BNT162b2 mRNA Vaccination Against COVID-19 is Associated with Decreased Likelihood of Multisystem Inflammatory Syndrome in U.S. Children Ages 5–18 Years

Laura D. Zambrano, PhD, MPH[1,*]; Margaret M. Newhams, MPH[2,*]; Samantha M. Olson, MPH[1]; Natasha B. Halasa, MD[3]; Ashley M. Price, MPH[1]; Amber O. Orzel, MPH[2]; Cameron C. Young[2]; Julie A. Boom, MD[4]; Leila C. Sahni, PhD, MPH[4]; Aline B. Maddux, MD[5]; Katherine E. Bline, MD[6]; Satoshi Kamidani, MD[7]; Keiko M. Tarquinio, MD[8]; Kathleen Chiotos, MD[9]; Jennifer E. Schuster, MD[10]; Melissa L. Cullimore, MD[11]; Sabrina M. Heidemann, MD[12]; Charlotte V. Hobbs, MD[13]; Ryan A. Nofziger, MD[14]; Pia S. Pannaraj, MD, MPH[15]; Melissa A. Cameron, MD[16]; Tracie C. Walker, MD[17]; Stephanie P. Schwartz, MD[17]; Kelly N. Michelson, MD[18]; Bria M. Coates, MD[18]; Heidi R. Flori, MD[19]; Elizabeth H. Mack, MD[20]; Laura Smallcomb, MD[21]; Shira J. Gertz, MD[22]; Samina S. Bhumbra, MD[23]; Tamara T. Bradford, MD[24]; Emily R. Levy, MD[25]; Michele Kong, MD[26]; Katherine Irby, MD[27]; Natalie Z. Cvijanovich, MD[28]; Matt S. Zinter, MD[29]; Cindy Bowens, MD[30]; Hillary Crandall, MD, PhD[31]; Janet R. Hume, MD[32]; Manish M. Patel, MD[1]; Angela P. Campbell, MD[1,†]; Adrienne G. Randolph, MD[2,33,†]; for the Overcoming COVID-19 Investigators**

[1]CDC COVID-19 Response Team, Atlanta, Georgia, USA
[2]Department of Anesthesiology, Critical Care, and Pain Medicine, Boston Children's Hospital, Boston, Massachusetts, USA
[3]Division of Pediatric Infectious Diseases, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, Tennessee, USA
[4]Department of Pediatrics, Baylor College of Medicine, Immunization Project, Texas Children's Hospital, Houston, Texas, USA
[5]Department of Pediatrics, Section of Critical Care Medicine, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora, Colorado, USA
[6]Division of Pediatric Critical Care Medicine, Nationwide Children's Hospital Columbus, Ohio, USA
[7]The Center for Childhood Infections and Vaccines of Children's Healthcare of Atlanta and the Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia, USA
[8]Division of Critical Care Medicine, Department of Pediatrics, Emory University School of Medicine, Children's Healthcare of Atlanta, Atlanta, Georgia, USA

Published by Oxford University Press on behalf of Infectious Diseases Society of America 2022.

[9]Division of Critical Care Medicine, Department of Anesthesiology and Critical Care, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA
[10]Division of Pediatric Infectious Diseases, Department of Pediatrics, Children's Mercy Kansas City, Kansas City, Missouri, USA
[11]Division of Pediatric Critical Care, Department of Pediatrics, Children's Hospital and Medical Center, Omaha, Nebraska, USA
[12]Division of Pediatric Critical Care Medicine, Children's Hospital of Michigan, Central Michigan University, Detroit, Michigan, USA
[13]Department of Pediatrics, Division of Infectious Diseases, University of Mississippi Medical Center, Jackson, Mississippi, USA
[14]Division of Critical Care Medicine, Department of Pediatrics, Akron Children's Hospital, Akron, Ohio, USA
[15]Division of Infectious Diseases, Children's Hospital Los Angeles and Departments of Pediatrics and Molecular Microbiology and Immunology, University of Southern California, Los Angeles, California, USA
[16]Division of Pediatric Hospital Medicine, UC San Diego-Rady Children's Hospital, San Diego, California, USA
[17]Department of Pediatrics, University of North Carolina at Chapel Hill Children's Hospital, Chapel Hill, North Carolina, USA
[18]Division of Critical Care Medicine, Department of Pediatrics, Northwestern University Feinberg School of Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois, USA
[19]Division of Pediatric Critical Care Medicine, Department of Pediatrics, Mott Children's Hospital and University of Michigan, Ann Arbor, Michigan, USA
[20]Division of Pediatric Critical Care Medicine, Medical University of South Carolina, Charleston, South Carolina, USA
[21]Department of Pediatrics, Medical University of South Carolina, Charleston, South Carolina, USA
[22]Division of Pediatric Critical Care, Department of Pediatrics, Cooperman Barnabas Medical Center, Livingston, New Jersey, USA
[23]The Ryan White Center for Pediatric Infectious Disease and Global Health, Department of Pediatrics, Indiana University School of Medicine, Indianapolis, Indiana, USA
[24]Department of Pediatrics, Division of Cardiology, Louisiana State University Health Sciences Center and Children's Hospital of New Orleans, New Orleans, Louisiana, USA

[25]Divisions of Pediatric Infectious Diseases and Pediatric Critical Care Medicine, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, Minnesota, USA
[26]Division of Pediatric Critical Care Medicine, Department of Pediatrics, University of Alabama at Birmingham, Birmingham, Alabama, USA
[27]Section of Pediatric Critical Care, Department of Pediatrics, Arkansas Children's Hospital, Little Rock, Arkansas, USA
[28]Division of Critical Care Medicine, UCSF Benioff Children's Hospital Oakland, California, USA
[29]Department of Pediatrics, Divisions of Critical Care Medicine and Allergy, Immunology, and Bone Marrow Transplant, University of California San Francisco, San Francisco, California, USA
[30]Department of Pediatrics, Division of Critical Care Medicine, University of Texas Southwestern, Children's Medical Center Dallas, Texas, USA
[31]Division of Pediatric Critical Care, Department of Pediatrics, University of Utah, Salt Lake City, Utah, USA
[32]Division of Pediatric Critical Care, University of Minnesota Masonic Children's Hospital, Minneapolis, Minnesota, USA
[33]Departments of Anaesthesia and Pediatrics, Harvard Medical School, Boston, Massachusetts, USA

*[†]These authors contributed equally
** Overcoming COVID-19 contributors are listed in the acknowledgement section

Corresponding author:
Laura D. Zambrano
U.S. Centers for Disease Control and Prevention
1600 Clifton Rd NE
MS H24-5
Atlanta, GA 30329 USA

Running title: BNT162b2 Vaccine and Likelihood of MIS-C

Abstract

Background: Multisystem inflammatory syndrome in children (MIS-C), linked to antecedent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, is associated with considerable morbidity. Prevention of SARS-CoV-2 infection or coronavirus disease 2019 (COVID-19) by vaccination might also decrease MIS-C likelihood.

Methods: In a multicenter case-control public health investigation of children ages 5–18 years hospitalized from July 1, 2021 to April 7, 2022, we compared the odds of being fully vaccinated (two doses of BNT162b2 vaccine ≥28 days before hospital admission) between MIS-C case-patients and hospital-based controls who tested negative for SARS-CoV-2. These associations were examined by age group, timing of vaccination, and periods of Delta and Omicron variant predominance using multivariable logistic regression.

Results: We compared 304 MIS-C case-patients (280 [92%] unvaccinated) with 502 controls (346 [69%] unvaccinated). MIS-C was associated with decreased likelihood of vaccination (aOR, 0.16; 95% CI, 0.10-0.26), including among children ages 5–11 years (aOR, 0.22; 95% CI, 0.10-0.52), ages 12–18 years (aOR, 0.10; 95% CI, 0.05–0.19), and during the Delta (aOR, 0.06; 95% CI, 0.02–0.15) and Omicron (aOR, 0.22; 95% CI, 0.11–0.42) variant-predominant periods. This association persisted beyond 120 days after the second dose (aOR, 0.08, 95% CI, 0.03–0.22) in 12–18 year-olds. Among all MIS-C case-patients, 187 (62%) required intensive care unit admission and 280 (92%) vaccine-eligible patients were unvaccinated.

Conclusions: Vaccination with two doses of BNT162b2 is associated with reduced likelihood of MIS-C in children ages 5–18 years. Most vaccine eligible hospitalized patients with MIS-C were unvaccinated.

Key words: MIS-C; vaccine effectiveness; Pfizer (BioNTech); COVID-19; children

Introduction

Multisystem inflammatory syndrome in children (MIS-C) is a severe hyperinflammatory condition occurring approximately four weeks post-acute infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19) [1–3]. In the United States, the Pfizer-BioNTech (BNT162b2) vaccine has been authorized for use in children and adolescents ages 6 months through 15 years under an Emergency Use Authorization by the U.S. Food and Drug Administration and is fully licensed for all persons ages ≥16 years [4,5]. Prelicensure trials indicate high immunogenicity and vaccine efficacy against laboratory-confirmed COVID-19 in children ages ≥5 years [6]. The Pfizer-BioNTech (BNT162b2) mRNA vaccine is also associated with preventing COVID-19 hospitalizations in children and adolescents [7,8].

We recently reported interim findings of an estimated 91% reduced likelihood of MIS-C hospitalization in the United States among adolescents 12–18 years old associated with two doses of BNT162b2 COVID-19 vaccine [9]. These data were among adolescents hospitalized with MIS-C through December 9, 2021, predominantly during Delta variant circulation. In this report, we extend those findings to include patients 5-11 years old who were first eligible for BNT162b2 vaccination beginning November 2, 2021 [10] and into the period of B.1.1.529 (Omicron) SARS-CoV-2 variant predominance, starting December 18, 2021 [11]. We evaluate the association of vaccination with MIS-C among patients ages 5–18 years hospitalized through April 7, 2022 by age group, by periods of predominant circulation with the Delta and Omicron SARS-CoV-2 variants, and by timing of vaccination.

Methods

Design and Setting

This evaluation of the association of COVID-19 vaccination with MIS-C was conducted across 29 hospitals in 22 U.S. states in the CDC-funded *Overcoming COVID-19* (OC-19) pediatric vaccine

effectiveness network (sites and investigators are listed in **Supplement 1**). Strengthening reporting of observational studies in epidemiology (STROBE) guidelines were followed [12]. The surveillance protocol was approved by CDC and by the other participating institutions as a public health surveillance activity; this review was conducted in accordance with applicable federal laws and CDC policy [13].

We applied a test-negative case-control design [14,15], often used to estimate vaccine effectiveness [8,16,17], to evaluate the association between MIS-C and prior vaccination with the BNT162b2 vaccine with case-patients hospitalized with MIS-C and SARS-CoV-2 negative control patients hospitalized for SARS-CoV-2-unrelated reasons. We secondarily aimed to describe organ system involvement and critical disease in vaccinated vs unvaccinated MIS-C patients.

Participants

Children ages 5 to 18 years hospitalized at OC-19 sites between July 1, 2021 and April 7, 2022, were enrolled through active surveillance for MIS-C. Case-patients were identified by review of hospital admission logs or electronic medical records and included those hospitalized with MIS-C as the primary reason for admission. Applying the CDC case definition for MIS-C [18], cases required multisystem (≥2) organ involvement, elevated inflammatory markers, recorded or subjective fever ≥38ºC lasting ≥24 hours, and laboratory evidence of recent SARS-CoV-2 infection by RT-PCR, antigen, or serology (**Supplemental Figure 1**). Controls tested negative for SARS-CoV-2 infection by RT-PCR or antigen-based assay either within 7 days prior to hospital admission or during their hospitalization, and were admitted for reasons unrelated to SARS-CoV-2 and did not meet clinical criteria for MIS-C. Controls were matched to case-patients by site, age group (5–11, 12–15, 16–18 years), and targeted admission within approximately +/- 3 weeks (maximum 4 weeks) of an enrolled case.

We excluded suspected MIS-C patients if they failed to meet all fever and organ system involvement criteria (including specification of ≥ 2 organ systems), or if they did not have molecular or serologic

evidence of current or recent SARS-CoV-2 infection within 90 days of admission or during their hospitalization. While a 2:1 control-to-case ratio was targeted, a minimum of one matched control per case-patient was required for inclusion. Information on vaccination status was collected after enrollment.

Data Collection

Demographic, clinical, and laboratory data were collected by trained personnel through standardized interviews and medical records abstraction. MIS-C patients were adjudicated at the site level, and clinical criteria were reviewed by CDC to ensure all MIS-C patients met inclusion criteria. COVID-19 vaccination status, including manufacturer, dates of vaccination, number of doses, and location, were ascertained through parent interviews and a review of source documentation. Documents acceptable for vaccine verification included patient vaccination cards, hospital records, electronic medical records, state immunization information systems, and vaccine records requested from clinics, pharmacies, and schools. Vaccinations were verified as received if source documentation was identified or if the interviewee provided a plausible date and location of vaccination.

Classification of Vaccination Status

Vaccination status was classified according to vaccine receipt before the case-patient hospital admission date (reference date). Participants were classified as unvaccinated if no vaccine was received before the reference date and fully vaccinated if they had received two BNT162b2 doses at least 28 days before the reference date. We chose 28 days as the cutoff for all cases and controls to account for a delay between potential infection with SARS-CoV-2 and MIS-C and to exclude the possibility of including cases of MIS-C potentially associated with vaccination, which are likely rare and would be expected to occur early after vaccination [19]. Partial vaccination was defined as having received only one vaccine dose before the reference date or receiving a second dose <28 days prior to the reference date. Patients

who received their 2nd dose between 14 and 27 days prior to the reference date were included in a sensitivity analysis, but were excluded from the primary analysis. Patients were excluded if they received a different type of COVID-19 vaccine, such as AD.26COV2.S (Janssen/Johnson & Johnson) or mRNA-1273 (Moderna) if they received heterologous doses (e.g., BNT162b2 for the first dose and mRNA-1273 for the second), or if they received >2 doses of any vaccine.

While full mRNA vaccination against acute COVID-19 is usually considered to be 14 days after a second dose [20], the timepoint at which vaccination may confer protection against MIS-C is unclear; therefore, we performed a sensitivity analysis including patients vaccinated at least 14 days before the reference date. Duration of immunity was assessed by separately comparing those hospitalized ≥121 days after the second dose. Patient inclusion in each of these sub-analyses was contingent upon hospitalization after the enrollment eligibility date (e.g. the date at which a patient could plausibly be considered fully vaccinated). Each eligibility date was calculated first using the date the vaccine was recommended for each age group by the Advisory Committee on Immunization Practices, adding 21 days required between the first and second dose, and finally adding the specified time interval between the second dose and hospitalization (**Supplemental Table 2**).

MIS-C Severity and Organ System Involvement

Data were collected on disease severity, survival, and organ system involvement up until the point of hospital discharge or death to characterize the clinical features and outcomes of included MIS-C case-patients (**Figures 2a-b and 3a-b**). Descriptive statistics were calculated for binary variables reflective of disease severity (ICU admission, noninvasive ventilation, invasive mechanical ventilation, vasopressor support, extracorporeal membrane oxygenation, or death). Organ system involvement among MIS-C case-patients was likewise assessed descriptively, with overlap of ≥2 organ systems analyzed and displayed graphically (**Figure 2b**). MIS-C severity and organ system involvement was also considered

in the context of median hospital length of stay and median number of organ systems involved. Findings on severity and organ system involvement were stratified by age group (5–11 years, 12–18 years).

Statistical Analysis

We compared the odds of being fully vaccinated with two doses of the BNT162b2 vaccine (exposed) vs. being unvaccinated (unexposed) in MIS-C case-patients compared with controls. We used multivariable logistic regression models, controlling for age at hospital admission (continuous, in years), sex, race and ethnicity, site of enrollment, and presence of an underlying medical condition. Adjusted odds ratios (aOR) <1.0 indicated that MIS-C was associated with a reduced likelihood of vaccination. The aOR can be used to estimate vaccine effectiveness for the prevention of MIS-C through the following equation: vaccine effectiveness (%) = (1 – aOR) X 100 [14,17,21].

This association between vaccination and MIS-C was further explored through stratified secondary analyses by age group (5–11 and 12–18 years). Given the earlier authorization date and longer follow-up time available among adolescents 12–18 years, we further stratified adolescents by time point since vaccination to examine the duration of immunity (28–120 days and ≥121 days). The later authorization date for 5-11 year olds precluded the ability to examine duration of immunity. The proportion of SARS-CoV-2 infections estimated to be attributable to the Omicron variant exceeded 50% during the week beginning December 18, 2021 [11,22], and the onset of MIS-C most frequently occurs within 2 to 4 weeks of SARS-CoV-2 infection [1–3]; therefore, we dichotomized the dates of patient hospitalization before and on/after January 1, 2022 (December 18, 2021, plus 2 weeks) to separately identify MIS-C cases attributed to periods of Delta vs. Omicron variant predominance. An additional model was constructed to evaluate the impact of time since vaccination by replacing the vaccination exposure variable with a time variable (unvaccinated, vaccinated 28–120 days before hospitalization, and

vaccinated ≥121 days before hospitalization). Analyses were conducted using SAS V9.4 (SAS Institute, Cary, NC) and R Studio (V1.2.5033).

Results

Participants

During July 1, 2021, to April 7, 2022, 1016 patients were enrolled from 29 pediatric hospitals in 22 states; 210 ineligible patients were excluded to yield 304 MIS-C case-patients and 502 controls (**Figure 1**, **Supplemental Table 3**). The most common reasons for exclusion from the primary analysis were partial vaccination (n=79), age-ineligible or hospitalization before the eligibility date (n=53), and receipt of the first vaccine dose <14 days prior to hospitalization (n=23). Twenty-six children who received their second dose between 14 and 27 days prior to hospitalization were excluded from the primary analysis, but included as a sensitivity analysis. If vaccinated, all patients were hospitalized ≥28 days after their second dose for the primary analysis.

Among enrolled patients, MIS-C case-patients differed from controls by sex and presence of underlying health conditions (**Table 1)**. Enrolled MIS-C case-patients were evenly distributed between periods of Delta (n=145, 48%) and Omicron (n=159, 52%) variant predominance; we assumed that the predominant variant shifted from Delta to Omicron after December 18, 2021 [11,22]. Of note, among MIS-C case-patients in the 12–18 year age group, 122/160 (84%) were hospitalized during the period of Delta predominance, whereas 121/144 (76%) of patients in the 5–11 year age group were hospitalized during the period of Omicron predominance. The majority of vaccinated MIS-C case-patients were hospitalized within 50 days of their 2nd vaccine dose (**Table 1, Supplemental Figure 2**).

Severe Clinical Outcomes and Organ System Involvement among MIS-C Case-Patients

Organ system involvement among MIS-C patients are shown in **Figure 2a** and the combinations of organ system involvement in **Figure 2b**. Of the 304 case-patients, 62% were admitted to the ICU, 21%

required noninvasive ventilation, 8% required invasive mechanical ventilation, and 43% required vasopressor support. **Figure 3a** shows the proportions of patients admitted to the ICU, receiving noninvasive ventilation or vasopressor support by age group (5–11 and 12–18 years).

Among 304 MIS-C case-patients, 280 (92%) were unvaccinated. Among case-patients 12–18 years of age, a lower proportion of vaccinated patients required life support or died (44.4% of unvaccinated vs 0% of vaccinated patients, p=0.05) during the period of Delta variant predominance; no significant difference in clinical outcomes by vaccination status was evident during the period of Omicron variant predominance. Among 5–11 year-olds, most of whom were hospitalized during Omicron predominance, MIS-C requiring life-support or resulting in death likewise did not differ by vaccination status (**Figure 3b, Supplemental Table 4**). One unvaccinated MIS-C case-patient in the 12–18 year-old age group required ECMO, and one unvaccinated patient in the 5–11 year-old age group died.

Association between MIS-C and BNT162b2 Vaccination

Full vaccination was less common in MIS-C case-patients compared with controls, (7.9% vs 31.1%) (**Figure 4)**. Overall, MIS-C was strongly associated with a lower likelihood of vaccination with two doses of BNT162b2 mRNA vaccine ≥28 days before hospitalization, with an aOR of 0.16 (95% CI, 0.10–0.26). Using a timeframe of ≥14 days before vaccination, the aOR was similar at 0.17 (95% CI, 0.10–0.27). When stratified by age, the aOR, was 0.22 (95% CI, 0.10–0.52) for children ages 5–11 years and 0.10 (95% CI, 0.05–0.19) for adolescents ages 12–18 years. Association between vaccination and protection against MIS-C was significant among children ages 12–18 years during both periods of variant predominance (aOR, 0.06; 95% CI, 0.02-0.17 for Delta; aOR, 0.08; 95% CI, 0.02-0.29 for Omicron). Among patients ages 12–18 years, MIS-C was also associated with a lower likelihood of hospitalization in patients vaccinated 120 to 200 days before hospitalization (aOR, 0.08; 95% CI, 0.03–0.22) (**Figure 4)**.

Discussion

In this public health investigation of children admitted to 29 U.S. pediatric hospitals between July 1, 2021, and April 7, 2022, BNT162b2 vaccination was less likely among patients with MIS-C than in children hospitalized for other non-SARS-CoV-2-related reasons. This finding was observed among children 5–11 years and 12–18 years, and in adolescents during periods of both Delta and Omicron predominance. Most children ages 5–18 years with MIS-C had severe clinical outcomes, including 62% requiring ICU admission and nearly half having a life-threatening illness. Overall 92% of the MIS-C patients were unvaccinated, including 93% of those with life-threatening or fatal illness. The aOR in this analysis corresponds to estimated overall vaccine effectiveness of 84% for vaccination with two doses of BNT162b2 to prevent MIS-C in patients ages 5-18 years. For 12–18 year olds who had a longer period of vaccine eligibility, the protective association persisted four to seven months after vaccination.

This investigation is one of the first to examine the association of BNT162b2 vaccination with prevention of MIS-C using a case-control design. We expand our prior preliminary findings of high vaccine effectiveness against MIS-C among 12–18 year-olds [9]. Our findings are also consistent with two prospective studies demonstrating decreased MIS-C incidence associated with vaccination prior to the emergence of the Omicron variant [23,24]. Levy et al. found that MIS-C incidence from September 1–October 31, 2021 decreased by 91% after dose one of BNT162b2 vaccine in France; no MIS-C cases were reported among fully vaccinated adolescents [23]. In a separate national cohort study in Denmark, Nygaard et al. found that MIS-C incidence among children ages 0–17 years declined by 94% among vaccinated children between August 1, 2021 and February 1, 2022 [24]. High VE has been reported against development of severe acute COVID-19 in children and adults [7,8,16,17], but MIS-C is a presumably post-infectious complication of SARS-CoV-2 infection. Waning vaccine-induced immunity has been highlighted as a concern, and the Omicron variant has been associated with immune escape and vaccine resistance among children and adults who have received two doses of the BNT162b2 vaccine [25–27]; however, the point estimates for the effect sizes we observed in preventing MIS-C after

vaccination during the period of Omicron predominance were overall larger than reported in pediatric vaccine effectiveness studies against symptomatic COVID-19 [25–27] and also in severe COVID-19 within the same OC-19 network [7,8]. This investigation also demonstrated sustained protection against MIS-C across both variant predominant periods in adolescents and among patients ages 5-18 years, as well as protection against severe clinical outcomes during the period of Delta variant predominance. These results reiterate the benefits of pediatric COVID-19 vaccinations and the public health imperative of improving pediatric vaccine acceptance and uptake.[28]

Limitations

This investigation has several limitations. First, this analysis used a control population of patients hospitalized for a non-SARS-CoV-2-related indication who tested negative for SARS-CoV-2. While hospitalized controls should support equivalent access to care between study arms, they may not represent the general population. Residual confounding may be present by unmeasured covariates and bias cannot be fully excluded in these observational evaluations. Second, because SARS-CoV-2-negative controls were included in this analysis, we could not separately examine protection from progression to MIS-C after infection and non-hospitalized patients with mild COVID-19 or asymptomatic SARS-CoV-2 infection 3-6 weeks later may be an alternate control group. Third, the case definition for MIS-C includes children up to age 20 years, and while mRNA-1273 (Moderna) is recommended for persons ages ≥18 years, this analysis assessed only the association between BNT162b2 and MIS-C. Fourth, the sample size was insufficient to assess the association between MIS-C and vaccination beyond 4 months after the second dose, and we had insufficient numbers of patients with a booster dose to assess effectiveness of booster vaccines. Fifth, given that most site investigators principally worked in the ICU, this investigation may not have captured all patients admitted to the general hospital ward. Finally, while the point estimate of the odds ratio appeared to be attenuated

among children ages 5–11 years, most of these children were hospitalized during the period of Omicron predominance. Children ages 5–11 years who received vaccination at the earliest opportunity (November 2, 2021) were only eligible for inclusion less than two weeks before the beginning of the Omicron-predominant period, so it is not possible to isolate the independent impact of age and variant predominance on the association between vaccination and MIS-C. Finally, if vaccination protects against the MIS-C, we cannot ascertain if it is due to prevention of SARS-CoV-2 infection or another mechanism.

Conclusions

Vaccination with two doses of BNT162b2 was was associated with lower frequency of MIS-C compared to hospitalized SARS-CoV-2 negative controls. MIS-C was generally associated with severe clinical outcomes, which might be averted by COVID-19 vaccination. These findings are consistent with MIS-C risk reduction associated with COVID-19 vaccination and add evidence to support the vaccination in the pediatric population.

NOTES:

Author contributions: Drs. Zambrano, Newhams and Randolph had full access to all of the data in the investigation and take responsibility for the integrity of the data. Dr. Zambrano takes responsibility for the accuracy of the data analysis.
Concept and design: Zambrano, Newhams, Olson, Price, Halasa, Patel, Campbell, Randolph
Acquisition, analysis, or interpretation of the data: Zambrano, Newhams, Halasa, Boom, Sahni, Kamidani, Tarquinio, Maddux, Heidemann, Bhumbra, Bline, Nofziger, Hobbs, Bradford, Cvijanovich, Irby, Mack, Cullimore, Pannaraj, Kong, Walker, Gertz, Michelson, Cameron, Chiotos, Maamari, Schuster, Orzel
Drafting of the manuscript: Zambrano, Patel, Campbell, Randolph
Critical revision of the manuscript for important intellectual content: Zambrano, Olson, Price, Patel, Campbell, Randolph
Statistical analysis: Zambrano, Olson, Price

Overcoming COVID-19 Network Study Group Investigators and Collaborators

(listed in PubMed, and ordered by U.S. State)

The following study group members were all closely involved with the design, implementation, and oversight of the Overcoming COVID-19 study.

Alabama: Children's of Alabama, Birmingham. Michele Kong, MD; Meghan Murdock, RN.

Arizona: University of Arizona, Tucson. Mary Glas Gaspers, MD, MPH; Katri V. Typpo, MD, MPH; Connor P. Kelley, MPH.

Arkansas: Arkansas Children's Hospital, Little Rock. Katherine Irby, MD; Ronald C. Sanders, MD; Masson Yates; Chelsea Smith.

California: Rady Children's Hospital, San Diego. Melissa A. Cameron, MD; Katheryn Crane, RN.

California: UCSF Benioff Children's Hospital Oakland, Oakland. Natalie Z. Cvijanovich, MD; Geraldina Lionetti, MD; Juliana Murcia-Montoya, BS.

California: UCSF Benioff Children's Hospital, San Francisco. Matt S. Zinter, MD; Denise Villarreal-Chico, BA.

California: Children's Hospital Los Angeles, Los Angeles. Pia S. Pannaraj, MD, MPH; Adam L. Skura, BS; Daniel Hakimi; Harvey Peralta, BA; Yea Ji Sea, MS; Kennis-Grace Mrotek.

Colorado: Children's Hospital Colorado, Aurora. Aline B. Maddux, MD, MSCS; Justin M. Lockwood, MD; Emily Port, BA, PMP; Imogene Carson, MS.

Florida: Holtz Children's Hospital, Miami. Brandon M. Chatani, MD.

Georgia: Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta. Satoshi Kamidani, MD; Keiko M. Tarquinio, MD; Laila Hussaini, MPH; Nadine Baida.

Illinois: Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago. Kelly N. Michelson, MD, MPH; Bria M. Coates, MD; Simone T. Rhodes, BS; Hassan A. Khan, BS.

Indiana: Riley Hospital for Children, Indianapolis. Samina S. Bhumbra, MD; Courtney M. Rowan, MD, MS; Mary Stumpf, MS, CCRC.

Louisiana: Children's Hospital of New Orleans, New Orleans. Tamara T. Bradford, MD; Marla S. Johnston, RN, MSN.

Massachusetts: Boston Children's Hospital, Boston. Adrienne G. Randolph, MD; Margaret M. Newhams, MPH; Suden Kucukak, MD; Amber O. Orzel, MPH; Cameron C. Young; Sabrina R. Chen, BS; Benjamin J. Boutselis; Timothy P. McCadden; Kasey R. Stewart; Edie Weller, PhD; Laura Berbert, MS; Jie He, MS.

Michigan: Children's Hospital of Michigan, Detroit. Sabrina M. Heidemann, MD.

Michigan: University of Michigan CS Mott Children's Hospital, Ann Arbor. Heidi R. Flori, MD, FAAP; Patrick Moran, MD.

Minnesota: University of Minnesota Masonic Children's Hospital, Minneapolis, Janet R. Hume, MD, PhD; Ellen R. Bruno, MS; Lexie A. Goertzen, BA.

Minnesota: Mayo Clinic, Rochester. Emily R. Levy, MD; Supriya Behl, MSc; Noelle M. Drapeau, BA.

Mississippi: Children's Hospital of Mississippi, Jackson. Charlotte V. Hobbs, MD; Lora Martin, MSN; Lacy Malloch, BS; Virginia Austin Harrison, MD; Cameron Sanders, BS; Kayla Patterson, MS; Chidinma A. Chikere, MPH, BSN, RN.

Missouri: Children's Mercy Kansas City, Kansas City. Jennifer E. Schuster, MD; Abigail Kietzman, BS, ACRP-CP; Melissa Sullivan, RN, BSN.

Nebraska: Children's Hospital & Medical Center, Omaha. Melissa L. Cullimore, MD, PhD; Valerie H. Rinehart, MD; Lauren A. Hoody.

New Jersey: Cooperman Barnabas Medical Center, Livingston. Shira J. Gertz, MD.

North Carolina: University of North Carolina at Chapel Hill, Chapel Hill. Stephanie P. Schwartz, MD; Tracie C. Walker, MD; Paris C. Bennett.

Ohio: Akron Children's Hospital, Akron. Ryan A. Nofziger, MD; Nicole A. Twinem, RN, ADN; Merry L. Tomcany, RN, BSN.

Ohio: Cincinnati Children's Hospital, Cincinnati. Mary Allen Staat, MD, MPH; Chelsea C. Rohlfs, BS, MBA.

Ohio: Nationwide Children's Hospital, Columbus. Katherine Bline, MD; Amber Wolfe, RN, BSN.

Pennsylvania: Children's Hospital of Philadelphia, Philadelphia. Kathleen Chiotos, MD, MSCE; Rebecca L. Douglas, RN, BSN; Kathlyn Phengchomphet, BA.

South Carolina: MUSC Children's Health, Charleston. Elizabeth H. Mack, MD, MS; Megan M. Bickford, MS; Lauren E. Wakefield, MHA; Laura Smallcomb, MD.

Tennessee: Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville. Natasha B. Halasa, MD, MPH; Haya Hayek, MD; Yesenia Romero, MS.

Texas: Texas Children's Hospital and Baylor College of Medicine, Houston. Julie A. Boom, MD; Leila C. Sahni, PhD, MPH; Jennifer N. Oates, MPH.

Texas: University of Texas Southwestern, Children's Medical Center Dallas, Dallas. Mia Maamari, MD; Cindy Bowens, MD, MSCS.

Utah: Primary Children's Hospital, Salt Lake City. Hillary Crandall, MD, PhD.

CDC COVID-19 Response Team on Overcoming COVID-19: Samantha M. Olson, MPH; Ashley M. Price, MPH; Laura D. Zambrano, PhD, MPH; Angela P. Campbell, MD, MPH; Manish M. Patel, MD, MPH.

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

Funding source: This investigation was funded through a contract (No. 75D30121C10297) from the Centers for Disease Control and Prevention National Center for Immunization and Respiratory Diseases, paid to institutions. Emily R. Levy reports the following support for this work, paid to institution: U.S. Centers for Disease Control and Prevention: CDC 75D30120C07725-01; Understanding COVID-19 among critically ill children in the PALISI network. Keiko M. Tarquinio reports CDC- subcontract GENFD000202411, primary contract 75D309121C10297.

Conflicts of interest: All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. Jennifer E. Schuster reports institutional support from Merck for an RSV research study, unrelated to the current work. Adrienne G. Randolph reports institutional support from the National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH), royalties from UpToDate as the Pediatric Critical Care Section Editor, and participation on a data safety monitoring board (DSMB) for a National Institute of Child Health and Human Development-funded study. Pia S. Pannaraj reports institutional support from AstraZeneca and Pfizer, consulting fees from Sanofi-Pasteur and Seqirus, payment from law firms for expert testimony, participation on a Division of Microbiology and Infectious Diseases DSMB (paid to author), and an unpaid leadership role in the California Immunization Coalition. Ryan A. Nofziger reports institutional support from NIH for participation in a multicenter influenza study. Satoshi Kamidani reports institutional support from NIH and Pfizer. Charlotte V. Hobbs reports consulting fees from Dynamed (clinical database, reviewer) and honoraria from Biofire/Biomerieux, and funding from CDC to University of Mississippi Medical Center. Natasha B. Halasa reports grants from Sanofi and Quidel and an educational grant from Genentech. Natalie Z. Cvijanovich reports a speaker's registration discount at the Society of Critical Care Medicine meeting and grants or contracts from the NIH, unrelated to this work and paid to institution. Samina S. Bhumbra reports receipt of an NIH, NIAID training grant during September 1, 2019–August 31, 2020 (T32AI007637). Melissa L. Cullimore reports grants or contracts unrelated to this work from the CDC, paid to institution. Heidi R. Flori reports grants or contracts unrelated to this work from the NHLBI and NICHD, paid to institution; support for attending meetings and/or travel from the Society of Critical Care Medicine; participation on DSMB for Cardiothoracic Surgery trial – single center and for intrathecal chemotherapy trial; unpaid leadership or fiduciary role on Michigan Thoracic Society Executive Committed and PALISI network Executive Committee, other financial or non-financial interests in Lucira Health advisory committee and Aerogen Pharma – advisory - unfunded. Janet R. Hume reports grants or contracts unrelated to this work from the NICHD, paid to institution; participation on DSMB for institutional study at the University of Minnesota, "Magnesium sulfate as adjuvant analgesia and its effect on opiate use by post-operative transplant patients in the pediatric ICU)" (Magnesium sulfate as IND per FDA; no financial reimbursements). Emily R. Levy reports the following grants or contracts unrelated to this work and paid to institution: AI 144301-01: An Observational Cohort Study to Determine Late Outcomes and Immunological Responses after Infection with SARS-CoV-2 in Children with and without MIS-C and NIH AI 154470-01: Immunobiology of Influenza Virus-related Critical Illness in Young Hosts. Elizabeth H. Mack reports an unpaid role as VP of SC Chapter of the American Academy of Pediatrics. Laura Smallcomb reports conference attendance allowance from Medical University of South Carolina. Matthew Zinter reports the following grant or contract unrelated to this work: NHLBI K23HL146936. No other potential conflicts of interest were disclosed.

References

1. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. N Engl J Med **2020**; 383:334–346.

2. Belay ED, Abrams J, Oster ME, et al. Trends in Geographic and Temporal Distribution of US Children With Multisystem Inflammatory Syndrome During the COVID-19 Pandemic. JAMA Pediatr **2021**;

3. Dufort EM, Koumans EH, Chow EJ, et al. Multisystem Inflammatory Syndrome in Children in New York State. N Engl J Med **2020**; 383:347–358.

4. Food and Drug Administration. FDA Approves First COVID-19 Vaccine. Silver Spring, MD: 2021. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-first-covid-19-vaccine.

5. Fleming-Dutra KE, Wallace M, 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. Available at: http://dx.doi.org/10.15585/mmwr.mm7126e2.

6. Frenck RW, Klein NP, Kitchin N, et al. Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents. N Engl J Med **2021**; 385:239–250.

7. Olson S, Newhams M, Halasa N, et al. Effectiveness of BNT162b2 Vaccine against Critical Covid-19 in Adolescents. N Engl J Med **2022**; 386:713–723.

8. Price A, Olson S, Newhams M, et al. BNT162b2 Protection against the Omicron Variant in Children and Adolescents. N Engl J Med **2022**; 386:1899–1909.

9. Zambrano LD, Newhams MM, Olson SM, Halasa NB, Price AM. Effectiveness of BNT162b2 (Pfizer-BioNTech) mRNA Vaccination Against Multisystem Inflammatory Syndrome in Children Among Persons Aged 12 – 18 Years — United States , July – December 2021. Morb Mortal Wkly Rep **2022**; 71:52–58.

10. Woodworth KR, Moulia D, 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. Morb Mortal Wkly Rep **2021**; 70:1579–1583.

11. Lambrou AS, Shirk P, Steele MK, et al. Genomic Surveillance for SARS-CoV-2 Variants: Predominance of the Delta (B.1.617.2) and Omicron (B.1.1.529) Variants — United States, June 2021–January 2022. Morb Mortal Wkly Rep **2022**; 71:206–211.

12. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. Lancet **2007**; 370:1453–1457.

13. Office of the Federal Register. Title 45. In: Code of federal regulations: a point in time eCFR system. February 22, 2022. 2022.

14. Foppa IM, Haber M, Ferdinands JM, Shay DK. The case test-negative design for studies of the effectiveness of influenza vaccine. Vaccine **2013**; 31:3104–3109. Available at: http://dx.doi.org/10.1016/j.vaccine.2013.04.026.

15. Lewnard JA, Patel MM, Jewell NP, et al. Theoretical Framework for Retrospective Studies of the Effectiveness of SARS-CoV-2 Vaccines. Epidemiology **2021**; 32:508–517.

16. Tenforde MW, Patel MM, Ginde AA, et al. Effectiveness of Severe Acute Respiratory Syndrome Coronavirus 2 Messenger RNA Vaccines for Preventing Coronavirus Disease 2019 Hospitalizations in the United States. Clin Infect Dis **2021**; 37232:1–10.

17. Tenforde MW, Self WH, Adams K, et al. Association Between mRNA Vaccination and COVID-19 Hospitalization and Disease Severity. JAMA **2021**; 326:2043–2054. Available at: https://jamanetwork.com/.

18. CDC Health Alert Network. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). Atlanta, GA USA: 2020. Available at: https://emergency.cdc.gov/han/2020/han00432.asp.

19. Yousaf AR, Cortese MM, Taylor AW, et al. Reported cases of multisystem inflammatory syndrome in children aged 12–20 years in the USA who received a COVID-19 vaccine, December, 2020, through August, 2021: a surveillance investigation. Lancet Child Adolesc Heal **2022**; Available at: www.thelancet.com/child-adolescentPublishedonline.

20. Centers for Disease Control and Prevention. Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Approved or Authorized in the United States. 2021. Available at: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html.

Accessed 10 December 2021.

21. Tenforde MW, Patel MM, Ginde AA, et al. Effectiveness of Severe Acute Respiratory Syndrome Coronavirus 2 Messenger RNA Vaccines for Preventing Coronavirus Disease 2019 Hospitalizations in the United States. Clin Infect Dis **2021**;

22. Marks KJ, Whitaker M, Anglin O, et al. Hospitalizations of Children and Adolescents with Laboratory-Confirmed COVID-19 — COVID-NET, 14 States, July 2021–January 2022. MMWR Morb Mortal Wkly Rep **2022**; 71:271–278.

23. Levy M, Recher M, Hubert H, et al. Multisystem Inflammatory Syndrome in Children by COVID-19 Vaccination Status of Adolescents in France. JAMA

24. 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 Heal **2022**; 2:1–7.

25. Fleming-Dutra KE, Britton A, Shang N, et al. Association of Prior BNT162b2 COVID-19 Vaccination With Symptomatic SARS-CoV-2 Infection in Children and Adolescents During Omicron Predominance. **2022**; :1–10.

26. Katz SE, Edwards K. Protecting Children Against Omicron. JAMA - J Am Med Assoc **2022**; 327:2195–2197.

27. Dorabawila V, Hoefer D, Bauer UE, Bassett MT, Lutterloh E, Rosenberg ES. Risk of Infection and Hospitalization Among Vaccinated and Unvaccinated Children and Adolescents in NewYork After the Emergence of the OmicronVariant. JAMA - J Am Med Assoc **2022**; 327:2242–2244.

28. Bilotta C, Perrone G, Zerbo S, Argo A. COVID-19 Vaccination in Pediatric Population: A Necessity or Obstruction to the Protection of the Right to Health? Biojuridical Perspective. Front Public Heal **2022**; 10:1–6.

Table 1. Characteristics of MIS-C Case-Patients and Control Patients Without COVID-19[a]

	No. (%)			
	5 to 11 years		12 to 18 years	
	MIS-C case-patients	Controls	MIS-C case-patients	Controls
Characteristic (no. unknown)	(n = 144)	(n = 230)	(n = 160)	(n = 272)
Median age, yrs (IQR)	8.5 (6.9 - 10.3)	7.9 (6.7 - 9.7)	14.3 (13.1 - 15.9)	14.6 (13.4 - 15.9)
Age, y				
12 - 15	n.a.	n.a.	127 (79.4)	210 (77.2)
16 - 18	n.a.	n.a.	33 (20.6)	62 (22.8)
Sex				
Female	52 (36.1)	108 (47.0)	44 (27.5)	150 (55.1)
Race/ethnicity				
White, non-Hispanic	60 (41.7)	96 (41.7)	53 (33.1)	101 (37.1)
Black, non-Hispanic	42 (29.2)	56 (24.3)	60 (37.5)	71 (26.1)
Asian, non-Hispanic	3 (2.1)	4 (1.7)	1 (0.6)	10 (3.7)
Hispanic, any race	23 (16.0)	55 (23.9)	26 (16.3)	65 (23.9)
Multiple/Other, non-Hispanic	11 (7.6)	16 (7.0)	13 (8.1)	15 (5.5)
Unknown	5 (3.5)	3 (1.3)	7 (4.4)	10 (3.7)
U.S. Census Region*				
Northeast	23 (16.0)	39 (17.0)	11 (6.9)	16 (5.9)
Midwest	63 (43.8)	93 (40.4)	44 (27.5)	69 (25.4)
South	36 (25.0)	64 (27.8)	68 (42.5)	118 (43.4)
West	22 (15.3)	34 (14.8)	37 (23.1)	69 (25.4)
Month of admission				
July 2021	n.a.	n.a.	5 (3.1)	4 (1.5)
August 2021	n.a.	n.a.	18 (11.3)	30 (11.0)
September 2021	n.a.	n.a.	37 (23.1)	39 (14.3)
October 2021	n.a.	n.a.	32 (20.0)	67 (24.6)
November 2021	n.a.	n.a.	17 (10.6)	38 (14.0)
December 2021	23 (16.0)	29 (12.6)	13 (8.1)	26 (9.6)
January 2022	74 (51.4)	119 (51.7)	25 (15.6)	41 (15.1)
February 2022	40 (27.8)	60 (26.1)	13 (8.1)	21 (7.7)
March 2022	6 (4.2)	21 (9.1)	0	6 (2.2)
April 2022	1 (0.7)	1 (0.4)	0	0
Attendance at in-person school or daycare (n=384)	76 (87.4)	61 (79.2)	71 (73.2)	82 (66.7)
≥1 chronic medical conditions	61 (42.4)	171 (74.3)	88 (55.0)	188 (69.1)
Respiratory disease, including asthma	20 (13.9)	94 (40.9)	25 (15.6)	83 (30.5)
Cardiovascular disease	0 0	16 (7.0)	5 (3.1)	22 (8.1)
Endocrine or metabolic (including obesity)	42 (29.2)	62 (27.0)	56 (35.0)	98 (36.0)
Other[b]	19 (13.2)	122 (53.0)	38 (23.8)	137 (50.4)
Vaccination status[c]				
BNT162b2 2-dose series 28 - 41 days prior to hospital admission	4 (2.8)	15 (6.5)	2 (1.3)	8 (2.9)

BNT162b2 2-dose series 42 - 120 days prior to hospital admission	6 (4.2)	28 (12.2)	5 (3.1)	44 (16.2)
BNT162b2 2-dose series ≥121 days prior to hospital admission	n.a.	n.a.	7 (4.4)	61 (22.4)
Unvaccinated	134 (93.1)	187 (81.3)	146 (91.3)	159 (58.5)
If fully vaccinated, median days from second vaccine to reference date of hospitalization (IQR)[δδ]	47 (31 - 71)	47 (36 - 56)	110 (63 - 158)	130 (75 - 189)

[a] Up to 2 controls were matched to each case by site, age group (5 - 11; 12 - 15; 16 - 18 years), and approximate +/- 3 week date of admission, with preferential selection of controls closest in age to each case-patient.

[b] Other underlying conditions include neurologic/neuromuscular disease, oncologic history, autoimmune disease or immunosuppresion)

[c] A total of 24 MIS-C case-patients and 55 controls were considered partially vaccinated (defined as 1st dose received ≥14 days before hospitalization; no 2nd dose or 2nd dose received 0 to 13 days before hospitalization). As a sensitivity analysis, patients who had been vaccinated between 14 and 27 days before vaccination and their matched controls were added to the cases included in our primary analysis. This added a total of 5 case-patients and 21 controls

FIGURE LEGENDS:

Figure 1: Participant Flow Through a Study of Association Between BNT162b2 COVID-19 mRNA Vaccination and MIS-C

[a] Children who received a 2nd vaccine dose between 14 and 27 days prior to hospitalization were included in a sensitivity analysis examining the association between vaccination ≥14 days prior to hospitalization and MIS-C; however, they were excluded from the primary analysis.

Figure 2 Organ System Involvement among MIS-C case-patients.

A. Organ System Involvement, by Age Group
B. Overlap in Organ System Involvement Among MIS-C Patients[b]

Figure 3. Clinical outcomes among MIS-C case-patients.

A. Proportion of MIS-C Patients requiring ICU admission, vasopressor support, and noninvasive or invasive mechanical ventilation.
B. Comparison of MIS-C cases resulting in life support or death between vaccinated and unvaccinated patients, by period of variant predominance and by age group

[a]Visualization of intersecting organ system involvement among included MIS-C patients, including the number of patients with involvement of each organ system (left) and a combination matrix representing the number of MIS-C patients with specific combinations of overlapping organ system involvement.

Figure 4. Association between MIS-C and Prior BNT162b2 Vaccination among children ages 5 - 18 years.

Subgroup	Vaccinated case-patients / total case-patients (%)	Vaccinated control patients / total control patients (%)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Overall				
≥28 Days since 2nd dose	24/304 (7.9)	156/502 (31.1)	0.19 (0.12 - 0.30)	0.16 (0.10 - 0.26)
By age group, y				
5 - 11	10/144 (6.9)	43/230 (18.7)	0.32 (0.16 - 0.67)	0.22 (0.10 - 0.52)
12 - 18	14/160 (8.8)	113/272 (41.5)	0.13 (0.07 - 0.25)	0.10 (0.05 - 0.19)
Ages 12 - 18 y, by period of variant predominance				
Delta	5/122 (4.1)	71/204 (34.8)	0.08 (0.03 - 0.21)	0.06 (0.02 - 0.17)
Omicron	9/38 (23.7)	42/68 (61.8)	0.19 (0.08 - 0.47)	0.08 (0.02 - 0.29)
Ages 12 - 18 y, interval				
28 - 120 Days since 2nd dose	7/153 (4.6)	52/211 (24.6)	0.15 (0.06 - 0.33)	0.10 (0.04 - 0.25)
≥121 Days since 2nd dose[c]	7/131 (5.3)	61/196 (31.1)	0.12 (0.06 - 0.28)	0.08 (0.03 - 0.22)

[a] Given similarities in the aOR point estimates by time interval between vaccine dose 2 and illness onset, the stratified analyses by period of variant predominance and age group used the subset of patients included at the 28-day timepoint

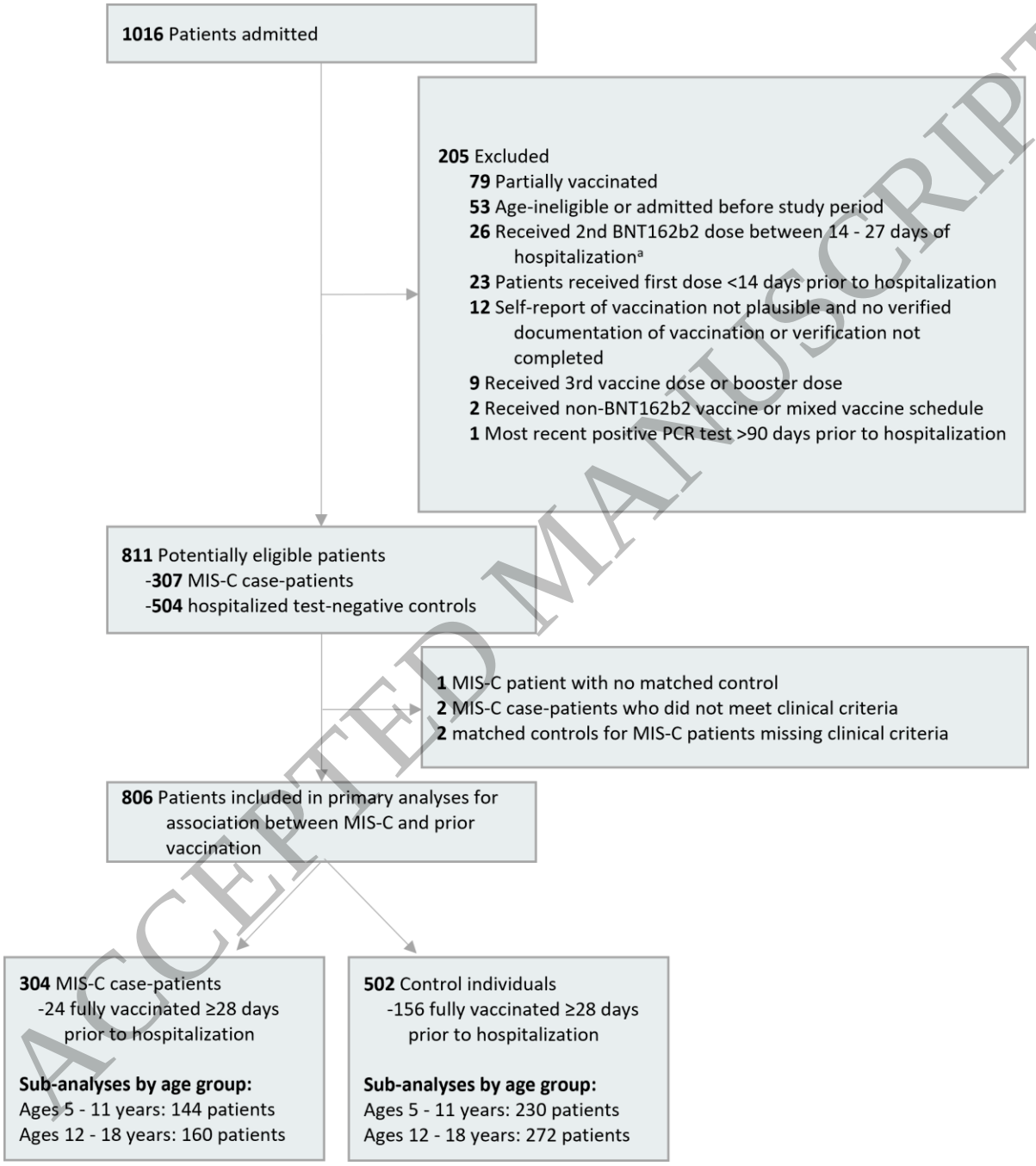

Figure 1
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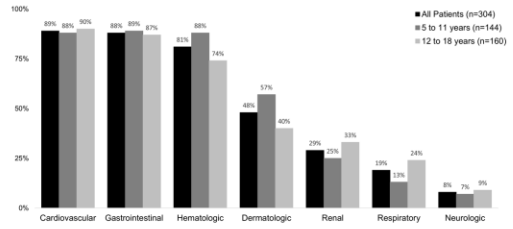
Figure 2 Organ System Involvement among MIS-C case-patients.

A. Organ System Involvement, by Age Group



B. Overlap in Organ System Involvement Among MIS-C Patients

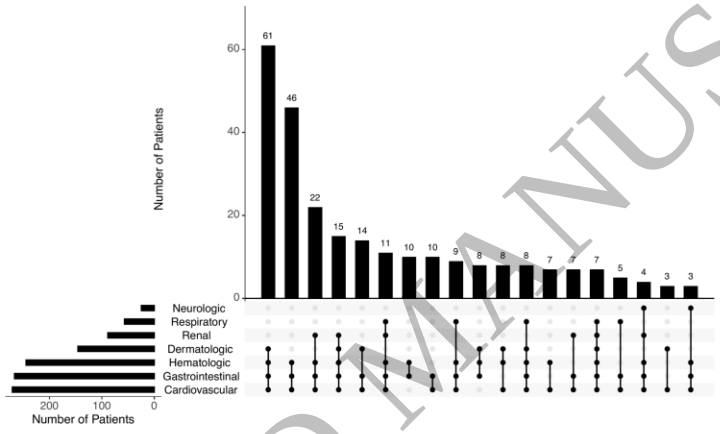


Figure 2
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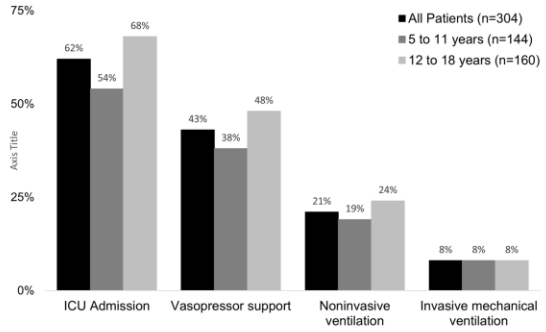
Figure 3. Clinical outcomes among MIS-C case-patients

A. Proportion of MIS-C Patients requiring ICU admission, vasopressor support, and noninvasive or invasive mechanical ventilation.



B. Comparison of MIS-C cases resulting in life support or death between vaccinated and unvaccinated patients, by period of variant predominance and by age group.

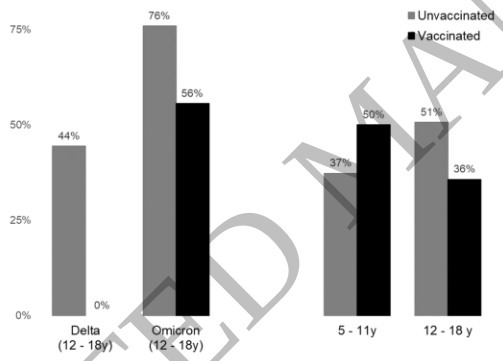


Figure 3
145x178 mm (x DPI)

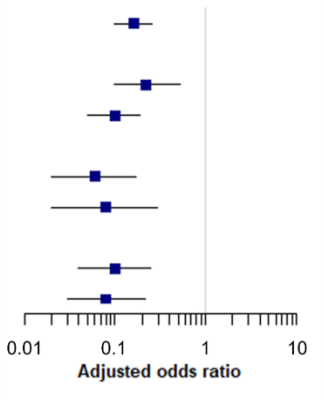


Figure 4
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