Multisystem Inflammatory Syndrome in Children (MIS-C) During SARS-CoV-2 Delta and Omicron Variant Circulation— United States, July 2021 – January 2022

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Abstract

We describe 2,116 multisystem inflammatory syndrome in children (MIS-C) cases reported to CDC during Delta and Omicron circulation from July 2021–January 2022. Half of MIS-C patients were aged 5-11 years, 52% received ICU-level care, and 1.1% died. Only 3.0% of eligible patients were fully vaccinated prior to MIS-C onset.

Keywords: multisystem inflammatory syndrome in children, COVID-19, child, epidemiology

Background

Multisystem inflammatory syndrome in children (MIS-C) is a post-acute hyperinflammatory condition generally occurring 2-6 weeks after SARS-CoV-2 infection, characterized by fever, systemic inflammation, and multisystem organ involvement in persons aged <21 years [1-3]. National reporting of possible MIS-C cases from health departments to the U.S. Centers for Disease Control and Prevention (CDC) began in May of 2020 [4]. In the United States, SARS-CoV-2 variants B.1.617.2 (Delta) and B.1.1.529 (Omicron) became the predominant circulating variants in July 2021 and December 2021, respectively [5].

The Advisory Committee on Immunization Practices (ACIP) issued interim recommendations for use of the Pfizer-BioNTech (BNT162b2) COVID-19 vaccine in persons aged ≥16 years on December 12, 2020, adolescents aged ≥12 years on May 12, 2021, and children aged 5–11 years on November 2, 2021 [6-8]. Expanded eligibility of vaccination to children and adolescents is especially important as continued transmission of SARS-CoV-2 variants places unvaccinated children at risk for SARS-CoV-2 infection and possible subsequent MIS-C [6-9].

We have previously summarized trends over the first 3 pandemic waves of MIS-C cases reported to CDC's national surveillance [3]. In this report, we describe characteristics, clinical features, and outcomes of MIS-C cases from a fourth period of Delta and Omicron predominance and compare them with MIS-C cases from the third pandemic wave, during which many pre-Delta variants circulated [5].

Methods

Health departments reported demographics, clinical presentation, and outcomes of suspected MIS-C cases using a standardized case report form [3]. We identified the nadir following the third wave on the U.S. MIS-C epi-curve to define a fourth wave of MIS-C pandemic activity: wave 4 was from July 9, 2021 through January 31, 2022, and wave 3 from October 18, 2020 through July 8, 2021 (**Supplement 1,** cases by U.S. Census region) [10]. Cases from wave 4 were largely attributable to SARS-CoV-2 infections

with the Delta or Omicron variants, which comprised >50% circulation for weeks ending on June 26, 2021, and December 25, 2021, respectively [5]. We compared wave 4 cases with cases occurring in wave 3 before Delta variant predominance. Using the onset date for each MIS-C case (or hospital admission when onset date not available), we included patients meeting CDC's MIS-C case definition with laboratory confirmation of SARS-CoV-2 infection reported on or before February 22, 2022 (**Supplement 2**). We reviewed case report form free-text responses and supplemented clinical findings (**Supplement 3)**. We adapted previously established frameworks to describe severe organ system involvement [1, 3, 11].

We assessed COVID-19 vaccination status for MIS-C cases and defined persons as fully vaccinated prior to MIS-C onset when MIS-C onset occurred ≥28 days after receipt of the second dose of a 2-dose mRNA primary vaccination series (at least 14 days after vaccination and at least 14 days for development of MIS-C). Using SAS version 9.4 (SAS Institute, Cary, NC) we calculated the frequency of patient characteristics and outcomes among cases stratified by wave. Differences between waves were tested using Kruskal-Wallis test for continuous variables and chi-square tests for categorical variables. Two-sided P values were considered significant at $\alpha<0.05$.

This activity was reviewed by CDC, determined to meet the requirements of public health surveillance, and was conducted in accordance with applicable federal law and CDC policy (45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq) [12, 13].

Results

A total of 5,670 MIS-C cases were reported from 53 jurisdictions: 3,554 in wave 3 and 2,116 in wave 4 (**Table 1, Supplement 1**). Most wave 4 cases (n=2,008; 95%) were during Delta variant predominance [5]. In wave 4, the proportion of patients aged 5-11 years was significantly higher compared with wave 3 (p<.001). Proportions of non-Hispanic White and non-Hispanic Black patients

significantly increased (both p≤.004). Nearly half (45.8%) of MIS-C patients in wave 4 were from the South.

Cases in wave 4 had a significantly lower reported proportion of severe organ involvement in 5 of the 6 systems evaluated compared with wave 3 (**Table 1**). Nearly all severe cardiovascular complications were reported in lower proportions including shock/receipt of vasopressors (p<.001), pericardial effusion/pericarditis (p<.001), coronary artery aneurysm/dilatation (p=0.001), and myocarditis (p<.001); cardiac dysfunction and need for extracorporeal membrane oxygenation did not change during wave 4. Reported pleural effusion (p<.001), invasive mechanical ventilation (p=0.049) and acute respiratory distress syndrome (p=0.043) decreased during wave 4, but pneumonia did not. Reported severe hematologic (p<.001), gastrointestinal (p<.001), and neurologic (p=0.011) involvement also significantly decreased during wave 4.

Length of hospitalization significantly decreased (p<.001), as did the proportions of patients receiving intensive care unit (ICU)-level care (p<.001) from wave 3 to 4. Twenty-three (1.1%) patients died during wave 4, a significantly increased proportion compared with the proportion of deaths (0.5%) during wave 3 (p=0.008). A higher but nonsignificant proportion (52.2%) of decedents from wave 4 were aged 16-20 years compared with wave 3 (41.2%) (**Supplement 4)**. Hospital and ICU length of stay were longer for decedents in wave 4 compared with wave 3 (median days in hospital 13 [IQR, 4–22] vs. 3 [IQR, 1–13] days, respectively; p=.095).

Overall, 763 MIS-C patients aged 5-20 years were eligible by age and date of MIS-C onset to be assessed for full vaccination status before MIS-C onset; 697 (91%) of these patients had no vaccine doses reported and 23 (3.0%) were fully vaccinated (**Table 1, Supplement 5**). ICU-level care was reported in a higher proportion of patients with no vaccination reported compared with fully vaccinated

patients (60.8% vs. 47.8%). None of the 15 patients who received ECMO or 17 who died had vaccination reported (**Supplement 5**).

Discussion

MIS-C continued to be an important complication of SARS-CoV-2 infection during the time periods before and during SARS-CoV-2 Delta and Omicron circulation. The proportion of cases with reported severe organ system involvement, including cardiovascular and respiratory complications, decreased during MIS-C wave 4 compared with wave 3. Duration of hospitalization was shorter and the proportion of patients receiving ICU-level care was significantly lower in wave 4. These differences in severity could be for several reasons, including variations in the host immune response, earlier clinical diagnosis and treatment of MIS-C, or a potentially altered clinical phenotype associated with some degree of pre-existing immunity conferred by SARS-CoV-2 infection or COVID-19 vaccination.

Among MIS-C patients who died in wave 4, 52% were aged 16-20, duration of hospitalization was prolonged (median, 13 days), and 65% were from the South, consistent with the geographical distribution of COVID-19 cases during the period of Delta predominance [14]. The proportion of patients who died during wave 4 (1.1%) was significantly higher than during wave 3 (0.5%), but similar to the proportions who died during wave 1 (2.4%) and wave 2 (1.6%) [11]. MIS-C surveillance is dynamic; at the time of this analysis, the denominator in wave 4 may comprise an under-represented proportion of non-fatal cases compared to earlier waves where case reporting may be more complete.

A recent study of MIS-C in Israel reported that MIS-C incidence was lower during the Omicron wave compared with the Alpha and Delta variant waves, and the proportion of cases with ICU admission decreased from the two previous waves [15]. In this report, 6% and 15% of patients in the Delta and Omicron waves, respectively, had received 2 doses of COVID-19 vaccine at least 2 weeks before admission [15]. In our study, of children eligible for full vaccination status by age and date of MIS-C onset, only 3% were fully vaccinated with a 2-dose mRNA COVID-19 vaccination series prior to MIS-C

onset. In conjunction with a recent study showing that the Pfizer-BioNTech vaccine was 91% (95% CI = 78%–97%) effective at preventing MIS-C in children 12 to 18 years during July 1-December 9, 2021, these findings highlight the importance of COVID-19 vaccination in persons aged ≥5 years [9].

This study is subject to limitations of passive surveillance including ascertainment bias and incomplete data. Jurisdictional participation is voluntary, and participation varies. MIS-C case reporting requires resource-intensive medical chart abstraction and misclassification based on varying levels of training and subjective interpretation of questions is possible. COVID-19 booster information was not collected, limiting analysis to the primary vaccination series. We also had a small proportion of cases from the period of Omicron-variant predominance. Finally, the CDC MIS-C case definition is broad and might have led to unintentional inclusion of patients experiencing other acute inflammatory illnesses such as severe acute COVID-19.

In conclusion, this study describes clinical characteristics of MIS-C patients during the periods before and during widespread Delta and early Omicron circulation as COVID-19 vaccinations were authorized for children and adolescents. MIS-C remained an important complication of SARS-CoV-2 infection during this period, although many indicators of severity showed improvement. Further investigation on the impact of SARS-CoV-2 variants on MIS-C case fatality is warranted, including a larger sample size to evaluate potential risk factors associated with death. Future analyses of MIS-C national surveillance data assessing the impact of SARS-CoV-2 variants and increased COVID-19 vaccination coverage among children and adolescents will be important to track the phenotype and outcomes of this unique syndrome.

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CONFLICT OF INTEREST

M. E. O. reports payment made to the institution where they have clinical responsibilities from the National Institutes of Health (NIH) (MUSIC Study) outside of the submitted work. AM, AY, EB, MJW, KL, MM, LZ, and AC report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Table 1. Characteristics of Patients with MIS-C by Pandemic Waves—October 18, 2020-July 8, 2021 (wave 3) and July 9, 2021-January 31, 2022 (wave 4), United States

Characteristic	All MIS-C cases (n=5,670) No. (%)	MIS-C onset, No. (%)		
		Wave 3 (n=3,554) (October 18, 2020 – July 8, 2021)	Wave 4 (n=2,116) (July 9, 2021 – January 31, 2022)	p value[a]
Age group, years [b]				
<1	175 (3.1)	98 (2.8)	77 (3.6)	0.064
1-4	1,131 (20.0)	730 (20.6)	401 (19.0)	0.146
5-11	2,662 (47.0)	1,603 (45.1)	1,059 (50.1)	<.001
12-15	1,140 (20.1)	736 (20.7)	404 (19.1)	0.140
16-20	558 (9.8)	384 (10.8)	174 (8.2)	0.002
Age, years, median (IQR)	9 (5–13)	9 (5–13)	9 (5–12)	0.192
Sex[c]				
Male	3,510 (62.0)	2,198 (61.9)	1,312 (62.1)	0.874
Race/Ethnicity [d]				
Non-Hispanic White	2,068 (38.3)	1,215 (35.5)	853 (43.0)	<.001
Non-Hispanic Black	1,647 (30.5)	996 (29.1)	651 (32.8)	0.004
Hispanic	1,241 (23.0)	915 (26.8)	326 (16.4)	<.001
Non-Hispanic Asian	143 (2.7)	107 (3.1)	36 (1.8)	0.004
Other/Multiple race	305 (5.6)	188 (5.5)	117 (5.9)	0.534
U.S. Census region				
Northeast	689 (12.2)	459 (12.9)	230 (10.9)	0.021
Midwest	1,390 (24.5)	850 (23.9)	540 (25.5)	0.191
South	2,278 (40.2)	1,309 (36.8)	969 (45.8)	<.001
West	1,313 (23.2)	936 (26.3)	375 (17.8)	<.001
Comorbidities				
Obesity [e]	1,404 (26.8)	921 (28.0)	483 (24.8)	0.012
Chronic lung disease including asthma	481 (8.5)	322 (9.1)	159 (7.5)	0.043
Cardiovascular involvement (N=5,064)				
Severe cardiovascular involvement	4,295 (75.8)	2,794 (78.6)	1,501 (70.9)	<.001
Elevated troponin	3,001 (52.9)	1,917 (53.9)	1,084 (51.2)	0.048
Shock/receipt of vasopressors	2,346 (41.4)	1,538 (43.3)	808 (38.2)	<.001
BNP or NT-pro BNP ≥ 1000 pg/mL	1,863 (32.9)	1,246 (35.1)	617 (29.2)	<.001
Cardiac dysfunction [f]	1,489 (28.8)	971 (28.9)	518 (28.7)	0.840
Pericardial effusion/pericarditis	1,063 (18.8)	744 (20.9)	319 (15.1)	<.001
Coronary artery aneurysm/dilatation [g]	762 (14.8)	535 (15.9)	227 (12.6)	0.001
Myocarditis[h]	669 (11.8)	462 (13.0)	207 (9.8)	<.001
ECMO	74 (1.3)	50 (1.4)	24 (1.1)	0.382
Hematologic involvement (N=5,080)				
Severe hematologic involvement	3,269 (57.7)	2,159 (60.8)	1,110 (52.5)	<.001
Thrombocytopenia [i]	2,258 (39.8)	1,497 (42.1)	761 (36.0)	<.001
Lymphopenia [j]	1,975 (34.8)	1,342 (37.8)	633 (29.9)	<.001

Respiratory involvement (N=3,888)				
Severe respiratory involvement	2,256 (39.8)	1,466 (41.3)	790 (37.3)	0.004
Pneumonia[k]	1,282 (22.6)	781 (22.0)	501 (23.7)	0.139
Pleural effusion	1,082 (19.1)	726 (20.4)	356 (16.8)	<.001
Oxygen, high flow nasal cannula	856 (15.1)	562 (15.8)	294 (13.9)	0.051
Invasive mechanical ventilation	403 (7.1)	271 (7.6)	132 (6.2)	0.049
Acute respiratory distress syndrome	290 (5.1)	198 (5.6)	92 (4.4)	0.043
Gastrointestinal involvement (N=5,207)				
Severe gastrointestinal involvement [l]	1,393 (24.6)	937 (26.4)	456 (21.6)	<.001
Mesenteric adenitis	711 (31.2)	479 (31.4)	232 (30.7)	0.736
Free fluid	536 (23.5)	359 (23.5)	177 (23.4)	0.952
Hepatomegaly/splenomegaly [m]	243 (10.7)	160 (10.5)	83 (11.0)	0.719
Colitis/enteritis	225 (9.9)	166 (10.9)	59 (7.8)	0.020
Cholecystitis/gallbladder abnormalities	176 (7.7)	117 (7.7)	59 (7.8)	0.908
Appendicitis/appendiceal changes	88 (3.9)	71 (4.7)	17 (2.3)	0.005
Renal involvement (N=1,088)				
Severe renal involvement	1,088 (19.2)	686 (19.3)	402 (19.0)	0.779
Acute kidney injury	1,050 (18.5)	656 (18.5)	394 (18.6)	0.879
Renal failure	131 (2.3)	86 (2.4)	45 (2.1)	0.477
Neurologic involvement (N=2,873)				
Severe neurologic involvement	459 (8.1)	313 (8.8)	146 (6.9)	0.011
Meningitis	322 (5.7)	208 (5.9)	114 (5.4)	0.464
Encephalopathy	171 (3.0)	125 (3.5)	46 (2.2)	0.004
Any mucocutaneous involvement	4,040 (71.3)	2,597 (73.1)	1,443 (68.2)	<.001
Treatment				
IVIG	4,772 (84.2)	3,082 (86.7)	1,690 (79.9)	<.001
Steroids	4,591 (81.0)	2,899 (81.6)	1,692 (80.0)	0.1358
Outcomes				
Total days in hospital, median (IQR) [n]	5 (4–8)	5 (4–8)	5 (3–7)	<.001
ICU-level care [o]	3,266 (57.6)	2,164 (60.9)	1,102 (52.1)	<.001
Days in ICU, median (IQR) [p]	3 (2–5)	3 (2–5)	3 (2–5)	0.080
Death	40 (0.7)	17 (0.5)	23 (1.1)	0.008
Vaccination status (among eligible, n=763) [q]				
Fully vaccinated	23 (3.0)	1 (12.5)	22 (2.9)	n/a[r]
Partially vaccinated	40 (5.2)	-	40 (5.3)	n/a[r]
Vaccination not received/reported [s]	697 (91.3)	7 (87.5)	690 (91.4)	n/a[r]

Abbreviations: BNP = brain natriuretic peptide; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; IQR = interquartile range; IVIG = intravenous immunoglobulin; NT-proBNP = N-terminal pro b-type natriuretic peptide

[a] P values from chi square test for categorical variables or where cell size <5 Fisher's exact test and Wilcoxon Rank Sum trend test for continuous variables.

[b] Percentages calculated among 5,666 persons with known age.

[c] Percentages calculated among 5,665 persons with known sex.

[d] Percentages calculated among 5,404 persons with known race and ethnicity data. Racial and ethnic classifications followed CDC's Office of Minority Health and Health Equity (OMHHE) guidance. Non-Hispanic ethnicity was assumed if Hispanic ethnicity was not noted. Hispanic ethnicity was top-coded over White, Black, and Asian race. Because of small patient sizes, American Indian/Alaskan and), Native Hawaiian/Pacific Islander were reported as such, regardless of ethnicity. Other/Multiple race category combines results from American Indian/Alaskan (N=45), Native Hawaiian/Pacific Islander (N=28), other race reported (N=190), and multiple races reported (N=42).

[e] By either clinician diagnosis of obesity or body mass index-based obesity; calculated only in children >2 years. Percentages calculated among 5,236 persons.

[f] Includes specified left ventricular dysfunction (n=1,348) and right ventricular dysfunction (n=354); percentages calculated among 5,163 persons with an echocardiogram performed.

[g] Percentages calculated among 5,163 persons with an echocardiogram performed.

[h] Indicated on case report form.

i Thrombocytopenia was collected under signs and symptoms or calculated from laboratory results as platelets <150 /µl

[j] Lymphopenia was defined as lymphocyte count <4,500 cells/µl if age <8 months or <1,500 cells/µl if age ≥8 months

[k] Information about pneumonia was collected on the case report form under signs and symptoms, complications, or chest imaging.

[l] Percentages calculated among 2,282 persons with an abdominal imaging performed.

[m] Includes hepatosplenomegaly.

[n] Percentages calculated among 5,072 patients with known hospitalization duration.

[o] ICU-level care was defined as having a documented date of ICU admission or known length of ICU stay or having received, ICU-level care including mechanical ventilation, vasopressor support, or extracorporeal membranous oxygenation (ECMO).

[p] Calculated among 2,171 patients with known ICU duration.

[q] Persons were defined as fully vaccinated prior to MIS-C onset when MIS-C onset occurred ≥28 days after receipt of the second vaccine dose of a 2-dose mRNA primary vaccination series. Partially vaccinated included 21 persons who had received only 1 dose of mRNA vaccine, 2 who received the Janssen [Johnson & Johnson] vaccine >6 months prior to MIS-C illness onset, and 17 who had MIS-C illness onset <28 days after receipt of the second dose. Three persons with unknown vaccination dates are not shown in table.

[r] P value n/a because no comparisons were performed for these columns.

[s] Three persons in the Not received/reported group were documented to have had vaccination after their MIS-C illness, the remaining 694 had no report of vaccination.