HHS Public Access

Author manuscript

Pediatr Infect Dis J. Author manuscript; available in PMC 2024 July 22.

Published in final edited form as:

Pediatr Infect Dis J. 2023 December 01; 42(12): e476–e478. doi:10.1097/INF.0000000000004103.

Multisystem Inflammatory Syndrome in Children (MIS-C) Among Persons who Completed a Two-Dose COVID-19 Vaccine Primary Series Compared with those Reporting No COVID-19 Vaccination, U.S. National MIS-C Surveillance

Anna R. Yousaf, MD[1], **Allison D. Miller, MPH**[1], **Katherine Lindsey, MPH**[1,2], **Ami B. Shah, MPH**[1,3], **Michael J. Wu, MSc**[1], **Michael Melgar, MD**[1], **Laura D. Zambrano, PhD, MPH**[1], **Angela P. Campbell, MD, MPH**[1]

[1]Coronavirus and Other Respiratory Viruses Division, CDC, Atlanta, Georgia, USA

[2]4ES Corporation, San Antonio, Texas, USA

[3]General Dynamics Information Technology, Fairfax, Virginia, USA

Abstract

We analyzed MIS-C cases by reported COVID-19 vaccination status (two-dose primary series versus no vaccination). Forty-six percent vaccinated versus 58% unvaccinated persons received ICU-level care (p=0.02); risk of ICU admission was 23% higher (adjusted relative risk: 1.23; 95% CI: 1.03-1.48) among unvaccinated patients; 21 unvaccinated persons died. MIS-C occurs after SARS-CoV-2 infection in vaccinated persons but may be less severe.

Keywords

MIS-C; COVID-19; children; vaccine

Introduction

Multisystem inflammatory syndrome in children (MIS-C) is a rare but serious condition that follows two to six weeks after SARS-CoV-2 infection.[1,2] Clinical features include fever, elevated laboratory markers of inflammation, and multi-organ system involvement.[1-3] CDC conducts national surveillance for MIS-C through voluntary reporting of cases by local, state, and territorial health departments. As of August 1, 2023, there were over 9,500 cases and 79 deaths reported among persons aged <21 years.[4]

The Advisory Committee on Immunization Practices (ACIP) issued interim recommendations on Pfizer-BioNTech (BNT162b2) COVID-19 vaccine use in persons

Corresponding Author Anna Yousaf, Centers for Disease Control and Prevention, 1600 Clifton Road NE, MS-H24-9, Atlanta, GA 30329, pgy6@cdc.gov. **Alternate Corresponding Author** Angela Campbell, Centers for Disease Control and Prevention, 1600 Clifton Road NE, MS-H24-9, Atlanta, GA 30329, app4@cdc.gov.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the US Centers for Disease Control and Prevention.

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.[5,6] On June 18, 2022, both the Pfizer-BioNTech and Moderna COVID-19 vaccines were recommended for all persons aged ≥6 months.[7] By the time of this analysis, all children aged ≥5 years who had completed their primary series were eligible to receive a booster dose.

COVID-19 vaccination is effective in preventing MIS-C. In a U.S. multicenter case-control investigation among children hospitalized from July 2021 through April 2022, MIS-C was 84% less likely among those aged ≥5 years who received two doses of the monovalent Pfizer-BioNTech vaccine.[11] A French population-based study from September 2021 through October 2021 found that most cases of MIS-C were among COVID-19 unvaccinated adolescents, and receipt of at least 1 COVID-19 vaccine dose reduced MIS-C incidence by 91%.[12] U.S. MIS-C cases from national surveillance data have not been evaluated by reported COVID-19 vaccination status. In this investigation we describe cases of MIS-C reported to CDC in children with reported completion of at least their two-dose COVID-19 vaccination primary series compared with those with no COVID-19 vaccination reported.

Methods

We identified all persons aged 5–20 years reported to MIS-C national surveillance as of December 31, 2022, with an illness meeting the 2020 CDC MIS-C case definition who were COVID-19 vaccine age-eligible per ACIP recommendations prior to MIS-C illness onset.[3,5,6,10] Children aged <5 years were excluded as they did not become vaccine-eligible until June 18, 2022, and there were none in our national surveillance dataset who completed a COVID-19 vaccine primary series.

Analysis was then restricted to persons who were vaccine age-eligible at the time of this investigation. The CDC MIS-C national surveillance case report form (CRF) was revised to begin collecting data on COVID-19 vaccine primary series doses in May of 2021. Because ACIP had recommended COVID-19 vaccination for children aged 16-20 years and children 12-15 years by May 12, 2021, these age groups were given the same vaccine eligibility start date for inclusion in this analysis.[5,10] The MIS-C national surveillance CRF did not collect data on COVID-19 booster doses at the time of this investigation. Persons aged 12-20 years were considered vaccine age-eligible if at least 21 days had elapsed from vaccination recommendation date (to allow for receipt of vaccine dose 1 and 2) followed by an additional 28 days (≥14 days to develop immunity from vaccine dose 2 and ≥14 days to account for the delay between infection and MIS-C). Therefore, persons aged 12-20 years were considered vaccine age-eligible if MIS-C illness onset was on or after June 30, 2021 and persons aged 5-11 years were considered vaccine age-eligible for analysis if MIS-C illness onset was on or after December 21, 2021(Supplemental Figure).[5,6,10]

Vaccine age-eligible persons with MIS-C were divided into two groups: those with reported completion of a COVID-19 vaccine series (referred to as “vaccinated”), and those with no COVID-19 vaccination reported. Primary COVID-19 vaccine series completion was defined as receipt of a two-dose mRNA primary vaccine series with MIS-C onset ≥28 days after vaccine dose 2. Persons with no vaccination reported were those eligible to receive

COVID-19 vaccine per ACIP recommendations at the time of the MIS-C illness but who had no vaccine doses noted on the MIS-C CRF. We compared demographic and clinical features, including previously defined categories of severe organ involvement[2], treatments, and outcomes between the two groups using SAS Chi square test for categorical variables (Fisher's Exact test used when cell sizes were <5) and Kruskal-Wallis for continuous variables. We used a multivariable Poisson model including age, race, ethnicity, social vulnerability index (SVI)[13], and obesity to estimate the relative risk of ICU-level care by vaccination status. Using a variable reduction approach, sex, census region, and presence of non-obesity comorbidities were also evaluated and removed as none demonstrated evidence of confounding. For 160 children with missing SVI, a value of 0.5 was imputed. All analysis were done using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA).

This activity was reviewed by CDC, was determined to meet the requirements of public health surveillance and was conducted consistent 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).

Results

Of 9,332 MIS-C cases reported as of December 31, 2022, 1,692 met vaccine-eligibility criteria for this investigation: 106 had completed a primary vaccination series, 109 had incomplete primary series, and 1,477 had no vaccination reported (Table). For those with vaccination reported, MIS-C onset occurred a median of 149 (IQR 70-237) days after vaccine dose 2.

There were no significant differences in any age group (5-11, 12-15, or 16-20 years) or sex between vaccinated and unvaccinated persons. A higher frequency of unvaccinated patients were non-Hispanic Black (435/1477, 29%) compared with those who were vaccinated (20/106, 19%) p=0.02. In addition, a higher proportion of vaccinated patients were from the Northeast compared with unvaccinated patients (31/106, 29% vs 226/1477, 15% [p<0.01]) while a significantly higher proportion of unvaccinated patients resided in the South compared with vaccinated patients (601/1477, 41% vs 27/106, 26% [p<0.01]). Persons with no vaccination reported had a higher median SVI (0.540) than those with vaccination reported (0.467), p<0.01. The vaccinated and unvaccinated groups did not differ by proportion of patients with comorbidities, although there was a trend toward a higher frequency of persons with obesity among the unvaccinated.

Among those with no vaccination reported, there was also a non-significant trend toward a higher proportion of persons with severe shock and/or receipt of vasopressors. Fewer vaccinated persons received intensive care unit (ICU)-level care compared with those with no vaccination reported, 49/106 (46%) versus 849/1477 (58%) respectively (p=0.02). After model adjustment, the risk of ICU-level care among unvaccinated MIS-C patients was 23% higher (adjusted relative risk: 1.23; 95% CI: 1.03 - 1.48) compared with vaccinated patients. There were no significant differences in hospital or ICU length of stay. Although not statistically significant, deaths were reported only among unvaccinated patients (21/1477; 1%).

Discussion

Although COVID-19 vaccination is associated with protection against MIS-C, MIS-C can still occur after SARS-CoV-2 infection in persons who have completed a two-dose primary COVID-19 vaccine series. those with primary series vaccination reported appear to have a milder clinical course. A significantly higher percentage of unvaccinated persons required ICU-level care and, in adjusted analysis, the risk of ICU admission was over 20% higher compared with vaccinated children. It is also notable that 21 deaths were reported during this surveillance period, all in persons whom were unvaccinated. These data suggest that MIS-C may be more severe among unvaccinated children compared with vaccinated children. While we cannot estimate vaccine effectiveness from these surveillance data, these findings suggest that COVID-19 vaccination is associated with decreased MIS-C clinical severity, in addition to the previously demonstrated protection vaccination confers against MIS-C overall.[11,14]

We found that a higher proportion of patients with MIS-C who were vaccinated resided in the Northeast compared with unvaccinated patients, and that unvaccinated patients more frequently were from the South compared with vaccinated patients. This pattern reflects national COVID-19 vaccine coverage data with higher uptake in the Northeast compared with the South.[15] We also observed that unvaccinated children had a significantly higher median SVI than vaccinated children, indicating residence in areas with greater social vulnerability among the unvaccinated.

A limitation of our investigation is that vaccination status was not systematically verified, and persons may be misclassified by vaccination status; specifically, persons with no reported vaccination may have received vaccine but misclassified as unvaccinated. Vaccination status was derived from the medical record, which may have been obtained from patient self-report or the state immunization information system. I Also, our investigation did not collect data on COVID-19 booster doses and their effect on MIS-C severity. These data do not account for trends in MIS-C over time, including the influence of circulating SARS-CoV-2 variants on MIS-C clinical manifestations. Additionally, we could not completely account for confounding factors associated with poor clinical outcomes given the small number of children reporting vaccination.

CDC will continue to monitor trends in MIS-C in both COVID-19 vaccinated and unvaccinated persons through national surveillance data. This investigation shows that while MIS-C can occur in persons after receipt of primary series COVID-19 vaccination, the clinical course may be less severe compared with MIS-C in unvaccinated persons. These findings add additional support to the recommendation for COVID-19 vaccination for children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Feldstein LR, Tenforde MW, Friedman KG, et al. Characteristics and Outcomes of US Children and Adolescents With Multisystem Inflammatory Syndrome in Children (MIS-C) Compared With Severe Acute COVID-19. JAMA. 2021;325(11):1074–1087. [PubMed: 33625505]
2. Miller AD, Yousaf AR, Bornstein E, et al. 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. Clin Infect Dis. 2022;75(Supplement_2):S303–S307. [PubMed: 35684958]
3. CDC. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). Available at: https://emergency.cdc.gov/han/2020/han00432.asp. Accessed November 28, 2022.
4. CDC. Health Department-Reported Cases of Multisystem Inflammatory Syndrome in Children (MIS-C) in the United States. Available at: https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance. Accessed November 15, 2022.
5. Wallace M WK, Gargano JW, et al. The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine in Adolescents Aged 12–15 Years — United States, May 2021. MMWR Morb Mortal Wkly Rep. 2021;70:749–752. [PubMed: 34014913]
6. Woodworth KR MD, Collins JP, et al. The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine in Children Aged 5–11 Years — United States, November 2021. MMWR Morb Mortal Wkly Rep. 2021;70:1579–1583. [PubMed: 34758012]
7. FDA. COVID-19 Vaccines. Available at: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines#authorized-vaccines. Accessed November 28, 2022.
8. FDA. Coronavirus (COVID-19) Update: FDA Expands Eligibility for Pfizer-BioNTech COVID-19 Vaccine Booster Dose to Children 5 through 11 Years. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-expands-eligibility-pfizer-biontech-covid-19-vaccine-booster-dose. Accessed November 28, 2022.
9. Fleming-Dutra KE WM, Moulia DL, et al. Interim Recommendations of the Advisory Committee on Immunization Practices for Use of Moderna and Pfizer-BioNTech COVID-19 Vaccines in Children Aged 6 Months–5 Years — United States, June 2022. MMWR Morb Mortal Wkly Rep. 2022;71:859–868. [PubMed: 35771731]
10. Oliver S GJ, Marin M, et al. The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine — United States, December 2020. MMWR Morb Mortal Wkly Rep. 2020;69:1922–1924. [PubMed: 33332292]
11. Zambrano LD, Newhams MM, Olson SM, et al. BNT162b2 mRNA Vaccination Against COVID-19 is Associated with Decreased Likelihood of Multisystem Inflammatory Syndrome in U.S. Children Ages 5-18 Years. Clin Infect Dis. 2022.
12. Levy M, Recher M, Hubert H, et al. Multisystem Inflammatory Syndrome in Children by COVID-19 Vaccination Status of Adolescents in France. JAMA. 2022;327(3):281–283. [PubMed: 34928295]
13. Flanagan BE, Hallisey EJ, Adams E, Lavery A. Measuring Community Vulnerability to Natural and Anthropogenic Hazards: The Centers for Disease Control and Prevention's Social Vulnerability Index. J Environ Health. 2018;80(10):34–36.
14. Nygaard U, Holm M, Hartling UB, et al. Incidence and clinical phenotype of multisystem inflammatory syndrome in children after infection with the SARS-CoV-2 delta variant by vaccination status: a Danish nationwide prospective cohort study. Lancet Child Adolesc Health. 2022;6(7):459–465. [PubMed: 35526537]
15. CDC. COVID-19 Vaccinations in the United States. Available at: https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-people-booster-percent-pop5. Accessed January 1, 2023.

Table.

Demographic and clinical characteristics of persons with MIS-C compared between those with reported completion of COVID-19 vaccination primary series reported and those with no COVID-19 vaccination reported

	Two-Dose COVID-19 Primary Series Vaccination Reported (N=106) %[1]	No Vaccination Reported (N=1,477) %	P-value[2]
Demographics			
Age group in years[3]			
5-11	43 (41)	635 (43)	0.63
12-15	41 (39)	594 (40)	0.76
16-20	22 (21)	248 (17)	0.29
Sex[4]			
Male	66 (62)	928 (63)	0.90
Race/Ethnicity[5]			
Non-Hispanic Black	20 (19)	435 (29)	0.02
Non-Hispanic White	52 (49)	591 (40)	0.07
Non-Hispanic Asian	6 (6)	42 (3)	0.10
Non-Hispanic Multiple/Other	4 (4)	50 (3)	0.78
Hispanic	16 (15)	254 (17)	0.58
Census Region			
Midwest	34 (32)	363 (25)	0.09
Northeast	31 (29)	226 (15)	<0.01
South	27 (26)	601 (41)	<0.01
West	14 (13)	284 (19)	0.12
Social Vulnerability Index, median (IQR)[6]	0.467 (0.270 – 0.643)	0.540 (0.368 – 0.708)	<0.01
Clinical Characteristics			
Comorbidities			
Any comorbidity present	37 (35)	553 (37)	0.60
Obesity[7]	20 (19)	408 (28)	0.05
Chronic lung disease	8 (8)	119 (8)	0.85
Seizures	4 (4)	35 (2)	0.33
Other neurologic disorder	6 (6)	43 (3)	0.11
Cardiovascular disorder	5 (5)	27 (2)	0.05
Immunosuppressive disorder/ malignancy	4 (4)	14 (1)	0.03
Diabetes (type 1 or 2)	3 (3)	12 (1)	0.07
Sickle cell disease	0 (0)	8 (1)	1.00
Other	7 (7)	111 (8)	1.00
Organ Involvement			

	Two-Dose COVID-19 Primary Series Vaccination Reported (N=106) %[1]	No Vaccination Reported (N=1,477) %	P-value[2]
Severe cardiovascular[8]	72 (68)	1100 (75)	0.14
Shock/vasopressor receipt	36 (34)	624 (42)	0.09
Severe gastrointestinal[9]	24 (23)	343 (23)	0.89
Severe hematologic[10]	65 (61)	887 (60)	0.80
Dermatologic/ mucocutaneous	69 (65)	1014 (69)	0.45
Treatment and Outcomes			
Intensive care unit (ICU)-level care[11]	49 (46)	849 (58)	0.02
Median hospital length of stay (IQR), days	5 (4 – 7)	5 (4 – 7)	0.25
Median ICU length of stay (IQR), days	3 (1 – 4)	3 (2 – 5)	0.13
Death	0 (0)	21 (1)	0.39

[1] For the 106 with vaccinated reported, 93 received monovalent Pfizer-BioNTech (BNT162b2) COVID-19 vaccine, 2 received monovalent Moderna *mRNA-1273* COVID-19 vaccine, and 11 received unknown vaccine type.

[2] P-values obtained using Chi square for categorical variables and Kruskal-Wallis for continuous. Fischer's Exact test used for categorical variables when cell sizes were <5.

[3] Age calculated at time of MIS-C illness onset.

[4] Sex missing for one person in unvaccinated group

[5] Race/ethnicity missing for 105 in the vaccine not reported group and 8 in the primary series vaccination group. Other race includes American Indian/Alaska Native, Pacific Islander, those listed as multiple, and those with race listed as other.

[6] SVI missing for 13 persons in vaccinated group and 147 in unvaccinated group.

[7] Either noted as a clinical diagnosis or BMI > 95th percentile when BMI percentile was available.

[8] Severe cardiovascular involvement defined as ventricular dysfunction, pericardial effusion/pericarditis, myocarditis, congestive heart failure, arrythmia, elevated troponin, elevated BNP, or NT-pro BNP ≥ 1,000 pg./mL, shock/receipt of vasopressors, or extracorporeal membranous oxygenation (ECMO) [2]

[9] Severe gastrointestinal involvement defined as mesenteric adenitis, free fluid, hepatomegaly/splenomegaly, colitis/enteritis, cholecystitis/ gallbladder abnormalities, or appendicitis/appendiceal changes [2]

[10] Severe hematologic defined as thrombocytopenia, lymphopenia, neutropenia, or thrombosis [2]

[11] Defined as ICU admission indicated on case report form or receipt of invasive ventilation, vasopressors, or extracorporeal membranous oxygenation (ECMO)