Clinical Infectious Diseases

MAJOR ARTICLE

Severe Acute Respiratory Syndrome Coronavirus 2 Infections Among Children in the Biospecimens from Respiratory Virus-Exposed Kids (BRAVE Kids) Study

Jillian H. Hurst,[1,2] Sarah M. Heston,[1] Hailey N. Chambers,[3] Hannah M. Cunningham,[3] Meghan J. Price,[3] Lilianna Suarez,[3] Carter G. Crew,[2] Shree Bose,[3] Jhoanna N. Aquino,[1] Stuart T. Carr,[1] S. Michelle Griffin,[4] Stephanie H. Smith,[5] Kirsten Jenkins,[1] Trevor S. Pfeiffer,[1] Javier Rodriguez,[4] C. Todd DeMarco,[5] Nicole A. De Naeyer,[5] Thaddeus C. Gurley,[5] Raul Louzao,[5] Congwen Zhao,[6] Coleen K. Cunningham,[1] William J. Steinbach,[1] Thomas N. Denny,[5] Debra J. Lugo,[1] M. Anthony Moody,[1,5] Sallie R. Permar,[1,2,5] Alexandre T. Rotta,[7] Nicholas A. Turner,[8] Emmanuel B. Walter,[5,9] Christopher W. Woods,[8] and Matthew S. Kelly[1]

[1]Department of Pediatrics, Division of Infectious Diseases, Duke University School of Medicine, Durham, North Carolina, USA, [2]Children's Health and Discovery Institute, Department of Pediatrics, Duke University School of Medicine, Durham, North Carolina, USA, [3]Duke University School of Medicine, Durham, North Carolina, USA, [4]Children's Clinical Research Unit, Department of Pediatrics, Duke University School of Medicine, Durham, North Carolina, USA, [5]Duke Human Vaccine Institute, Duke University School of Medicine, Durham, North Carolina, USA, [6]Department of Biostatistics and Bioinformatics, Duke University School of Medicine, Durham, North Carolina, USA, [7]Department of Pediatrics, Division of Pediatric Critical Care Medicine, Duke University School of Medicine, Durham, North Carolina, USA, [8]Department of Medicine, Division of Infectious Diseases, Duke University School of Medicine, Durham, North Carolina, USA, and [9]Department of Pediatrics, Division of Primary Care Pediatrics, Duke University School of Medicine, Durham, North Carolina, USA

Background. Child with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection typically have mild symptoms that do not require medical attention, leaving a gap in our understanding of the spectrum of SARS-CoV-2-related illnesses that the viruses causes in children.

Methods. We conducted a prospective cohort study of children and adolescents (aged <21 years) with a SARS-CoV-2-infected close contact. We collected nasopharyngeal or nasal swabs at enrollment and tested for SARS-CoV-2 using a real-time polymerase chain reaction assay.

Results. Of 382 children, 293 (77%) were SARS-CoV-2-infected. SARS-CoV-2-infected children were more likely to be Hispanic (P < .0001), less likely to have asthma (P = .005), and more likely to have an infected sibling contact (P = .001) than uninfected children. Children aged 6-13 years were frequently asymptomatic (39%) and had respiratory symptoms less often than younger children (29% vs 48%; P = .01) or adolescents (29% vs 60%; P < .001). Compared with children aged 6-13 years, adolescents more frequently reported influenza-like (61% vs 39%; P < .001) , and gastrointestinal (27% vs 9%; P = .002), and sensory symptoms (42% vs 9%; P < .0001) and had more prolonged illnesses (median [interquartile range] duration: 7 [4-12] vs 4 [3-8] days; P = 0.01). Despite the age-related variability in symptoms, wWe found no difference in nasopharyngeal viral load by age or between symptomatic and asymptomatic children.

Conclusions. Hispanic ethnicity and an infected sibling close contact are associated with increased SARS-CoV-2 infection risk among children, while asthma is associated with decreased risk. Age-related differences in clinical manifestations of SARS-CoV-2 infection must be considered when evaluating children for coronavirus disease 2019 and in developing screening strategies for schools and childcare settings.

Keywords. COVID-19; pediatric; community; asymptomatic; viral load.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been responsible for more than 20 million infections and 750 000 deaths as of August 2020. Current epidemiological data suggest that children are less susceptible to SARS-CoV-2 infection than adults. Population screening in Iceland found SARS-CoV-2 was detected at a lower rate among children aged <10 years compared with adolescents and adults (6.7% vs 13.7%) [1]. Further, mathematical modeling from Asia and Europe estimated susceptibility of individuals aged <20 years to the virus was approximately half that of older adults [2]. Finally, in a household transmission study, the secondary attack rate was lower among children aged <20 years (5%) than among adults aged 20–59 years (15%) or ≥60 years (18%) [3]. The extent to which these findings reflect differences in SARS-CoV-2 exposures among adults and children or age-related biological differences in SARS-CoV-2 susceptibility is unknown. To date, few factors that influence infection risk among SARS-CoV-2–exposed children have been identified.

Children infected with SARS-CoV-2 generally have milder illnesses than adults. In a recent meta-analysis of data from 371 children aged <18 years, fever (51%) and cough (37%) were the most frequently reported symptoms, while 17% of children were asymptomatic [4]. In a large cohort of children tested for SARS-CoV-2 in the United States, around half of

Received 24 August 2020; editorial decision 28 October 2020; published online 3 November 2020.

Correspondence: Matthew S. Kelly, 2301 Erwin Rd, Durham, NC 27710 (matthew.kelly@duke.edu).

Clinical Infectious Diseases® 2021;73(9):e2875–82

© The Author(s) 2020. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com.

DOI: 10.1093/cid/ciaa1693

children who tested positive had cough or fever, while 15% reported shortness of breath [5]. To date, studies that describe the clinical characteristics of SARS-CoV-2 infections among children have been limited by cross-sectional designs, small sample sizes, or inclusion of only hospitalized or symptomatic children [6–10]. Given that a small minority of children with SARS-CoV-2 infection require hospitalization, the spectrum of illnesses caused by SARS-CoV-2 in children has not been well characterized. Such data are critical for providers who evaluate children with possible coronavirus disease 2019 (COVID-19) and for the development of effective screening strategies in order for children to attend schools and other congregate childcare settings.

Here, we describe risk factors, clinical manifestations, and nasopharyngeal viral loads of SARS-CoV-2 infection among 382 children and adolescents living within the catchment area of a health system in central North Carolina, constituting the largest nonhospitalized pediatric cohort described to date.

METHODS

Study Design

The Duke Biospecimens from RespirAtory Virus-Exposed Kids (BRAVE Kids) study is a prospective cohort study of children and adolescents with confirmed SARS-CoV-2 infection or close contact with an individual with confirmed SARS-CoV-2 infection. This study is being conducted within the Duke University Health System (DUHS) in Raleigh–Durham, North Carolina. The DUHS is a large, integrated health system that consists of 3 hospitals and more than 100 outpatient clinics. The DUHS Institutional Review Board approved the study.

Study Participants

Eligible participants were aged <21 years and had close contact with an individual with laboratory-confirmed SARS-CoV-2 infection. Participants were identified either through presentation to the health system themselves or through presentation of a close contact with laboratory-confirmed SARS-CoV-2 infection. We defined close contact as an unprotected exposure within 6 feet to a confirmed case between 2 days before and 7 days after symptom onset or laboratory confirmation of SARS-CoV-2 infection in asymptomatic contacts. Close contacts included, but were not limited to, siblings, parents, other caregivers, partners, and relatives. Potential study participants were recruited through review of positive SARS-CoV-2 test results for individuals aged <21 years within the DUHS or review of positive SARS-CoV-2 test results for individuals aged ≥21 years who may have had close contact with children and adolescents within their households. Households with individuals who tested positive for SARS-CoV-2 were contacted by phone. All individuals aged <21 years identified in the household who had close contact with a SARS-CoV-2–infected individual were eligible for study enrollment. Informed consent was obtained from study participants or their legal guardians; assent was obtained for children aged 8–17 years. Written consent was provided using an electronic consent document. We obtained a waiver of documentation for participants who did not have an email address or were unable to complete the electronic consent document.

Study Procedures

We collected exposure, sociodemographic, and clinical data at enrollment through review of electronic medical records and a directed caregiver questionnaire conducted by telephone. We recorded symptoms that occurred up to 14 days prior to enrollment. Research staff completed follow-up questionnaires by phone for all participants 7 days after study enrollment to document new symptoms and healthcare encounters. For participants with ongoing symptoms 7 days after study enrollment, additional questionnaires were administered 14 and 28 days after enrollment or until the participant reported complete symptom resolution. We recorded the results of SARS-CoV-2 testing performed for clinical care. Research staff collected nasopharyngeal swabs from participants who consented to a home visit. Participants who declined a home visit received a kit for self-collection of a midturbinate nasal swab. Nasopharyngeal and nasal samples were collected with nylon flocked swabs (Copan Italia, Brescia, Italy) into RNAProtect (Qiagen, Hilden, Germany).

Viral Load Assay

SARS-CoV-2 RNA copies per milliliter was determined using a 2-step real-time quantitative polymerase chain reaction (PCR) assay developed in the Clinical Laboratory Improvement Amendments-certified Immunology and Virology Quality Assessment Center at the Duke Human Vaccine Institute. DSP Virus/Pathogen Midi Kits (Qiagen, Hilden, Germany) were used to extract viral RNA on a QIAsymphony SP automated sample preparation platform. A reverse primer specific to the SARS-CoV-2 envelope gene was annealed to the extracted RNA and reverse transcribed into cDNA using SuperScript III Reverse Transcriptase and RNaseOut (Thermo Fisher Scientific, Waltham, MA). cDNA was treated with RNase H and then added to a custom 4× TaqMan Gene Expression Master Mix (Applied Biosystems, Foster City, CA) that contained envelope gene-specific primers and a fluorescently labeled hydrolysis probe; quantitative PCR was carried out on a QuantStudio 3 Real-Time PCR system (Thermo Fisher Scientific, Waltham, MA) [11]. SARS-CoV-2 RNA copies per reaction were interpolated using quantification cycle data and a serial dilution of a highly characterized custom DNA plasmid that contained the SARS-CoV-2 envelope gene sequence. The limit of quantification was 62 RNA copies/mL of sample as determined by an extensive validation process consistent for use in a clinical setting.

Data Analyses

We described characteristics of the study population by SARS-CoV-2 infection status using frequencies and percentages for categorical variables and medians and interquartile ranges (IQRs) for continuous variables. We used the χ^2 or Fisher exact test for categorical variables and Wilcoxon rank sum tests or analysis of variance (ANOVA) for continuous variables to compare the characteristics of SARS-CoV-2–infected and uninfected children and to evaluate age-related differences in symptoms among SARS-CoV-2–infected children. We compared nasopharyngeal SARS-CoV-2 viral loads (measured as $\log_{10}$ copies per milliliter) by age, illness characteristics, and timing of sample collection relative to symptom onset using ANOVA or linear regression. We used a quantile-quantile plot to verify normality of the nasopharyngeal viral load data. Study data were managed using REDCap electronic data capture tools hosted at Duke University [11]. Analyses were performed using R version 3.6.1 [12].

RESULTS

Patient Characteristics

Among the 382 children enrolled between 7 April 2020 and 16 July 2020 (Figure 1), median (IQR) age was 9.7 years (4.8, 15.9), 204 (53%) children were female, and 307 (81%) were of Hispanic ethnicity. These children and adolescents were in 204 households, with a mean of 1.9 participants per household. To provide additional context for our cohort's demographics, we identified all individuals aged <21 years within the DUHS who were tested for SARS-CoV-2 by PCR from 1 April 2020 to 31 July 2020 (Supplementary Table 1). Hispanic children represented 21% of those individuals tested for SARS-CoV-2 infection but accounted for 59% of SARS-CoV-2–infected patients. Most children were healthy, with the most commonly identified comorbidities being obesity (body mass index ≥95th percentile for age; 28%) and having a history of provider-diagnosed asthma (9%). A total of 293 (77%) children were SARS-CoV-2–infected and 89 (23%) were SARS-CoV-2–uninfected (Table 1). History of provider-diagnosed asthma was less common in SARS-CoV-2–infected children than in uninfected children (6% vs 17%; $P = .005$). SARS-CoV-2–infected children were more likely to be of Hispanic ethnicity (88% vs 57%; $P < .0001$) and to have an infected sibling contact than uninfected children (49% vs 29%; $P = .001$). Of 145 SARS-CoV-2–infected children with an infected sibling, 46 of 145 (32%) did not have any identified adult close contacts with confirmed SARS-CoV-2 infection. Among these 46 children, median (IQR) age of the infected sibling contacts was 12.0 years (8.2–16.2).

Symptoms of SARS-CoV-2 Infection

One or more symptoms were reported by 206 (70%) patients with confirmed SARS-CoV-2 infection (Supplementary Table 2). The most commonly reported symptoms were subjective

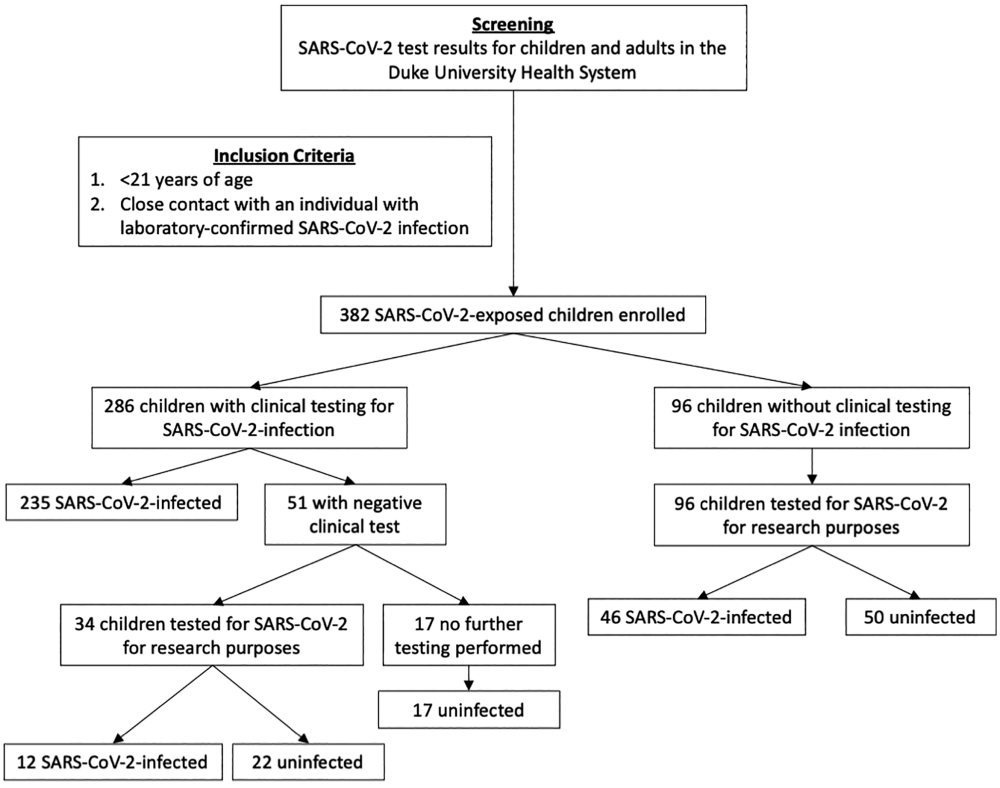

Figure 1. Flow chart of enrollment and determination of SARS-CoV-2 infection status in the study population. Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 1. Characteristics of the Study Population

Characteristic	Total (N = 382)		SARS-CoV-2–Infected (n = 293)		SARS-CoV-2–Uninfected (n = 89)		*P* Value
	n (or median)	% (or IQR)	n (or median)	% (or IQR)	n (or median)	% (or IQR)	
Age, y	9.7	(4.8–15.9)	10.4	(4.8–16.4)	8.7	(5.0–14.4)	.37
Sex							.80
Female	204	53%	158	54%	46	52%	
Male	178	47%	135	46%	43	48%	
Race							<.0001
Black or African-American	26	7%	17	6%	9	10%	
Latino or Hispanic-American	307	81%	256	88%	51	57%	
Non-Hispanic White	45	12%	17	6%	28	31%	
Other	2	<1%	1	<1%	1	1%	
Number of household members	5	(4–6)	5	(4–6)	5	(4–6)	.97
Close contacts with SARS-CoV-2							
Parent	217	57%	159	54%	134	46%	.09
Sibling	171	45%	145	49%	26	29%	.001
Other	103	27%	77	26%	26	29%	.68
Comorbidities							
Provider-diagnosed asthma	34	9%	19	6%	15	17%	.005
Obesity (body mass index ≥95th percentile for age)	108	28%	88	30%	20	22%	.18

Abbreviations: IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

fever (42%), cough (34%), and headache (26%). The median (IQR) duration of symptoms was 5 days (3–10); 90% of symptomatic children reported full symptom resolution within 15 days. The clinical manifestations of SARS-CoV-2 infection varied by age (Figure 2). Symptoms were reported at enrollment or in follow-up in 75% of children aged 0–5 years, 61% of children aged 6–13 years, and 76% of adolescents aged 14–20 years ($P = .04$). Children aged 6–13 years reported respiratory symptoms less often than younger children (29% vs 48%; $P = .01$) and adolescents aged 14–20 years (29% vs 60%; $P < .0001$). Compared with children aged 6–13 years, adolescents aged 14–20 years also more frequently reported influenza-like (61% vs 39%; $P = .002$), gastrointestinal (27% vs 9%; $P = .002$), and sensory symptoms (42% vs 9%; $P < .0001$). Adolescents had more prolonged illnesses than either children aged 0–5 years (median [IQR] duration: 7 [4–12] vs 4 [3–7.5] days; $P = .002$) or children aged 6–13 years (median [IQR] duration: 7 [4–12] vs 4 [3–8] days; $P = .01$). One infant with a prior history of severe bronchiolitis required hospitalization for respiratory distress and was given remdesivir.

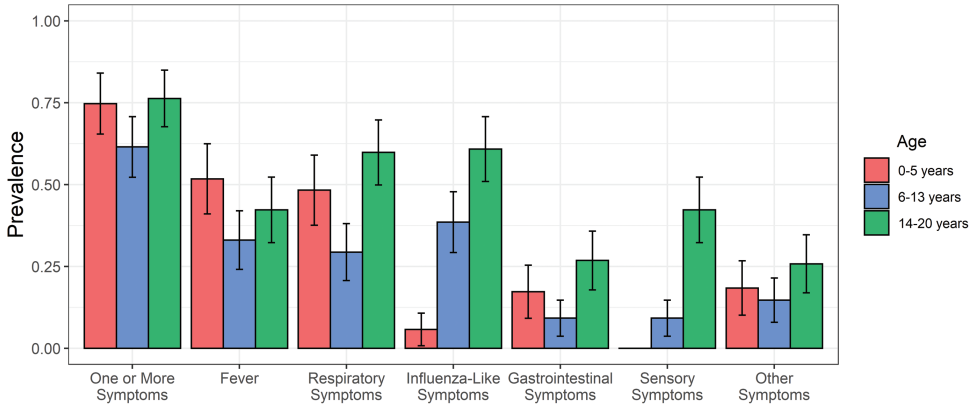

Figure 2. Prevalence of reported symptom complexes in 293 severe acute respiratory syndrome coronavirus 2–infected children by age. Age was categorized into 3 groups (0–5 years, 6–13 years, and 14–20 years), and the prevalence of specific symptom complexes are reported for children in each age group. Symptom complexes include respiratory symptoms (cough, difficulty breathing, nasal congestion, or rhinorrhea), influenza-like symptoms (headache, myalgias, or pharyngitis), gastrointestinal symptoms (abdominal pain, diarrhea, or vomiting), and sensory symptoms (anosmia or dysgeusia). Error bars correspond to the 95% confidence interval for each symptom complex in each age group.

Nasopharyngeal Viral Loads

We performed quantitative SARS-CoV-2 PCR on nasopharyngeal samples from 258 study participants. SARS-CoV-2 was detected in 178 (69%) samples at a median (IQR) viral load of 4.0 log copies/mL (3.0–5.6). We evaluated associations between nasopharyngeal viral load and age, symptoms, and the timing of sample collection relative to symptom onset (Figure 3). SARS-CoV-2 viral loads did not differ by age group ($P = .80$). Among symptomatic children, nasopharyngeal viral loads were highest in the 3 days before and after onset of symptoms and declined with increasing time from symptom onset ($P < .0001$). Nasopharyngeal viral loads did not differ in symptomatic and asymptomatic children of any age (median [IQR]: 4.1 [3.0–5.5] vs 3.8 [2.8–6.5] log copies/mL; $P = .56$). Similarly, we found no association between viral load and the presence of fever, respiratory symptoms, or other reported symptom complexes.

DISCUSSION

We describe the clinical and epidemiological characteristics of 382 children and adolescents who had close contact with a SARS-CoV-2–infected individual. We found that Hispanic ethnicity and a SARS-CoV-2–infected sibling were risk factors for SARS-CoV-2 infection, while history of provider-diagnosed asthma was associated with a decreased infection risk. We also report that the characteristics and duration of illnesses among SARS-CoV-2–infected children vary by age. Finally, we demonstrate that nasopharyngeal SARS-CoV-2 viral loads do not

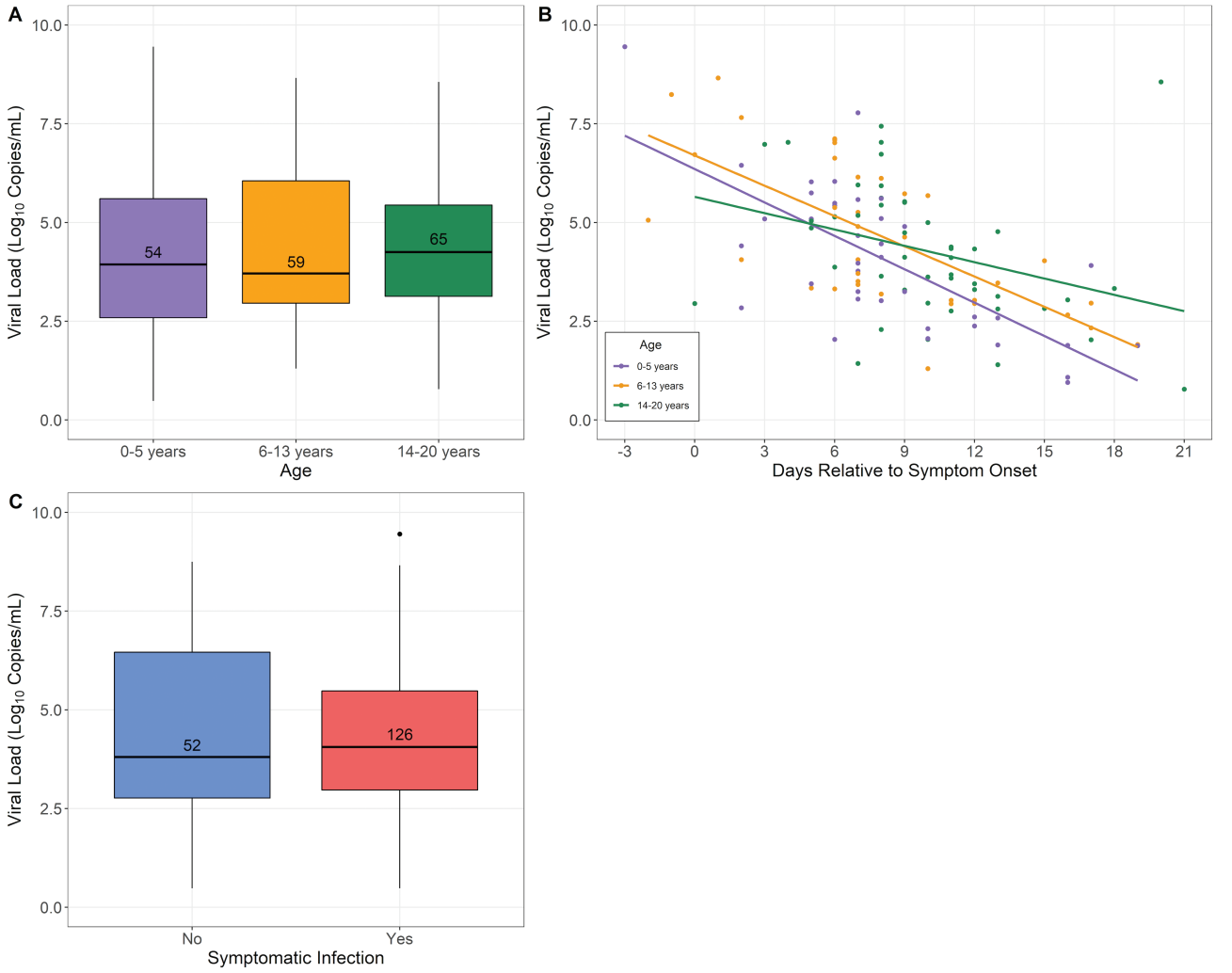

Figure 3. Evaluation of nasopharyngeal severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral load among 178 SARS-CoV-2–infected children by age, symptoms, and timing of sample collection relative to symptom onset. *A,* Viral loads among SARS-CoV-2–infected children by age group. No difference in viral load was seen with respect to age ($P = .80$). *B,* Viral loads in symptomatic SARS-CoV-2–infected children relative to the timing of symptom onset (days –3 to 21). SARS-CoV-2 viral loads were highest in the 3 days before and after symptom onset (median [interquartile range]: 6.5 log copies/mL [4.4–7.7]) and declined with increasing time from symptom onset ($P < .0001$). Adjusting for the timing of sample collection relative to symptom onset, there were no differences in nasopharyngeal viral load by age group (0–5 years vs 14–20 years, $P = .27$; 6–13 years vs 14–20 years, $P = .94$). *C,* Viral loads among SARS-CoV-2–infected children who reported 1 or more symptoms and children who reported no symptoms. Viral loads were similar among asymptomatic children and children with symptomatic coronavirus disease 2019 ($P = .56$).

differ by age or between symptomatic and asymptomatic children and decrease sharply after symptom onset in children and adolescents.

More than 80% of children in our cohort were Hispanic, and Hispanic ethnicity was associated with an increased risk of SARS-CoV-2 infection. Individuals of Hispanic ethnicity accounted for 59%–62% of all SARS-CoV-2 cases reported in the catchment area during the study period [13]. Similarly, data from our cohort and the DUHS are consistent with national data that demonstrate that 42% of the 161 387 school-aged children who tested positive for SARS-CoV-2 were of Hispanic ethnicity [14]. Moreover, Hispanic ethnicity was more commonly reported among children who were hospitalized or admitted to an intensive care unit [14]. The factors that underlie the racial and ethnic disparities in SARS-CoV-2 infection rates and outcomes will require further study, though they are likely linked to structural inequities, including higher prevalence of essential workers, dense living conditions, and socioeconomic factors.

We also found that having an infected sibling was a risk factor for SARS-CoV-2 infection. Early studies suggested that children transmit SARS-CoV-2 less effectively than adults, but evidence for efficient transmission from children has been accumulating [9, 15–17]. Further, there have been increasing reports of infections among children as schools, camps, and other childcare facilities reopen in the United States and other countries [16, 18, 19]. Future studies should carefully evaluate the nature of child-to-child contacts in order to understand the conditions under which the virus is most readily transmitted within this age group.

Our findings suggest that a history of provider-diagnosed asthma is associated with a lower susceptibility to SARS-CoV-2 infection among children. Though many viral respiratory infections are associated with asthma exacerbations, a recent study of adults hospitalized with SARS-CoV-2 pneumonia found no difference in disease severity between asthmatic and nonasthmatic patients [20]. Several prior studies reported that individuals with asthma are underrepresented in cohorts of patients with COVID-19 [21–23]. In a study of 1590 individuals hospitalized for COVID-19 in China, not a single patient had a history of provider-diagnosed asthma [23]. These observations have led to speculation that asthma may lower SARS-CoV-2 susceptibility or alternatively protect from severe COVID-19 by promoting a Th2-dominant immune response or through reduced expression of the SARS-CoV-2 receptor (angiotensin-converting enzyme 2) [24].

Consistent with prior reports, we found that the majority of SARS-CoV-2–infected children had mild illnesses and that symptoms reported in our cohort were broadly similar to those seen in other pediatric studies [4, 5, 7, 8]. Among 291 SARS-CoV-2–infected children with symptom data reported to the Centers for Disease Control and Prevention, fever, cough, and headache were most commonly reported [8]. Similar to recent studies of SARS-CoV-2–infected adults, gastrointestinal and sensory symptoms (anosmia or dysgeusia) were relatively common in our cohort [25, 26]. Clinical manifestations appear to vary by age, both in our cohort and in other reports. Symptoms reported by SARS-CoV-2–infected adolescents have been generally similar to those described in adults, with high prevalence of respiratory, influenza-like, gastrointestinal, and sensory symptoms [27]. Additionally, illness duration appears to correspond with age, though illness durations were generally shorter than have been reported in adults [28, 29]. In a study of 270 outpatient SARS-CoV-2–infected adults in the United States, 35% of adults reported not having returned to their usual state of health 14 to 21 days after SARS-CoV-2 testing [28].

Recent studies that evaluated associations between age and nasopharyngeal viral load reported conflicting results. Among 145 children and adults with symptomatic SARS-CoV-2 infection in Chicago, higher amounts of viral nucleic acid were detected in samples from 46 children aged <5 years than from 51 older children and 48 adults [30]. This study used cycle threshold values from a PCR assay that has been approved for clinical use but has not been calibrated for quantitation [30]. A study conducted in Switzerland showed no difference in nasopharyngeal viral loads between 53 children aged <11 years and adults [31]. In this largest pediatric cohort reported to date, we found no association between age and nasopharyngeal SARS-CoV-2 viral load among children and adolescents aged <21 years. Conflicting data have also been reported with regard to associations between nasopharyngeal viral load and illness severity [32–34]. A higher nasopharyngeal viral load predicted a shorter duration of illness among adults who presented for emergency care, while a higher viral load was associated with an increased risk of intubation in hospitalized adults [33, 34]. Moreover, a prior study suggested that asymptomatic patients have viral loads that approximate those of patients with symptomatic COVID-19 [35]. In our pediatric cohort, nasopharyngeal viral loads were similar across age groups and did not differ based on symptoms. However, we found a strong association between the timing of symptom onset and nasopharyngeal viral load, similar to what has been reported previously in adults in whom viral loads are highest around the time of symptom onset [36].

Our study has several limitations. First, study recruitment was influenced by local SARS-CoV-2 testing availability and guidelines, which changed during the study period and may differ from those in other areas. Early in the pandemic, the North Carolina Department of Health and Human Services (NCDHHS) recommended testing of all individuals with symptoms of SARS-CoV-2 infection. Later, these guidelines were expanded to include those who had close contact with a known SARS-CoV-2–infected individual, regardless of symptoms. Given a disproportionate number of cases identified in racial and ethnic populations, NCDHHS updated their guidance in

mid-May to specifically recommend testing in historically marginalized populations, including Hispanic individuals. Thus, testing procedures varied over time as our understanding of SARS-CoV-2 clinical presentations and risk factors evolved, influencing the composition of our cohort. Additionally, we are unable to estimate the number of children who may have had close contact with a SARS-CoV-2–infected individual within the study catchment area. It is therefore possible that our cohort is biased toward inclusion of symptomatic SARS-CoV-2–infected children. Another limitation is that we did not attempt to identify the settings in which family members and participants may have been infected. Future work should examine the contributions of employment, school and daycare attendance, and other social exposures to infection risk. Given our study design and the relatively high rate of asymptomatic infection among children in our cohort, we were unable to determine the direction of SARS-CoV-2 transmission within households. Nearly one-third (30%) of children in our cohort were tested for SARS-CoV-2 infection at only a single time point, and some children who ultimately developed SARS-CoV-2 infection may have been misclassified as uninfected because of the timing of sample collection. The prevalence of influenza-like sensory symptoms and symptom duration should be interpreted with caution in children aged <5 years, given that many children in this age group are unable to verbalize these symptoms. Further, viral loads from nasopharyngeal swabs are likely affected by sampling technique. Finally, analyses were limited to detection of viral nucleic acid, although a prior study reported a close correlation between viral load and infectious virus in symptomatic neonates, children, and adolescents [37].

In summary, we identify risk factors for SARS-CoV-2 infection among children and present further evidence of probable child-to-child transmission within household settings. Moreover, we demonstrate that the clinical manifestations of SARS-CoV-2 infection among children and adolescents are dependent on age. Finally, we show that children and adolescents with SARS-CoV-2 infection have similar nasopharyngeal viral loads. Future studies are needed to elucidate the biological and immunological factors that account for the age-related differences in infection susceptibility and illness characteristics among children.

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

Acknowledgments. We offer sincere gratitude to the children and families who participated in this research.

Financial support. This work was supported by the Translating Duke Health Children's Health and Discovery Initiative and the Children's Miracle Network hospitals. M. S. K. was supported by a National Institutes of Health Career Development award (K23-AI135090). S. M. H. was supported by a training grant from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (T32HD094671).

Potential conflicts of interest. S. R. P. consults for cytomegalovirus vaccine programs at Merck, Sanofi, Moderna, and Pfizer and receives support for research from Moderna, Merck, and the Gates Foundation. E. B. W. is an investigator for clinical trials funded by Pfizer and Moderna. A. R. reports consulting fees from Vapotherm, scientific advisory board fees from Breas US, and royalties from Elsevier outside the submitted work. C. W. reports advisory board fees from Roche Molecular Sciences, nonfinancial support from BioMerieux and Becton Dickinson, research collaboration from Biofire, and being cofounder of Predigen outside the submitted work. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Gudbjartsson DF, Helgason A, Jonsson H, et al. Spread of SARS-CoV-2 in the Icelandic population. N Engl J Med **2020**; 382:2302–15.
2. Davies NG, Klepac P, Liu Y, Prem K, Jit M, Eggo RM; CMMID COVID-19 Working Group. Age-dependent effects in the transmission and control of COVID-19 epidemics. Nat Med **2020**; 26:1205–11.
3. Jing QL, Liu MJ, Zhang ZB, et al. Household secondary attack rate of COVID-19 and associated determinants in Guangzhou, China: a retrospective cohort study. Lancet Infect Dis **2020**; 20:1141–50.
4. Ding Y, Yan H, Guo W. Clinical characteristics of children with COVID-19: a meta-analysis. Front Pediatr **2020**; 8:431.
5. Zhang C, Gu J, Chen Q, et al. Clinical and epidemiological characteristics of pediatric SARS-CoV-2 infections in China: a multicenter case series. PLoS Med **2020**; 17:e1003130.
6. Du W, Yu J, Wang H, et al. Clinical characteristics of COVID-19 in children compared with adults in Shandong Province, China. Infection **2020**; 48:445–52.
7. Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. Lancet Infect Dis **2020**; 20:689–96.
8. Coronavirus disease 2019 in children—United States, February 12-April 2, 2020. MMWR Morb Mortal Wkly Rep **2020**; 69:422–6.
9. Posfay Barbe C, Wagner N, Gauthey M, et al. COVID-19 in children and the dynamics of infection in families. Pediatrics **2020**:e20201576.
10. Corman VM, Landt O, Kaiser M, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill **2020**; 25:2000045. Available at: https://doi.org/10.2807/1560-7917.ES.2020.25.3.2000045.
11. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) —a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform **2009**; 42:377–81.
12. R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, **2013**. Available at: http://www.R-project.org/. Accessed 1 August 2020.
13. North Carolina Department of Health and Human Services. COVID-19 cases. Available at: https://covid19.ncdhhs.gov/dashboard/cases. Accessed 14 August 2020.
14. Leeb RT, Price S, Sliwa S, et al. COVID-19 trends among school-aged children—United States, March 1–September 19, 2020. MMWR Morb Mortal Wkly Rep **2020**; 69:1410–15.
15. Wu Q, Xing Y, Shi L, et al. Coinfection and other clinical characteristics of COVID-19 in children. Pediatrics **2020**; 146:e20200961.
16. Park YJ, Choe YJ, Park O, et al; COVID-19 National Emergency Response Center, Epidemiology and Case Management Team. Contact tracing during coronavirus disease outbreak, South Korea, 2020. Emerg Infect Dis **2020**; 26:2465–8.
17. Teherani MF, Kao CM, Camacho-Gonzalez A, et al. Burden of illness in households with SARS-CoV-2 infected children. Pediatr Infect Dis J **2020**; 9:613–16.
18. Szablewski CM. SARS-CoV-2 transmission and infection among attendees of an overnight camp—Georgia, June 2020. MMWR Morb Mortal Wkly Rep **2020**; 69:1023–5.
19. Stein-Zamir C, Abramson N, Shoob H, et al. A large COVID-19 outbreak in a high school 10 days after schools' reopening, Israel, May 2020. Euro Surveill **2020**; 25:2001352.
20. Grandbastien M, Piotin A, Godet J, et al. SARS-CoV-2 pneumonia in hospitalized asthmatic patients did not induce severe exacerbation. J Allergy Clin Immunol Pract **2020**; 8:2600–7.

21. Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol **2020**; 146:110–8.
22. Lupia T, Scabini S, Mornese Pinna S, Di Perri G, De Rosa FG, Corcione S. 2019 novel coronavirus (2019-nCoV) outbreak: a new challenge. J Glob Antimicrob Resist **2020**; 21:22–7.
23. Guan W-J, Liang W-H, Zhao Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J **2020**; 55:2000547.
24. Camiolo M, Gauthier M, Kaminski N, Ray A, Wenzel SE. Expression of SARS-CoV-2 receptor ACE2 and coincident host response signature varies by asthma inflammatory phenotype. J Allergy Clin Immunol **2020**; 146:315–324.e7.
25. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA **2020**; 323:1061–9.
26. Giacomelli A, Pezzati L, Conti F, et al. Self-reported olfactory and taste disorders in patients with severe acute respiratory coronavirus 2 infection: a cross-sectional study. Clin Infect Dis **2020**; 71:889–90.
27. Gandhi RT, Lynch JB, Del Rio C. Mild or moderate Covid-19. N Engl J Med **2020**; 383:1757–66.
28. Tenforde MW, Kim SS, Lindsell CJ, et al; IVY Network Investigators; CDC COVID-19 Response Team. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network—United States, March-June 2020. MMWR Morb Mortal Wkly Rep **2020**; 69:993–8.
29. Carfì A, Bernabei R, Landi F; Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. JAMA **2020**; 324:603–5.
30. Heald-Sargent T, Muller WJ, Zheng X, Rippe J, Patel AB, Kociolek LK. Age-related differences in nasopharyngeal severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) levels in patients with mild to moderate coronavirus disease 2019 (COVID-19). JAMA Pediatr **2020**; 174:902–3.
31. Baggio S, L'Huillier AG, Yerly S, et al. SARS-CoV-2 viral load in the upper respiratory tract of children and adults with early acute COVID-19. Clin Infect Dis **2020**.
32. He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med **2020**; 26:672–5.
33. Argyropoulos KV, Serrano A, Hu J, et al. Association of initial viral load in SARS-CoV-2 patients with outcome and symptoms. Am J Clin Pathol **2020**; 190:1881–7.
34. Magleby R, Westblade LF, Trzebucki A, et al. Impact of SARS-CoV-2 viral load on risk of intubation and mortality among hospitalized patients with coronavirus disease 2019. Clin Infect Dis **2020**; ciaa851.
35. Bi Q, Wu Y, Mei S, et al. Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study. Lancet Infect Dis **2020**; 20:911–19.
36. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. N Engl J Med **2020**; 382:1177–9.
37. L'Huillier AG, Torriani G, Pigny F, Kaiser L, Eckerle I. Culture-competent SARS-CoV-2 in nasopharynx of symptomatic neonates, children, and adolescents. Emerg Infect Dis **2020**; 26:2494–7.