Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby gran to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Kacy Nowak Date

A Comprehensive Assessment of Pediatric COVID-19 in Atlanta, GA: Risk Factors for Infection and Severity Level, and the Role Children Play in Household Transmission

By

Kacy Nowak

MPH

Hubert Department of Global Health

Robert Breiman, MD
Committee Chair

Jessica Fairley, MD, MPH
Committee Member

A Comprehensive Assessment of Pediatric COVID-19 in Atlanta, GA: Risk Factors for Infection and Severity Level, and the Role Children Play in Household Transmission

By

Kacy Nowak

Bachelor of Science

Colorado State University

2017

Thesis Committee Chair: Robert Breiman, MD

Thesis Committee Member: Jessica Fairley, MD, MPH

An abstract of

A thesis submitted to the Faculty of the Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health

in Hubert Department of Global Health

2021

Abstract

A Comprehensive Assessment of Pediatric COVID-19 in Atlanta, GA: Risk Factors for Infection and Severity Level, and the Role Children Play in Household Transmission

By Kacy Nowak

Background: To date, there have been over 3.4 million reported pediatric COVID-19 cases and 379 pediatric COVID-19 deaths in the US. Although severe infections and death rates are low among the total US pediatric population (0.19%), there has been a 4% increase in weekly pediatric incidence during the Spring of 2021. Furthermore, the Centers for Disease Control and Prevention reports disproportionate health outcomes among racial/ethnic minority groups. Black children make up only 14% of the US pediatric population, yet they account for 29% of MIS-c patients. Hispanic/Latino children represent 25% of the US pediatric population yet account for 34% of MIS-c patients.

Objective: This study aims to better understand risk factors associated with an increased likelihood of pediatric COVID-19 infections and severe outcomes. Furthermore, this study aims to explore the role children play in household transmission of COVID-19.

Methods: COVID-19 test results (n=18,507) and infection severity (n=2,848) data of children ≤ 18 from CHOA were analyzed using univariate, multivariate, and polytomous logistic regression to compare children with and without COVID-19 and children with and without a severe infection across demographic, socioeconomic, and health characteristics. Survey data from 15 households were collected to compare secondary infection rates across household characteristics.

Results: Black (aOR= 1.65, 95% CI: 1.02-2.71) and Hispanic/Latino children (aOR= 5.19, 95% CI: 3.07-8.83) had a higher likelihood of a positive COVID-19 test. Among infected individuals, black children were more likely to have MIS-c (aOR=1.47, 95% CI: 1.02-2.15). Obesity was significantly associated with disease severity including ICU admission (aOR= 2.07, 95% CI: 1.28-3.39) and MIS-c diagnosis (aOR= 21.35, 95% CI: 13.39-34.49). Household survey data showed three children served as an index case in their households (20% of total index cases), and all three cases were infected from a school or sport exposure. The average number of secondary infections among children index cases was 3.0 members/ household.

Discussion: Like with adults, the disproportionate likelihood of COVID-19 infection and severe outcome among minority groups highlights the need for improved public health policies with optimal use of resources for health equity. Increased understanding of co-morbidities leading to more severe infections is needed to reduce morbidity and mortality of SARS-CoV-2.

A Comprehensive Assessment of Pediatric COVID-19 in Atlanta, GA: Risk Factors for Infection and Severity Level, and the Role Children Play in Household Transmission

By

Kacy Nowak

Bachelor of Science

Colorado State University

2017

Thesis Committee Chair: Robert Breiman, MD

Thesis Committee Member: Jessica Fairley, MD, MPH

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health

in Hubert Department of Global Health

2021

Acknowledgments

I would like to express my sincere gratitude for my thesis advisor and committee member Dr. Robert Breiman and Dr. Jessica Fairley for their unwavering support and mentorship during this process. I would also like to thank collaborators at Emory University including Dr. Parmi Suchdev and the Emory-Kaiser COVID Household Study team for technical support and guidance.

I would also like to thank the Children's Healthcare of Atlanta (CHOA) including Dr. Evan Orenstein and Dr. Preeti Jaggi for making it possible for me to work with CHOA data for this study, as well as the Global Health Crisis Coordination Center for providing me initial support and the opportunity to work on this project.

Table of Contents

Chapter I: Introduction

The novel coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to devastating health outcomes globally. As of April 2021, there have been over 138 million cases and almost three million deaths around the world [1]. The United States has seen over 30 million COVID-19 cases and over 550,000 deaths due to COVID-19 [2]. Since emergency use authorizations, about 112 million (33.7%) of the US population has received at least one dose of a vaccine [2]. However, even with increasing vaccination coverage, we are still seeing rising weekly COVID-19 case counts among both adults and children. The Centers for Disease Control and Prevention (CDC) reported between March 20th, 2021 and April 9th, 2021, the seven-day moving average of new cases has been higher than the previous week [2].

Cumulatively, there have been four million reported pediatric COVID-19 cases (13% of total cases) since the onset of the pandemic in the US [2]. Data suggests children have a much lower COVID-19 infection prevalence than adults: 1.2% compared to 9.2% for adults (95% CI, 0.02-0.95) [3]. To the public, this low prevalence may translate as “no risk”, which is not accurate. Children are not immune to infection. The CDC suggests children are likely to have similar viral loads, secondary infection rates, and can spread the disease, influencing overall transmission [4]. Furthermore, pediatric cases are likely underreported due to lack of widespread testing and a high proportion of asymptomatic infections in children [4].

While overall case rates per 100,000 individuals declined in January and February 2021 [2], weekly case incidence of pediatric COVID-19 infections has been increasing for several months. The American Academy of Pediatrics (AAP) first reported an increase in weekly confirmed cases of pediatric COVID-19 in November 2020. Over the course of late March 2021

into early April, rates of weekly pediatric infection have increased 4% [5]. In addition to rising cases, hospitalization events have also increased among children. The University of Minnesota School of Public Health looked at hospitalization trends for children with COVID-19 in several states from May 2020 to November 2020 and found an increase in average hospitalization rate per 100,000 children from 2.0 at the start of the study to 17.2 at the end of the study [6].

Trends of pediatric case incidence and case severity are not only increasing in the pediatric population as a whole, but there are clear disproportionately higher frequencies of COVID-19 cases and severe outcomes in minority groups and vulnerable populations. Data suggests black children have higher odds of a COVID-19 infection than white children (OR:3.1, 95% CI: 1.23-5.34) and both black and Hispanic/Latino children have higher cumulative rates of COVID-19 infections (1 6.4 and 10.5 per 100,000, respectively) than white children. [7,8].

The COVID-19 pandemic has highlighted race/ethnicity and socioeconomic health disparities and the deep-rooted systemic racism of this country. Discrimination, healthcare access, segmented labor markets, housing, education, and income all play a role in this increased risk of exposure to COVID-19 and hospitalization or death. [9]. Emphasis on better understanding the disproportionate burden of disease among minority and vulnerable populations is needed. From this, more effective allocation of resources and economic aid and concrete actions to address health equity can occur in order to reduce future morbidity and mortality among these higher-risk groups.

As schools open for in-person classes, children may be at a higher risk for COVID-19 exposure and infection. School closures during the earlier months of the pandemic may have skewed the reported impact of SARS-CoV-2 on the pediatric population, making the role of children and school-exposures on disease transmission unclear [4, 10, 11]. Therefore, it is crucial

to focus on better understanding the risks of acute and long-term infections among children, which children are more at risk for severe outcomes, and the role children play in transmission.

To provide insight on these gaps in knowledge of pediatric COVID-19 risk factors and household transmission, this study aims to:

1. Identify health and socioeconomic risk factors for COVID-19 infection
2. Assess potential risk factors for severe COVID-19 infection
3. Investigate the occurrences of pediatric index cases and resulting secondary transmission to household members

Definition of terms:

Pediatric/child: Persons 18 years old and under

Index case: First test-positive COVID-19 case or symptomatic individual in a household cluster

Household Contact: Anyone living in the same residence as the index case at the time of first infection.

Secondary Infection Rate (SIR): The proportion of infected household contacts following exposure to the index case over the total number of household contacts

ICU/PICU: Intensive care unit/ Pediatric intensive care unit

Chapter II: Literature Review

As SARS-CoV-2 continues to strike the global population with calamitous health impacts, investigations continue to explore factors that influence infection severity and transmission rates. As of April 2021, there have been over 138 million cases and almost 3 million deaths around the world [1]. The United States has seen over 30 million COVID-19 cases and over 550,000 deaths due to COVID-19 [2].

Demographic and epidemiological characteristics of severe COVID-19 infections among the adult population show older adults are more likely to develop severe disease with a median age of 52 years [12]. Data also suggest the asymptomatic infection rate among adults lies between 17%-20% [13]. Having a co-morbidity increases the likelihood for severe COVID-19 infection. The CDC reports adults with cancer, chronic kidney disease, COPD and other heart conditions, Down syndrome, obesity, sickle cell disease, and diabetes have an increased risk for severe illness from SARS-CoV-2 [14].

Cumulatively, there have been four million reported pediatric COVID-19 cases (13% of total cases) in the US since the onset of the pandemic [2]. Children have a cumulative case incidence of 1.2% compared to 9.2% for adults (95% CI, 0.02-0.95) [3]. Even though children are less likely to get infected with SARS-CoV-2 or have symptomatic infections, when they do become infected, children are likely to have similar viral loads and secondary infection rates and can still transmit the virus [4]. Furthermore, children are more likely to be asymptomatic-- a meta-analysis found the proportion of asymptomatic cases in children was 27.7% versus 15.6% in adults [15].

Severe Pediatric COVID-19 Infections

Hospitalization and death rates for pediatric COVID-19 infections are lower than adult infections. CDC reported that 20% of pediatric cases were hospitalized compared to 33% of adult cases [16]. However, these cases were reported and described shortly before the publication of the study which introduces potential bias since there was inadequate follow-up to define the scope and severity of illness [16]. Therefore, full clinical manifestations and course of illness for many cases were unknown. This can skew severity results and introduce information bias. Recent reports show hospitalization rates among children are increasing and about 33% of children hospitalized are admitted to the ICU which is similar to adult rates. [5,7]

Severe COVID-19 illness can include a variety of manifestations including respiratory failure, myocarditis, shock renal failure, coagulopathy, intussusception, and multi-system organ failure [4]. Another severe outcome due to COVID-19 is Multisystem Inflammatory Syndrome in Children (MIS-c). According to the CDC case definition, a diagnosis for MIS-c is based on the presence of all of the following: 1) fever (≥38.0°C), 2) laboratory evidence of inflammation or evidence of clinically severe illness involving two or more multisystem organ involvement, 2) hospitalization, 3) SARS-CoV-2 infection confirmed by PCR, serology, or antigen test [17]. Clinical manifestations of MIS-c usually occur 4-6 weeks after primary infection with COVID-19 [18]. As of late March 2021, there had been 3,185 cases of MIS-c and 36 deaths [18].

Risk Factors for Severe COVID-19 Infections

Early studies suggested infected children between 1 year to 6 years of age were more likely to have severe illness compared with other children. [16, 19]. A study conducted in Italy showed that children under the age of one had higher rates of hospitalization (36.6% for children under one versus an overall rate of 13.3%), and children ages 2-6 years had the highest rates of

ICU admission (9.5% increase, p=0.010) [16]. However, as the course of the pandemic continued and more MIS-c cases have appeared, median age for severe pediatric COVID-19 infection has increased. Based on current literature, the median age for MIS-c patients is nine years [17, 18, 20].

Other common factors found to be associated with a higher risk of severe disease among children include pre-existing medical conditions, such as chronic lung disease, cardiovascular disease and immunosuppression or oncologic diseases [21, 22]. Using multivariate regression models, data have shown a correlation between having pre-existing medical conditions and the odds of severe COVID-19 infection (OR: 2.80, 95% CI: 1.74-4.48) [19]. Data from the CDC showed 77% of children who were hospitalized had at least one underlying medical condition (as opposed to 12% for those not hospitalized) [21]. Furthermore, a recent CDC update in 2021 stated data there is an increased risk of severe illness among children with sickle cell disease and chronic kidney disease [14]. The New York School of Medicine found children with previous renal dysfunction had higher rates of critical care admission than acute care admission (43% vs. 10%, P=0.002) [23]. Another study out of Paris, France saw all pediatric patients who had sickle cell disease and tested positive for COVID-19, experienced acute chest syndrome (an indicator for severe illness) [24]. However, the sample size for those who had sickle cell disease and tested positive for COVID-19 was made up of four children, so more data is needed to better understand the relationship between sickle cell disease and severe COVID-19 infection.

Increased body mass index (BMI) and obesity, diabetes, and hypertension are potential factors associated with severe COVID-19 disease in adults; however, the relationship between obesity and severe disease in pediatric COVID-19 cases is less conclusive. In adult COVID-19 studies, cases with severe obesity (BMI ≥ 30) had higher odds of severe disease, consistent with

data for other diseases like influenza [25, 26, 27]. A study from New York University School of Medicine found patients under the age of 60 who had a BMI ≥ 35 were 3.6-fold (95% CI, 2.5–5.3) more likely to be admitted to an ICU than those with a BMI under 30 and of the same age [27]. Children infected with SARS-CoV2 with obesity or asthma were shown to have a higher proportion of MIS-c than other children without those conditions [6,7].

Although gender has been shown to be a risk factor associated with COVID-19 infections in adults, pediatric data do not show this correlation. Across data, there was a slightly higher proportion (51.4%-58.2%) of male pediatric COVID-19 positive cases compared to female pediatric cases; however, these small differences in positive cases by gender were not statistically significant [16, 21, 28].

Many analyses exploring risk factors for disease among the pediatric population have small sample sizes due to the low incidence of COVID-19 in children and, perhaps because they may not be using large datasets optimally [8, 9, 19, 24, 25]. This limits the ability to use statistical analysis and modelling to evaluate the evidence of relationships between risk factors and disease uncovered through the studies. Therefore, there is a need for additional studies with larger study populations in order to evaluate COVID-19 in children using multivariate models to gain stronger and more reliable findings.

Disproportionate Risk of COVID-19 Infections and Severe Outcomes among Minority Groups

The pandemic has shown disproportionate risk of infection and severe outcomes among racial and ethnic minority groups, especially among Black, Native American, and Hispanic individuals. The CDC states 33% of reported cases with known demographic information are Hispanic/Latino and 22% are black [29]. However, these groups only make up 18% and 13% of the total US population, respectively.

The CDC found that black race and lack of insurance were independently associated with hospitalization due to COVID-19 infection (aOR = 3.2, 95% CI = 1.8–5.8 and aOR = 2.8, 95% CI 1.1–7.3) [30]. Furthermore, among those infected, black and Hispanic individuals were more likely to require invasive-mechanical ventilation due to COVID-19 than white adults (OR: 1.54, 95% CI: 1.18-2.03) and experienced longer hospital length-of-stay after controlling for age, gender, and comorbidities [31]. Another study that looked at COVID-related deaths for each state saw that in Michigan, black individuals comprised 40% of the state's COVID-19 deaths, yet black people only make up 13.5% of the state's population; in New York, black COVID-19 deaths comprised 14.9% of the state's Covid-19 associated mortality but only make up 8.8% of the state population [32]. A nationwide cross-sectional study that looked at COVID-19 mortality rates by racial/ethnicity found mortality rate ratios for Hispanic/Latino adults were 7.0 (95% CI: 5.8-8.4) times higher than non-Hispanic white adults for ages 25-34 and 8.8 (95% CI: 7.8-9.9) times higher for ages 35-44 [33].

Pediatric studies have also seen a higher incidence of positive cases among black children compared to white children. A study at Rush University in Chicago, Illinois found 6.8% of black children vs. 1.7% of white children tested positive for COVID-19 ($p = 0.046$) [8]. After adjusting for age and gender, they found black children were at a higher risk for a positive COVID-19 test compared to white children (aOR:3.1, 95% CI:1.23-5.34). Another study from The Children's Hospital of Philadelphia saw 10.6% of black children tested positive for COVID-19 versus 3.3% of white children [34].

Going beyond infection incidence, severity risk was also shown to be disproportionate among racial/ethnic minority groups among pediatric populations. Black children account for 14% of the US pediatric population and 12.6% of overall pediatric cases; however, black

children make up 29% of MIS-c cases [2]. Hispanic/Latino children make up 34% of MIS-c cases even though they represent only 25% of the pediatric US population. Furthermore, a report from Rush University found, of the children who required hospitalization, 80% were black [8]. Additionally, all PICU- admitted patients in the study were black.

Structural inequalities rooted in neighborhood segregation, housing and education inequalities, and unequal access to medical care have led to drastic health inequities during the COVID-19 pandemic [32, 35]. The U.S. Census Bureau reported Hispanic/Latino people were three times more likely and black people two times more likely to be uninsured than non-Hispanic white people [36]. Lack of insurance and access to medical providers can lead to undiagnosed, and therefore, untreated medical conditions such as chronic heart diseases, diabetes, and chronic liver disease which put these populations at an increased risk for severe COVID-19 infections [37]. Additionally, data looking into discrepancies of health insurance type found a higher proportion of pediatric patients with government or public insurance tested positive for COVID-19 compared to pediatric patients with commercial insurance [34].

Factors leading to health disparities seen in minority populations during the COVID-19 pandemic are also linked to increased exposure to SARS-CoV-2. Black and Hispanic/Latino groups were more likely to work in jobs considered essential, and therefore remained open throughout the pandemic [37, 38]. In South Carolina, black people were more likely to work in cleaning and maintenance jobs than non-Hispanic white people (7.88% vs. 1.98%). In New York, health-care support jobs were made up by 10.02% black/AA individuals versus only 1.74% non-Hispanic whites [37]. Furthermore, essential occupations like transportation, health-care support, food preparation, and maintenance and repair tend to involve working conditions in close-proximity to other people. The disparities seen among minority and low-income

communities not only lead to increased risk of exposure of SARS-CoV-2 for adults, but also increased exposure risk to SARS-CoV-2 in children who live in the same household [37].

Influence of School Closures on Child Health and Well-Being

The role children and school-exposures play in transmission is still unclear since previous school closures might have skewed the impact of child transmission rates [4, 10, 11]. As schools open for in-person classes, children may be at a higher risk for COVID-19 exposure and infection [4, 10, 11]. It is important to better understand the risks of re-opening on children infection rates and household transmission in order for in-person classes to safely re-open and contribute to the education, health, and well-being of children.

In-person learning undoubtably benefits children and their educational experience, and reopening schools will help to disrupt some of the indirect negative effects of the pandemic on children. First, remote learning has led to unhealthy nutritional changes for many students living below the poverty line. Schools are not only a place for education, but for many children, especially those living in poverty, school is the main way for children to get a consistent, nutritious meal [39]. The School Nutrition Association recorded schools served 20.2 million free school lunches, 1.8 million reduced-priced lunches per day, and 14.7 million breakfasts to students in 2018 [40]. With remote learning, these students may not be getting adequate nutrition for the meals they routinely relied on before school closures. According to the United States Department of Agriculture, 14% of households with children experienced food insecurity (irregular or unhealthy diets) in 2018 [41]. With job layoffs occurring frequently as a result of the pandemic, this number may be even higher now, which means children are at a greater risk of facing food insecurity during the pandemic while schools are closed.

Furthermore, remote learning is widening the learning gap between children of high and low socioeconomic status [39]. Online learning requires resources like computers and adequate internet that many families might not have, which prevents academic growth and achievement among the children who face these challenges. The National Center for Homeless Education and the National Center for Homeless Children and Youth reported over five million enrolled students were homeless or living in an unstable residence [42]. This value only accounts for children enrolled in the public-school districts of local educational agencies so it is likely and underestimation of the true number of children who have experienced homelessness or unstable living conditions. These children likely have a harder time completing assignments and accessing the learning resources needed due to their living circumstances. In general, it has been found that learning abilities decrease when children are not in a school environment during in-person learning. The Massachusetts General Hospital Institute of Health Professions and Georgia Institute of Technology reported kindergarten children without formal education would have a 67% decrease in literacy ability to those with formal education since children are likely exposed less to reading at home without a teacher to assist [43]. Reading and early education is a crucial foundation for continued growth and learning as children get older so these drastic consequences of education outcomes due to the pandemic is concerning.

Lastly, many children view school as a safe space and a place to escape from hostile family environments. It has been shown increased stress due to a disaster leads to increased rates of household abuse [44]. If a child lives in these dangerous environments, school closures take away direct contact with teachers, counselors, and other adult figures who can recognize child abuse and be a main point of contact for a child to confide in. The Federal Interagency Forum on Child and Family Statistics reported 9.1 per 1,000 children experienced maltreatment (physical

abuse, sexual abuse, psychological abuse, and neglect), and education staff were the most common personal to report these cases [45].

Schools provide critical resources and services to their students which are being taken away for many children due to the COVID-19 pandemic and remote learning. Therefore, it is crucial to better understand COVID-19 infection frequency and the risk of severe infections among children. Additionally, it is important to better understand transmission dynamics between children and their close contacts in order to successfully limit the spread of SARS-CoV-2 in households. Better understanding of the risks of re-opening schools on infection rates in children and household transmission can help schools safely re-open and contribute to the education, health, and well-being of children.

Household Transmission of COVID-19

Household data, to date, show children are less likely to get infected within the household than adults. One household study from Huazhong University of Science and Technology reported secondary transmission of SARS-CoV-2 occurred in 16.3% of household contacts. The secondary attack rate among children was 4% compared to 17.1% to adults (OR 0.18, 95% CI 0.06-0.54, p=0.002) [46]. Another retrospective cohort study out of Wuhan, China used a statistical transmission model to estimate the secondary attack rate from 27,101 households. This study found a mean secondary attack rate of 15.6% (95% CI: 15.2-16.0) [47]. They also found infants less than one year were more likely to be infected than children ages 2-5 years (OR: 2.20, 95% CI: 1.40-3.44) and children 6-12 years old (OR:1.53, 95% CI:1.01-2.34). Household secondary attack rate from other studies ranged from 4.6% in Taiwan to 31.6% in Zhejiang province; The United States study reporting a secondary attack rate of 10.5% [48, 49, 50].

Data on the secondary infection rate from children to other household members are still unclear. An investigation in Barcelona, Spain found that only 7.7% of households in the study population had a pediatric index case that went on to infect household members [51]. However, another cohort study done by the CDC found adults (SIR= 30%) and children (SIR=28%) had similar secondary infection rates [52].

Factors contributing to these varying results for secondary infection rates among children are the detection and use of asymptomatic transmission in data analysis and transmission models. Many household transmission studies focus on symptomatic cases only, which can lead to an underestimation of reported cases since asymptomatic infection rates in children range from 16%-27% [53, 54]. If antibody tests are performed to capture asymptomatic cases in household transmission studies, secondary infection rates are usually much higher. The CDC recruited laboratory-confirmed COVID-19 patients and their household contacts to interview and perform antibody tests to identify asymptomatic cases that could be involved in household transmission. They found 55% of the 58 households examined had evidence of secondary infection, with an overall secondary infection rate of 29% (95% CI: 23-36%), 42% among children, and 33% among spouses/partners [55].

The gap in knowledge about asymptomatic transmission renders household transmission dynamics difficult to accurately map since it is difficult to determine who infected who or who was infected first with asymptomatic or pauci-symptomatic cases. Data suggests asymptomatic cases are less likely to transmit to other people. One study from Bond University in Australia found the relative risk of asymptomatic transmission was 42% lower than for symptomatic transmission (RR: 0.58, 95% CI 0.34-0.99, p=0.047) [56]. Even though less likely, asymptomatic transmission events have been reported from adult and pediatric index cases [57, 58]. Therefore,

including asymptomatic and pauci-symptomatic cases in household transmission studies involving children is particularly important due to the high percentage of asymptomatic and pauci-symptomatic cases in this age demographic.

Data on household transmission collected during the first few months of the pandemic found that children are most commonly infected through familial clusters compared to school or daycare clusters [16]. Furthermore, data suggest the majority of pediatric cases are diagnosed after exposure to a known infected adult within a household [59, 60, 61]. However, this sequence appears to be shifting; as schools reopen and children sports and other activities resume, school exposures have become are a major source for pediatric case surges. Michigan state has seen a 47% increase in school-related outbreaks over the last week of March into the first week of April [62, 63]. This has led to a pause of in-person classes and suggest school clusters are actually a large contributor to overall transmission.

Pediatric cases across the country are continuing to rise with a reported 4% increase in weekly pediatric COVID-19 incidence for multiple consecutive weeks in late March into early April 2021 [5]. Additionally, the American Academy of Pediatrics reported more than 64,000 new pediatric COVID-19 cases between March 18th and March 25th in the United states. Due to the increasing rates of pediatric COVID-19 and school-related outbreaks, a better understanding of risk factors associated with severe infection among children and the role they play in transmission is necessary.

Chapter III: Original Study Manuscript

Risk Factors for Severe COVID-19 and MIS-c Outcomes for Pediatric Patients in Atlanta, GA

Kacy D. Nowak[1], Evan W. Orenstein, MD[3], Jessica K. Fairley, MD, MPH[1,2], Robert F. Breiman, MD[1]

Affiliations

1 Rollins School of Public Health, Emory University, Atlanta, GA

2 Department of Pediatrics, Emory University School of Medicine, Atlanta, GA

3 Children's Healthcare of Atlanta, Atlanta, GA

Address for Correspondence: Kacy Nowak, MPH candidate, Rollins School of Public Health, Emory University, 1518 Clifton Rd, Atlanta, GA 30322. Telephone: (808)348-9792.

Email: kacy.danielle.nowak@emory.edu

Sources of support

Children's Healthcare of Atlanta, Atlanta, GA

Global Health Crisis Coordination Center (GHC3)

Keywords: Severe acute respiratory syndrome coronavirus, SARS-CoV-2, COVID-19, MIS-c, Pediatric, epidemiology, risk factors

Abstract

Background: Pediatric COVID-19 cases have surpassed 3.9 million in the United States, and a disproportionate number of cases and hospitalizations have occurred in racial/ethnic minority groups. Information about socioeconomic and health risk factors for severe pediatric COVID-19 is still limited. This study aims to describe epidemiological characteristics and identify risk factors for severe COVID-19 infections in children.

Methods: Data from the Children's Healthcare of Atlanta (CHOA) were examined in this retrospective cohort study. Regression analyses were conducted to examine relationships between socioeconomic factors and testing positive for COVID-19. Furthermore, univariate and multivariate logistic regression analyses were performed to identify risk factors for severe COVID-19 defined by hospital and ICU admission, MIS-c diagnosis, and presence of severe symptoms.

Results: Hispanic/Latino (OR: 4.86, 95% CI: 2.98-7.99) and black children (1.92, 95% CI: 1.26-2.97 were more likely to receive a positive COVID-19 test result than white children. Furthermore, children with Medicare/Medicaid had the highest frequency of positive COVID-19 tests (47.17%, $p < 0.001$). Black children (aOR:1.47, 95% CI: 1.02-2.15) were also at a higher risk for MIS-c relative to white children. Obesity was a predictor for ICU admission (aOR: 2.14, 95% CI: 1.34-3.48) and MIS-c (aOR:21.35, 95% CI: 13.39-34.49).

Conclusion: Racial/ethnic minority groups, children in low-income families (indicated by insurance status), and obese children are more likely to be infected by COVID-19 and are more likely to have severe infections. Findings from this study can help inform future pandemic planning, resource allocation and vaccine distribution, and steps to address structural inequities that exacerbate health disparities in the US.

Introduction

The United States has seen over 30 million cases and over 550,000 deaths due to COVID-19 as of April 2021[2]. The American Academy of Pediatrics (AAP) reported over 3.4 million pediatric COVID-19 cases (13% of total cases) since the onset of the pandemic in the US. Furthermore, pediatric cases make up 1.3-3.1% of COVID-19 related hospitalizations [5]. COVID-19-related death is a rare phenomenon among children. The CDC and AAP report 379 deaths among individuals under 18 years which makes up to 0.19% of the total COVID-19 deaths in the US [2, 5]. Although severe infections and deaths rates are low among the pediatric population, data is showing pediatric cases have seen a 4% increase in cumulative cases over late March 2021 into early April.

As schools reopen for in-person classes, there is continued need to characterize the magnitude and risk factors for severe disease. Defining sociodemographic, comorbidities and other risk factors that influence severity of COVID-19 infections is important in order to better target prevention strategies and resource allocation to reduce morbidity.

One serious outcome of COVID-19 is multisystem inflammatory syndrome in children (MIS-c). As of late March 2021, there have been 3,185 cases of MIS-c and 36 deaths [17]. Clinical presentations of MIS-c usually occur 4-6 weeks after primary infection with COVID-19 and include fever and inflammation of multiple organ systems [17].

Based on current literature, the median age for MIS-c patients is nine years [17, 20, 64]. Furthermore, children infected with SARS-CoV2 with obesity or asthma have a higher proportion of MIS-c than other children without those co-morbidities [65, 66, 67, 68]. A higher proportion of COVID-19-infected black children (29%) have developed MIS-c when compared to white children (27%) [2]. However, black children only account for 12.6% of overall pediatric

cases and 14% of the child population in the US. Hispanic/Latino children also show this increased risk of severe disease, making up 34% of MIS-c cases but only 30% of overall pediatric cases and 25% of the pediatric US population [2].

Even though severe COVID-19 cases are less common in children overall than among adults, children are not immune to infection. As in-person classes resume and increases in pediatric COVID-19 and MIS-c increase, it is important to better understand which pediatric groups may be at an increased risk for MIS-c and other negative health outcomes from COVID-19. This study aims to characterize pediatric COVID-19 by analyzing demographic and health data among test-positive and test-negative children in order to find any discrepancies in case frequencies between age, race, ethnicity, and co-morbidity status. Additionally, the study aims to assess if any differences in case frequency are linked to an increased likelihood of developing MIS-c or another severe COVID-19 infection.

Materials and Methods

1) Analyzing test positive frequencies among different age and demographic groups

Population and sample:

The study population included 18,507 individuals in a cohort of hospitalized and non-hospitalized children ≤ 18 years who were tested at a facility of the Children's Healthcare of Atlanta (CHOA). Children were tested by PCR using nasal or nasopharyngeal swabs at out-patient settings, including drive through testing centers, emergency rooms, and at in-hospital settings.

Procedure:

Descriptive statistical analyses were performed to compare children who received at least one positive COVID-19 test versus children who received negative COVID-19 test(s) results

during their interaction with CHOA. Anthropometric z-scores of bmi-for-age were interpreted using WHO and CDC guidelines [69, 70]. Regression models were used to examine the relationship between age, race/ethnicity, insurance status, and obesity with a positive COVID-19 test result.

2) Analyzing risk factors associated with severe COVID-19 and MIS-c outcomes

Population and sample:

A second data set including 2,848 COVID-19 positive patients ≤ 18 years from CHOA was used for this analysis. A positive COVID-19 diagnosis was confirmed using either PCR or IgG test results.

Procedure and statistical analysis:

To examine risk factors for severe COVID-19 infection, analyses on four outcomes were performed:

1. Admission to a hospital facility versus no hospitalization
2. Admission to the ICU/PICU versus general hospital admission
3. Diagnosed with MIS-c versus not diagnosed with MIS-c
4. Evidence of severe illness versus non-severe clinical manifestations

We defined MIS-c following CDC criteria which includes all of the following: 1) fever (≥38.0°C), 2) laboratory evidence of inflammation or evidence of clinically severe illness involving two or more multisystem organ involvement, 2) hospitalization, 3) SARS-CoV-2 infection confirmed by PCR, serology, or antigen test. For the fourth outcome assessed, a 3-level severity classification was constructed (mild, moderate, and severe infection). Mild infection included children who were not admitted to the hospital or ICU; Moderate infection included patients admitted to the hospital or ICU but did not present with severe symptoms related to

COVID-19; Severe infection included patients who were admitted to the hospital or ICU and presented with at least one severe symptom related to COVID-19. Severe manifestations included: requiring dialysis, deep vein thrombosis, liver failure, pericarditis, myocarditis, syncope, congestive heart failure, arrhythmia, encephalopathy, meningitis, renal failure, acute kidney disease/failure, pneumonia, ARDS, ventilation use, and ECMO.

Statistical Analysis

Demographic and clinical characteristics of patients in both data sets were summarized, and the $\chi 2$ test and Fisher's Exact test were used to compare test results and disease severity among categorical predictor variables. Continuous variables were compared using the Wilcoxon rank sum test. Binary risk factors for a positive COVID-19 test and severe infection were assessed using univariate and multivariate logistic regression models including age, sex, race, ethnicity, insurance status, and co-morbidities. Risk of a severe infection using the three-level severity outcome was performed using polytomous logistic regression. Since the proportional odds ratio was not met for this model, ordinal logistic regression was not performed. Output from these models were interpreted as relative risk ratios since a severe pediatric COVID-19 infection is a rare outcome so relative risk ratios and odds ratios are approximately equal.

For disease severity analyses, American Indian/Alaskan Native (0.74% of total population), Native Hawaiian/other Pacific Islander (0.14% of total population), Asian (2.88% of total population), and other race (0.04% of total population) were combined to create a single "Other race" group for regression modelling. This was done due to their low frequencies and statistical power which could lead to inflated false discovery rates. For similar reasons, co-morbidities with low frequencies were not assessed individually in multivariate models.

Instruments

Study data were collected and retrieved from patient survey responses using REDCap electronic data capture tools hosted at CHOA [71, 72]. All statistical analyses were performed using Rstudio 1.3.1073. Calculating anthropometric z-scores was conducted using the online WHO Anthro Survey Analyser for children under the age of five, and the WHO AnthroPlus R macro based on the 2007 WHO Growth Reference for children 5-18 [69]. CDC z-score interpretation guidelines were used to interpret and categorize BMI z-score results for individuals [70].

Ethical Considerations

These secondary analyses of deidentified health data from CHOA were determined to be non-human subjects research and would not require protocol review and approval by the CHOA IRB on July 30th, 2020.

Results

Positive Versus Negative COVID-19 Test

Of 18,507 children tested for COVID-19, 1,696 (9.16%) children tested positive. Table 1 describes the demographic and epidemiological characteristics of test-positive and test-negative children in the study. Females made up 47% of the study population and the median age was 76 months (mean= 90.46). Most confirmed COVID-19 test results occurred in children ages 16-18 (17.87%). Even though Hispanic/Latino children made up only 20.6% of the study population, this group contributed 40.68% of COVID-19 positive cases. Children with Medicare/Medicaid had the highest frequency of positive COVID-19 tests (47.17) and had a greater likelihood of receiving a positive COVID-19 test than children with private insurance (OR: 2.2, 95% CI: 1.91-2.56). Furthermore, children with “self-pay” (OR: 4.08, 95% CI: 3.1-5.32) and children with

unknown insurance status (OR: 2.65, 95% CI: 2.27-3.1) were also more likely to receive a positive COVID-19 test than children with private insurance.

Figure 1. discusses the results from the multiple logistic regression model including age, race/ethnicity, insurance status, and BMI class. After controlling for age, race, insurance status, and BMI, Hispanic/Latino children were five times (aOR: 5.19, 95% CI: 3.07-8.83) more likely to have a positive COVID-19 test than non- Hispanic/Latino children. Black children were almost two times (aOR:1.65, 95% CI: 1.02-2.71) more likely to receive a positive test result than white children. After controlling for age, race, ethnicity, and insurance status, obese children were two times (aOR:2.1, 95% CI: 1.35-3.3) more likely to receive a positive test result than children at a "normal" BMI range.

Risk Factors for Different Levels of COVID-19 Infection Severity

Pediatric Cohort Epidemiological and Clinical Characteristics

Of the 2,848 pediatric patients from the second CHOA data set used to assess disease severity, nearly all (97%) children were symptomatic; 553 (19%) patients were admitted to the hospital. Of the 553 patients admitted, 238 (8%) were admitted to the ICU or PICU. Furthermore, 215 individuals were diagnosed with MIS-c. The median age for all children was eight years and 53% of the patients were male. Forty-four percent of patients were white, 43% of patients were black, 4% of patients were "Other race", and 9% of patients refused to provide or didn't know their race information. Furthermore, 29% of patients were Hispanic/Latino.

Outcome: Admitted to Hospital

The median age for those admitted to the hospital was eight years (versus seven years for those not admitted) and the age group with the highest admissions was children ages 15-18 years (Table 2). Male patients made up 55% of hospitalizations. Black children made up 51% of

admitted patients, but only made up 41% of the non-admitted population and only 43% of total sample population. Hispanic/Latino children made up 23% of those who were hospitalized versus 31% for those not hospitalized. (Table 2). Out of those who were admitted, 229 (41%) presented with at least one co-morbidity and 49 of those individuals presented with more than one co-morbidity (Table 2). Specifically, 101 (18%) and 79 (14%) of children admitted presented with obesity or chronic lung disease respectively. Hospitalized children were more likely to have obesity (aOR: 39.22, 95% CI: 22.65-73.88), and 3.4 times more likely to have chronic lung disease (a95% CI: 2.5-4.6) than non-admitted patients (Figure 2).

After controlling for race, ethnicity, and co-morbidities, children ages 10-14 years, were 30% (aOR: 0.71, 95% CI: 0.51-0.99) less likely to be admitted to the hospital than children under the age of 1 year (Figure 2). Furthermore, Hispanic/Latino children were 38% (aOR: 0.62, 95% CI: 0.46-0.83) less likely to be admitted to the hospital than non-Hispanic/Latino children after controlling for age, race, and co-morbidities. Children with a co-morbidity were 6.4 (aOR: 6.39, 95% CI: 5.0-8.18) times more likely to be admitted to the hospital than those without a co-morbidity after controlling for age, race, and ethnicity. When assessing ungrouped co-morbidities, obesity (aOR: 39.98, 95% CI: 22.51-77.14), diabetes (aOR: 5.32, 95% CI: 2.31-12.3), heart disease (aOR: 3.07, 95% CI: 1.06-8.43), and lung disease (aOR: 2.35, 95% CI:1.63-3.36), were all predictors for hospital admission after controlling for age, race, and ethnicity (Figure 2).

Outcome: Admitted to ICU/PICU

Among the 238 pediatric patients admitted to the ICU or PICU, 59% were diagnosed with MIS-c (Table 3). The median age for those admitted to the ICU was 10 years versus seven years for general hospital admission ($p < 0.001$). Children aged 10-14 years had the highest

frequency of ICU admissions (29%). There was not a statistically significant difference between ICU admission and general hospital admission among race and ethnicity groups. When assessed individually in a univariate model, obesity (OR: 2.66, 95% CI: 1.71-4.20), diabetes (OR: 2.91, 95% CI: 1.04-9.34), chronic lung disease (OR: 2.10, 95% CI: 1.3-3.44), and having more than one co-morbidity (OR: 2.17, 95% CI: 1.20- 4.02) were all associated with ICU admission.

After controlling for race, ethnicity, and co-morbidities, all age groups were more likely to be admitted to the ICU than children under one year (Figure 3). When controlling for age, race, and ethnicity, children with at least one co-morbidity were 1.5 (95% CI: 1.03-2.27) times more likely to be admitted to an ICU than those without a co-morbidity. In a multivariate model looking at obesity, lung disease, and diabetes ungrouped, obesity (aOR: 2.07, 95% CI: 1.28-3.39) was a predictor for ICU admission after controlling for age, race, ethnicity, lung disease, and diabetes (Figure 3). There was no statistically significant relationship between ICU admission and lung disease or diabetes.

Outcome: MIS-c Diagnosis

Of the 215 patients diagnosed with MIS-c, 65% were admitted to the ICU (35% admitted to the general hospital ward) where the average hospital stay was five days (versus three for children not diagnosed with MIS-c) (Table 4). Fifty-six percent of MIS-c patients were male, and the average age was eight years. Children 5-9 years made up the largest percent of those with MIS-c (37%). Fifty-eight percent of MIS-c patients were black compared to 42% without MIS-c ($p<0.001$). Obesity ($p<0.001$), chronic lung disease ($p=0.02$), prematurity ($p=0.007$), and having more than one co-morbidity ($p<0.001$) were all associated with having a MIS-c diagnosis (Table 4).

After controlling for race, ethnicity, and co-morbidities, all age groups were more likely to be diagnosed with MIS-c than children under the age of one year (Figure 4). Children with at least one co-morbidity were three times more likely to have MIS-c than children without a co-morbidity (aOR: 3.1, 95% CI: 2.25-4.24). When further analyzing obesity as a predictor for MIS-c, obese children were 21 times (aOR: 21.35, 95% CI: 13.39-34.49) more likely to have MIS-c than children without obesity after holding age, race, ethnicity, and lung disease at a fixed value. Furthermore, after controlling for age, ethnicity, obesity, and lung disease, the odds of having MIS-c among black children were 1.47 (95% CI: 1.02-2.15) times higher than for white children (Figure 4).

Multi-level severity outcome

There were 2,305 (81%) children with mild infection, 372 (13%) patients with moderate infection, and 171 (6%) patients with severe infection (Table 5). Children 15-18 showed a higher proportion of moderate (22%) and severe (26%) than mild infections (19%). Children ages 10-14 had the highest frequency of severe infections (33%) compared to mild infections (22%), followed by children 5-9 years (27% severe infection and 10% mild infection). Black children also had a higher frequency of both moderate (52%) and severe (50%) infections than mild infections (41%). Hispanic/Latino children had a higher frequency of mild infections (31%); however, they had more severe infections (30%) than moderate infections (20%) when admitted to the hospital (Table 5).

After controlling for race, ethnicity, and co-morbidities, patients ages 5-9 (RR:4.2, p=0.001), 10-14 (RR: 3.2, p=0.01) and 15-18 (RR:2.47, p=0.048) were more likely to have severe infections than mild or moderate infections (Table 6). Furthermore, after controlling for age, race, and ethnicity, the relative risk of a severe COVID-19 infection increased for those with

a co-morbidity as severity level increased (RR:5.47, $p < 0.001$ for moderate severity and RR: 9.96, $p < 0.001$ for high severity).

Discussion

Hispanic/ Latino and black children are more likely to receive a positive COVID-19 test result than white children. This association between race/ethnicity and a positive test result may be due to a higher recorded frequency of COVID-19 infections among individuals in certain racial/ ethnic groups for many reasons. First, since racial/ethnic minority groups are more likely to work in essential businesses during the pandemic, more adults in minority households are in public facing or crowded conditions that increase their risk of exposure [37, 38]. Adults can then come home and expose their children. Another possible explanation for the association between race/ethnicity and a positive test result may be certain minority groups develop more severe infections and are more likely to present with severe symptoms and get tested at a hospital facility. Causes for increased severity in these groups might be related to the individual patient's health and co-morbidities, but it is also likely influenced by racism and the structural and health inequities present in the United States that prevent minority groups from accessing timely and affordable health care.

To further explore the relationship between racial/ethnic groups and COVID-19 infection outcomes, a second analysis was performed to look at potential risk factors of severe infection. This analysis shows black children are not only more likely to receive a positive COVID-19 test than white children, but they are also more likely to be diagnosed with MIS-c (aOR: 1.47, 95% CI: 1.02-2.15). Next, even though this study found a high test-positive frequency among Hispanic/Latino children, this group is less likely to be admitted to the hospital. Additionally, unlike many previous studies done, this study did not find a statistically significant relationship

between Hispanic/Latino ethnicity and severe COVID-19 disease outcomes. These results suggest there are factors not included in this study that might better describe why Hispanic/Latino children are more likely than non-Hispanic children to get a positive test result but not be admitted to the hospital or ICU. A limitation of this severity outcome analysis is the absence of insurance status which could play a role in the reasoning to opt out of hospital admission. Attitude towards healthcare might also play a role in the decreased hospital admission results. Additional analyses working with members of the Hispanic/Latino community are needed to assess if insurance status, attitudes related to hospital admission, or other factors absent from this study influence hospitalization rates among Hispanic/Latino groups.

Along with race/ethnicity, obesity and having a co-morbidity are also predictors for COVID-19 infections and severe outcomes. Children classified as obese are two times more likely to have a positive COVID-19 test than children with a “normal” BMI. This association does not necessarily suggest obese children are more likely to get infected when exposed. Rather, obese children may present with more severe COVID-19 infections and therefore are more likely to get tested at a hospital facility. Obesity is significantly associated with general hospital admission (aOR: 39.98, 95% CI: 22.51-77.14), ICU admission (aOR: 2.66, 95% CI: 1.71-4.20), and MIS-c diagnosis (aOR: 21.35, 95% CI: 13.39-34.49) when controlling for age, race, ethnicity, and other co-morbidities.

The CDC states obesity is linked to decreased T cell quantity and function [73] and decreased lung capacity [74] which could result in more severe COVID-19 symptoms. The CDC also suggests obesity might lead to increased severity because obesity increases the risk for developing other chronic diseases like diabetes and heart disease [75]. In this study analysis, diabetes was associated with higher likelihood for ICU admission when analyzed on its own;

however, diabetes was not significantly associated with MIS-C, and heart disease was not associated with a higher likelihood of ICU admission or MIS-C when modelled alone.

Having a co-morbidity increases the likelihood of a severe infection across all severity classifications used as outcome variables in this analysis. However, there was not a statistically significant difference between having one co-morbidity or having more than one co-morbidity on severity outcome. In univariate model analyses, diabetes and chronic lung disease were significant predictors for ICU admission among pediatric COVID-19 patients. Additionally, chronic lung disease and prematurity were associated with MIS-C diagnosis. However, there were only four children who had a history of prematurity, and none of these patients were under one year (two between ages 1-4 years and two between ages 10-14 years). Furthermore, three of the four premature patients had either obesity or chronic lung disease. Therefore, the association between prematurity and severe disease may be the result of other co-morbidities the patients had. A larger sample size containing premature infants needs to be assessed to better understand this relationship.

With a better understanding of higher-risk groups, careful considerations for pediatric vaccination trials and future vaccine distribution can be performed. First, it is important to assess how children with co-morbidities will react to a vaccine since it is unknown how immunosuppressed children will respond. Next, if racial/ethnic minority groups and children with obesity, chronic lung, or another co-morbidity are more susceptible to getting COVID-19 and having a severe reaction, vaccine distribution needs to focus on these populations. Furthermore, since data shows there are disproportionate rates of both COVID-19 infections and severe outcomes among black children and Hispanic/Latino children, it is crucial to explore this relationship further in order to better inform future actions to allocate resources and economic

aid to these communities, initiate policy change to improve health equity, increase focus on structural inequities in the US such as neighborhood segregation, housing and education inequalities, and unequal access to medical care, and to reduce future morbidity and mortality among at-risk groups.

Analyses for this study had a few limitations. Health records for some patients were not complete or updated into the database at the time of analysis. Missing age, gender, and race/ethnicity data prevented the inclusion of a few individuals with severe outcomes in the analysis. However, the number of pediatric cases excluded was small enough where no introduced bias is anticipated. Next, there are several variables that were unavailable for this analysis that could be confounders for the relationships assessed and could have provided more insight on why Hispanic/Latino children were less likely to be admitted to the hospital. Lastly, the reason for hospital or ICU admission among several patients with co-morbidities could have been the result of the co-morbidity rather than a severe COVID-19 infection. However, it wasn't possible to confirm that patients were admitted the hospital or ICU due to COVID-19 beyond excluding those who were admitted for a known unrelated cause or patients who did not experience COVID-like symptoms.

Conclusion

This multi-outcome analysis supports current literature showing an overrepresentation of case prevalence and disease severity among racial/ethnic minority groups. Black and Hispanic/Latino children were two and five times more likely to test positive with COVID-19, and black children were 1.47 times more likely to have MIS-c than white children. Furthermore, this analysis shows obesity in children significantly contributes to disease severity, even after controlling for other demographic and co-morbidity variables. Findings show obese children

have almost three times higher odds of ICU admission and 21 times higher odds of MIS-c than non-obese children. Additionally, diabetes, heart disease, and lung disease were all predictors for hospital admission among pediatric COVID-19 patients. Additional studies should evaluate approaches to alleviate the disproportionate likelihood of infection and severe outcome among minority groups and address co-morbidities leading to more severe infections. Findings from this study can help inform pediatric vaccine trials and distribution as well as public health policy and future pandemic planning.

Tables and Figures

Table 1. Demographic and Epidemiological Characteristics of Test-Positive versus Test-Negative Children (0-18 years) in CHOA System

		Test Result, n (%)			
Patient Characteristics		**Positive**	**Negative**	**Total**	**p value**
Total		n= 1696 (9.16)	n= 16811 (90.84)	18507	
Age Ranges					p < .001
	Less than 1	223(13.09)	1867(11.05)	2090(11.23)	
	1-3	231(13.56)	2879(17.14)	3110(16.81)	
	4-6	211(12.56)	3412(20.31)	3623(19.6)	
	5-8	204(12.03)	2394(14.23)	2598(14.03)	
	9-12	248(14.62)	2034(12.11)	2282(12.34)	
	13-15	276(16.27)	2087(12.43)	2363(12.78)	
	16-18	303(17.87)	2138(12.74)	2441(13.21)	
Gender					0.37
	Female	790(46.58)	8029(47.76)	8819(47.65)	
	Male	906(53.42)	8782(52.24)	9688(52.35)	
Race					p < .001
	White	757(44.63)	8774(52.2)	9531(51.5)	
	American Indian/ Alaska Native	41(2.42)	100(0.60)	141(0.76)	
	Asian	58(3.42)	643(3.83)	701(3.79)	
	Black/AA	589(34.73)	5893(35.05)	6482(35.02)	
	Native Hawaiian/ Pacific Islander	10(0.59)	52(0.31)	62(0.34)	
	Unknown	23(1.36)	234(1.39)	257(1.39)	

	Declined	218(12.85)	1115(6.63)	1333(7.20)	
Ethnicity					p < .001
	Non-Hispanic/ Latino	992(58.49)	13512(80.38)	14504(78.37)	
	Hispanic/ Latino	690(40.68)	3123(18.58)	3813(20.6)	
	Declined/Unknown	14(0.8)	176(1.0)	190(1.0)	
Financial Class					p < .001
	Private Insurance	249(14.68)	4908(29.19)	5157(27.87)	
	Medicare/Medicaid	800(47.17)	7156(42.57)	7956(42.99)	
	Champva	0(0.00)	1(0.01)	1(0.01)	
	Tricare	10(0.59)	221(1.31)	231(1.25)	
	Shared Service	0(0.00)	2(0.01)	2(0.01)	
	Self-Pay	82(4.83)	396(2.36)	478(2.58)	
	Null	555(32.72)	4127(24.55)	4682(25.30)	
ECMO					0.17
	Yes	0(0.00)	27(0.16)	27(0.15)	
	No	1696(100)	16784(99.84)	18480(99.85)	
Ventilator					p < .001
	Yes	12(0.71)	570(3.39)	582(3.14)	
	No	1684(99.29)	16241(96.61)	17925(96.86)	
Age (Months), median (IQR)		105(134)	76(114)	78(116)	p < .001
Days Admitted, median (IQR)		0(0)	0(1)	0(1)	0.055
BMI Status					p < .001
	Severe Wasting/Thinness	5(0.29)	82(0.49)	87(0.47)	
	Moderate Wasting/Thinness	7(0.41)	195(1.16)	202(1.1)	
	Normal	77(4.54)	2297(13.66)	2374(12.83)	
	Overweight	36(2.12)	723(4.3)	759(4.10)	
	Obese	58(3.42)	723(4.3)	781(4.22)	
	NA	1513(89.20)	12791(76.09)	14304(77.29)	

Note: χ2 or Fisher's Exact (categorical data) and Wilcoxon rank sum (continuous variables) were used to compare admitted versus non-admitted patients.

Table 2: Demographic and Epidemiological Characteristics of CHOA COVID-19 Patients Based on General Hospital Admission Status

Patient Characteristics		Hospital Admission Status, n (%)		p value
		Admitted to Hospital	Not Admitted to Hospital	
Total		n=553 (19.42)	n=2295 (80.58)	
Age Range				0.031
	< 1 Year Old	80 (14.47)	358 (15.60)	
	1-4 Years	103 (18.63)	547 (23.83)	
	5-9 Years	117 (21.16)	445 (19.39)	
	10-14 Years	124 (23.33)	509 (22.18)	
	15-18 Years	129 (23.77)	436 (19.00)	
Age in Years, Median (IQR)		8.0 (12.0)	7.0 (11.0)	0.013
Gender				0.26
	Female	250 (45.21)	1101 (47.97)	
	Male	303 (54.79)	1194 (52.03)	
Race				p < 0.001
	White	205 (37.07)	1036 (45.14)	
	Black/AA	283 (51.18)	949 (41.35)	
	Other Race	18 (3.25)	90 (3.92)	
	Refused or Unknown	47 (8.50)	220 (9.59)	
Ethnicity				p < 0.001
	Not Hispanic or Latino	422 (79.93)	1562 (68.06)	
	Hispanic or Latino	128 (23.15)	710 (30.94)	
	Refused or Unknown	3 (0.54)	23 (1.00)	
Co-Morbidities		229 (41.41)	197 (8.58)	p < 0.001
	Immunosuppressive/ Blood Disorder	55 (9.95)	46 (2.00)	p < 0.001
	Obesity	101 (18.26)	13 (0.57)	p < 0.001

Diabetes (Type 1 and Type 2)	16 (2.89)	12 (0.52)	p < 0.001
Congenital Heart Disease	10 (1.81)	10 (0.44)	0.002
Chronic Lung Disease (Including Asthma)	79 (14.29)	107 (4.66)	p < 0.001
Chronic Liver Disease	6 (1.08)	0 (0.00)	p < 0.001
Chronic Kidney Disease	2 (0.36)	5 (0.22)	0.628
Seizure Disorder	18 (3.25)	6 (0.26)	p < 0.001
Prematurity	9 (1.63)	2 (0.087)	p < 0.001
Autism	3 (0.54)	12 (0.52)	1
Other Condition	19 (3.44)	7 (0.31)	p < 0.001
More than one co-morbidity	49 (8.86)	10 (0.44)	p < 0.001

Note: χ2 or Fisher's Exact for categorical data and Wilcoxon rank sum for continuous variables were used to compare admitted versus non-admitted patients

Table 3: Demographic and Epidemiological Characteristics of CHOA COVID-19 Patients based on ICU/PICU Admission vs General Hospital Admission

Patient Characteristics		**Type of Hospital Admission, n (%)**		**p value**
		Admitted to ICU/PICU	**General Hospital Admission**	
Total		n= 238 (8.36)	n=305 (10.71)	
Age Range				p < 0.001
	< 1 Year Old	13 (5.46)	66 (21.64)	
	1-4 Years	41 (17.23)	59 (19.34)	
	5-9 Years	59 (24.79)	58 (19.02)	
	10-14 Years	69 (28.99)	51 (16.72)	
	15-18 Years	56 (23.53)	71 (23.28)	

Age in Years, Median (IQR)		10 (9.0)	7 (13.0)	p < 0.001
Gender				0.45
	Female	103 (43.28)	143 (46.0)	
	Male	135 (56.72)	162 (53.11)	
Race				0.32
	White	82 (34.45)	119 (39.02)	
	Black/AA	132 (55.46)	146 (47.87)	
	Other Race	6 (2.52)	12 (3.93)	
	Refused/Unknown	18 (7.56)	28 (9.18)	
Ethnicity				0.2
	Not Hispanic/ Latino	181 (76.05)	234 (76.72)	
	Hispanic/ Latino	54 (22.69)	71 (23.28)	
	Refused/ Unknown	3 (1.26)	0 (0.0)	
Days in Hospital, Median (IQR)		5.0 (3.0)	3.0 (3.0)	p < 0.001
Final Diagnosis				p < 0.001
	COVID-19 Infection	98 (41.18)	234 (76.72)	
	MIS-c	140 (58.82)	71 (23.28)	
Co-Morbidities				0.03
	Immunosuppressive/ Blood Disorder	16 (6.72)	39 (12.79)	p < 0.001
	Obesity	64 (26.89)	37 (12.13)	p < 0.001
	Diabetes (Type 1 and Type 2)	11 (4.62)	5 (1.64)	0.07
	Congenital Heart Disease	6 (2.52)	4 (1.31)	0.35

Chronic Lung Disease (Including Asthma)	47 (19.75	32 (10.49)	0.004
Chronic Liver Disease	3 (1.26)	3 (0.98)	1
Chronic Kidney Disease	2 (0.84)	0 (0.0)	0.19
Seizure Disorder	10 (4.20)	8 (2.62)	0.34
Prematurity	6 (2.52)	3 (0.98)	0.19
Autism	13 (5.46)	1 (0.33)	0.58
Other Condition	11 (4.62)	8 (2.62)	0.24
More than one co-morbidity	30 (12.61)	19 (6.23)	0.02

Note: $\chi 2$ or Fisher's Exact for categorical data and Wilcoxon rank sum for continuous variables were used to compare ICU versus general hospital admitted patients

Table 4. Demographic and Epidemiological Characteristics of CHOA COVID-10 Patients Based on MIS-c Diagnosis

Patient Characteristics		MIS-c Diagnosis Status, n (%) Diagnosed with MIS-c	Not Diagnosed with MIS-c	p value
Total		n= 215 (7.55)	n= 2633 (92.45)	
Age Range				p < 0.001
	< 1 Year Old	5 (2.33)	433 (16.45)	
	1-4 Years	36 (16.74)	614 (23.19)	
	5-9 Years	80 (37.21)	482 (18.31)	
	10-14 Years	62 (28.84)	571 (21.69)	
	15-18 Years	32 (14.88)	533 (20.24)	
Age in Years, Median (IQR)		8.0 (7.0)	8.0 (13.0)	0.0026
Gender				0.36
	Female	95 (44.19)	1256 (47.70)	
	Male	120 (55.81)	1377 (52.30)	
Race				p < 0.001
	White	72 (33.49)	1169 (44.40)	
	Black/AA	124 (57.67)	1108 (42.08)	
	Other Race	4 (1.86)	105 (3.99)	
	Refused/ Unknown	15 (6.98)	252 (9.57)	
Ethnicity				0.018
	Not Hispanic/ Latino	166 (77.21)	1818 (69.05)	
	Hispanic/ Latino	46 (21.40)	792 (30.08)	
	Refused/ Unknown	3 (1.40)	23 (0.87)	
ICU/PICU Admission				p < 0.001

	No	75 (34.88)	2535 (96.28)	
	Yes	140 (65.12)	98 (3.72)	
Days in Hospital, Median (IQR)		5.0 (3.0)	3.0 (4.0)	p < 0.001
Co-Morbidities		75 (34.88)	351 (13.33)	p < 0.001
	Immunosuppressive/ Blood Disorder	3 (1.40)	98 (3.72)	0.11
	Obesity	58 (26.98)	56 (2.13)	p < 0.001
	Diabetes (Type 1 and Type 2)	0 (0.0)	28 (1.06)	0.27
	Congenital Heart Disease	3 (1.40)	17 (0.65)	0.19
	Chronic Lung Disease (Including Asthma)	23 (10.70)	163 (6.19)	0.02
	Chronic Liver Disease	0 (0.0)	6 (0.23)	1
	Chronic Kidney Disease	1 (0.47)	6 (0.23)	0.42
	Seizure Disorder	1 (0.47)	23 (0.87)	1
	Prematurity	4 (1.86)	7 (0.27)	0.007
	Autism	1 (0.47)	14 (0.53)	1
	Other Condition	2 (0.93)	24 (0.91)	1
	More than one co-morbidity	14(6.51)	45 (1.71)	p < 0.001

Note: $\chi 2$ or Fisher's Exact for categorical data and Wilcoxon rank sum for continuous variables were used to compare MIS-c diagnosis status

Table 5. Demographic and Epidemiological Characteristics of CHOA COVID-19 Patients Based on Infection Severity Level (Mild, Moderate, Severe)

		Infection Severity, n (%)		
Patient Characteristics		**Mild Infection**	**Moderate Infection**	**Severe Infection**
Total		n = 2305 (80.93)	n = 372 (13.06)	n = 171 (6.0)
Age Ranges (Years)				
	< 1	359 (15.57)	73 (19.62)	6 (3.51)
	1-4	550 (23.86)	81 (21.77)	19 (11.11)
	5-9	445 (19.31)	70 (18.82)	47 (27.49)
	10-14	513 (22.26)	65 (17.47)	55 (32.16)
	15-18	438 (19.00)	83 (22.31)	44 (25.73)
Age (Years), median (IQR)		7.0 (11.0)	7.0 (13.0)	11.0 (8.5)
Gender				
	Female	1105 (47.94)	175 (47.04)	71 (41.52)
	Male	1200 (52.06)	197 (52.96)	100 (58.48)
Race				
	White	1040 (45.12)	141 (37.90)	60 (35.09)
	Black/ AA	954 (41.39)	192 (51.61)	86 (50.29)
	Other Race	90 (3.9)	14 (3.76)	4 (2.34)
	Refused/ Unknown	221 (9.59)	25 (6.72)	21 (12.28)
Ethnicity				
	White	1569 (68.07)	298 (80.11)	117 (68.42)
	Hispanic/ Latino	713 (30.93)	74 (19.89)	51 (29.82)
	Unknown/ Declined	23 (1.0)	0 (0.00)	3 (1.75)

Symptomatic				
	No	90 (3.90)	0 (0.0)	0 (0.0)
	Yes	2215 (96.10)	372 (100.0)	171 (100.0)
Days Admitted		NA	3.0 (3.0)	6.0 (4.0)
Co-morbidities				
	No	2108 (91.45)	242 (65.05)	72 (42.11)
	Yes	197 (8.55)	130 (34.95)	99 (57.89)
More than one co-morbidity				
	No	2295 (99.57)	351 (94.35)	143 (83.63)
	Yes	10 (0.43)	21 (5.65)	28 (16.37)

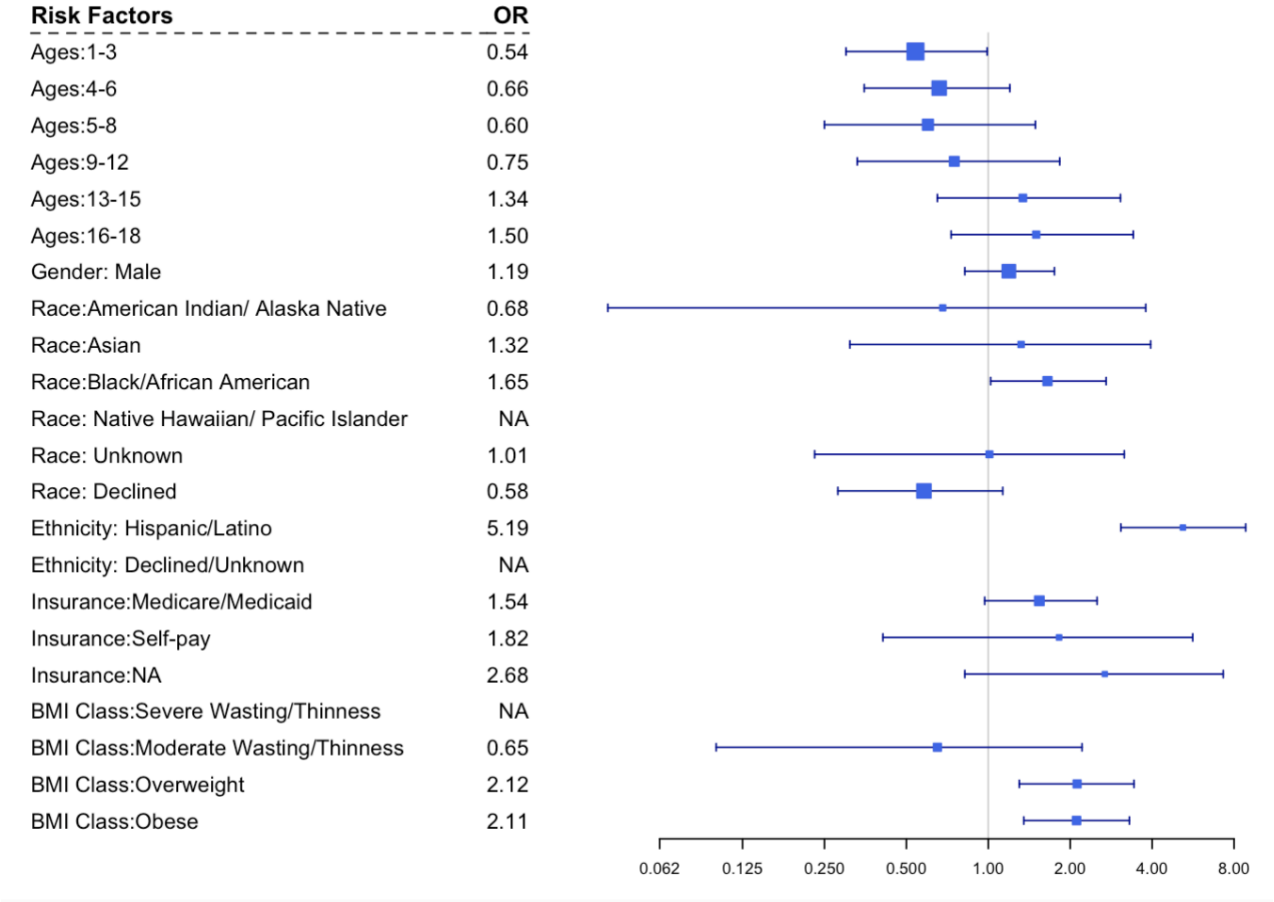
Note: Mild Infection= symptomatic but no hospital admission; moderate infection= symptomatic and admitted to hospital but no severe symptoms present; severe infection= admitted to hospital and at least one severe symptom is present; See Methods section for severe symptom list; — not applicable

Table 6. Potential Risk Factors for severe COVID-19 infection among CHOA Patients with COVID-19 40

		Mild Infection Compared to Moderate Infection		Mild Infection Compared to Severe Infection	
Patient Characteristics		**Relative Risk Ratio**	**p value**	**Relative Risk Ratio**	**p value**
Age	Ref= <1				
	1-4	0.62	0.01	1.53	0.37
	5-9	0.62	0.01	4.17	0.001
	10-14	0.45	$p < 0.001$	3.22	0.009
	15-18	0.56	0.002	2.47	0.048
Race	Ref= White				
	Black/AA	1.03	0.81	1.1	0.69
	Other Race	2.03	0.93	1.38	0.77
	Refused/ Unknown	2.02	0.92	1.62	0.11
Ethnicity	Ref= Not Hispanic/Latino				
	Hispanic/Latino	0.6	0.003	0.96	0.87
	Unknown/Refused	0	0.96	1.07	0.93
Co-Morbidity	Ref= "No"				
	Yes	5.47	$p < 0.001$	9.96	$p < 0.001$
More than 1 Co-morbidity	Ref= "No"				
	Yes	3.99	$p < 0.001$	7.24	$p < 0.001$

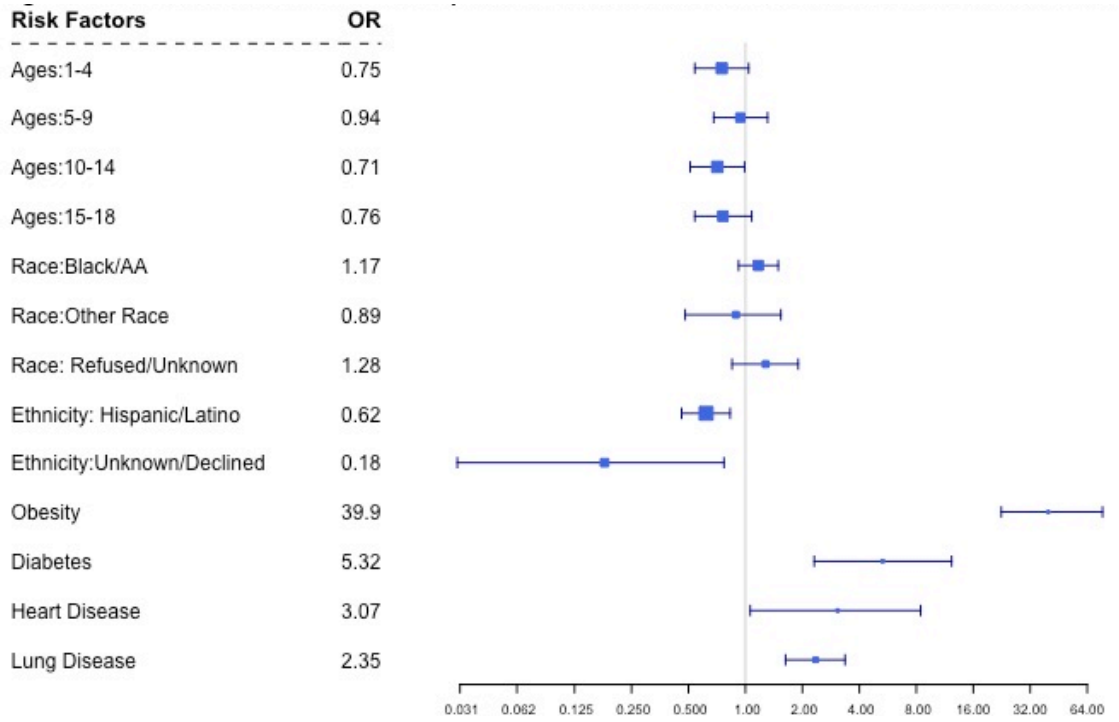
Note: Mild Infection= symptomatic but no hospital admission; moderate infection= symptomatic and admitted to hospital but no severe symptoms present; severe infection= admitted to hospital and at least one severe symptom is present; See Methods section for severe symptom list; RR were estimated using polytomous logistic regression since the proportional odds assumption wasn't met for ordinal logistic regression

Figure 1. Assessing Potential Characteristics Associated with a Positive COVID-19 Test Result among Children Tested at CHOA



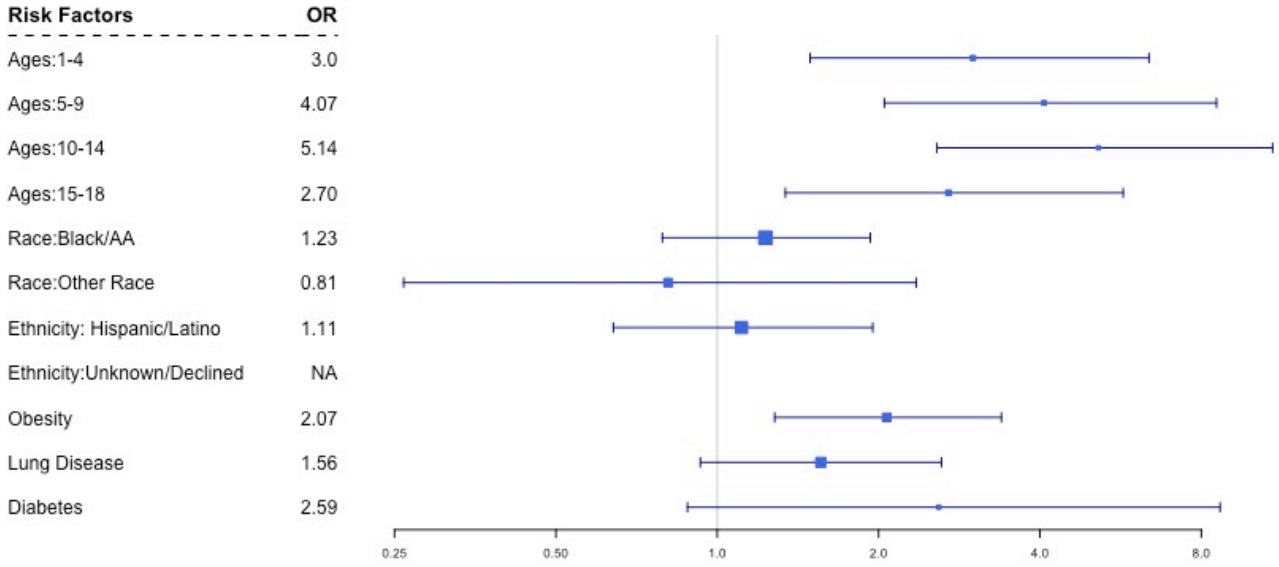
Note: Odds ratios estimated using Multiple logistic regression model. Reference groups = 'Ages: < 1', 'Race: White, 'Ethnicity: Non-Hispanic/Latino', Insurance: 'Private Insurance', BMI Class: 'Normal'; "NA" = Not available due to small sample size.

Figure 2. Potential Risk Factors Associated with Hospitalization among Pediatric Patients at CHOA



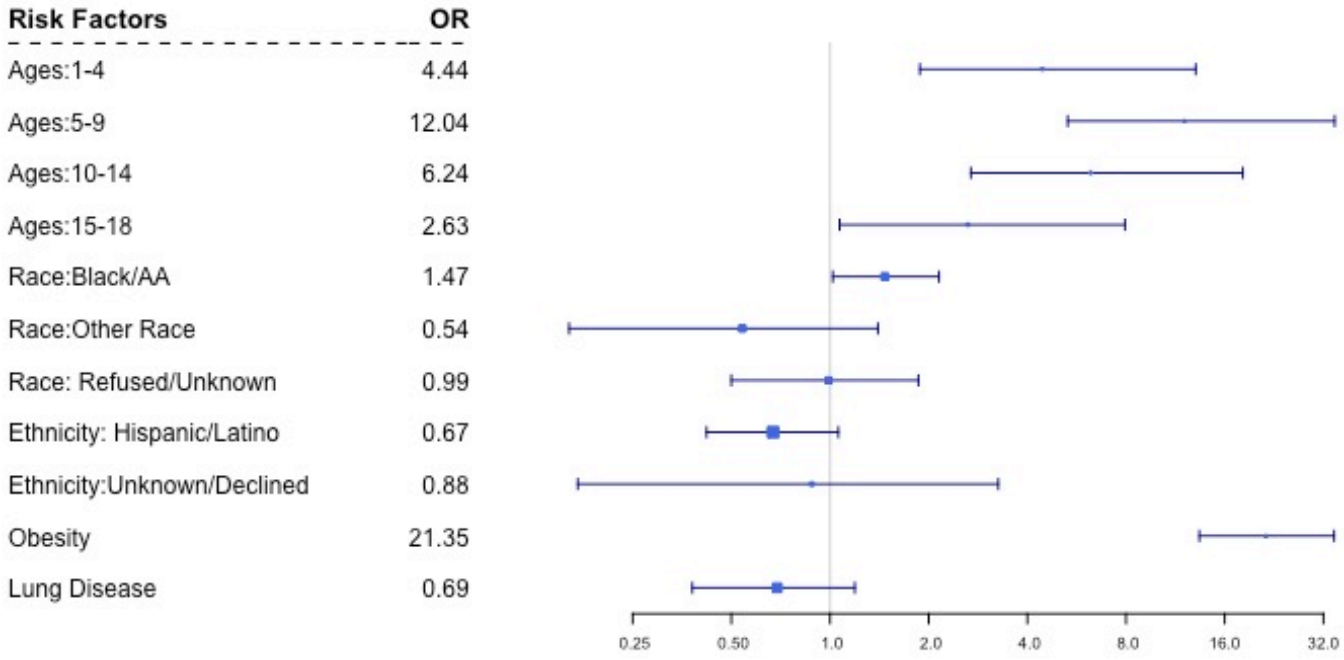
Note: Odds ratios estimated using Multiple logistic regression model. Reference groups = 'Ages: < 1', 'Race: White', 'Ethnicity: Not Hispanic/Latino', co-morbidities = 'No'

Figure 3: Potential Risk Factors Associated with ICU Admission versus General Hospital Admission among COVID-19 Pediatric Patients at CHOA



Note: Odds ratios estimated using Multiple logistic regression model. Reference groups = 'Ages: < 1', 'Race: White', 'Ethnicity: Not Hispanic/Latino', co-morbidities: = 'No'

Figure 4: Potential Risk Factors of MIS-c among COVID-19 Pediatric Patients at CHOA



Note: Odds ratios estimated using Multiple logistic regression model. Reference groups = 'Ages: < 1', 'Race: White', 'Ethnicity: Not Hispanic/Latino', co-morbidities: = 'No'

Analyzing Household Transmission Dynamics of COVID-19 and the Role Children Play in Transmission

Kacy D. Nowak[1], Morgan A. Lane[2], Armand N. Mbanya, MPH[3] Robert F. Breiman, MD[1], R.L.F Lobelo, MD, PhD[1,3] Jessica D. Fairley, MD, MPH[1,2]

Affiliations

1 Rollins School of Public Health, Emory University, Atlanta, GA

2 Department of Pediatrics, Emory University School of Medicine, Atlanta, GA

3 Kaiser Permanente, Atlanta, GA

Address for Correspondence: Kacy Nowak, MPH candidate, Rollins School of Public Health, Emory University, 1518 Clifton Rd, Atlanta, GA 30322. Telephone: (808)348-9792.

Email: kacy.danielle.nowak@emory.edu

Sources of support

SOM I3 /WHSC Synergy/Kaiser Permanente Georgia COVID-19 Collaboration

Keywords: Severe acute respiratory syndrome coronavirus, SARS-CoV-2, COVID-19, Pediatric, household transmission

Abstract

A better understanding of the role children play in household transmission is needed. This brief report summarizes preliminary data from a pilot study which saw a mean secondary infection rate (SIR) of 54% The proportion of index cases/ household who were under 18 years was 20%. Every child index case participated in in-person class or sports during the time of infection. Additional households and antibody test results will be analyzed to better understand this relationship.

Introduction

Understanding the role children play in the transmission of SARS-CoV-2 has been a challenge during the early stages of the pandemic due to low pediatric case numbers and high estimated proportion of asymptomatic infections in children (between 16%-50%.) [53, 76, 77]. However, pediatric cases have been increasing as adult cases have decreased during March and April 2021. The American Academy of Pediatrics (AAP) reported a 4% increase in cumulative cases for multiple weeks in late March and Early April [5]. Furthermore, more severe pediatric COVID-19 infections and hospitalization are being reported [17]. A closer look at household transmission during this time of increased pediatric cases and severity will help develop a better idea of pediatric COVID-19 transmission potential. Also, as schools continue to resume in-person classes, surveillance of how this might influence COVID-19 exposure and infections at school and how that will play a role in household transmission is necessary.

We aim to investigate transmission potential of children in the household including symptomatic cases as well as asymptomatic infections using saliva antibody testing results. The objective of this pilot study brief report is to assess patterns of household infection rates,

proportion of pediatric index cases, and secondary infection rates in the household based on individual and household-level characteristics in order to inform future study direction and focus.

Methods

Population and sample:

This pilot cross-sectional study included fifteen households. The population for this analysis was recruited between December 2020- March 2021 using COVID-19 test records at an Emory Hospital facility as well as flyers distributed across Emory University facilities and local grade schools and social media advertisements. Households were eligible to participate if at least one member was under the age of 18 years and if the household received at least one positive COVID-19 test within 4-16 weeks prior to the study visit date.

Procedures:

The consent/assent process was completed at the start of the study visit. All participants 18 or older provided informed written consent. Children ages 6 -10 years provided verbal assent and children ages 11-17 will provided written assent.

During study visits, each household member received two saliva receptacles to self-collect saliva samples by rubbing a swab with a sponge at the end in the gingival space on both sides of the participant's mouth for two minutes. Saliva samples will be sent to Johns Hopkins Bloomberg School of Public Health for detection of IgG antibodies that bind to the SARS-COV-2 RBD and nucleocapsid (N) proteins [78].

Individual and household surveys were distributed after study visits through RedCap survey links [71, 72]. Household were asked to complete individual surveys discussing individual demographics, symptoms, pre-existing medical conditions, exposures, and a household survey discussing testing and symptom timelines and isolation and quarantine

procedures in the household. The outcome variable assessed was the secondary infection rate (SIR) which was dichotomized in order to compare households with an SIR below the cohort mean above the cohort mean. SIR is defined as the number of secondary cases in a household infected from the index case over the total number of household contacts. Survey data was extracted from RedCap and descriptive statistical analysis was performed using a t-test or Fisher's Exact test as appropriate to explore differences between household secondary infection rate in each household and household characteristics during time of infection. All statistical analyses were performed using Rstudio 1.3.1073.

A household index case was defined as the individual who received the first confirmed COVID-19 test result or had the earliest symptom onset date among the household cluster. A household contact was defined as anyone living in the same residence as the index case at the time of first infection. Protocol and research instruments for the household transmission pilot study were submitted to Emory's IRB and expedited approval was granted on October 4th, 2020.

Results

The mean household size for this cohort was 3.87. The overall incidence of *known* COVID-19 for the 15 households was 53.45% (54% per household). On average, 80% of household members took a COVID-19 test (51% excluding the index case). Two members per household on average received a confirmed positive COVID-19 test (1.07 per household when excluding the index case). Furthermore, the average percentage of symptomatic individuals per household was 54.45% (Table 1). On average, the secondary infection rate per household was 54%. The median age for household contacts per household was 19.0 (IQR=6.1) years and the median age for the identified index case was 38.0 (IQR=11.5) years. There were 11 female and 4 male index cases. Sixty-seven percent of index cases were symptomatic and 26.7% had a

previous medical history. The average proportion of male household contacts was 55% (Table 1). Additionally, the mean proportion of male household contacts differed between households with an SIR below (0.75, SD=0.29) and above (0.42, SD=0.26) the cohort average SIR of 54% ($p = 0.04$).

Children under 18 years made up 52% of the total household cohort, but only 3 (20%) index cases were under the age of 18. There was 1 (6.7%) index case in each of the 1-3-year age range, 9-year age range, and 12-15-year age range. Two child index cases attended either daycare or school in-person (one of which had a known school exposure), and the third child index case attended an indoor sport activity during the time of possible exposure.

In households with a child index case, the average number of secondary cases was 3 individuals, and the average proportion of secondary infections per household was 62.5%. However, there was no significant difference of the proportion of secondary infections per household between child and index cases ($p= 0.23$).

When asked about isolation and quarantine procedures, 5 (33.33%) households said they wore masks in the household around the sick index case all of the time, 3 (20%) wore a mask most of the time, 2 (13.33%) wore a mask occasionally, and 4 (26.7%) never wore a mask within the household after the first COVID-19 household case was diagnosed or showed symptoms. Sixty-seven percent of households isolated from the index case, and 9 (60%) households quarantined in the household after the index case was diagnosed or showed symptoms. There was no significant difference in the mean proportion of secondary infections between those who did and did not practice isolation and quarantine methods (Table 1).

Discussion

The preliminary data collected for this pilot study show an overall secondary household infection rate of 54% and a pediatric index case frequency of 20%. All pediatric index cases had SIR's above the cohort average, with a mean SIR of 0.75 (SD=0.23). Additionally, households with a lower proportion of male contacts had a lower SIR than households with a higher proportion of male contacts ($p=0.04$).

Although this study did not provide the statistical power and analysis in order to make any conclusions, observing pediatric index cases who are transmitting SARS-CoV-2 to multiple household members is notable and aligns with another study out of Emory University who found 7 potential pediatric index cases with an average SIR of 45.7% [79]. Furthermore, since all pediatric cases either attended in-person school or sporting activities, looking at index case frequencies and secondary infection rates from children as most schools are transitioning or already transitioned back to in-person classes will be important to understand the impact of increased school-exposure on pediatric infections and household transmission. As more data comes in from additional household participants and as antibody test results are assessed, secondary infection rates for index cases be better analyzed to look at the possible relationships between index case age and secondary infections.

Household-level characteristics and isolation and quarantine measures practiced in the household did not show to have any influence on secondary infection rate. Additional and more diverse data will be necessary to take a better look at these potential influencing factors on transmission within households.

A major limitation of this study is the assumption that secondary infections resulted from the index case in the household, which can lead to an overestimation of the secondary infection

rate. Although, many households participated in at-home practices which reduces potential community spread. Another limitation is potential for misclassification of the index case which could influence the analysis, since an index case could be asymptomatic. Basing index cases on confirmed test result dates and symptoms helps confirm the index case role, and the addition of antibody test results in future analyses will help mitigate this limitation.

Overall, this pilot study analysis showed households with a child index cases have higher than average SIR's and school or sport exposures was the likely source of infection for the pediatric index cases for the study population. Furthermore, household contact gender may play a role in the overall household SIR. However, a larger and more diverse sample size as well as antibody test results are needed in order to perform analyses to better understand the role children have on household transmission and occurrences of school exposure.

Tables and Figures

Table 1. Household Characteristics During Infection Duration and Secondary Infection Rate

Characteristics	Household Secondary Infection Rate, n (%)		Overall	p value
	Below Average SIR	Above Average SIR		
	(n=6)	(n=9)	(n=15)	
Index Case Characteristics				
Age (Years)				0.16
Mean (SD)	40.2 (7.60)	29.2 (16.7)	33.6 (14.5)	
Median (IQR)	39.0 (6.5)	33.0 (28.0)	38.0 (11.5)	
Child Index Case				0.23
No	6 (100)	6 (66.7)	12 (80.0)	
Yes	0 (0)	3 (33.3)	3 (20.0)	
Gender				0.6
Male	1 (16.7)	3 (33.3)	4 (26.7)	
Female	5 (83.3)	6 (66.7)	11 (73.3)	
Co-Morbidities				1
No	4 (66.7)	7 (77.8)	11 (73.3)	
Yes	2 (33.3)	2 (22.2)	4 (26.7)	
Symptomatic				0.33
No	3 (50.0)	2 (22.2)	5 (33.3)	
Yes	3 (50.0)	7 (77.8)	10 (66.7)	
Household Contact Characteristics				
Average Age				0.86
Mean (SD)	20.7 (4.11)	20.1 (6.93)	20.3 (5.80)	
Median (IQR)	19.2 (5.72)	19.0 (7.0)	19.0 (6.1)	

Proportion of Male Gender				0.04
Mean (SD)	0.75 (0.29)	0.42 (0.26)	0.55 (0.31)	
Median (IQR)	0.83 (0.46)	0.50 (0.24)	0.5 (0.25)	
Proportion with a Co-Morbidity				0.08
Mean (SD)	0.32 (0.19)	0.11 (0.22)	0.19 (0.23)	
Median (IQR)	0.33 (0.19)	0.0 (0.0)	0.0 (0.42)	
Household-Level Characteristics				
Household Size				0.43
Mean (SD)	3.50 (1.05)	4.11 (1.62)	3.87 (1.41)	
Median (IQR)	3.50 (1.0)	4.00 (1.0)	4.00 (1.0)	
Mask Use in the HH				0.89
Never	1 (16.7)	3 (33.3)	4 (26.7)	
Occasionally	1 (16.7)	2 (22.2)	3 (20.0)	
Most of the Time	1 (16.7)	2 (22.2)	3 (20.0)	
All of the Time	3 (50.0)	2 (22.2)	5 (33.3)	
Isolated from Index Case				0.58
No	1 (16.7)	4 (44.4)	5 (33.3)	
Yes	5 (83.3)	5 (55.6)	10 (66.7)	
Shared a Bedroom/Bathroom with Index Case				1
Neither	3 (50.0)	3 (33.3)	6 (40.0)	
Only Bathroom	0 (0)	1 (11.1)	1 (6.7)	
Only Bedroom	0 (0)	1 (11.1)	1 (6.7)	
Both	3 (50.0)	4 (44.4)	7 (46.7)	
Quarantined in the Household				0.29
No	1 (16.7)	5 (55.6)	6 (40.0)	

Yes	5 (83.3)	4 (44.4)	9 (60.0)	
At Least One Person in the HH Worked In- Person				1
No	2 (33.3)	4 (44.4)	6 (40.0)	
Yes	4 (66.7)	5 (55.6)	9 (60.0)	
At Least One Child in the HH went to School/Daycare In-Person				1
No	4 (66.7)	5 (55.6)	9 (60.0)	
Yes	2 (33.3)	4 (44.4)	6 (40.0)	

Note: The average secondary infection rate (SIR) for this cohort was 0.54; P values were estimated with fisher's exact test for categorical variables and t-test for continuous variables

Chapter V: Conclusion/ Public Health Implications

This study found race and co-morbidities, particularly obesity, are important risk factors for severe COVID-19 infections. Black children and children with obesity were both more likely to have MIS-c than white or non-obese children. Furthermore, this study found race, ethnicity, and insurance status are predictors for getting infected with COVID-19. Black and Hispanic/Latino children were both more likely to receive a positive COVID-19 test than white-non-Hispanic children. Children with Medicare/Medicaid or no insurance were also more likely to receive a positive COVID-19 test than children with private insurance. The household transmission study provided information to show children can infect others in their household and school or sports team exposures are contributing sources of this transmission. Children made up 20% of household index cases, and all children went on to infect household members. The average household secondary infection rate for child index cases was 0.75 (SD=0.23) which is above the mean cohort secondary infection rate of 0.54. All child index cases were attending school or recreational sporting events during the time of likely exposure.

Results from this study identify important information which can help fill in knowledge gaps found in current literature on how the COVID-19 pandemic is affecting children. Specifically, these findings show, like in adults, there is an overrepresentation of COVID-19 cases and MIS-c patients among racial/ethnic and lower-income minority groups. Additionally, the household transmission study results provide information on the role children play in transmission. There are conflicting opinions in current literature on if children are likely to get infected in a school setting and if children are likely to transmit SARS-CoV-2 to household members. This study found that both events are possible, and therefore, more attention and research on the often-overlooked pediatric population is necessary.

The systemic health and social inequities present in this country have been very apparent during the course of the pandemic, and results from this study support this unacceptable reality. Additional studies need to explore this relationship to better understand the driving factors leading to this increased risk for minority groups and those with government insurance or no insurance. Additionally, reasonings behind low hospital admission among Hispanic/Latino children needs to be explored to understand why this group has higher rates of COVID-19 infections yet are less likely to be admitted to the hospital. Although more evidence is needed to better understand these relationships, it is clear the disproportionate economic, environmental, healthcare, occupation, and education opportunities contribute to the increased risk among these minority and economically vulnerable groups.

Along with socioeconomic risk factors leading to increased risk for COVID-19 and severe outcomes, this study showed obesity and chronic lung disease were health factors associated with severe COVID-19 infection outcomes including ICU admission and MIS-c. Research about what physiological characteristics of obese children contribute to this increased risk such as decreased immune cell functionality is limited. Therefore, an increased focus in this area of research is needed, especially among pediatric populations.

Findings from this study along with additional research and understanding of the socioeconomic and health factors associated with COVID-19 and severe disease can help inform future public health interventions and policy implications. A better understanding can inform future pediatric vaccine trials for COVID-19 by focusing on higher-risk groups with co-morbidities to ensure vaccines are safe and effective for these populations. Furthermore, better understanding of the socioeconomic and health risk factors for COVID-19 can inform vaccine and additional resource distribution. The unanimous findings of the health consequences

resulting from systemic racism in this country can help drive policy change to better address disproportionate economic, occupation, and education opportunities as well as healthcare access to minority and vulnerable communities in this country. Lastly, a better understanding of school and household transmission can help inform safer decisions and actions for in-person classes. This is especially critical due to the rising pediatric case incidence and school outbreak events occurring in the US. Children need the resources and services schools provide that greatly benefit children's' health and well-being. However, informed and cautious school re-opening plans are needed to prevent unnecessary disease exposure and consequential household transmission to family members.

References

1. CoronaVirus Resource Center (April 2021). *COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU).* https://coronavirus.jhu.edu/map.html
2. Centers for Disease Control and Prevention (April 2021). *COVID Data Tracker*. https://covid.cdc.gov/covid-data-tracker/#datatracker-home.
3. Milani, G.P., Bottino, I., Rocchi, A., et al. (2020). Frequency of Children vs Adults Carrying Severe Acute Respiratory Syndrome Coronavirus 2 Asymptomatically. *JAMA Pediatr.*, 175(2):193-194. doi:10.1001/jamapediatrics.2020.3595
4. National Center for Immunization and Respiratory Diseases (NCIRD), Division of Viral Diseases (Dec 2020). *Information for Pediatric Healthcare Providers*. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/hcp/pediatric-hcp.html
5. American Academy of Pediatrics (April 2021). *Children and COVID-19: State-Level Data Report*. https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/
6. Levin Z., Choyke K., Georgiou A., et al. (2021). Trends in Pediatric Hospitalizations for Coronavirus Disease 2019. *JAMA Pediatr,* 175(4):415–417. doi:10.1001/jamapediatrics.2020.5535
7. Kim, L., Whitaker, M., O'Halloran, A., et al. (2020). 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. Morbidity and mortality weekly report*, *69*(32), 1081–1088. https://doi.org/10.15585/mmwr.mm6932e3

8. Bandi, S., Nevid, M. Z., & Mahdavinia, M. (2020). African American children are at higher risk of COVID-19 infection. *Pediatr Allergy Immunol, 31*(7), 861-864. doi:10.1111/pai.13298
9. National Center for Immunization and Respiratory Diseases (NCIRD), Division of Viral Diseases (Feb 2021). *Health Equity Considerations and Racial and Ethnic Minority Groups*. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/community/health-equity/race-ethnicity.html
10. World Health Organization (Oct 2020). *What we know about COVID-19 transmission in schools.* https://www.who.int/docs/default-source/coronaviruse/risk-comms-updates/update39-covid-and-schools.pdf?sfvrsn=320db233_2
11. National Center for Immunization and Respiratory Diseases (NCIRD), Division of Viral Diseases (Mar 2021). *Science Brief: Transmission of SARS-CoV-2 in K-12 schools.* Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/transmission_k_12_schools.html
12. Pollock, A. M., & Lancaster, J. (2020). Asymptomatic transmission of covid-19. *BMJ, 371*, m4851. doi:10.1136/bmj.m4851
13. Nogrady, B. (2020). What the data say about asymptomatic COVID infections. *Nature*, 587, 534-535. doi: https://doi.org/10.1038/d41586-020-03141-3
14. Center for Disease Control and Prevention (Mar 2021). *People with Certain Medical Conditions.* https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html
15. He, J., Guo, Y., Mao, R., & Zhang, J. (2021). Proportion of asymptomatic coronavirus disease 2019: A systematic review and meta-analysis. *Journal of medical virology*, *93*(2), 820–830. https://doi.org/10.1002/jmv.26326

16. Bellino, S., Punzo, O., Rota, M. C., et al. (2020). COVID-19 Disease Severity Risk Factors for Pediatric Patients in Italy. *Pediatrics, 146*(4). doi:10.1542/peds.2020-009399

17. National Center for Immunization and Respiratory Diseases (NCIRD) (April 2021). *Health Department-Reported Cases of Multisystem Inflammatory Syndrome in Children (MIS-C) in the United States*. Centers for Disease Control and Prevention. https://www.cdc.gov/mis-c/cases/index.html

18. National Center for Immunization and Respiratory Diseases (NCIRD) (July 2020*). Infographic: Early Cases of MIS-C: Multi-System Inflammatory Syndrome in U.S. Children.* Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/covid-data/infographic-mis-c.html

19. Alfraij, A., Alamir, A., Al-Otaibi, A., et al. (2020). Characteristics and outcomes of coronavirus disease 2019 (COVID-19) in critically ill pediatric patients admitted to the intensive care unit: A multicenter retrospective cohort study. *Journal of Infection and Public Health, ISSN 1876-0341,*https://doi.org/10.1016/j.jiph.2020.12.010

20. L.R. Feldstein, E.B. Rose, S.M. Horwitz, et al. (2020). Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. N Engl J Med, 383(4), 334-346. doi:10.1056/NEJMoa2021680

21. CDC COVID-19 Response Team (2020). Coronavirus Disease 2019 in Children - United States, February 12-April 2, 2020. *MMWR*, *69*(14), 422–426. https://doi.org/10.15585/mmwr.mm6914e4

22. Rabinowicz, S., Leshem, E., & Pessach, I. M. (2020). COVID-19 in the Pediatric Population-Review and Current Evidence. *Curr Infect Dis Rep, 22*(11), 29. doi:10.1007/s11908-020-007396

23. Lumba R, Dapul HM, et al. (2020). Characteristics of hospitalized children with SARSCoV-2 in the New York City metropolitan area. *Hosp Pediatr*. doi: 10.1542/hpeds.2020- 001917

24. Heilbronner, C., Berteloot, L., Tremolieres, P., et al. (2020). Patients with sickle cell disease and suspected COVID-19 in a paediatric intensive care unit. *Br J Haematol*, 190(1): e21-e24. doi: 10.1111/bjh.16802

25. Moser, J., Galindo-Fraga, A., Ortiz-Hernández, A.A., et al. Underweight, overweight, and obesity as independent risk factors for hospitalization in adults and children from influenza and other respiratory viruses. Influenza Other Respir Viruses. 2019; 13(1): 3– 9.

26. Malik, P, Patel, U, Patel, K, et al. Obesity a predictor of outcomes of COVID-19 hospitalized patients- A systematic review and meta-analysis. *J Med Virol*. 2021; 93: 1188– 1193. https://doi.org/10.1002/jmv.26555

27. Lighter, J., Phillips, M., Hochman, S., et al. (2020). Obesity in Patients Younger Than 60 Years Is a Risk Factor for COVID-19 Hospital Admission. *Clinical Infectious Diseases,* 71(15): 896-897. doi: https://doi.org/10.1093/cid/ciaa415

28. Wang, M., Nie, X., Huang, S., Pi, W., et al. (2020). Epidemiological characteristics and transmission dynamics of paediatric cases with coronavirus disease 2019 in Hubei province, China. *J Paediatr Child Health*. doi:10.1111/jpc.15287

29. Stokes, E.K., Zambrano, L.D., Anderson, K.N., Marder, E.P., Raz, K.M., Felix, S.E.B., Tie.Y., Fullerton, K.E. (2020). Coronavirus Disease 2019 Case Surveillance — United States, January 22–May 20, 2020. *MMWR,* 69(24), 759–765. Doi:

30. Killerby, M. E., Link-Gelles, R., Haight, S. C., et al. (2020). Characteristics Associated with Hospitalization Among Patients with COVID-19 Metropolitan Atlanta, Georgia, March-April 2020. *MMWR Morb Mortal Wkly Rep, 69*(25), 790-794. doi:10.15585/mmwr.mm6925e1

31. Alnababteh, M., Drescher, G., Jayaram, L., et al. (2020). Investigating the relationship between race/ethnicity and clinical outcomes in COVID-19. *Chest 4(158)*, A2477-A2478. https://doi.org/10.1016/j.chest.2020.09.054

32. Rogers, T.N., Rogers, C.R., VanSant-Webb, E., et al. (2020). Racial Disparities in COVID-19 Mortality Among Essential Workers in the United States. *World Medical & Health Policy*, 12: 311-327. https://doi.org/10.1002/wmh3.358

33. Bassett, M.T., Chen, J.T., & Krieger, N. (2020) Variation in racial/ethnic disparities in COVID-19 mortality by age in the United States: A cross-sectional study. *PLoS Med* 17(10): e1003402. https://doi.org/10.1371/journal.pmed.1003402

34. Otto, W. R., Geoghegan, S., Posch, L. C., et al. (2020). The Epidemiology of Severe Acute Respiratory Syndrome Coronavirus 2 in a Pediatric Healthcare Network in the United States. *J Pediatric Infect Dis Soc, 9*(5), 523-529. doi:10.1093/jpids/piaa074

35. Anyane-Yeboa, A., Sato, T., & Sakuraba, A. (2020). Racial disparities in COVID-19 deaths reveal harsh truths about structural inequality in America. *Journal of Internal Medicine, 288*(4), 479-480. doi:https://doi.org/10.1111/joim.13117

36. United States Census Bureau. (2019). *Health Insurance Coverage in the United States: 2018: Current Population Reports*, Washington DC: U.S. Government Printing Office. https://www.census.gov/content/dam/Census/library/publications/2019/demo/p60-267.pdf.

37. Kim, E.J., Marrast, L., Conigliaro, J. (2020). COVID-19: Magnifying the Effect of Health Disparities. *J Gen Intern Med* 35(8): 2441-2. doi: 10.1007/s11606-020-05881-4

38. Raifman, M. A., & Raifman, J. R. (2020). Disparities in the Population at Risk of Severe Illness From COVID-19 by Race/Ethnicity and Income. *American journal of preventive medicine*, *59*(1), 137–139. https://doi.org/10.1016/j.amepre.2020.04.003

39. Van Lancker, W., & Parolin, Z. (2020). COVID-19, school closures, and child poverty: a social crisis in the making. *The Lancet Public Health, 5*(5), e243-e244. doi:10.1016/S2468-2667(20)30084

40. School Nutrition Association. n.d. (2020). *School Meal Trends and Stats.* Arlington, VA: School Nutrition Association. https://schoolnutrition.org/aboutschoolmeals/schoolmealtrendsstats/.

41. United States Department of Agriculture (9 Sept 2020). *Food security in the United States*. https://www.ers.usda.gov/data-products/food-security-in-the-united-states/

42. National Center for Homeless Education (Jan 2020). *Federal Data Summary School Year 2015–16 through 2017–18.* https://nche.ed.gov/wp-content/uploads/2020/01/Federal-Data-Summary-SY-15.16-to-17.18-Published-1.30.2020.pdf.

43. Bao, X., Qu, H., Zhang, R., et al. (2020). Literacy Loss in Kindergarten Children during COVID-19 School Closures. https://doi.org/10.3390/ijerph17176371

44. Swedo, E., Idaikkadar, N., Leemis, R., et al. (2020). Trends in U.S. Emergency Department Visits Related to Suspected or Confirmed Child Abuse and Neglect Among Children and Adolescents Aged <18 Years Before and During the COVID-19 Pandemic - United States, January 2019-September 2020. *MMWR Morb Mortal Wkly Rep, 69*(49), 1841-1847. doi:10.15585/mmwr.mm6949a1

45. Federal Interagency Forum on Child and Family Statistics. 2019. *America's Children: Key National Indicators of Well-Being, 2019*. Washington, DC: U.S. Government Printing Office. Retrieved from: https://www.childstats.gov/pdf/ac2019/ac_19.pdf.

46. Li, W., Zhang, B., Lu, J., et al. (2020). Characteristics of Household Transmission of COVID-19. *Clin Infect Dis, 71*(8), 1943-1946. doi:10.1093/cid/ciaa450

47. Li, F., Li, Y.-Y., Liu, M.-J., et al. (2021). Household transmission of SARS-CoV-2 and risk factors for susceptibility and infectivity in Wuhan: a retrospective observational study. *The Lancet Infectious Diseases*. doi:10.1016/S1473-3099(20)30981-6

48. Sun, W. W., Ling, F., Pan, J. R., et al. (2020). Epidemiological characteristics of COVID-19 family clustering in Zhejiang Province. *Zhonghua yu fang yi xue za zhi [Chinese journal of preventive medicine], 54*(6), 625-629. doi:10.3760/cma.j.cn112150-20200227-00199

49. Cheng, H.-Y., Jian, S.-W., Liu, D.-P., et al. (2020). Contact Tracing Assessment of COVID-19 Transmission Dynamics in Taiwan and Risk at Different Exposure Periods Before and After Symptom Onset. *JAMA Internal Medicine, 180*(9), 1156-1163. doi:10.1001/jamainternmed.2020.2020

50. Burke, R. M., Midgley, C. M., Dratch, A., et al. (2020). Active Monitoring of Persons Exposed to Patients with Confirmed COVID-19 - United States, January-February 2020. *MMWR Morb Mortal Wkly Rep, 69*(9), 245-246. doi:10.15585/mmwr.mm6909e1

51. Soriano-Arandes, A., Gatell, A., Serrano, P., et al. (2021). Household SARS-CoV-2 transmission and children: a network prospective study. *Clinical Infectious Diseases: pre-published.* https://doi.org/10.1093/cid/ciab228

52. Laws, R.L., Chancey, R.J., Rabold, E.M., et al. (2020). Symptoms and Transmission of SARS-CoV-2 Among Children — Utah and Wisconsin. *Pediatrics*, 146(6):e2020027268. doi:10.1542/peds.2020-027268external icon.

53. Assaker, R., Colas, A. E., Julien-Marsollier, F., et al. (2020). Presenting symptoms of COVID-19 in children: a meta-analysis of published studies. *British journal of anaesthesia*, *125*(3), e330–e332. https://doi.org/10.1016/j.bja.2020.05.026

54. He, J., Guo, Y., Mao, R., et al. (2020). Proportion of asymptomatic coronavirus disease 2019: A systematic review and meta-analysis. J Med Virol. 93(2); 820-830. doi: https://doi.org/10.1002/jmv.26326

55. Lewis, N. M., Chu, V. T., Ye, D., et al. (2020). Household Transmission of SARS-CoV-2 in the United States. *Clin Infect Dis,* ciaa1166. Advance online publication. https://doi.org/10.1093/cid/ciaa1166

56. Byambasuren, O., Cardona, M., Bell, K., et al. (2020). Estimating the extent of asymptomatic COVID-19 and its potential for community transmission: Systematic review and meta-analysis. *JAMMI*, 5(4), 223-234. doi: 10.3138/jammi-2020-0030

57. Yu, X. & Yang, R. (2020). COVID-19 transmission through asymptomatic carriers is a challenge to containment. *Influenza Other Respi Viruses*, 14(4); 474-475. doi: https://doi.org/10.1111/irv.12743

58. Lopez, A. S., Hill, M., Antezano, J., et al. (2020). Transmission Dynamics of COVID-19 Outbreaks Associated with Child Care Facilities - Salt Lake City, Utah, April-July 2020. *MMWR. Morbidity and mortality weekly report*, *69*(37), 1319–1323. https://doi.org/10.15585/mmwr.mm6937e3

59. Hobbs, C. V., Martin, L. M., Kim, S. S., et al. (2020). Factors Associated with Positive SARS-CoV-2 Test Results in Outpatient Health Facilities and Emergency Departments Among Children and Adolescents Aged <18 Years - Mississippi, September-November 2020. *MMWR Morb Mortal Wkly Rep, 69*(50), 1925-1929. doi:10.15585/mmwr.mm6950e3

60. Guo, C. X., He, L., Yin, J. Y., et al. (2020). Epidemiological and clinical features of pediatric COVID-19. *BMC Med, 18*(1), 250. doi:10.1186/s12916-020-01719-2

61. Liguoro, I., Pilotto, C., Bonanni, et al. (2020). SARS-COV-2 infection in children and newborns: a systematic review. *Eur J Pediatr, 179*(7), 1029-1046. doi:10.1007/s00431-020-03684-7

62. State of Michigan (14 Apr 2021). *School-Related Outbreak Reporting.* https://www.michigan.gov/coronavirus/0,9753,7-406-98163_98173_102480---,00.html

63. Herbart, P. (14 Apr 2021). *Labor Voices: COVID surge makes classroom too dangerous for students.* Michigan Education Association. https://mea.org/labor-voices-covid-surge-makes-classroom-too-dangerous-for-students/

64. Rafferty, M.S., Burrows, H., Joseph, J.P., et al (2021). Multisystem inflammatory syndrome in children (MIS-C) and the coronavirus pandemic: Current knowledge and implications for public health. *J Infect Public Health***,** 14(4), 484-494. https://doi.org/10.1016/j.jiph.2021.01.008

65. Ahmed, M., Advani, S., Moreira, A., et al. (2020). Multisystem inflammatory syndrome in children: A systematic review. *EClinicalMedicine, 26*, 100527. doi:10.1016/j.eclinm.2020.100527

66. Lee, P. Y., Day-Lewis, M., Henderson, L. A., Friedman, K. G., Lo, J., Roberts, J. E., . . . Son, M. B. F. (2020). Distinct clinical and immunological features of SARS-CoV-2-induced multisystem inflammatory syndrome in children. *J Clin Invest, 130*(11), 5942-5950. doi:10.1172/JCI141113

67. Cheung, E. W., Zachariah, P., Gorelik, M., Boneparth, A., Kernie, S. G., Orange, J. S., & Milner, J. D. (2020). Multisystem Inflammatory Syndrome Related to COVID-19 in Previously Healthy Children and Adolescents in New York City. *JAMA*, *324*(3), 294–296. https://doi.org/10.1001/jama.2020.10374

68. Nogueira-de-Almeida, C. A., Del Ciampo, L. A., Ferraz, I. S., et al. (2020). COVID-19 and obesity in childhood and adolescence: a clinical review. *Jornal de pediatria*, *96*(5), 546–558. https://doi.org/10.1016/j.jped.2020.07.001

69. World Health Organization (2019). *WHO Anthro Survey Analyser: Quick Guide*. https://www.who.int/nutgrowthdb/about/anthro-survey-analyser-quickguide.pdf

70. Division of Nutrition, Physical Activity, and Obesity (2019). *A SAS Program for the 2000 CDC Growth Charts (ages 0 to <20 years).* https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm

71. PA Harris, R Taylor, R Thielke, et al. (2009). Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform, 42*(2), 377-381. doi:10.1016/j.jbi.2008.08.010

72. PA Harris, R Taylor, BL Minor, et al. (2019). The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform, 95*, 103208. doi:10.1016/j.jbi.2019.103208

73. Tanaka, S., Isoda, F., Ishihara, Y., Kimura, M., et al. (2001). T lymphopaenia in relation to body mass index and TNF-alpha in human obesity: adequate weight reduction can be corrective. *Clinical endocrinology*, *54*(3), 347–354.

74. Simonnet, A., Chetboun, M., Poissy, J., et al. (2020). High Prevalence of Obesity in Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) Requiring Invasive Mechanical Ventilation. *Obesity (Silver Spring, Md.)*, *28*(7), 1195–1199. https://doi.org/10.1002/oby.22831

75. Division of Nutrition, Physical Activity, and Obesity, National Center for Chronic Disease Prevention and Health Promotion (Mar 2021). *Obesity, Race/Ethnicity, and COVID-19. Centers*

for Disease Control and Prevention. https://www.cdc.gov/obesity/data/obesity-and-covid-19.html#References

76. Chen, C., Zhu, C., Yan, D., et al. (2021). The epidemiological and radiographical characteristics of asymptomatic infections with the novel coronavirus (COVID-19): A systematic review and meta-analysis. *Int J Infect Dis, 104*, 458-464. doi:10.1016/j.ijid.2021.01.017
77. Almadhi, M. A., Abdulrahman, A., Sharaf, S. A., et al. (2021). The high prevalence of asymptomatic SARS-CoV-2 infection reveals the silent spread of COVID-19. *Int J Infect Dis, 105*, 656-661. doi:10.1016/j.ijid.2021.02.100
78. Randad, P. R., Pisanic, N., Kruczynski, K., et al. (2020). COVID-19 serology at population scale: SARS-CoV-2-specific antibody responses in saliva. *medRxiv*, preprint. https://doi.org/10.1101/2020.05.24.20112300
79. Teherani,M.F., Kao, C.M., Camacho-Gonzalez, C., et al. (2020) Burden of Illness in Households With Severe Acute Respiratory Syndrome Coronavirus 2–Infected Children, J *Pediatric Infect Dis Soc*, 9 (5), 613-616. https://doi.org/10.1093/jpids/piaa097