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Laura D. Zambrano

Margaret M. Newhams

Samantha M. Olson

Natasha B. Halasa

Ashley M. Price

See next page for additional authors

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MAJOR ARTICLE

BNT162b2 mRNA Vaccination Against Coronavirus Disease 2019 is Associated With a Decreased Likelihood of Multisystem Inflammatory Syndrome in Children Aged 5–18 Years—United States, July 2021 – April 2022

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

[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; [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]Division of Infectious Diseases, Department of Pediatrics, 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]Division of Cardiology, Department of Pediatrics, 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]Divisions of Critical Care Medicine and Allergy, Immunology, and Bone Marrow Transplant, Department of Pediatrics, 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; and [33]Departments of Anesthesia and Pediatrics, Harvard Medical School, Boston, Massachusetts, USA

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 1 July 2021 to 7 April 2022, we compared the odds of being fully vaccinated (2 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 (adjusted OR [aOR]: .16; 95% CI: .10–.26), including among children ages 5–11 years (aOR: .22; 95% CI: .10–.52), ages 12–18 years (aOR: .10; 95% CI: .05–.19), and during the Delta (aOR: .06; 95% CI: .02–.15) and Omicron (aOR: .22; 95% CI: .11–.42) variant-predominant periods. This association persisted beyond 120 days after the second dose (aOR: .08; 95% CI: .03–.22) in 12–18-year-olds. Among all MIS-C case-patients, 187 (62%) required intensive care unit admission and 280 (92%) vaccine-eligible case-patients were unvaccinated.

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[a]L. D. Z., M. M.N., A. P. C., and A. G. R. contributed equally.

[b]Overcoming COVID-19 Investigators are listed in the Acknowledgments section.

Correspondence: L. D. Zambrano, US Centers for Disease Control and Prevention, 1600 Clifton Rd NE, MS H24-5, Atlanta, GA 30329, USA (xbs6@cdc.gov).

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Conclusions. Vaccination with 2 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.

Keywords. MIS-C; vaccine effectiveness; Pfizer (BioNTech); COVID-19; children.

Multisystem inflammatory syndrome in children (MIS-C) is a severe hyperinflammatory condition occurring approximately 4 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 US Food and Drug Administration and is fully licensed for all persons ages 16 years and older [4, 5]. Prelicensure trials indicate high immunogenicity and vaccine efficacy against laboratory-confirmed COVID-19 in children ages 5 years and older [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 2 doses of BNT162b2 COVID-19 vaccine [9]. These data were among adolescents hospitalized with MIS-C through 9 December 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 2 November 2021 [10] and into the period of B.1.1.529 (Omicron) SARS-CoV-2 variant predominance, starting 18 December 2021 [11]. We evaluate the association of vaccination with MIS-C among patients ages 5–18 years hospitalized through 7 April 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 US states in the Centers for Disease Control and Prevention (CDC)–funded Overcoming COVID-19 (OC-19) pediatric vaccine effectiveness network (see Supplementary Material for sites and investigators). 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 versus unvaccinated patients with MIS-C.

Participants

Children ages 5–18 years hospitalized at OC-19 sites between 1 July 2021 and 7 April 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 of 38°C or higher lasting 24 hours or more, and laboratory evidence of recent SARS-CoV-2 infection by reverse transcription–polymerase chain reaction (RT-PCR), antigen, or serology (see Supplementary 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 patients with suspected MIS-C 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 1 matched control per case-patient was required for inclusion. Information on vaccination status was collected after enrollment.

Data Collection

Demographic and laboratory data and clinical information, including presence of underlying medical conditions (see Supplementary Table 1), were collected by trained personnel through standardized interviews and medical records abstraction. Patients with MIS-C were adjudicated at the site level, and clinical criteria were reviewed by CDC to ensure all patients with MIS-C met inclusion criteria. COVID-19 vaccination status, including manufacturer, dates of vaccination, number of doses, and location, was 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 2 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 1 vaccine dose before the reference date or receiving a second dose less than 28 days prior to the reference date. Patients who received their second 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 (eg, BNT162b2 for the first dose and mRNA-1273 for the second), or if they received more than 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 time point 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 or more after the second dose. Patient inclusion in each of these subanalyses was contingent upon hospitalization after the enrollment eligibility date (eg, 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 (see Supplementary 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 2 and 3). Descriptive statistics were calculated for binary variables reflective of disease severity (intensive care unit [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 or more organ systems analyzed and displayed graphically (Figure 2*B*). 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 2 doses of the BNT162b2 vaccine (exposed) with 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 (aORs) less than 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) × 100 [14, 16, 17].

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 aged 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 at the time this analysis was undertaken. The proportion of SARS-CoV-2 infections estimated to be attributable to the Omicron variant exceeded 50% during the week beginning 18 December 2021 [11, 21], 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 1 January 2022 (18 December 2021, plus 2 weeks) to separately identify MIS-C cases attributed to SARS-CoV-2 infection during the periods of Delta versus 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 version 9.4 (SAS

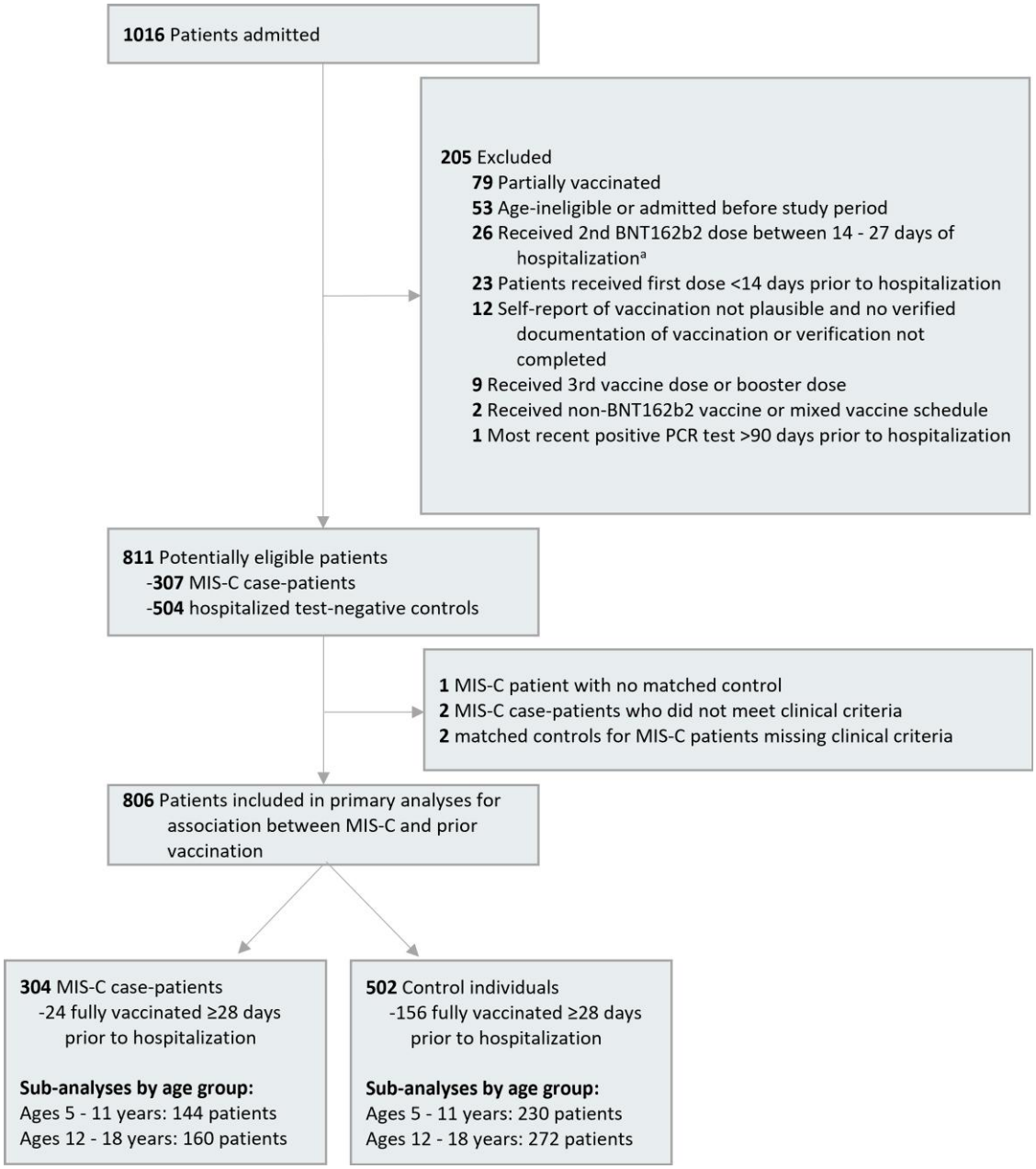

Figure 1. Participant flow through a study of association between BNT162b2 (Pfizer-BioNTech) COVID-19 mRNA vaccination and MIS-C. [a]Children who received a second vaccine dose between 14 and 27 days prior to hospitalization were included in a sensitivity analysis examining the association between vaccination ≥14 days prior to hospitalization and MIS-C; however, they were excluded from the primary analysis. Abbreviations: COVID-19, coronavirus disease 2019; MIS-C, multisystem inflammatory syndrome in children; PCR, polymerase chain reaction.

Institute, Cary, NC) and R Studio (V1.2.5033; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Participants

During 1 July 2021 to 7 April 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, Supplementary 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 less than 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

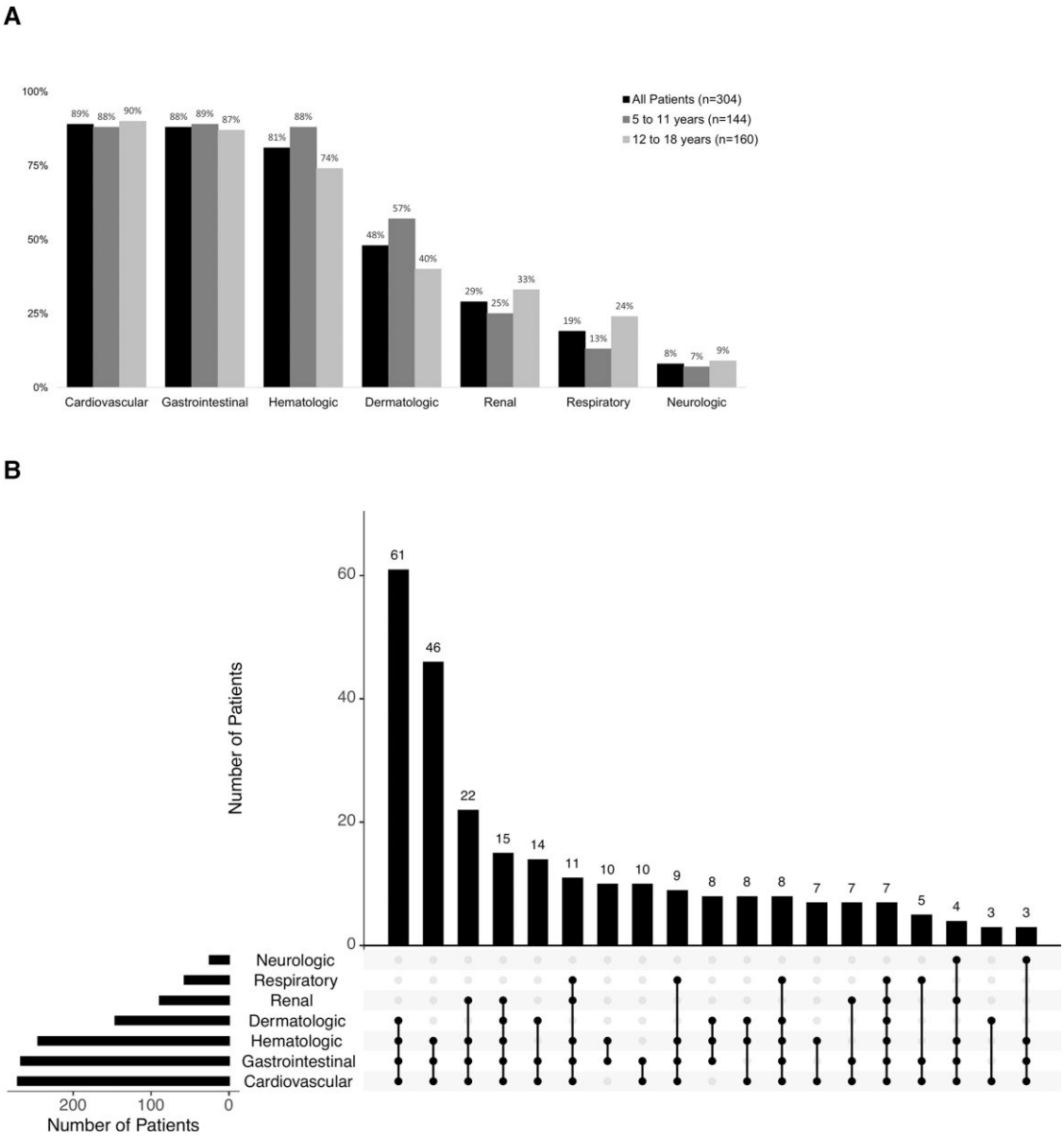

Figure 2. Organ system involvement among MIS-C case-patients. (*A*) Organ system involvement, by age group. (*B*) Overlap in organ system involvement among patients with MIS-C, including the number of patients with involvement of each organ system (left) and a combination matrix representing the number of MIS-C patients with specific combinations of overlapping organ system involvement. Abbreviation: MIS-C, multisystem inflammatory syndrome in children.

the primary analysis but included as a sensitivity analysis. If vaccinated, all patients were hospitalized 28 days or more 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 18 December 2021 [11, 21]. Of note, among MIS-C case-patients in the 12–18-year-age group, 122 of 160 (84%) were hospitalized during the period of Delta predominance, whereas 121 of 144 (76%) 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 second vaccine dose (Table 1, Supplementary Figure 2).

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

Organ system involvement among MIS-C patients is shown in Figure 2*A* and the combinations of organ system involvement in Figure 2*B*. Of the 304 case-patients, 62% were admitted to the ICU, 21% required noninvasive ventilation, 8% required invasive mechanical ventilation, and 43% required vasopressor

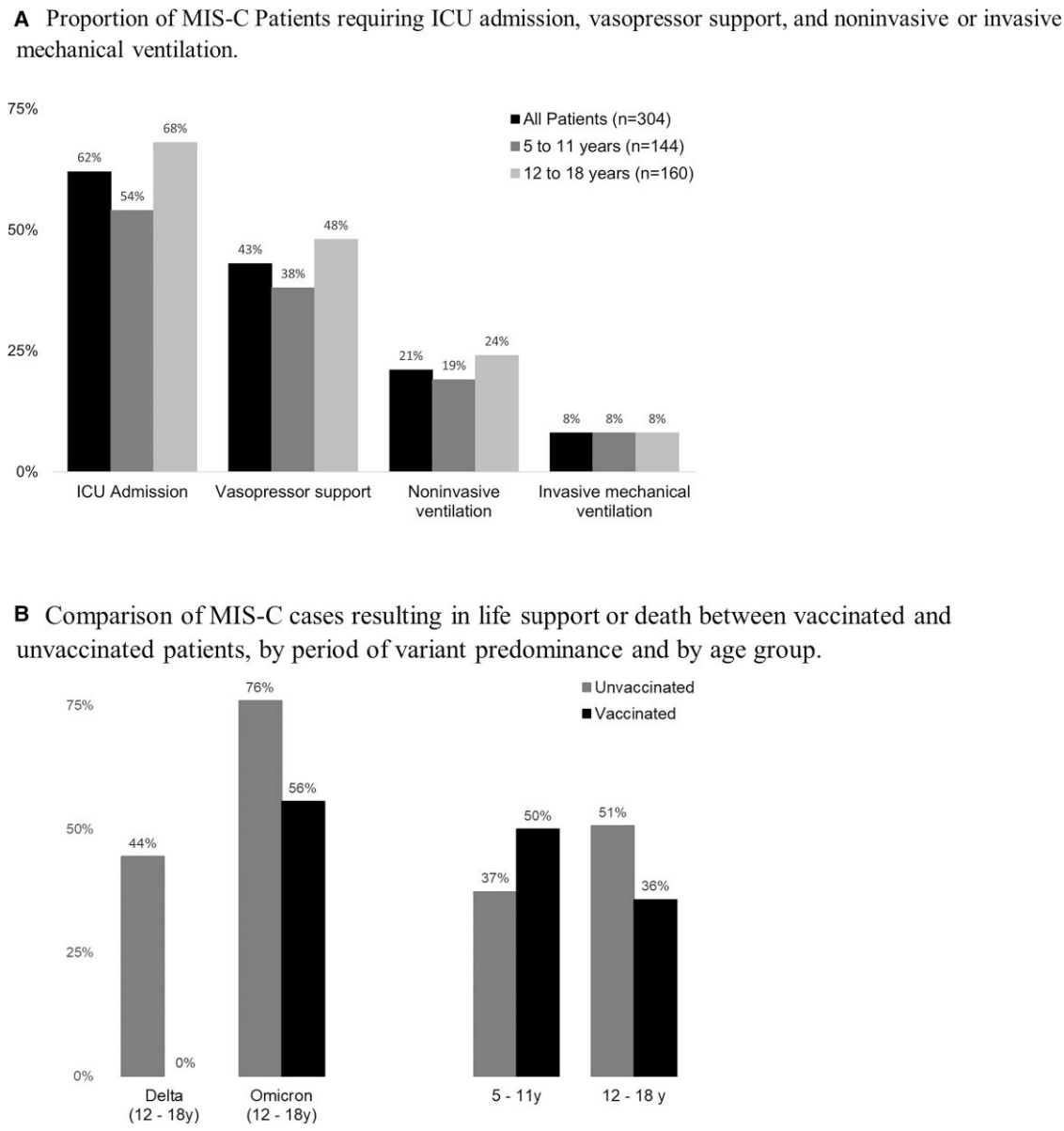

Figure 3. Clinical outcomes among MIS-C case-patients. (*A*) Proportion of patients with MIS-C requiring ICU admission, vasopressor support, and noninvasive or invasive mechanical ventilation. (*B*) Comparison of MIS-C cases resulting in life support or death between vaccinated and unvaccinated patients, by period of variant predominance and by age group. Abbreviations: ICU, intensive care unit; MIS-C, multisystem inflammatory syndrome in children.

support. Figure 3*A* 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; $P = .05$) 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 3*B*, Supplementary Table 4). One unvaccinated MIS-C case-patient in the 12–18-year-old age group required extracorporeal membrane oxygenation, and 1 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 2 doses of BNT162b2 mRNA vaccine 28 days or more before hospitalization, with an aOR of .16 (95% CI: .10–.26).

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

Characteristics	5–11 Years		12–18 Years	
	MIS-C Case-Patients (n = 144)	Controls (n = 230)[a]	MIS-C Case-Patients (n = 160)	Controls (n = 272)
Median (IQR) age, years	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				
12–15 years	n.a.	n.a.	127 (79.4)	210 (77.2)
16–18 years	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)
US 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	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 (Pfizer-BioNTech) 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)	47 (31–71)	47 (36–56)	110 (63–158)	130 (75–189)

Data are presented as n (%) unless otherwise indicated. Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range; MISC, MIS-C, multisystem inflammatory syndrome in children; n.a., not applicable.

[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 patients included in our primary analysis. This added a total of 5 case-patients and 21 controls.

Using a time frame of 14 days or more before vaccination, the aOR was similar at .17 (95% CI: .10–.27). When stratified by age, the aOR was .22 (95% CI: .10–.52) for children ages 5–11 years and .10 (95% CI: .05–.19) for adolescents ages 12–18 years. The association between vaccination and protection against MIS-C was significant among children ages 12–18 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[a]	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	7/131 (5.3)	61/196 (31.1)	0.12 (0.06 - 0.28)	0.08 (0.03 - 0.22)

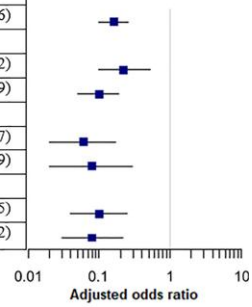

Figure 4. Association between MIS-C and prior BNT162b2 (Pfizer-BioNTech) vaccination among children ages 5–18 years. [a]Given similarities in the aOR point estimates by time interval between vaccine dose 2 and illness onset, the stratified analyses by period of variant predominance and age group used the subset of patients included at the 28-day time point. Abbreviations: aOR, adjusted odds ratio; MIS-C, multisystem inflammatory syndrome in children.

during both periods of variant predominance (aOR: .06; 95% CI: .02–.17 for Delta; aOR: .08; 95% CI: .02–.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: .08; 95% CI: .03–.22) (Figure 4).

DISCUSSION

In this public health investigation of children admitted to 29 US pediatric hospitals between 1 July 2021 and 7 April 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 aged 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 an estimated overall vaccine effectiveness of 84% for vaccination with 2 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 4 to 7 months after vaccination.

This investigation is one of the first to examine the association of BNT162b2 vaccination with the 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 2 prospective studies demonstrating decreased MIS-C incidence associated with vaccination prior to the emergence of the Omicron variant [22, 23]. Levy et al [22] found that MIS-C incidence from 1 September to 31 October 2021 decreased by 91% after dose 1 of the BNT162b2 vaccine in France; no MIS-C cases were reported among fully vaccinated adolescents. In a separate national cohort study in Denmark, Nygaard et al [23] found that MIS-C incidence among children ages 0–17 years declined by 94% among vaccinated children between 1 August 2021 and 1 February 2022. High vaccine effectiveness has been reported against the 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 2 doses of the BNT162b2 vaccine [24–26]; 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 [24–26] 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 [27].

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 nonhospitalized 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 and older, 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 the 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 OR 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 (2 November 2021) were only eligible for inclusion less than 2 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 MIS-C, we cannot ascertain if it is due to prevention of SARS-CoV-2 infection or another mechanism.

Conclusions

Vaccination with 2 doses of BNT162b2 was associated with a lower frequency of MIS-C compared with 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.

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

Authors' 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.

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Overcoming COVID-19 Network Study Group Investigators and Collaborators (listed in PubMed, and ordered by US 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.

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