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Editorial: Long-Term Effects of Symptomatic and Asymptomatic SARS-CoV-2 Infection in Children and the Changing Pathogenesis of Common Childhood Viruses Driven by the COVID-19 Pandemic

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Abstract The range of long-term clinical conditions following SARS-CoV-2 infection in adults is now recognized. However, the prevalence, presentation, and risk factors for long COVID, or post-COVID-19, in children are less well understood because there have been few follow-up studies or long-term clinical trials in children with COVID-19. However, recent studies have shown that children with mild or asymptomatic COVID-19 may develop long-term sequelae that include cough, fatigue, and lethargy. The incidence and severity of common childhood respiratory viruses have changed in the past year, including respiratory syncytial virus (RSV). Hepatitis of unknown cause in children with SARS-CoV-2 infection is increasingly reported. Although both a viral cause and an autoimmune cause have been proposed, adenovirus type 41 infection is of current interest. These findings support immunization programs for SARS-CoV-2 in children, and infection surveillance and monitoring of the changing patterns and severity of other pediatric viral infections, including adenovirus type 41 and RSV, to develop and administer effective vaccines. This Editorial aims to highlight what is currently known of the long-term effects of symptomatic and asymptomatic SARS-CoV-2 infection in children and the changing epidemiology and pathogenesis of previously common childhood viral infections now driven by the COVID-19 pandemic.

Keywords: COVID-19 • SARS-CoV-2 • Pediatric • Adenovirus • Respiratory Syncytial Virus • Editorial

The range of long-term clinical conditions following SARS-CoV-2 infection in adults, and their pathogenesis, are now increasingly recognized [1,2]. Long COVID in adults involves the respiratory, cardiovascular, and neurological systems [1,2]. However, in children, the prevalence, presentation, and risk factors for long COVID or post-COVID-19 conditions are less well understood [3]. SARS-CoV-2 infection in children and young adults is assumed to be less severe, but few follow-up studies have been undertaken [3]. Few clinical trials have involved children with a history of COVID-19 [3]. Importantly, changing patterns in the epidemiology and pathogenesis of other viral infections in children are increasingly recognized due to the COVID-19 pandemic [3,4].

Following lockdown and absence from school and social events during the beginning of the COVID-19 pandemic, children experienced fewer common childhood infections [4]. The pathogenesis of common childhood respiratory viruses, such as a respiratory syncytial virus (RSV), has changed during the past year [4]. RSV is a significant cause of lower respiratory tract infection that can result in infant hospitalization, which also affects older adults. In temperate regions, infections with RSV peak in the winter months [4]. In the US, the incidence

of childhood infection with RSV is monitored by the Centers for Disease Control and Prevention (CDC) [4,5]. Until March 2021, RSV activity remained low to normal [4,5]. However, since March 2021, infections from RSV reported to the National Respiratory and Enteric Virus Surveillance System (NREVSS) have increased [5,6]. Also, an unusual wave of RSV infection occurred in the spring and summer of 2021 and 2022 [5,6]. The NREVSS is a nationwide laboratory-based surveillance network that has begun to advise clinicians and healthcare providers on increasing RSV vaccination rates [6].

Acute hepatitis is now recognized as a presenting symptom of SARS-CoV-2 infection in children and may be present without respiratory symptoms [7]. Hepatitis of unknown cause in children with SARS-CoV-2 infection can occur in clusters, and a viral cause or an autoimmune cause has been proposed [7,8]. Hepatitis A, B, and C infections have not been identified, but adenovirus has been identified in some cases [7,8]. Because the reported cases of hepatitis of unknown cause are not associated with SARS-CoV-2 vaccination, this condition does not appear to be a vaccine-associated adverse event [7]. The CDC and the National Center for Immunization and Respiratory Disease

(NCIRD) are currently working with health departments in the US to identify children with hepatitis of unknown cause [9]. Investigators are examining a possible association with adenovirus type 41 infection [9]. The US CDC now recommends adenovirus testing and typing in children with hepatitis [9]. Testing can be performed on upper respiratory tract samples, blood, or archival liver biopsy tissue using a nucleic acid amplification test (NAAT) or reverse transcription-polymerase chain reaction (RT-PCR) [9].

Studies have shown that children with mild or asymptomatic COVID-19 may develop long-term sequelae [10]. In 2021, a study from a tertiary pediatric center in Melbourne, Australia, reported the medium-term clinical outcomes at 3-6 months after diagnosis in children aged ≤ 18 years with COVID-19 [10]. The study included 171 children from 137 households [10]. Data were collected on medical history and post-acute COVID-19 symptoms, including dyspnea, rash, fatigue, and abdominal pain [10]. The study included 171 children from 137 households, with 80% of children diagnosed between July and August 2020 [10]. The median age was 3 years (IQR 1-8), 53% were boys, most children (58%) had mild COVID-19, and 36% were asymptomatic, with 5% having moderate clinical symptoms [10]. Fourteen children (8%) were briefly admitted to hospital [10]. Follow-up data at 3-6 months were available for 151 (88%) of 171 children, with 12 (8%) of children with post-acute COVID-19 symptoms, including mild post-viral cough in 4%, fatigue in 2%, or both post-viral cough and fatigue in 1% [10]. The duration of post-viral cough ranged from between 3-8 weeks, and post-viral fatigue ranged from 6-8 weeks from symptom onset [10].

On July 22, 2022, the findings from a prospective cohort study from 36 emergency departments in eight countries that included children who were positive for SARS-CoV-2 infection and underwent a 90-day follow-up were reported [11]. The study was conducted between March 2020 and January 2021, with the study population frequency matched by country, hospitalization status, and recruitment date with controls who were negative for SARS-CoV-2 [11]. Post-COVID-19 conditions were identified as any new, persistent, or recurrent health conditions

reported during the 90-day follow-up [11]. The findings from this prospective study showed that of 2,368 children who were SARS-CoV-2 positive, 2,365 (99.9%) had index emergency department data available, and 1,884 children (79.7%) completed the 9-month follow-up [11]. The median age of the study population was 3 years (IQR, 0-10 years), and 994 (52.8%) were male children [11]. There were 110 SARS-CoV-2-positive children who reported long COVID symptoms (5.8%; 95% CI, 4.8-7.0%) [11]. Also, 44 of 447 children were hospitalized during the acute illness (9.8%; 95% CI, 7.4-13.0%), and 66 of 1437 children were not hospitalized (4.6%; 95% CI, 3.6-5.8%) [11]. The most common symptoms during the 9-month follow-up among the SARS-CoV-2-positive children were fatigue or weakness in 21 cases (1.1%) [11]. Factors associated with at least one episode of long COVID in children during 90 days following hospital admission, who were SARS-CoV-2 positive, included: being hospitalized for 48 hours or more (95% CI, 1.63-4.38%); having four or more symptoms present on initial hospital admission, when compared with fewer symptoms [95% CI, 2.50-8.44]; and an age of 14 years compared with age < 1 year (95% CI, 1.43-4.99%) [11]. At 90-day follow-up, 5.8% of patients, including 9.8% of hospitalized children and 4.6% of discharged children, reported long COVID symptoms. Characteristics associated with long COVID in children included being hospitalized 48 hours or more, having four or more symptoms reported at the index emergency department visit, and being 14 years of age or older [11].

Conclusions

Recent clinical and epidemiological studies support that appropriate clinical guidance and clinical follow-up are required for children who test positive for SARS-CoV-2, particularly when infection requires hospitalization. The long-term clinical consequences of pediatric SARS-CoV-2 infection support immunization programs for SARS-CoV-2 in children. Infection surveillance and monitoring of the changing patterns and severity of other pediatric viral infections, including adenovirus type 41 and RSV, are required to develop and administer effective vaccines.

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