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SUPPLEMENT ARTICLE

# Multisystem Inflammatory Syndrome in Children During Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Delta and Omicron Variant Circulation—United States, July 2021–January 2022

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We describe 2116 multisystem inflammatory syndrome in children (MIS-C) cases reported to the Centers for Disease Control and Prevention during Delta and Omicron circulation from July 2021 through January 2022. Half of MIS-C patients were aged 5–11 years, 52% received intensive care unit–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.

Multisystem inflammatory syndrome in children (MIS-C) is a post-acute hyperinflammatory condition that generally occurs 2–6 weeks after severe acute respiratory syndrome coronavirus 2 (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 Centers for Disease Control and Prevention (CDC) began in May 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 issued interim recommendations for use of the Pfizer-BioNTech (BNT162b2) coronavirus disease 2019 (COVID-19) vaccine for persons aged ≥16 years on 12 December 2020, for adolescents aged ≥12 years on 12 May 2021, and for children aged 5–11 years on 2 November 2021 [6–8]. Expanded eligibility for 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].

Previously, we summarized trends over the first 3 pandemic waves of MIS-C cases reported to the CDC's national surveillance [3]. Here, 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 US MIS-C epi-curve to define a fourth wave of MIS-C pandemic activity: wave 4 was from 9 July 2021 through 31 January 2022, and wave 3 was from 18 October 2020 through 8 July 2021 (cases by US Census region; Supplementary Materials 1) [10]. Cases from wave 4 were largely attributable to SARS-CoV-2 infections with the Delta or Omicron variant, which comprised >50% circulation for weeks ending on 26 June 2021 and 25 December 2021, respectively [5]. We compared wave 4 cases with cases that occurred in wave 3 before Delta variant predominance. Using the onset date for each MIS-C case (or hospital admission when onset date were not available), we included patients who met CDC's MIS-C case definition with laboratory confirmation of SARS-CoV-2 infection reported on or before 22 February 2022 (Supplementary Materials 2). We reviewed case report form free-text responses and supplemented clinical findings (Supplementary Materials 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

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**Table 1. Characteristics of Patients With Multisystem Inflammatory Syndrome in Children by Pandemic Wave: Wave 3, 18 October 2020–8 July 2021, and Wave 4, 9 July 2021–31 January 2022—United States**

| Characteristic | All MIS-C Cases (N = 5670) No. (%) | MIS-C Onset, No. (%) | | |
|---|---|---|---|---|
| | | Wave 3 (n = 3554) (18 October 2020–8 July 2021) | Wave 4 (n = 2116) (9 July 2021–31 January 2022) | *P* Value[a] |
| Age group, years[b] | — | — | — | — |
| <1 | 175 (3.1) | 98 (2.8) | 77 (3.6) | .064 |
| 1–4 | 1131 (20.0) | 730 (20.6) | 401 (19.0) | .146 |
| 5–11 | 2662 (47.0) | 1603 (45.1) | 1059 (50.1) | <.001 |
| 12–15 | 1140 (20.1) | 736 (20.7) | 404 (19.1) | .140 |
| 16–20 | 558 (9.8) | 384 (10.8) | 174 (8.2) | .002 |
| Age, median (IQR), years | 9 (5–13) | 9 (5–13) | 9 (5–12) | .192 |
| Sex[c] | — | — | — | — |
| Male | 3510 (62.0) | 2198 (61.9) | 1312 (62.1) | .874 |
| Race/Ethnicity[d] | — | — | — | — |
| Non-Hispanic White | 2068 (38.3) | 1215 (35.5) | 853 (43.0) | <.001 |
| Non-Hispanic Black | 1647 (30.5) | 996 (29.1) | 651 (32.8) | .004 |
| Hispanic | 1241 (23.0) | 915 (26.8) | 326 (16.4) | <.001 |
| Non-Hispanic Asian | 143 (2.7) | 107 (3.1) | 36 (1.8) | .004 |
| Other/Multiple race | 305 (5.6) | 188 (5.5) | 117 (5.9) | .534 |
| US Census region | — | — | — | — |
| Northeast | 689 (12.2) | 459 (12.9) | 230 (10.9) | .021 |
| Midwest | 1390 (24.5) | 850 (23.9) | 540 (25.5) | .191 |
| South | 2278 (40.2) | 1309 (36.8) | 969 (45.8) | <.001 |
| West | 1313 (23.2) | 936 (26.3) | 375 (17.8) | <.001 |
| Comorbidities | — | — | — | — |
| Obesity[e] | 1404 (26.8) | 921 (28.0) | 483 (24.8) | .012 |
| Chronic lung disease including asthma | 481 (8.5) | 322 (9.1) | 159 (7.5) | .043 |
| Cardiovascular involvement (N = 5064) | — | — | — | — |
| Severe cardiovascular involvement | 4295 (75.8) | 2794 (78.6) | 1501 (70.9) | <.001 |
| Elevated troponin | 3001 (52.9) | 1917 (53.9) | 1084 (51.2) | .048 |
| Shock/receipt of vasopressors | 2346 (41.4) | 1538 (43.3) | 808 (38.2) | <.001 |
| BNP or NT-pro BNP ≥ 1000 pg/mL | 1863 (32.9) | 1246 (35.1) | 617 (29.2) | <.001 |
| Cardiac dysfunction[f] | 1489 (28.8) | 971 (28.9) | 518 (28.7) | .840 |
| Pericardial effusion/pericarditis | 1063 (18.8) | 744 (20.9) | 319 (15.1) | <.001 |
| Coronary artery aneurysm/dilatation[g] | 762 (14.8) | 535 (15.9) | 227 (12.6) | .001 |
| Myocarditis[h] | 669 (11.8) | 462 (13.0) | 207 (9.8) | <.001 |
| Extracorporeal membrane oxygenation | 74 (1.3) | 50 (1.4) | 24 (1.1) | .382 |
| Hematologic involvement (N = 5080) | — | — | — | — |
| Severe hematologic involvement | 3269 (57.7) | 2159 (60.8) | 1110 (52.5) | <.001 |
| Thrombocytopenia[i] | 2258 (39.8) | 1497 (42.1) | 761 (36.0) | <.001 |
| Lymphopenia[j] | 1975 (34.8) | 1342 (37.8) | 633 (29.9) | <.001 |
| Respiratory involvement (N = 3888) | — | — | — | — |
| Severe respiratory involvement | 2256 (39.8) | 1466 (41.3) | 790 (37.3) | .004 |
| Pneumonia[k] | 1282 (22.6) | 781 (22.0) | 501 (23.7) | .139 |
| Pleural effusion | 1082 (19.1) | 726 (20.4) | 356 (16.8) | <.001 |
| Oxygen, high-flow nasal cannula | 856 (15.1) | 562 (15.8) | 294 (13.9) | .051 |
| Invasive mechanical ventilation | 403 (7.1) | 271 (7.6) | 132 (6.2) | .049 |
| Acute respiratory distress syndrome | 290 (5.1) | 198 (5.6) | 92 (4.4) | .043 |
| Gastrointestinal involvement (N = 5207) | — | — | — | — |
| Severe gastrointestinal involvement[l] | 1393 (24.6) | 937 (26.4) | 456 (21.6) | <.001 |
| Mesenteric adenitis | 711 (31.2) | 479 (31.4) | 232 (30.7) | .736 |
| Free fluid | 536 (23.5) | 359 (23.5) | 177 (23.4) | .952 |
| Hepatomegaly/splenomegaly[m] | 243 (10.7) | 160 (10.5) | 83 (11.0) | .719 |
| Colitis/enteritis | 225 (9.9) | 166 (10.9) | 59 (7.8) | .020 |
| Cholecystitis/gallbladder abnormalities | 176 (7.7) | 117 (7.7) | 59 (7.8) | .908 |
| Appendicitis/appendiceal changes | 88 (3.9) | 71 (4.7) | 17 (2.3) | .005 |
| Renal involvement (N = 1088) | — | — | — | — |

**Table 1. Continued**

| Characteristic | All MIS-C Cases (N = 5670) No. (%) | MIS-C Onset, No. (%) | | *P* Value[a] |
|---|---|---|---|---|
| | | Wave 3 (n = 3554) (18 October 2020–8 July 2021) | Wave 4 (n = 2116) (9 July 2021–31 January 2022) | |
| Severe renal involvement | 1088 (19.2) | 686 (19.3) | 402 (19.0) | .779 |
| Acute kidney injury | 1050 (18.5) | 656 (18.5) | 394 (18.6) | .879 |
| Renal failure | 131 (2.3) | 86 (2.4) | 45 (2.1) | .477 |
| Neurologic involvement (N = 2873) | — | — | — | — |
| Severe neurologic involvement | 459 (8.1) | 313 (8.8) | 146 (6.9) | .011 |
| Meningitis | 322 (5.7) | 208 (5.9) | 114 (5.4) | .464 |
| Encephalopathy | 171 (3.0) | 125 (3.5) | 46 (2.2) | .004 |
| Any mucocutaneous involvement | 4040 (71.3) | 2597 (73.1) | 1443 (68.2) | <.001 |
| Treatment | — | — | — | — |
| Intravenous immunoglobulin | 4772 (84.2) | 3082 (86.7) | 1690 (79.9) | <.001 |
| Steroids | 4591 (81.0) | 2899 (81.6) | 1692 (80.0) | .1358 |
| Outcomes | — | — | — | — |
| Total days in hospital, median (IQR)[n] | 5 (4–8) | 5 (4–8) | 5 (3–7) | <.001 |
| ICU-level care[o] | 3266 (57.6) | 2164 (60.9) | 1102 (52.1) | <.001 |
| Days in ICU, median (IQR)[p] | 3 (2–5) | 3 (2–5) | 3 (2–5) | .080 |
| Death | 40 (0.7) | 17 (0.5) | 23 (1.1) | .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; ICU, intensive care unit; IQR, interquartile range; MIS-C, multisystem inflammatory syndrome in children; NT, *N*-terminal.

[a] *P* values from $\chi^2$ test for categorical variables or where cell size <5. Fisher exact test and Wilcoxon rank sum trend test for continuous variables.

[b] Percentages calculated among 5666 persons with known age.

[c] Percentages calculated among 5665 persons with known sex.

[d] Percentages calculated among 5404 persons with known race and ethnicity data. Racial and ethnic classifications followed the Centers for Disease Control and Prevention's Office of Minority Health and Health Equity 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 numbers, 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 aged >2 years. Percentages calculated among 5236 persons.

[f] Includes specified left ventricular dysfunction (n = 1348) and right ventricular dysfunction (n = 354). Percentages calculated among 5163 persons with an echocardiogram performed.

[g] Percentages calculated among 5163 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 <4500 cells/μL if aged <8 months or <1500 cells/μL if aged ≥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 2282 persons with abdominal imaging performed.

[m] Includes hepatosplenomegaly.

[n] Percentages calculated among 5072 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.

[p] Calculated among 2171 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 messenger RNA (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 the table.

[r] *P* value not calculated 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.

dose of a 2-dose messenger RNA (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 the Kruskal–Wallis test for continuous variables and $\chi^2$ tests for categorical variables. Two-sided *P* values were considered significant at $\alpha<.05$.

This activity was reviewed by the 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 5670 MIS-C cases were reported from 53 jurisdictions: 3554 in wave 3 and 2116 in wave 4 (Table 1, Supplementary Materials 1). Most wave 4 cases (n = 2008;

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 $P \leq .004$). 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 ($P = .001$), 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 ($P = .049$), and acute respiratory distress syndrome ($P = .043$) decreased during wave 4, but pneumonia did not. Reported severe hematologic ($P < .001$), gastrointestinal ($P < .001$), and neurologic ($P = .011$) involvement also significantly decreased during wave 4.

Length of hospitalization significantly decreased ($P < .001$), as did the proportions of patients who received 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 ($P = .008$). A higher but nonsignificant proportion (52.2%) of decedents from wave 4 were aged 16–20 years compared with wave 3 (41.2%; Supplementary Materials 4). Hospital and ICU length of stay were longer for decedents in wave 4 compared with wave 3 (median days in the hospital 13, interquartile range [IQR], 4–22 vs 3 days, IQR, 1–13, 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, Supplementary Materials 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 extracorporeal membrane oxygenation or the 17 who died had vaccination reported (Supplementary Materials 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 who received 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 preexisting 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 years, 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 underrepresented proportion of nonfatal cases compared with earlier waves where case reporting may be more complete.

A recent study of MIS-C in Israel showed that MIS-C incidence was lower during the Omicron wave compared with the Alpha and Delta variant waves and that the proportion of cases with ICU admission decreased from the 2 previous waves [15]. In that 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 that showed that the Pfizer-BioNTech vaccine was 91% (95% confidence interval, 78%–97%) effective at preventing MIS-C in children aged 12–18 years during 1 July 2021–9 December 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 who experienced other acute inflammatory illnesses such as severe acute COVID-19.

In conclusion, we describe 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 to assess 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.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

## Notes

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