COVID-19 in Childhood: Transmission, Clinical Presentation, Complications and Risk Factors

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Abbreviations:

SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2
COVID-19 – coronavirus disease 2019
MIS-C – multisystem inflammatory syndrome in children
WHO – World Health Organization
UK – United Kingdom
SAR – secondary attack rate
ACE-2 – angiotensin-converting enzyme 2
CXR – chest radiography
NP – nasopharyngeal
RT-PCR – reverse transcription polymerase chain reaction
RNA – ribonucleic acid
UNICEF – United Nation Children's Fund
ICU – intensive care unit
CRP – C-reactive protein
CDC – Center for Disease Control and Prevention
KD – Kawasaki disease

TSS – toxic shock syndrome
US – United States
SARS-CoV – severe acute respiratory syndrome coronavirus 1
MERS-CoV – Middle Eastern respiratory syndrome coronavirus
RSV – respiratory syncytial virus

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Abstract

Children less than 18 years of age account for an estimated 500,000 to 1.5 million global SARS-CoV-2 cases. Lower prevalence of COVID-19 among children, in addition to higher numbers of mild and asymptomatic cases, continues to provide challenges in determining appropriate prevention and treatment courses. Here, we summarize the current evidence on the transmission, clinical presentation, complications and risk factors in regards to SARS-CoV-2 in children and highlight crucial gaps in knowledge going forward. Based on current evidence, children are rarely the primary source of secondary transmission in the household or in child care and school settings and are more likely to contract the virus from an adult household member. Higher transmission rates are observed in older children (10-19 years old) compared to younger children (<10 years old). While increasing incidence of COVID-19 in neonates raises the suspicion of vertical transmission, it is unlikely that breast milk is a vehicle for transmission from mother to infant. The vast majority of clinical cases of COVID-19 in children are mild, but there are rare cases that have developed complications such as multisystem inflammatory syndrome in children (MIS-C), which often presents with severe cardiac symptoms requiring intensive care. Childhood obesity is associated with a higher risk of infection and a more severe clinical presentation. Although immediate mortality rates among children are low, long-term respiratory and developmental implications of the disease remain unknown in this young and vulnerable population.

Introduction

Children less than 18 years of age account for an estimated 1.7% of SARS-CoV-2 clinical infections in the US,[1] with global estimates ranging from 2.0[2] to 4.8%.[3] The low prevalence of pediatric cases has made it difficult to draw conclusive statements about many aspects of the virus in this population, but the reported cases numbers are likely an underestimation of the true pediatric case load, as many cases in children are asymptomatic.[4] Initial observations report that the clinical course is generally milder and outcomes are better in children.[5] Also, as the pandemic progresses, clinicians report an increasing number of children with a severe inflammatory syndrome following COVID-19 exposure or infection. Though rare, this syndrome has the potential to cause devastating outcomes in children and as the pandemic continues cases of MIS-C are likely to increase. These findings have underscored the limitations of current knowledge regarding COVID-19 in children and have raised questions about the implications for long-term respiratory and developmental prognosis. We seek to comprehensively examine what is currently known and what knowledge we still lack about transmission, clinical presentation, complications and risk factors as they pertain to SARS-CoV-2 infection in the pediatric population.

Transmission

According to the WHO,[6] SARS-CoV-2 is transmitted directly and indirectly through the respiratory secretions of those infected. Several studies have also looked at the prevalence and implications of fecal viral shedding in the pediatric population and the implications for transmission.[7] Based on a systematic review of contact tracing programs and population studies,

the susceptibility of children to COVID-19 was lower than adults, although the role that they played in transmission was not conclusive.[8]

The prominence of mild and asymptomatic illness in pediatric patients has created concern that the true prevalence of disease in this age group has been underreported.[4, 5] Population-based seroprevalence studies have had conflicting results.[9-11] The seroprevalence of antibodies in children was consistent with that of adults in the same area in the UK,[9] implying that children and adults are equally susceptible to the virus, however, in Italy seroprevalence increased with age.[11]

Household Transmission

Table 1 presents transmission sources as reported in several pediatric studies. Available data indicate that SARS-CoV-2-positive adults living in the household are the primary source of infection for children. It should be noted that shelter-in-place orders decreased outdoor activities in most countries and likely led to the increase of viral spread within households.[12] In an investigation of 110 cases stemming from 11 infection clusters in Japan, close contact in an indoor setting contributed to all 11 clusters.[13] In South Korea, household cases were the primary source of infection until mid-March, 2020, when imported cases became the most prevalent.[4] In the UK, a population-based seroprevalence study of children reported that neither age nor gender had any association with positive results, but contact with a household member with confirmed COVID-19 was a significant predictor for seropositivity.[9]

Although children are usually infected by SARS-CoV-2-positive adults living in the household, several studies have shown that the overall risk of contagion to children is lower than that of other adults residing in the same household.[12, 14] In a meta-analysis looking at secondary attack rates (SAR) in the household setting (n=46 studies),[12] the overall SAR for household

contacts was almost 19%, while that of close contacts was just 4.3%. Spouses of infected individuals were at greater risk than other household members (43.4% vs. 18.3%), whereas the rate of secondary household transmission to children was significantly lower than adults (15.7% vs. 31%).[12]

Child's age may also affect the risk of transmission. In South Korea, analysis of data for 59,000 contacts of 5,700 index cases found that a total of 11.8% of household contacts tested positive for COVID-19.[15] When further stratified by age, the infection rate was 18.6% for index cases aged 10-19 years, and 5.3% for ages 0-9 years.[15] Consistently, in a study of Swiss students, the seroprevalence of SARS-CoV-2 antibodies decreased with age.[10]

Maternal-fetal and perinatal transmission

Vertical transmission was demonstrated with SARS-CoV-1, and the same risk theoretically exists for SARS-CoV-2, as the viral receptor (angiotensin-converting enzyme 2, ACE-2) is widely expressed in the placenta.[16] Consequently, the growing number of confirmed neonatal cases of COVID-19 infection has reinforced the suspicion that SARS-CoV-2 is similarly capable of crossing the placenta to infect fetal lungs. A recent study identified 3 neonates delivered from COVID-positive mothers with pneumonia on chest radiography (CXR) obtained at birth and nasopharyngeal (NP) swabs positive for SARS-CoV-2 on days 2 and 4 of life and negative on day 6-7.[17] One of these patients was born at 31 weeks of gestation via cesarean delivery due to fetal distress and required resuscitation. Although vertical transmission was not found in several other neonates born to COVID-19 infected mothers, it is critical to note that most of such data have been limited by extremely small sample size (frequently n=1), a lack of cord blood or amniotic fluid (the gold standard to prove vertical transmission) evidence, and provide little or no information on the outcome of the infants. As pregnant women are more susceptible than the

general population to respiratory pathogens including COVID-19, maternal infection and inflammation in response to virus could affect the developing fetus and even postnatal life. With the continuing pandemic of COVID-19, there is general consensus further studies are warranted to investigate pregnant women with COVID-19, follow-up the pregnancy outcomes, and monitor postnatal development of the fetus.

Breastfeeding

Based on the earliest 13 case studies/series (n = 48 milk samples from 32 women combined), only one sample contained virus, while SARS-CoV-2 antibodies were found in two other samples.[18] However, the sample collection and analytical methods were not provided in detail in these case reports, raising questions on methodological quality and potential for contamination. In a longitudinal study of two COVID-19 positive mothers following delivery (day 0), the first mother's samples were all negative for SARS-CoV-2 RNA, but milk samples from days 10, 12 and 13 post-delivery were positive for the second mother.[19] The positive milk samples coincided with mild symptoms in the second mother and her infant tested positive for COVID-19 on day 11. The first infant also tested positive for COVID-19, although viral RNA was absent in the first mother's samples.[19] In another study (n=64 breastmilk samples from 18 COVID-19 positive mothers) viral RNA was isolated in one sample, but no replication-competent virus was detected.[20] Both breastmilk samples (n=37 milk samples) and breast swabs (n=70 swabs collected before and after cleaning the breast with soap and water prior to feeding) were analyzed from 18 COVID-19-positive women.[21] SARS-CoV-2 RNA was not present in the milk samples, but was present on one of the pre-cleaning swabs. Further, SARS-CoV-2 antibodies were detected in all 37 milk samples.[21] As SARS-CoV-2 transmission through breastmilk is unlikely, both World Health Organization (WHO) and UNICEF currently

recommend mothers with suspected or confirmed COVID-19 initiate or continue breastfeeding while following guidance on hygiene and mask use.[22, 23] For situations requiring donor milk, pasteurization of human milk by the Holder method (62.5°C for 30 minutes) inactivates SARS-CoV-2.[24]

Child Care

As of July 31, 52 (33 confirmed) SARS-CoV-2 cases had occurred in 29/666 (4.3%) child care facilities in Rhode Island.[25] Twenty of these facilities only reported a single case, with no evidence of secondary transmission, while possible secondary transmission occurred in 4 centers, accounting for 17 cases. Contact tracing and testing data for child care facilities in Salt Lake City, Utah.in April–July, 2020, reported 31 confirmed cases of COVID-19 between three facilities, 42% (13/31) of which occurred in children.[26] Asymptomatic transmission from children to adult contacts was confirmed in two cases. Index cases for all three facilities were determined to be adult staff members.[26]

School Opening and Transmission

Table 2 provides data from studies analyzing secondary transmission of SARS-CoV-2 in the school setting. In South Korea, children were not the primary source of transmission within schools, as secondary cases were all a result of contact with an infected staff member.[27] In Ireland, no secondary transmission of COVID-19 was reported in a follow-up of 1,025 exposed school contacts.[28] These exposures included activities such as music lessons and choir practice, both of which are assumed to be high-risk activities for transmission.[28] Of 18 cases of secondary transmission in Australia, 5 cases occurred in 3 schools and the other 13 occurred in a single early childhood education center where the cluster outbreak was traced to a single adult staff member.[29] The overall child-to-child SAR was 0.3% (2/649) and the child to staff SAR was 1.0%

(1/103), while the staff-to-staff SAR was 4.4% (7/160) and the staff-to-child SAR was 1.5% (8/536).[29] In Switzerland, researchers randomly analyzed seroprevalence among 2,585 students (6 to 16 years old) in 55 schools and found that at least one seropositive case was reported in 36/55 schools with no evidence of clustered outbreaks or secondary transmission.[10] In Hong Kong, only 5 of 20 cases in children (5 to 17 years old) were associated with 2 clustered school outbreaks.[30] In Germany, 137 COVID-19-positive students attended school for at least one day while infectious.[31] Only 6 of these cases contributed to the transmission of SARS-CoV-2 to an additional 11 students. No additional secondary transmission was reported despite extensive screening and monitoring of more than 2,300 close school contacts.[31] Authors of both papers acknowledged the contribution of infection-control measures, such as social distancing and masking, to the low transmission rates.[30, 31] Child-to-child transmission within the school setting was uncommon and not the primary source of SARS-CoV-2 infection in children.[31]

Ten days after schools reopened in Jerusalem in May, 2020 two separate cases of COVID-19 in the same high-school led to the infection of almost 260 people.[32] Within the school community, 153 students and 25 staff members were infected. Overly crowded classrooms without appropriate social distancing and the suspension of mask-wearing for several days in response to a heat wave likely contributed to the outbreak.[32]

School infections peaked in Victoria, Australia when community transmission was high, but transmission among children was not school-driven.[33] In Sweden and Finland, the cumulative incidence rates of COVID-19 among school-age children were similar across both countries despite Sweden's decision not to close childcare facilities or primary schools. Health officials in Sweden concluded that school closures did not significantly impact the overall prevalence of

COVID-19 among 1 to 19 year-olds.[34] Daycare, primary, or secondary school teachers were not at increased risk for SARS-CoV-2 infection.[34]

Clinical Presentation in Children

Table 3 summarizes 12 studies reporting clinical data of children with diagnosed or suspected COVID-19.[5] The heterogeneity in study participant selection criteria must be noted among these studies, which may have affected both clinical presentation and severity of the cases reported.

In a systematic review of literature regarding the clinical presentation of COVID-19 in children, the most commonly reported symptoms were fever and cough.[35] In a cohort study involving 651 pediatric cases in the UK, fever and a runny nose were more common in younger children, while vomiting, abdominal pain, headache and a sore throat showed an increasing trend with age.[36] Older children were more likely to present with respiratory distress than infants (44% vs. 7%).[37] Less common symptoms include seizures[36, 38, 39] and loss of taste and smell.[4, 37]

A study of 2,143 (731 laboratory-confirmed) pediatric cases reported to the Chinese Center for Disease Control and Prevention found that 94.1% of cases could be classified as asymptomatic, mild or moderate.[5] The mild category (50.9%) included symptoms such as fever, fatigue, myalgia, cough, sore throat, runny nose and sneezing.[5] In Turkey, of 220 positive pediatric cases, 145 (70.5%) were classified as asymptomatic (25.5%) or mild (45%).[40] In South Korea, 22% of COVID-19-positive study participants remained asymptomatic throughout a three-week monitoring period.[4] A systematic review of studies (n=4,300 confirmed pediatric cases) reported that 18.9% of children were asymptomatic.[41] The majority of studies reported a mortality rate of less than 2% (**Table 3**).

There is a significant difference in the median age between studies, with the lowest being 2.3 years old[38] and the highest 13 years.[42] Infants (aged <1 year) account for between 30-40% of participants in half of the studies (**Table 3**). The high proportion of infants could be influenced by a tendency for parents to seek medical attention for this age group and an increased likelihood that physicians will admit them to hospitals.[38] A multivariate analysis reported an association between neonatal period (<1 month of age) and ICU admission (Odd Ratio 5.06).[36, 43]

Several studies noted that COVID-19 positive patients had elevated blood markers indicative of inflammation.[36, 37, 39, 40, 42] One study reported that 38.8% (47/121) of participants had high concentrations of the inflammatory marker C-reactive protein (CRP).[38] Moreover, children with more serious symptoms were found to have significantly higher CRP levels than those with a milder presentation.[37] In Turkey, lymphopenia was the most common abnormal lab value found amongst participants (13.5%; 85/220).[40]

Complications in Children

Multisystem Inflammatory Syndrome in Children (MIS-C)

Starting in late April 2020, a hyperinflammatory syndrome likely related to COVID-19 has been reported in growing numbers of children.[44, 45] This syndrome has been named multisystem inflammatory syndrome in children (MIS-C) and its clinical presentation has many similarities to Kawasaki Disease (KD)[46] and Toxic Shock Syndrome (TSS), particularly the elevation of multiple inflammatory markers with severe cardiac involvement.[36, 44, 47-50] In the UK, MIS-C is referred to as pediatric inflammatory multisystem syndrome temporarily associated with SARS-CoV-2 (PIMS-TS).[51]

Table 4 summarizes 14 studies looking at patients with potential or diagnosed cases of MIS-C. The information is presented in table format for ease of viewing, but not necessarily for comparison among studies as they vary greatly in size and scope. Patient selection also varies among studies, with earlier studies responding to an unusual increase in KD cases in the pediatric population and selecting study cases from those with a definitive KD diagnosis. Later, as the medical and scientific community became aware of MIS-C as a distinct condition, more formal diagnostic characteristics were sought.[52] Since then, the WHO,[53] the Centers for Disease Control (CDC)[54] in the US, and the Royal College of Paediatrics and Child Health[51] in the UK have all provided separate case definitions.

Clinical Presentation of MIS-C

Fever, gastrointestinal complaints, rash, and conjunctivitis have been reported as the most prevalent symptoms MIS-C (**Table 4**), although a combination of these symptoms must be present in order for patients to meet the case definition for MIS-C or PIMS-TS.[52] Due to the overlapping clinical features of MIS-C and KD, RT-PCR and antibody testing are needed to confirm MIS-C.[46, 48, 55]

MIS-C and SARS-CoV-2 Testing Results

Although the causality of MIS-C is currently inconclusive, several studies have noted an increase in cases 4 to 6 weeks following a spike in COVID-19 cases within a population.[36, 50, 56-58] In several studies, patients found to be negative for SARS-CoV-2 by RT-PCR were positive for SARS-CoV-2 antibodies.[44, 47] SARS-CoV-2 RT-PCR was positive in 52% of cases, while SARS-CoV-2 antibodies were found in almost 71% of cases across all available studies (**Table 4**). Riphagen et al. reported that all 8 cases in their study tested negative for SARS-CoV-2 by RT-PCR, but no mention of antibody testing was noted.[55] Serum samples from 29 pediatric patients,

showed that cases classified as MIS-C had higher IgG antibody titers than their non-MIS-C counterparts,[59] which is consistent with the delayed onset of MIS-C cases following COVID-19 exposure and/or infection.[59] UK Patients with MIS-C who were antibody-positive were younger (median age 10.0 years vs. 12.4 years) and more likely to be of non-white ethnicity than those who were positive by RT-PCR,[36] suggesting that more testing is needed in younger and minority children. Conjunctivitis (71% vs. 16%) and abdominal pain (95% vs. 44%) were more common in patients positive for SARS-CoV-2 antibodies, whereas those who were diagnosed by RT-PCR testing were more likely to present with shortness of breath (52% vs. 14%).[36]

MIS-C and Patient Characteristics

Due to the severity of the clinical presentation, children with MIS-C often require ICU-level care, especially to manage cardiac complications. In one study, children with MIS-C were 5 times more likely to be admitted to the ICU,[36] while another study reported that 14 of 15 MIS-C patients were admitted to the ICU within 24 hours of hospital admission.[47] In Latin America, lower socioeconomic status was found to have a significant association with MIS-C diagnosis and the need for mechanical ventilation.[60] Different from adults, there are conflicting data regarding comorbidities that place children at higher risk for COVID-19 complications, and several studies reported that the majority of their pediatric subjects did not have any significant past medical history.[44, 47, 50, 55, 60] A possible exception to these findings was reported where 5 of 6 patients diagnosed with MIS-C had a pre-existing medical condition, 4 of whom were immunocompromised.[61]

Comorbidities and Severity

Obesity, chronic respiratory diseases (particularly asthma), and a compromised or suppressed immune system are the most common underlying medical conditions that have been cited. **Table 5** summarizes 12 studies that have included comorbidity data.

Obesity

Obesity was the most common comorbidity among hospitalized COVID-positive children, with a significant association between obesity and severe cases requiring mechanical ventilation in children 2 years and older.[37] A retrospective study from Wuhan, China reported that an elevated body mass index (BMI) was correlated with an increased mortality risk in COVID-19 patients aged 14 to 45 years).[62] In another study, 30% (14/46) of admitted pediatric patients testing positive for COVID-19 were obese, but no correlation was noted between obesity and ICU admissions.[63] Finally, an analysis of nationwide data from pediatric cases in Mexico reported that obese children were 39% more likely to have a SARS-CoV-2 infection.[64]

The effect of the COVID-19 lockdown policies on weight gain in children is another concern. A cross-sectional survey of 584 households in the US reported that families are buying more non-perishable and highly processed foods, and a third of families also reported an increase in their consumption of snack foods and desserts.[65] In a longitudinal study of 41 obese youth in Italy, the intake of food items linked to obesity, such as potato chips, red meat and sugary drinks had increased significantly while time spent in sports activities had decreased during the first 3 weeks of the national lockdown.[66] The wide disruption in the diet and activities of children due to lockdown policies has the potential of worsening the ongoing obesity epidemic, which in turn places children at greater risk for COVID-19 infection.[67]

Chronic Respiratory Disease

As COVID-19 is primarily as respiratory illness, asthma and other respiratory conditions were initially thought to place children at higher risk for more severe symptoms. However, there are conflicting data about the risk of COVID-19 in children with chronic respiratory illnesses. A study looking exclusively at COVID-19 patients receiving ICU care[42] did not show a significantly higher proportion of asthmatics than studies looking at all hospitalized children.[57] Underlying respiratory conditions were present in only 4.3% (21/491) of those requiring general care, while 10.4% (12/115) of those requiring ICU care reported the same.[36] In a study of COVID-19 pediatric cases in Mexico, asthma was reported in 3.8% (806) of all cases, but was not associated with increased severity of infection; those reporting asthma were not more likely to develop pneumonia, nor were they at higher risk for hospitalization.[64] Surprisingly, there was a much lower prevalence of asthma in their pediatric COVID-19 cohort than in the general population (2% vs. 11%) in Italy.[68] Researchers postulated the potential for asthma to act as a protectant due to adaptation in the immune response of pediatric asthmatics.[68]

Immune System Compromise

Immunocompromised comorbidities include organ transplants, malignancies, and aplastic anemia (**Table 5**). Notably, some studies used immunocompromised and immunodeficient interchangeably.[43] Individuals using immunosuppressants and those receiving chemotherapy and/or radiation are all considered to be immunosuppressed.

Available data concerning the risk of COVID-19 in patients with immunodeficiencies and/or immunosuppression are contradictory. In a study of 91 pediatric cases in South Korea, none reported an existing immunodeficiency.[4] These 91 cases account for 76.5% of all pediatric cases in the country, excluding a cluster outbreak within a religious community.[4] In Spain, 8/51 (15%) of the total pediatric COVID-19 cases for the month were immunocompromised.[69] Only

8.1% (53/599) of pediatric cases in the UK reported use of immunosuppressants prior to being hospitalized for COVID-19.[36] There was no association between immunosuppressant use and critical care admission.[36] In Mexico, immunodeficiencies were reported in 3.8% (808) of all cases and were associated with a 4-fold increase of COVID-19 pneumonia and 8-fold increase in the risk of hospital admission.[64]

Viral Co-Infections

In a retrospective study from China, researchers reported that 47.06% (16/34) of COVID-19-positive pediatric patients were infected with additional respiratory pathogens, including *Mycoplasma pneumoniae*, influenza type A and B, and respiratory syncytial virus (RSV).[70] In another study from China, 10 pediatric patients were extensively evaluated and all were negative for both common viruses (RSV, influenza, etc.) and SARS-CoV and MERS-CoV.[7] In Italy, 5.9% (10/168) of study participants had co-infections,[38] while in Perú, *M. pneumoniae* was found in 10% (9/91) of participants.[39] In Latin America, 3.4% (14/409) of participants tested positive for a viral co-infection, although no significant association was found between co-infections and ICU admission or mechanical respiratory support.[60] In contrast, in Europe, 5% (29/582) of participants tested positive for a viral co-infection and patients with one or more viral co-infections were more likely to have signs or symptoms of upper or lower respiratory tract infection at presentation.[43] Individuals with viral co-infection were also significantly more likely to require ICU admission, respiratory support, and vasoactive medications.[43]

Overall, there is still limited data regarding the presence of viral coinfections within the COVID-19-positive pediatric population. There is also limited evidence regarding the influence of these coinfections in either increasing a patient's susceptibility to COVID-19 or in contributing to a more severe course of disease in those who are infected. With expected peaks

of additional respiratory pathogens like influenza and respiratory syncytial virus during the coming winter season, we will likely experience the true impact of multi-viral respiratory infections in the context of COVID-19 in terms of both incidence and clinical severity.

Summary

Preliminary findings are generally optimistic respecting incidence and severity of SARS-CoV-2 infection in the pediatric population. Children do not appear to be the primary source of transmission within either the household or school environments, and are most likely to contract the virus from an adult household member. As SARS-CoV-2 transmission through breastmilk is unlikely, the current recommendation for mothers with suspected or confirmed COVID-19 is to initiate or continue breastfeeding while following guidance on hygiene and mask use. Findings on perinatal transmission are inconclusive, and further studies of the pregnancy outcomes and post-natal fetal development of infants of COVID-positive women are warranted.

The large proportion of cases studied thus far have shown that children often have a mild or asymptomatic presentation. While rare, there are hundreds of children in the US that have met case definition for MIS-C.[57] Despite the potential for catastrophic outcomes, the WHO, the CDC, and the Royal College of Paediatrics and Child Health have all provided formal diagnostic criteria for MIS-C,[51, 53, 54] allowing for an overall positive prognosis for those children who are diagnosed.[57] In addition, mortality rates remain low.[36, 44, 52, 57] Findings on chronic respiratory illnesses, compromised immunity, and viral co-infections as risk factors for COVID-19 in children are inconclusive, but comorbidities such as obesity are associated with a higher risk of infection and a more severe clinical course of disease.[37, 62-64]

The lower incidence and severity of SARS-CoV-2 infections in children should not allow our focus to shift away from a highly vulnerable population with potential developmental implications. The novelty of COVID-19 has presented many challenges, but there are also unique opportunities to study longitudinally children that have been affected from infancy through childhood and into adulthood. Continued testing and longer-term investigations are warranted to provide data on risk factors for infection and MIS-C, long-term respiratory and developmental outcomes, as well as behavioral and lifestyle influences. Indeed, such knowledge may assist in framing public policy responses that would protect children and mitigate future epidemics.

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