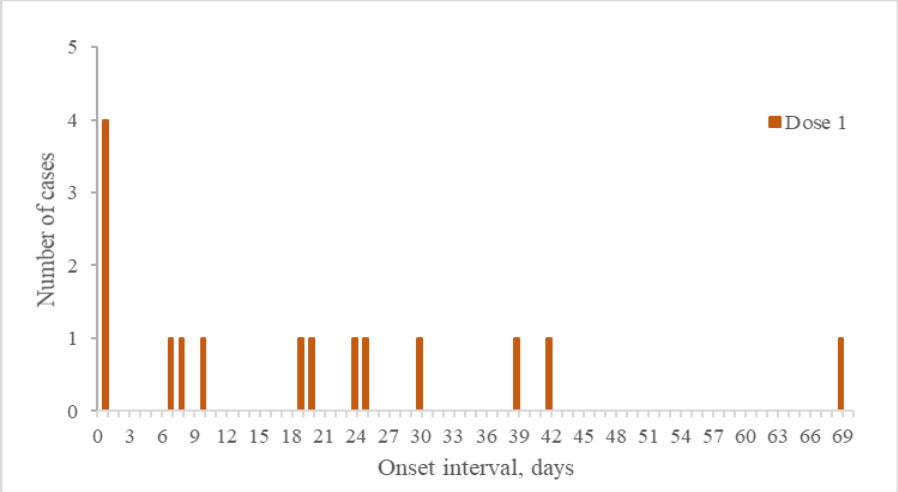
A. Number of cases by number of days from last COVID-19 vaccine dose to onset of MIS-C



B. Number of cases by number of days from last COVID-19 vaccine dose to hospital admission.

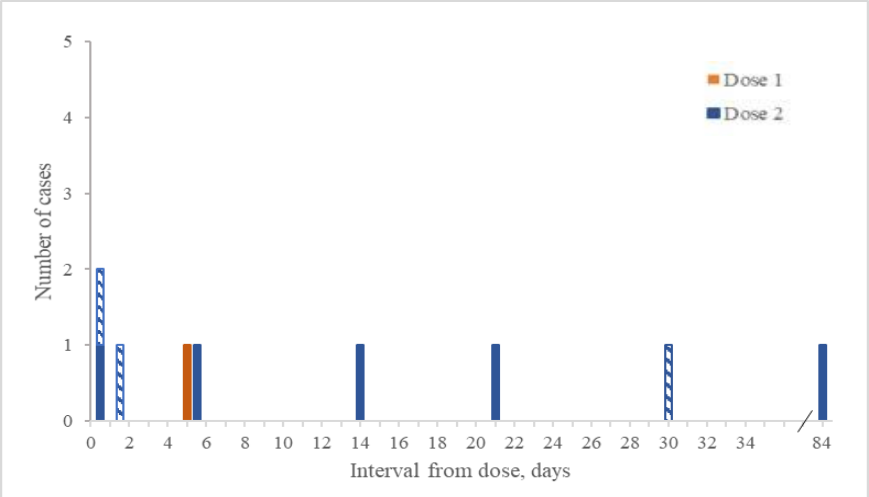


C. Number of cases by number of days from Dose 1 of COVID-19 vaccine to onset of MIS-C.

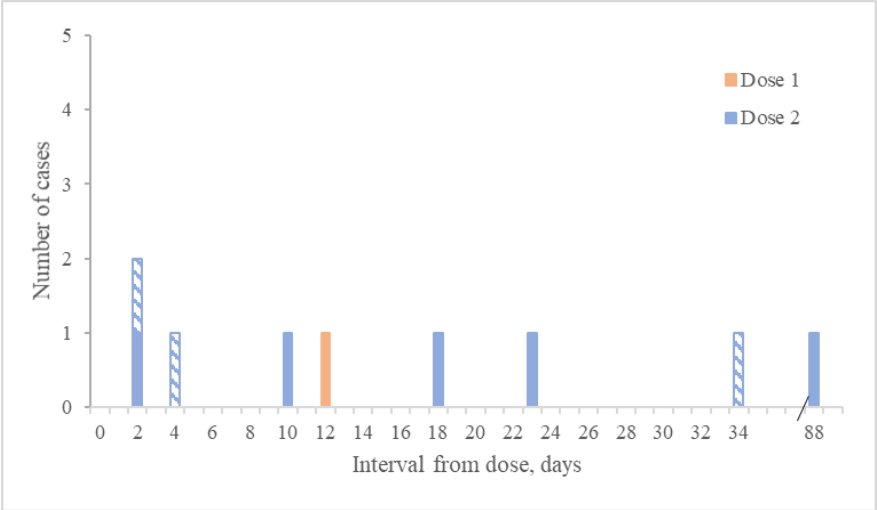


Supplemental Figure 2. Number of MIS-C cases without laboratory evidence of SARS-CoV-2 infection (solid bars, n=6) and those with illness meeting MIS-C clinical and inflammatory criteria except for a positive SARS-CoV-2 test (hashed bars, n=3), by days from COVID-19 vaccine— United States, December 2020 through August 2021. Note break in x-axes.

A. Number of persons by number of days from last COVID-19 vaccine dose to onset of MIS-C.



B. Number of persons by number of days from last COVID-19 vaccine dose to hospital admission.



C. Number of persons by number of days from Dose 1 of COVID-19 vaccine to onset of MIS-C.