Risk Factors for Severe COVID-19 in Children

Rebecca C. Woodruff, PhD, MPH,[a,b] Angela P. Campbell, MD, MPH,[a] Christopher A. Taylor, PhD,[a] Shua J. Chai, MD, MPH,[c,d] Breanna Kawasaki, MPH,[e] James Meek, MPH,[f] Evan J. Anderson, MD,[g,h,i] Andy Weigel, MSW,[j] Maya L. Monroe, MPH,[k] Libby Reeg, MPH,[l] Erica Bye, MPH,[m] Daniel M. Sosin, MD, MPH,[n,o] Alison Muse, MPH,[p] Nancy M. Bennett, MD, MS,[q] Laurie M. Billing, MPH,[r] Melissa Sutton, MD, MPH,[s] H. Keipp Talbot, MD, MPH,[t] Keegan McCaffrey, BA,[u] Huong Pham, MPH,[a] Kadam Patel, MPH,[a,v] Michael Whitaker, MPH,[a] Meredith McMorrow, MD, MPH,[a,b] Fiona Havers, MD, MHS,[a,b] COVID-NET Surveillance Team

abstract

OBJECTIVES: Describe population-based rates and risk factors for pediatric severe coronavirus disease 2019 (COVID-19) (ie, ICU admission, invasive mechanical ventilation, or death).

METHODS: During March 2020 to May 2021, the COVID-19–Associated Hospitalization Surveillance Network identified 3106 children hospitalized with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 infection in 14 states. Among 2293 children primarily admitted for COVID-19, multivariable generalized estimating equations generated adjusted risk ratios (aRRs) and 95% confidence intervals (CIs) of the associations between demographic and medical characteristics abstracted from patient electronic medical records and severe COVID-19. We calculated age-adjusted cumulative population-based rates of severe COVID-19 among all children.

RESULTS: Approximately 30% of hospitalized children had severe COVID-19; 0.5% died during hospitalization. Among hospitalized children aged <2 years, chronic lung disease (aRR: 2.2; 95% CI: 1.1–4.3), neurologic disorders (aRR: 2.0; 95% CI: 1.5–2.6), cardiovascular disease (aRR: 1.7; 95% CI: 1.2–2.3), prematurity (aRR: 1.6; 95% CI: 1.1–2.2), and airway abnormality (aRR: 1.6; 95% CI: 1.1–2.2) were associated with severe COVID-19. Among hospitalized children aged 2 to 17 years, feeding tube dependence (aRR: 2.0; 95% CI: 1.5–2.5), diabetes mellitus (aRR: 1.9; 95% CI: 1.6–2.3) and obesity (aRR: 1.2; 95% CI: 1.0–1.4) were associated with severe COVID-19. Severe COVID-19 occurred among 12.0 per 100 000 children overall and was highest among infants, Hispanic children, and non-Hispanic Black children.

CONCLUSIONS: Results identify children at potentially higher risk of severe COVID-19 who may benefit from prevention efforts, including vaccination. Rates establish a baseline for monitoring changes in pediatric illness severity after increased availability of COVID-19 vaccines and the emergence of new variants.

[a]*Coronavirus Disease 2019–Associated Hospitalization Surveillance Network, Division for Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia;* [b]*US Public Health Service Commissioned Corps, Rockville, Maryland;* [c]*Division of State and Local Readiness, Center for Preparedness and Response, Centers for Disease Control and Prevention, Atlanta, Georgia;* [d]*California Emerging Infections Program, Oakland, California;* [e]*Colorado Department of Public Health and Environment, Denver, Colorado;* [f]*Connecticut Emerging Infections Program, Yale School of Public Health, New Haven, Connecticut;* [g]*Departments of Medicine and Pediatrics, Emory School of Medicine, Atlanta, Georgia;* [h]*Georgia Emerging Infections Program, Georgia Department of Public Health, Atlanta, Georgia;* [i]*Atlanta Veterans Affairs Medical Center, Atlanta, Georgia;* [j]*Iowa Department of Public Health, Des Moines, Iowa;* [k]*Maryland Department of Health, Baltimore, Maryland;* [l]*Michigan Department of Health and Human Services, Lansing, Michigan;* [m]*Minnesota Department of Health, St Paul, Minnesota;* [n]*New Mexico Emerging Infections Program, Santa Fe, New Mexico;* [o]*New Mexico Department of Health, Santa Fe, New Mexico;* [p]*New York State Department of Health, Albany, New York;* [q]*University of Rochester School of Medicine and Dentistry, Rochester, New York;* [r]*Ohio Department of Health, Columbus, Ohio;* [s]*Public Health Division, Oregon Health Authority, Portland, Oregon;* [t]*Vanderbilt University Medical Center, Nashville, Tennessee;* [u]*Utah Department of Health, Salt Lake City, Utah; and* [v]*General Dynamics Information Technology, Atlanta, Georgia*

WHAT'S KNOWN ON THIS SUBJECT: Children can experience severe disease outcomes because of COVID-19 illness, including ICU admission, invasive mechanical ventilation, and death. However, more information is needed to identify the pediatric subgroups at greatest risk of severe disease to inform prevention efforts.

WHAT THIS STUDY ADDS: Using data from 2293 hospitalized children primarily admitted for COVID-19 in 14 states during March 2020 to May 2021, we found that specific underlying conditions were associated with increased risk of severe COVID-2019, and these varied by age group.

To cite: Woodruff RC, Campbell AP, Taylor CA, et al. Risk Factors for Severe COVID-19 in Children. *Pediatrics.* 2022;149(1):e2021053418

As of August 31, 2021, >4 million cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have been documented in US children aged <18 years.[1] Although children have lower rates of hospitalization for coronavirus disease 2019 (COVID-19) compared with that of adults,[2,3] severe illness and death have occurred.[4–8] Children with SARS-CoV-2 infection may develop serious complications, including acute respiratory distress syndrome, myocarditis, acute renal failure, multisystem organ failure, and multisystem inflammatory syndrome in children (MIS-C).[3–6,8–14] Among children hospitalized with COVID-19, ~28% to 40% were admitted to an ICU, 6% to 18% required invasive mechanical ventilation, and up to 3% have died.[3,4,6,10–12]

As of September 2021, the Food and Drug Administration has approved the Pfizer-BioNTech vaccine for use in children aged ≥16 years and has authorized 2 vaccines for emergency use in children aged 12 to 17 years.[15–17] Multiple clinical trials testing vaccine efficacy for preventing severe illness and death in the pediatric population are ongoing.[18–22] However, until these vaccines are authorized for use in younger age groups, children may continue to be at risk for severe illness. Information about the demographic and medical characteristics associated with severe COVID-19 in this population can be used to inform clinical decision-making, risk communication, and recommendations for vaccination and other preventive measures. Although several descriptive investigations have characterized the demographic and clinical characteristics of pediatric COVID-19–associated hospitalizations[3,10,11] and ICU admissions,[5,9] most studies that have identified risk factors for severe COVID-19 among children have been conducted among geographically limited populations during the initial months of the pandemic.[4,6,12,23] Additionally, population-based rates of severe COVID-19 in children are needed to establish a baseline for monitoring trends as COVID-19 vaccines are approved for use in younger age groups, to compare with rates of severe adverse vaccine reactions, and as new SARS-CoV-2 variants emerge.

The objectives of this investigation were to identify demographic characteristics and underlying medical conditions associated with increased relative risk of severe COVID-19 among children hospitalized with SARS-CoV-2 infection and calculate population-based rates of severe COVID-19 among children during March 2020 to May 2021.

METHODS

As described previously,[2,24] the Coronavirus Disease 2019–Associated Hospitalization Surveillance Network (COVID-NET) conducts population-based surveillance of laboratory-confirmed COVID-19–associated hospitalizations in 250 acute-care hospitals located in a defined catchment area that includes ~10% of the US population. COVID-NET conducts surveillance in 99 counties across 14 states (California, Colorado, Connecticut, Georgia, Iowa, Maryland, Michigan, Minnesota, New Mexico, New York, Ohio, Oregon, Tennessee, and Utah) located in each of the 10 Health and Human Services Department regions.

Hospitalizations that meet the case definition of a COVID-19–associated hospitalization are included in surveillance if the patient resided in the catchment area and had a positive molecular or rapid antigen SARS-CoV-2 test during hospitalization or up to 14 days before admission. COVID-NET cases can include patients with acute COVID-19, MIS-C, or asymptomatic SARS-CoV-2 infection detected through screening. Trained surveillance officers identify cases using notifiable disease and laboratory databases as well as hospital admission and infection control practitioner logs. Medical chart abstraction is completed for all COVID-19–associated hospitalizations among children aged <18 years by using a standard case report form; hospitalizations are then reported to COVID-NET. This activity was reviewed by the Centers for Disease Control and Prevention (CDC) and conducted consistent with applicable federal law and CDC policy.[1] Participating sites obtained approval from their respective state and local institutional review boards, as required.

Participants

During March 2020 to May 2021, 3106 children with COVID-19 –associated hospitalization were identified by COVID-NET. To identify risk factors for severe COVID-19 among hospitalized children, we analyzed data from 2293 (73.8%) hospitalizations. Hospitalizations were excluded if chart abstraction was incomplete (n = 81; 2.6%), the patient was pregnant at the time of admission (n = 127; 4.1%), or outcome data were unknown (n = 15; 0.5%). Additionally, we excluded 718 children who had any of the following primary reasons for admission, which were not likely related to COVID-19: psychiatric admissions (n = 270), obstetrics or gynecology (n = 162), trauma (n = 136), inpatient procedures (n = 118), or other with no symptoms consistent with COVID-19 at the time of admission (n = 32).

Excluded children differed on demographic and medical characteristics, compared with included children (Supplemental Table 4).

Measures

Severe COVID-19

The dependent variable was severe COVID-19, defined as requiring ICU admission or invasive mechanical ventilation or in-hospital death.

Demographic Characteristics

Demographic variables included age group, sex, housing type, and race and/or Hispanic ethnicity group (Hispanic, non-Hispanic Black, non-Hispanic White, non-Hispanic Asian or Pacific Islander, non-Hispanic other or unknown). Children with unknown ethnicity ($n = 79$; 3.5%) were presumed to be non-Hispanic.

Clinical Characteristics

COVID-NET collects information on 14 categories of underlying medical conditions (Supplemental Table 5); other medical conditions reported in free text were categorized after review by a pediatrician. The underlying conditions considered for each age group were determined on the basis of clinical relevance and sample size. Among children aged <2 years, 7 underlying conditions were considered: airway abnormality, cardiovascular disease, chronic lung disease, feeding tube dependence, neurologic disorders, prematurity (gestational age: <37 weeks), or other conditions (immunocompromised condition, gastrointestinal or liver disease, chronic metabolic disease, blood disorders, renal disease, or other condition). Among children aged 2 to 17 years, 13 underlying conditions were considered: airway abnormality, asthma, blood disorders, cardiovascular disease, developmental delay, diabetes mellitus (type I or 2), feeding tube dependence, immunocompromised conditions, obesity (BMI kg/m^2 ≥95th percentile for age and sex based on CDC growth charts; *International Classification of Diseases, 10th Revision*, codes for obesity; or obesity selected on the case report form), nonasthma chronic lung disease, nondiabetes chronic metabolic disease, nondevelopmental delay neurologic disorders, or other conditions (gastrointestinal or liver disease; renal disease; or rheumatologic, autoimmune, or inflammatory disease).

Statistical Analysis

To identify risk factors for severe COVID-19, we specified bivariate and multivariable log-linked Poisson generalized estimating equations in SAS (version 9.4; SAS Institute, Inc, Cary, NC) using robust variance estimators to account for clustering of hospitalizations within 10 Health and Human Services Department regions. We present unadjusted and adjusted risk ratios (aRRs), 95% confidence intervals (CIs), and *P* values using a type I error rate of 5%. Multivariable models identifying demographic characteristics associated with severe COVID-19 included all children aged <18 years and were adjusted for the presence of ≥1 underlying medical conditions. Multivariable models identifying underlying medical conditions associated with severe COVID-19 were adjusted for demographic characteristics and specified separately for children aged <2 years and 2 to 17 years because some underlying medical conditions (eg, prematurity and obesity) are only clinically relevant for specific pediatric subgroups. In supplementary analyses, we stratified models by additional age groups (ie, <6 months, 6–23 months, 2–4 years, 5–11 years, and 12–17 years) and by race and ethnicity group among children aged 2 to 17 years. We also conducted sensitivity analyses, excluding patients with a discharge diagnosis of MIS-C.[8]

Age-adjusted cumulative population-based rates of severe COVID-19 during March 2020 to May 2021 were calculated by using the number of catchment area residents aged <18 years hospitalized with severe COVID-19 as the numerator and 2019 bridged-race postcensal population estimates from the National Center for Health Statistics as the denominator.[25] Rates and rate ratios (RRs) by age group, sex, and race and ethnicity groups are presented. Hospitalizations with complete data on age group, sex, and race and ethnicity were included; no additional exclusion criteria were applied to the numerator data. Rates with relative SEs ≥30% were suppressed.

RESULTS

Of 2293 pediatric hospitalizations, 745 (32.5%) were infants and children aged <2 years; 1548 (67.5%) were children aged 2 to 17 years (Table 1). One-half (53.4%) were male, and the median age was 7 years (interquartile range [IQR]: 1–14). Most were Hispanic (33.7%) or non-Hispanic Black (32.1%), followed by non-Hispanic White (22.9%) or non-Hispanic Asian/Pacific Islander (5.2%). More than one-half (55.0%) had ≥1 underlying medical conditions, although the prevalence varied by age group (28.7% among infants and children <2 years old; 67.7% among children 2–17 years old). The most common underlying conditions were obesity, chronic lung disease, neurologic disorders, cardiovascular disease, and blood disorders. Within the latter categories, asthma, developmental delay, congenital heart disease, and sickle cell disease

TABLE 1 Demographic Characteristics and Underlying Medical Conditions Among Hospitalized Children Aged <18 Years Identified Through the COVID-NET, March 2020 to May 2021

	Total (N = 2293)		Infants and Children Aged <2 y (n = 745)		Children Aged 2–17 y (n = 1548)	
Characteristic	No.	%	No.	%	No.	%
Age, median and IQR[a]	7	1–14	2	1–11	12	7–16
Age group						
<6 mo	450	19.6	450	60.4	—	—
6–23 mo	295	12.9	295	39.6	—	—
2–4 y	249	10.9	—	—	249	16.1
5–11 y	470	20.5	—	—	470	30.4
12–17 y	829	36.2	—	—	829	53.6
Sex						
Male	1224	53.4	409	54.9	815	52.7
Female	1069	46.6	336	45.1	733	47.4
Race and ethnicity						
Hispanic	773	33.7	267	35.8	506	32.7
NH Black	737	32.1	192	25.8	545	35.2
NH White	525	22.9	181	24.3	344	22.2
NH Asian or Pacific Islander	118	5.2	53	7.1	65	4.2
NH other[b]	140	6.1	52	7.0	88	5.7
Residential type						
Private residence[c]	2240	97.7	717	96.2	1523	98.4
Congregate setting, other or unknown[d]	53	2.3	28	3.8	25	1.6
Hospitalized since birth	25	1.1	25	3.4	0	0.0
Underlying medical conditions						
≥1 underlying medical conditions	1262	55.0	214	28.7	1048	67.7
Obesity[e]	478	20.9	—	—	478	30.9
Chronic lung disease	468	20.4	38	5.1	430	27.8
Asthma	373	16.3	13	1.7	360	23.3
Neurologic disorder	348	15.2	49	6.6	299	19.3
Developmental delay	218	9.5	30	4.0	188	12.1
Cardiovascular disease	146	6.4	57	7.7	89	5.8
Congenital heart disease	94	4.1	44	5.9	50	3.2
Blood disorder	142	6.2	21	2.8	121	7.8
Sickle cell	102	4.5	16	2.2	86	5.6
Chronic metabolic disease	136	5.9	8	1.1	128	8.3
Diabetes mellitus (type I or II)	89	3.9	1	0.1	88	5.7
Immunocompromised condition	129	5.6	7	0.9	122	7.9
Feeding tube dependent	114	5.0	33	4.4	81	5.2
Prematurity[f]	100	4.4	100	13.4	—	—
Airway abnormality	58	2.5	24	3.2	34	2.2
Renal disease	46	2.0	9	1.2	37	2.4
Liver disease	41	1.8	6	0.8	35	2.3
Rheumatologic, autoimmune, inflammatory condition	14	0.6	0	0.0	14	0.9
Other	133	5.8	36	4.8	97	6.3
Discharge diagnosis of MIS-C	198	8.6	15	2.0	183	11.8
Outcomes						
ICU admission or invasive mechanical ventilation	691	30.1	164	22.0	527	34.0
Invasive mechanical ventilation	122	5.3	34	4.6	88	5.7
In-hospital deaths	12	0.5	4	0.5	8	0.5

NH, non-Hispanic; —, not applicable.

[a] Reported in months for children aged <2 y and in years for all other age groups.

[b] Includes NH American Indian or Alaska Native (n = 20; 0.9%), NH multiple races (n = 25; 1.1%), or unknown (n = 95; 4.1%).

[c] Includes private residence or home with services.

[d] Includes hospitalized since birth, group home or retirement, homeless shelter, psychiatric facility, facility, long-term acute-care hospital, corrections facility, other, and unknown.

[e] Children aged 2 to 17 y were classified as having obesity if they had BMI (kg/m^2) ≥95th percentile for age and sex on the basis of CDC growth charts, ICD-10 codes for obesity in the electronic medical record, or obesity selected on the case report form.

[f] Gestational age <37 wk at birth among children aged <2 y.

were the most common conditions respectively.

Demographic Characteristics Associated With Severe COVID-19

Among hospitalized children aged <18 years, 30.1% had severe COVID-19 (Table 1). In multivariable analyses, the risk of severe COVID-19 among hospitalized children was higher among children with ≥1 underlying medical condition (aRR: 1.5; 95% CI: 1.2–1.9; $P = .001$; Fig 1). Severe disease was significantly less likely in infants aged <6 months (aRR: 0.7; 95% CI: 0.5–0.9; $P = .004$). Race and ethnicity group were not statistically significantly associated with severe COVID-19. In sensitivity analyses excluding children with MIS-C, children living in a congregate, other, or unknown residence type also had a higher risk of severe disease (aRR: 1.5; 95% CI: 1.0–2.2; $P = .3$) and children aged 5 to 11 years had a lower risk of severe COVID-19, relative to children aged 12 to 17 years (aRR: 0.9; 95% CI: 0.8–1.0; $P = .3$; Supplemental Table 6).

Underlying Medical Conditions Associated With Severe COVID-19

Among hospitalized children aged <2 years, 22.0% had severe COVID-19 (Table 1). In multivariable analyses, the risk of severe COVID-19 was higher among children with chronic lung disease (aRR: 2.2; 95% CI: 1.1–4.3; $P = .03$), neurologic disorders (aRR: 2.0; 95% CI: 1.5–2.6; $P < .0001$), cardiovascular disease (aRR: 1.7; 95% CI: 1.2–2.3; $P = .004$), prematurity (aRR: 1.6; 95% CI: 1.3–2.1; $P \leq .0001$) or airway abnormality (aRR: 1.6; 95% CI: 1.1–2.2; $P = .02$; Fig 2A). Other conditions were not significantly associated with an increased risk of severe COVID-19. Results from sensitivity analyses excluding children with MIS-C were similar (Supplemental Table 7).

Among hospitalized children aged 2 to 17 years, 34.0% had severe COVID-19 (Table 1). In multivariable analyses, the risk of severe COVID-19 was higher among children with feeding tube dependence (aRR: 2.0; 95% CI: 1.5–2.5; $P < .0001$), diabetes mellitus (aRR: 1.9; 95% CI: 1.6–2.3; $P < .0001$) and obesity (aRR: 1.2; 95% CI: 1.0–1.4; $P = .0003$; Fig 2B). Other conditions were not significantly associated with increased risk of severe COVID-19. In sensitivity analyses excluding children with MIS-C, developmental delay was also a risk factor for severe COVID-19 (aRR: 1.3; 95% CI: 1.1–1.6; $P = .004$; Supplemental Table 7).

Sensitivity Analyses

In sensitivity analyses among additional age groups, the categories of underlying medical conditions associated with increased risk of severe disease varied by age groups (Supplemental Table 8). Among

Demographic Characteristic	Severe Disease $n = 691$ n (%)		No Severe Disease $n = 1,602$ n (%)		Bivariate Models RR (95% CI)		Multivariable Models aRR (95% CI)	
Age group								
<6 mo	88	(12.7)	362	(22.6)	0.6	(0.4–0.8)	0.7	(0.5–0.9)
6–23 mo	76	(11.0)	219	(13.7)	0.8	(0.6–1.0)	0.9	(0.6–1.2)
2–4 y	80	(11.6)	169	(10.6)	0.9	(0.7–1.2)	1.0	(0.8–1.2)
5–11 y	166	(24.0)	304	(19.0)	1.0	(0.9–1.2)	1.1	(0.9–1.2)
12–17 y	281	(40.7)	548	(34.2)	1.0	Reference	1.0	Reference
Sex								
Male	384	(55.6)	840	(52.4)	1.1	(0.9–1.3)	1.1	(0.9–1.3)
Female	307	(44.4)	762	(47.6)	1.0	Reference	1.0	Reference
Race and ethnicity group								
Hispanic	213	(30.8)	560	(35.0)	1.0	(0.7–1.4)	1.0	(0.7–1.4)
NH Black	263	(38.1)	474	(29.6)	1.2	(1.0–1.6)	1.1	(0.9–1.5)
NH Asian Pacific Islander	31	(4.5)	87	(5.4)	1.0	(0.7–1.4)	1.0	(0.7–1.3)
NH other[a]	42	(6.1)	98	(6.1)	1.2	(0.9–1.4)	1.2	(0.9–1.5)
NH White	142	(20.6)	383	(23.9)	1.0	Reference	1.0	Reference
Residential type[b]								
Congregate setting or other	22	(3.2)	31	(1.9)	1.4	(1.0–2.1)	1.5	(1.0–2.2)
Private residence	669	(96.8)	1,571	(98.1)	1.0	Reference	1.0	Reference
≥1 underlying medical conditions[c]								
Yes	461	(66.7)	801	(50.0)	1.7	(1.3–1.7)	1.5	(1.2–1.9)
No	230	(33.3)	801	(50.0)	1.0	Reference	1.0	Reference

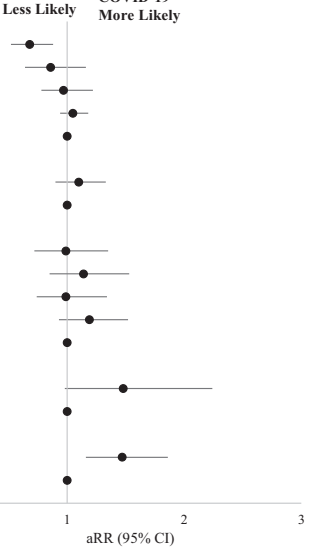
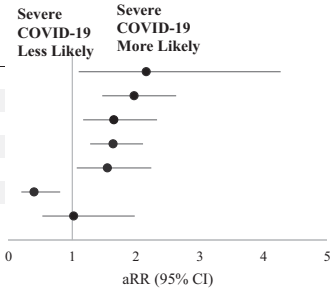


FIGURE 1

Demographic characteristics associated with severe COVID-19. Demographic characteristics and ≥1 underlying conditions associated with ICU admission, invasive mechanical ventilation, or death among children <18 years hospitalized with COVID-19: 14 states, March 2020 to May 2021. [a] Includes non-Hispanic American Indian or Alaskan Native, non-Hispanic multiple races, or unknown. [b] Private residence includes home with services. Congregate setting includes hospitalized since birth, group home/retirement, homeless shelter, psychiatric facility, facility, long-term acute care hospital, corrections facility, other, and unknown. [c] Includes obesity (among those aged 2–17 years); prematurity (among those aged <2 years); chronic lung disease; airway abnormality; neurologic disorders; immunocompromised conditions; feeding tube dependence; cardiovascular disease; chronic metabolic disease; blood disorders; gastrointestinal or liver disease; renal disease; rheumatologic, autoimmune, or inflammatory conditions; or other conditions.

Underlying Medical Condition	Severe Disease *n* = 164 *n*	(%)	No Severe Disease *n* = 581 *n*	(%)	Bivariate Models RR	(95% CI)	Multivariable Models[a] aRR	(95% CI)
Chronic lung disease	21	(12.8)	17	(2.9)	2.8	(2.0, 3.9)	2.2	(1.1, 4.3)
Neurologic disorder	27	(16.5)	22	(3.8)	2.9	(2.2, 3.8)	2.0	(1.5, 2.6)
Cardiovascular disease	23	(14.0)	34	(5.9)	2.0	(1.5, 2.7)	1.7	(1.2, 2.3)
Prematurity[b]	39	(23.8)	61	(10.5)	2.1	(1.5, 2.9)	1.6	(1.3, 2.1)
Airway abnormality	12	(7.3)	12	(2.1)	2.4	(1.4, 4.1)	1.6	(1.1, 2.2)
Feeding tube dependent	11	(6.7)	22	(3.8)	1.6	(1.0, 2.6)	0.4	(0.2, 0.8)
Other[c]	11	(6.7)	25	(6.7)	1.5	(0.8, 2.7)	1.0	(0.5, 2.0)



Underlying Medical Condition	Severe Disease *n* = 527 *n*	(%)	No Severe Disease *n* = 1,021 *n*	(%)	Bivariate Models RR	(95% CI)	Multivariable Models[a] aRR	(95% CI)
Feeding tube dependence	49	(9.3)	32	(3.1)	2.0	(1.7, 2.2)	2.0	(1.5, 2.5)
Diabetes mellitus (type I or 2)	53	(10.1)	35	(3.4)	1.9	(1.6, 2.3)	1.9	(1.6, 2.3)
Obesity[d]	191	(36.2)	287	(28.1)	1.3	(1.1, 1.5)	1.2	(1.0, 1.4)
Chronic lung disease[e]	32	(6.1)	38	(3.7)	1.5	(1.2, 1.8)	1.2	(0.9, 1.5)
Developmental delay	84	(15.9)	104	(10.2)	1.4	(1.3, 1.6)	1.2	(1.0, 1.4)
Immunocompromised condition	37	(7.0)	85	(8.3)	0.9	(0.6, 1.2)	1.1	(0.8, 1.6)
Airway abnormality	18	(3.4)	16	(1.6)	1.6	(1.1, 2.3)	1.0	(0.7, 1.5)
Cardiovascular disease	32	(6.1)	57	(5.6)	1.1	(0.8, 1.4)	1.0	(0.8, 1.3)
Chronic metabolic disease[e]	12	(2.3)	28	(2.7)	0.9	(0.6, 1.4)	0.9	(0.6, 1.3)
Asthma	120	(22.8)	240	(23.5)	1.0	(0.8, 1.2)	0.9	(0.7, 1.2)
Neurologic disorder[e]	34	(6.5)	66	(6.5)	1.0	(0.8, 1.3)	1.9	(0.7, 1.2)
Blood disorder	25	(4.7)	96	(9.4)	0.5	(0.4, 0.7)	0.5	(0.4, 0.7)
Other[f]	17	(3.2)	80	(7.8)	0.5	(0.3, 0.7)	0.4	(0.3, 0.7)

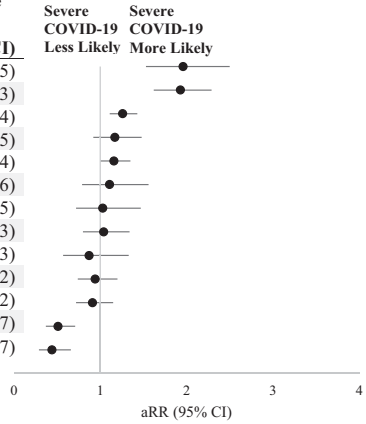


FIGURE 2

Underlying conditions associated with severe COVID-19 by age group. Underlying conditions associated with ICU admission, invasive mechanical ventilation, or death among children (A) aged <2 years and (B) aged 2–17 years hospitalized with COVID-19: 14 states, March 2020 to May 2021. [a] Multivariable models are adjusted for age group, sex, race and ethnicity group, and housing type. [b] Born <37 weeks' gestational age. [c] Includes immunocompromised conditions, liver disease, chronic metabolic disease, blood disorders, renal disease, and other disease specified on the case report form. [d] Children aged 2 to 17 years were classified as having obesity if they had body mass index (kg/m^2) ≥95th percentile for age and sex based on CDC growth charts, ICD-10 codes for obesity in the electronic medical record, or obesity selected on the COVID-NET case report form. [e] Chronic lung disease excludes asthma, chronic metabolic disease excludes type 1 or 2 diabetes mellitus, and neurologic disorder excludes developmental delay. [f]Includes liver disease; renal disease; rheumatologic, autoimmune, and inflammatory conditions; and other conditions specified on the case report form.

children aged 6 to 23 months, chronic lung disease (aRR: 2.4; 95% CI: 1.3–4.3), neurologic disorders (aRR: 2.3; 95% CI: 1.8–2.9), and cardiovascular disease (aRR: 1.4; 95% CI: 1.2–1.5) were associated with increased risk of severe COVID-19. Among children aged 2 to 4 years, feeding tube dependence (aRR: 2.1; 95% CI: 1.1–3.9) and chronic metabolic disease (aRR: 1.3; 95% CI: 1.1–1.5) were associated with increased risk of severe COVID-19. Among children aged 5 to 11 years, obesity (aRR: 1.4; 95% CI: 1.2–1.6) was associated with increased risk of severe COVID-19. Among children aged 12 to 17 years, feeding tube dependence (aRR: 3.0; 95% CI: 2.6–3.5), chronic metabolic disease (aRR: 1.7; 95% CI: 1.5–1.9), and obesity (aRR: 1.3; 95% CI: 1.0–1.6) were associated with increased risk of severe COVID-19. Other conditions were not significantly associated with increased risk of severe COVID-19.

In sensitivity analyses among children aged 2 to 17 years hospitalized with COVID-19, the categories of underlying medical conditions associated with increased risk of severe disease varied by race and ethnicity group (Supplemental Table 9). Among Hispanic children aged 2 to 17 years, chronic metabolic disease (aRR: 1.6; 95% CI: 1.1–2.5; $P = .03$) and obesity (aRR: 1.4; 95% CI: 1.0–1.8; $P = .03$) were associated with increased risk of severe COVID-19. Among non-Hispanic Black children aged 2 to 17 years, obesity (aRR: 1.2; 95% CI: 1.0–1.4; $P = .01$) and cardiovascular disease (aRR: 1.1; 95% CI: 1.1–1.1; $P < .0001$) were associated with increased risk of severe COVID-19. Among non-Hispanic White children aged 2 to 17 years, chronic metabolic disease (aRR: 1.6; 95% CI: 1.1–2.3; $P = .01$), obesity (aRR: 1.5; 95% CI: 1.0–2.2; $P = .04$), and feeding tube dependence (aRR: 2.1; 95% CI: 1.3–3.3; $P = .002$) were associated with increased risk of severe COVID-19. Other underlying medical conditions were not significantly associated with increased risk of severe COVID-19 among race and ethnicity groups.

In-Hospital Deaths

Among children <18 years of age hospitalized with COVID-19, 12

TABLE 2 Demographic Characteristics and Underlying Medical Conditions Among Children Aged <18 Years Who Died While Hospitalized With COVID-19: COVID-NET, March 2020–May 2021

	Children Aged <18 y (n = 12)	
Characteristic	No.	%
Age, mean and range, y	7	0–14
Age group		
<6 mo	1	8.3
6–23 mo	3	25.0
2–4 y	2	16.7
5–11 y	2	16.7
12–17 y	4	33.3
Sex		
Male	7	58.3
Female	5	41.7
Race and ethnicity		
Hispanic	6	50.0
NH Black	4	33.3
NH White	0	0.0
Unknown	2	14.3
Residential type[a]		
Private residence	12	100
Congregate setting, other or unknown	0	0
Underlying medical conditions		
≥1 underlying medical conditions	10	83.3
Neurologic disorder	7	58.3
Chronic lung disease	2	16.7
Immunocompromised condition	2	16.7
Feeding tube dependence	2	16.7
Outcomes		
ICU admission	12	100
Invasive mechanical ventilation	10	83.3

NH, non-Hispanic.

[a] Private residence includes home with services. Congregate setting includes hospitalized since birth, group home/retirement, homeless shelter, psychiatric facility, facility, long-term acute-care hospital, corrections facility, other, and unknown.

(0.5%) died during hospitalization (Table 2). The median age was 7 years (IQR: 0–14), and most were male (n = 7; 58%), Hispanic (n = 6; 50%), or non-Hispanic Black (n = 4; 33%). The majority (n = 10; 83%) had ≥1 underlying medical conditions; neurologic disorders (n = 7; 58%) were the most common underlying condition.

Population-Based Rates of Severe COVID-19 Among Children ≤18 Years of Age

During March 2020 to May 2021, the overall cumulative population-based rate of hospitalization was 43.2 per 100 000 children aged <18 years, and the rate of severe COVID-19 was 12.0 per 100 000 children aged <18 years (Table 3). Hospitalization rates were highest among infants aged <12 months (177.5 per 100 000; RR: 3.2 versus children aged 2–17 years), Hispanic children (71.2 per 100 000; RR: 3.3 versus non-Hispanic White children), and non-Hispanic Black children (63.0 per 100 000; RR: 2.9 versus non-Hispanic White children). Rates of severe disease were highest among infants aged <12 months (36.8 per 100 000; RR: 2.4 versus children 2–17 years), Hispanic children (17.6 per 100 000; RR: 3.3 versus non-Hispanic White children), and non-Hispanic Black children (21.1 per 100 000; RR: 3.9 versus non-Hispanic White children).

DISCUSSION

Almost one-third of hospitalized children with SARS-CoV-2 infection required ICU admission or invasive mechanical ventilation, and children with specific underlying medical conditions were at greater risk of severe COVID-19. A strength of this investigation was the large, geographically diverse sample of children hospitalized with SARS-CoV-2 infection, which enabled the identification of demographic and medical characteristics associated with severe COVID-19 among pediatric subgroups, including by age and race and ethnicity. These results provide needed descriptive information about COVID-19 severity in children before widespread availability of pediatric COVID-19 vaccination and can serve as a baseline to assess changes in trends as COVID-19 vaccines are approved for use in younger age groups, to compare with severe adverse vaccine reactions, and as new SARS-CoV-2 variants emerge. Additionally, information about pediatric risk factors for severe COVID-19 can inform clinical decision-making by identifying children who may benefit from closer monitoring after hospitalization. These results may also guide other prevention measures, including health education and risk communication campaigns and recommendations for vaccination,[26–28] once COVID-19 vaccines are approved for use among younger children.

Similar to previous investigations,[29,30] we found that the presence of ≥1 underlying medical conditions was associated with increased risk of severe COVID-19 and identified the specific underlying conditions associated with severe COVID-19 within pediatric subgroups. Results underscore the importance of obesity and diabetes, which have previously been documented as risk factors for severe COVID-19 among both adults and children[4,12,24,30–33] and identify

TABLE 3 Age-Adjusted Cumulative Population-Based Rates of Hospitalization and Severe COVID-19 per 100 000 Children Aged <18 Years by Age Group, Sex, and Race and Hispanic Ethnicity Identified Through the COVID-NET, March 2020–May 2021

	Hospitalization			Severe COVID-19		
Group	No.	Rate	RR	No.	Rate	RR
Overall	3106	43.2	—	860	12.0	—
Age group						
<2 y	862	113.7	—	199	26.3	—
<12 mo	671	177.5	3.2	139	36.8	2.4
12–23 mo	191	50.3	0.9	60	15.8	1.03
2–17 y	2244	34.9	—	661	10.3	—
2–5 y	375	23.8	0.4	123	7.8	0.5
6–11 y	493	20.5	0.4	159	6.6	0.4
12–17 y	1376	56.1	Reference	379	15.5	Reference
Sex						
Male	1556	42.5	0.97	476	13.0	1.2
Female	1550	44.0	Reference	384	10.9	Reference
Race and Hispanic ethnicity group[a]						
Hispanic	1051	71.2	3.3	259	17.6	3.3
NH Black	936	63.0	2.9	314	21.1	3.9
NH Asian or Pacific Islander	149	25.3	1.2	36	6.0	1.1
NH White	767	21.4	Reference	193	5.4	Reference

Age-adjusted cumulative rates reflect the number of ICU admissions or invasive mechanical ventilations among children aged <18 y divided by the 2019 bridged-race postcensal population estimates from the National Center for Health Statistics. NH, non-Hispanic; —, not applicable.

[a] Rates not presented for the following race and ethnicity groups because of insufficient sample size: NH American Indian or Alaska Native, NH multiple races, NH other, or unknown.

additional risk factors, including neurologic and cardiovascular disease, feeding tube dependence, airway abnormality, and prematurity among specific pediatric subgroups. These results highlight the potential importance of neurologic disorders (including developmental delay), which were reported in more than one-half of the 12 in-hospital pediatric deaths and were associated with increased risk of severe COVID-19 across several pediatric population subgroups, including children 2 to 17 years of age without a discharge diagnosis of MIS-C and infants and children <2 years. Neurologic disorders have been shown to increase risk of severe illness in other respiratory diseases, potentially through decreased muscle tone and strength, impaired mobility, or structural conditions that diminish pulmonary function.[34–36] Consistent with findings from influenza-associated hospitalizations,[37] we found that some underlying medical conditions, including immunocompromised conditions and blood disorders, were not associated with increased risk of severe COVID-19, which may be explained by lower thresholds for hospital admission among children with conditions such as sickle cell disease.

When we examine population-based rates, which have not been calculated in most other studies, infants aged <12 months had the highest rates of hospitalization and severe COVID-19, compared with those of all other pediatric age groups, an important finding when assessing infant risk from COVID-19 disease.[3] However, similar to other studies,[4,12,29] we found that, once hospitalized with SARS-CoV-2 infection, infants were not at significantly increased risk of severe COVID-19 relative to older children. Young infants may have a lower threshold for admission compared with older children and, therefore, some hospitalized infants may not be as seriously ill from COVID-19 illness as hospitalized older children, potentially obscuring the true risk to infants compared with older children. More research is needed to evaluate the risk of severe COVID-19 among infants relative to older children.

Consistent with other studies,[2,3] Hispanic and non-Hispanic Black children had higher population-based rates of hospitalization and severe disease relative to non-Hispanic White children. However, as reported elsewhere,[6,12,23,29] once hospitalized with SARS-CoV-2 infection, Hispanic and Black children aged 2 to 17 years were not at increased risk of severe COVID-19 relative to White children, after controlling for the presence of ≥1 underlying medical conditions. These results may suggest that Hispanic and non-Hispanic Black children may be at greater risk of SARS-CoV-2 infection, COVID-19 illness, and associated hospitalization but are not necessarily at greater risk of severe disease outcomes after accounting for variation in the prevalence of

underlying medical conditions. Hispanic and non-Hispanic Black children may be at greater risk of SARS-CoV-2 infection relative to non-Hispanic White children by, for example, increased risk of infection with SARS-CoV-2 among household members who may be disproportionately represented among essential occupations, structural barriers to accessing health care, or other mechanisms.[38–40]

Limitations of this investigation include geographic and temporal variability in testing availability, capacity, and performance across contributing sites. Additionally, this investigation may have had limited statistical power to detect differences in severe COVID-19, particularly by less prevalent underlying medical conditions or among pediatric subgroups. In addition, ICU admission and invasive mechanical ventilation may not be proxies for disease severity for all children, particularly if the threshold for admission to the ICU for monitoring varied by pediatric subgroup. Also, children could have been misclassified if underlying conditions were not noted on their electronic medical records or case report form. Finally, these results are from a network of acute-care hospitals in 14 states and may not be generalizable to all hospitalized children with SARS-CoV-2 infection in the United States.

CONCLUSION

Children experience severe COVID-19, and, in hospitalized children, the presence of specific underlying medical conditions may be associated with greater risk of severe COVID-19 outcomes. Results provide baseline information about disease severity among children before widespread pediatric COVID-19 vaccination, and can be used to inform clinical decision-making, monitor population-based trends over time, and improve risk communication.

ACKNOWLEDGMENTS

The COVID-NET Surveillance Team Authors and Affiliations are as follows: Pam Daily Kirley, MPH (California Emerging Infections Program); Nisha Alden, MPH (Colorado Department of Public Health and Environment); Kimberly Yousey-Hindes, MPH, CPH (Connecticut Emerging Infections Program, Yale School of Public Health); Emily Fawcett, MPH (Georgia Emerging Infections Program; Georgia Department of Public Health; Atlanta Veterans Affairs Medical Center); Patricia A. Ryan, MS (Maryland Department of Health); Justin Henderson, MPH (Michigan Department of Health and Human Services); Ruth Lynfield, MD (Minnesota Department of Health); Sarah A. Khanlian, MPH (University of New Mexico, New Mexico Emerging Infections Program); Grant Barney, MPH (New York State Department of Health); Christina B. Felsen, MPH (University of Rochester School of Medicine); Jess Shiltz, MPH (Ohio Department of Health); Nasreen Abdullah, MD, MPH (Public Health Division, Oregon Health Authority); William Schaffner, MD (Vanderbilt University Medical Center); Mary Hill, MPH (Salt Lake County Health Department)

We acknowledge with gratitude the clinicians and surveillance officers at the COVID-NET sites included in this study. We also wish to acknowledge the following people: Onika Anglin (COVID-NET Surveillance Team, Centers for Disease Control and Prevention; General Dynamics Information Technology); Jennifer L. Milucky (COVID-NET Surveillance Team, Centers for Disease Control and Prevention); Roxanne Archer, Brooke Heidenga, Jeremy Roland, Maria Rosales, Monica Napoles (California Emerging Infections Program); Rachel Herlihy, Sarah McLafferty, Millen Tsegaye (Colorado Department of Public Health and Environment); Amber Maslar, Paula Clogher, Adam Misiorski, Christina Parisi, Maria Correa, Tessa Carter, Carol Lyons, Daewi Kim, Gaggan Brar, Linda Niccolai (Connecticut Emerging Infections Program, Yale School of Public Health); Allison Roebling, Katelyn Ward, Jana Manning, Asmith Joseph, Chandler Surell, Gracie Chambers, Grayson Kallas, Lauren Russell, Daniel Pizarro, Jeremiah Williams, Rayna Ceaser, Stephanie Lehman, Taylor Eisenstein, Suzanne Segler, Kyle Openo (Georgia Emerging Infections Program, Georgia Department of Public Health; Veterans Affairs Medical Center; Foundation for Atlanta Veterans Education and Research); Kenzie Teno (Iowa Department of Public Health); Elisabeth Vaeth, Cindy Zerrlaut, David Blythe, Alicia Brooks (Maryland Department of Health); Rachel Park, Michelle Wilson (Maryland Emerging Infections Program – The Johns Hopkins Bloomberg School of Public Health); Jim Collins, Shannon Johnson, Sue Kim, Alexander Kohrman, Sam Hawkins, Val Tellez Nunez, Lauren Leegwater, Sierra Peguies-Khan, Chloe Brown (Michigan Department of Health and Human Services); Kathy Como-Sabetti, Austin Bell, Kalyla Bilski, Emma Contestabile, Claire Henrichsen, Katherine Schleiss, Samantha Siebman, Emily Holodick, Lisa Nguyen, Kristen Ehresmann, Richard Danila (Minnesota Department of Health); Kathy M. Angeles, Emily B. Hancock, Yadira Salazar-Sanchez, Meaghan Novi, Nancy Eisenberg,

Melissa Christian, Dominic Rudin (New Mexico Emerging Infections Program); Nancy Spina, Suzanne McGuire, Adam Rowe, Kerianne Engesser (New York State Department of Health); Sophrena Bushey, Kevin Popham, Virginia Cafferky, Christine Long, RaeAnne Kurtz, Maria Gaitan (University of Rochester School of Medicine and Dentistry); Ama Owusu-Dommey, Breanna McArdle (Public Health Division; Oregon Health Authority); Kylie Seeley (Oregon Health & Science University School of Medicine); Katie Dyer, Karen Leib, Tiffanie Markus, Terri McMinn, Danielle Ndi, John Ujwok, Anise Elie, Kathy Billings, Manideepthi Pemmaraju (Vanderbilt University Medical Center); Amanda Carter, Andrea George, Andrea Price, Andrew Haraghey, Ashley Swain, Caitlin Shaw, Ian Buchta, Ilene Risk, Jake Ortega, Laine McCullough, Melanie Crossland, Ryan Chatelain, Tyler Riedesel (Salt Lake County Health Department).

ABBREVIATIONS

aRR: adjusted risk ratio
CDC: Centers for Disease Control and Prevention
CI: confidence interval
COVID-19: coronavirus disease 2019
COVID-NET: Coronavirus Disease 2019–Associated Hospitalization Surveillance Network
ICD-10: *International Classification of Diseases, 10th Revision*
IQR: interquartile range
MIS-C: multisystem inflammatory syndrome in children
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
RR: rate ratio

Dr Woodruff conceptualized and designed the study, analyzed and interpreted the data, and drafted the manuscript; Drs Campbell, Taylor, and Havers conceptualized and designed the study; interpreted the data, drafted the manuscript, critically revised the manuscript for important intellectual content, and supervised the investigation; Drs Chai, Anderson, Sosin, Bennett, Sutton, and Talbot and Ms Kawasaki, Mr Meek, Anderson, Mr Weigel, Ms Monroe, Ms Reeg, Ms Bye, Ms Muse, Ms Billing, and Mr McCaffrey participated in designing the study, interpreted the data and critically revised the manuscript for important intellectual content; Ms Pham, Mr Patel, and Mr Whitaker participated in designing the study, analyzed the data, and critically revised the manuscript for important intellectual content; Dr McMorrow participated in designing the study, interpreted the data, and critically revised the manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.
DOI: https://doi.org/10.1542/peds.2021-053418

Accepted for publication October 19, 2021

Address correspondence to Rebecca C. Woodruff, PhD, MPH, Division for Heart Disease and Stroke Prevention, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, 4770 Buford Hwy NE, Chamblee, GA 30341. E-mail: okp9@cdc.gov

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by the Centers for Disease Control and Prevention through an Emerging Infections Program cooperative agreement (grant CK17-1701) and through a Council of State and Territorial Epidemiologists cooperative agreement (grant NU38OT000297-02-00). The findings and conclusions in this report are those of the authors do not necessarily represent the official position of the US Department of Health and Human Services, the US Public Health Service Commissioned Corps, the Centers for Disease Control and Prevention, or the authors' institutions. The Centers for Disease Control and Prevention was involved in all aspects of the study, including its design, data collection, analysis, and writing the article.

POTENTIAL CONFLICT OF INTEREST: Mr Meek and Dr Sutton report receiving funding from the Centers for Disease Control and Prevention (CDC) Emerging Infections Program cooperative agreement. Ms Reeg and Ms Billing report receiving a CDC federal grant from the Council of State and Territorial Epidemiologists. Ms Billing reports receiving Epidemiology and Laboratory Capacity grant funding from CDC to support vaccine preventable disease epidemiology staffing and additionally report receiving Immunizations and Vaccines for Children grant funding from CDC. Dr Anderson has consulted for Pfizer, Sanofi Pasteur, Janssen, and Medscape, and his institution receives funds to conduct clinical research unrelated to this article from MedImmune, Regeneron, PaxVax, Pfizer, GSK, Merck, Sanofi Pasteur, Janssen, and Micron. He also serves on a safety monitoring board for Kentucky BioProcessing, Inc. and Sanofi Pasteur. His institution has also received funding from National Institutes of Health to conduct clinical trials of Moderna and Janssen COVID-19 vaccines.

REFERENCES

1. Centers for Disease Control and Prevention. COVID data tracker. Available at: https://covid.cdc.gov/covid-data-tracker/#datatracker-home. Accessed February 1, 2021
2. Garg S, Kim L, Whitaker M, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019 - COVID-NET, 14 states, March 1-30, 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(15):458–464
3. Kim L, Whitaker M, O'Halloran A, et al; COVID-NET Surveillance Team. Hospitalization rates and characteristics of children aged< 18 years hospitalized with laboratory-confirmed COVID-19 - COVID-NET, 14 states, March 1-July 25, 2020. *MMWR Morb Mortal Wkly Rep.* 2020; 69(32):1081–1088
4. Fernandes DM, Oliveira CR, Guerguis S, et al; Tri-State Pediatric COVID-19 Research Consortium. Severe acute respiratory syndrome coronavirus 2 clinical syndromes and predictors of disease severity in hospitalized children and youth. *J Pediatr.* 2021;230:23–31.e10
5. Shekerdemian LS, Mahmood NR, Wolfe KK, et al; International COVID-19 PICU Collaborative. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian pediatric intensive care units. *JAMA Pediatr.* 2020;174(9):868–873
6. Fisler G, Izard SM, Shah S, et al; Northwell COVID-19 Research Consortium. Characteristics and risk factors associated with critical illness in pediatric COVID-19. *Ann Intensive Care.* 2020; 10(1):171
7. Bixler D, Miller AD, Mattison CP, et al; Pediatric Mortality Investigation Team. SARS-CoV-2-associated deaths among persons aged 21 years - United States, February 12-July 31, 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(37):1324–1329
8. Feldstein LR, Tenforde MW, Friedman KG, et al; Overcoming COVID-19 Investigators. Characteristics and outcomes of US children and adolescents with multisystem inflammatory syndrome in children (MIS-C) compared with severe acute COVID-19. *JAMA.* 2021;325(11):1074–1087
9. Derespina KR, Kaushik S, Plichta A, et al. Clinical manifestations and outcomes of critically ill children and adolescents with coronavirus disease 2019 in New York City. *J Pediatr.* 2020;226:55–63.e2
10. Kainth MK, Goenka PK, Williamson KA, et al; NORTHWELL HEALTH COVID-19 RESEARCH CONSORTIUM. Early experience of COVID-19 in a US children's hospital. *Pediatrics.* 2020;146(4):e2020003186
11. Verma S, Lumba R, Dapul HM, et al. Characteristics of hospitalized children with SARS-CoV-2 in the New York City metropolitan area. *Hosp Pediatr.* 2021;11(1):71–78
12. Zachariah P, Johnson CL, Halabi KC, et al; Columbia Pediatric COVID-19 Management Group. Epidemiology, clinical features, and disease severity in patients with coronavirus disease 2019 (COVID-19) in a children's hospital in New York City, New York. *JAMA Pediatr.* 2020;174(10):e202430
13. Feldstein LR, Rose EB, Horwitz SM, et al; Overcoming COVID-19 Investigators; CDC COVID-19 Response Team. Multisystem inflammatory syndrome in U.S. children and adolescents. *N Engl J Med.* 2020; 383(4):334–346
14. Abrams JY, Oster ME, Godfred-Cato SE, et al. Factors linked to severe outcomes in multisystem inflammatory syndrome in children (MIS-C) in the USA: a retrospective surveillance study. *Lancet Child Adolesc Health.* 2021;5(5):323–331
15. US Food and Drug Administration. BLA approval. Available at: https://www.fda.gov/media/151710/download. Accessed May 1, 2021
16. Frenck RW Jr, Klein NP, Kitchin N, et al; C4591001 Clinical Trial Group. Safety, immunogenicity, and efficacy of the BNT162b2 Covid-19 vaccine in adolescents. *N Engl J Med.* 2021;385(3):239–250
17. US Food & Drug Administration. ModernaTX, Inc. COVID-19 vaccine emergency use authorization letter of authorization. Available at: https://www.fda.gov/media/144636/download. Accessed May 1, 2021
18. ModernaTX, Inc. A study to evaluate the safety, reactogenicity, and effectiveness of mRNA-1273 vaccine in adolescents 12 to <18 years old to prevent COVID-19 (TeenCove). Available at: https://clinicaltrials.gov/ct2/show/NCT04649151?cond=covid+vaccine&age=0&draw=2&rank=6. Accessed May 1, 2021
19. ModernaTX, Inc. A study to evaluate safety and effectiveness of mRNA-1273 vaccine in healthy children between 6 months of age and less than 12 years of age. Available at: https://clinicaltrials.gov/ct2/show/NCT04796896?term=moderna+children&cond=Covid19&draw=2&rank=1. Accessed May 1, 2021
20. Pfizer-BioNTech. Study to evaluate the safety, tolerability, and immunogenicity of an RNA vaccine candidate against COVID-19 in healthy children <12 years of age. Available at: https://clinicaltrials.gov/ct2/show/NCT04816643. Accessed May 1, 2021
21. Pfizer-BioNTech. Study to describe the safety, tolerability, immunogenicity, and efficacy of RNA vaccine candidates against COVID-19 in healthy individuals. Available at: https://clinicaltrials.gov/ct2/show/NCT04368728. Accessed May 1, 2021
22. Janssen Vaccines & Prevention B.V. A study to evaluate a range of dose levels and vaccination intervals of Ad26.COV2.S in healthy adults and adolescents. Available at: https://clinicaltrials.gov/ct2/show/NCT04535453. Accessed May 1, 2021
23. Graff K, Smith C, Silveira L, et al. Risk factors for severe COVID-19 in children. *Pediatr Infect Dis J.* 2021;40(4):e137–e145
24. Kim L, Garg S, O'Halloran A, et al. Risk factors for intensive care unit admission and in-hospital mortality among hospitalized adults identified through the US coronavirus disease 2019 (COVID-19)-associated hospitalization surveillance network (COVID-NET). *Clin Infect Dis.* 2020;72(9): e206–e214
25. Centers for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET) purpose and methods. Available at: https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covid-net/purpose-methods.html. Accessed May 1, 2021
26. Oliver SE, Gargano JW, Marin M, et al. The Advisory Committee on Immunization Practices' interim recommendation for use of Pfizer-BioNTech COVID-19 vaccine - United States, December 2020. *MMWR Morb Mortal Wkly Rep.* 2020; 69(50):1922–1924

27. Oliver SE, Gargano JW, Marin M, et al. The Advisory Committee on Immunization Practices' interim recommendation for use of Moderna COVID-19 vaccine - United States, December 2020. *MMWR Morb Mortal Wkly Rep*. 2021;69(5152): 1653–1656

28. Oliver SE, Gargano JW, Scobie H, et al. The Advisory Committee on Immunization Practices' interim recommendation for use of Janssen COVID-19 vaccine - United States, February 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(9): 329–332

29. Preston L, Chevinsky J, Kompaniyets L, et al. Characteristics and disease severity of US children and adolescents diagnosed with COVID-19. *JAMA Netw Open*. 2021;4(4):e215298

30. Tsankov BK, Allaire JM, Irvine MA, et al. Severe COVID-19 infection and pediatric comorbidities: a systematic review and meta-analysis. *Int J Infect Dis*. 2021;103: 246–256

31. Del Sole F, Farcomeni A, Loffredo L, et al. Features of severe COVID-19: a systematic review and meta-analysis. *Eur J Clin Invest*. 2020;50(10):e13378

32. Yang J, Ma Z, Lei Y. A meta-analysis of the association between obesity and COVID-19. *Epidemiol Infect*. 2020; 149:e11

33. Kompaniyets L, Agathis NT, Nelson JM, et al. Underlying medical conditions associated with severe COVID-19 illness among children. *JAMA Netw Open*. 2021;4(6):e2111182

34. Havers F, Fry AM, Chen J, et al. Hospitalizations attributable to respiratory infections among children with neurologic disorders. *J Pediatr*. 2016;170:135–141.e1-5

35. Inal-Ince D, Savci S, Arikan H, et al. Effects of scoliosis on respiratory muscle strength in patients with neuromuscular disorders. *Spine J*. 2009;9(12):981–986

36. Keren R, Zaoutis TE, Bridges CB, et al. Neurological and neuromuscular disease as a risk factor for respiratory failure in children hospitalized with influenza infection. *JAMA*. 2005;294(17): 2188–2194

37. Collins JP, Campbell AP, Openo K, et al. Clinical features and outcomes of immunocompromised children hospitalized with laboratory-confirmed influenza in the United States, 2011-2015. *J Pediatric Infect Dis Soc*. 2019;8(6):539–549

38. Raine S, Liu A, Mintz J, Wahood W, Huntley K, Haffizulla F. Racial and ethnic disparities in COVID-19 outcomes: social determination of health. *Int J Environ Res Public Health*. 2020; 17(21):E8115

39. Hawkins D. Differential occupational risk for COVID-19 and other infection exposure according to race and ethnicity. *Am J Ind Med*. 2020; 63(9):817–820

40. Mackey K, Ayers CK, Kondo KK, et al. Racial and ethnic disparities in COVID-19-related infections, hospitalizations, and deaths : a systematic review. *Ann Intern Med*. 2021; 174(3):362–373