The Challenge of Studying Long COVID: An Updated Review

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Abstract: Accurately determining the risk of long COVID is challenging. Existing studies in children and adolescents have considerable limitations and distinguishing long-term SARS-CoV-2 infection-associated symptoms from pandemic-related symptoms is difficult. Over half of individuals in this age group, irrespective of COVID-19, report physical and psychologic symptoms, highlighting the impact of the pandemic. More robust data is needed to inform policy decisions.

Keywords: SARS-CoV-2, coronavirus, persistent, post COVID, neurologic mental, fatigue, headache

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The majority of children with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have asymptomatic or mild disease.[1] The long-term effects of the infection might therefore have greater weight in coronavirus disease 2019 (COVID-19) vaccination and other policy decisions in this age group. We recently reported that the frequency of persistent symptoms after COVID-19 in children and adolescents is uncertain.[2,3] Almost all of the studies on 'long COVID' in this age group have considerable limitations, for example, the inclusion of children without confirmed SARS-CoV-2 infection and a lack of appropriate control groups.[3,4] As the number of published studies on this topic has doubled, we reassessed the current evidence on long COVID in children and adolescents.

We identified 27 studies (13 cross-sectional studies,[5–17] 9 prospective cohort studies,[18–26] 4 case series[27–30] and 1 retrospective cohort study[31]) investigating persistent symptoms in a total of 34,664 SARS-CoV-2-infected and 38,988 uninfected children and adolescents. The number of children in each study varied from 5 to 30,117 [median 105, interquartile range (IQR) 30–859]. The study findings are detailed in the Table, Supplemental Digital Content, http://links.lww.com/INF/E684. Studies which followed children after a SARS-CoV-2 infection but did not evaluate symptoms of long COVID,[32–34] did not evaluate more than 1 symptom[35] and those which did not report separate results for children and adolescents[36–39] were not included.

Nine of the 27 studies included an uninfected control group.[5–8,18–22] Six studies compared the proportion of children and adolescents with persistent symptoms in those with and without evidence of prior SARS-CoV-2 infection.[5,8,19–22] The difference in proportions varied between Please replace by -0.5% and 13.2% (median 3.0%, IQR 1.4%-3.6%) (Fig. 1). In all but one study,[22] the difference was less than 4%. The study which reported a difference of 13.2% had a response rate of only 13.4% and therefore a major risk of sampling bias. A further study reported a difference of 45.2% in persistent symptoms when comparing children after SARS-CoV-2 infection with those after other respiratory infections.[7] However, it is likely that a large part of this difference is attributable to the considerable difference in age between the two groups (median of 10 vs. 2 years). Two studies did not report the proportion of children affected by long COVID symptoms in the control group.[6,18]

Although many studies included a control group, they all had other deficiencies meaning their results need to be viewed with caution. Many had low response rates or differences in response and inclusion rates between children with and without SARS-CoV-2 infection (Table, Supplemental Digital Content 1, http://links.lww.com/INF/E684).

The 11 studies which investigated persisting symptoms after SARS-CoV-2 infection without control groups reported prevalences of long COVID symptoms between 7.9% and 58.1% (median 27.1%, IQR 12.5%–41.4%).[9,13–15,17,23–26,30,31] However, many of these studies included children without laboratory-confirmed infections, studied children at arbitrary time points, relied on self- or parent-reported symptoms without clinical assessment and objective parameters or varied in the proportion of children with preexisting medical conditions.

The large variation in results from studies underlines how difficult it is to accurately determine the risk of long COVID. In addition to the lack of a clear case definition, it is impossible to blind participants to whether they have been infected with SARS-CoV-2 or not. Another unavoidable limitation includes the possibility that the uninfected control group is contaminated by children who have been infected with SARS-CoV-2 but who were not tested or who did not seroconvert.[40] Further, studies that evaluate a single time point might miss transitory or intermittent symptoms of long COVID. Finally, the range and the number of symptoms sought in studies vary considerably and some studies have been criticized for evaluating certain key symptoms.

In future studies, it is important to collect age-aggregated data, as the incidence and characteristics of long COVID will be different in young children and adolescents. Moreover, more studies are needed to investigate the association between the initial severity of COVID-19 and the number and duration of persistent symptoms. Additionally, other risk factors for long COVID should be identified. It is also important to unravel the mechanisms underlying persistent symptoms after COVID-19 and to identify similarities to and differences from other postviral syndromes. This will help find treatment options and define the role of vaccination in the prevention of long COVID.

The fact that nearly all symptoms reported by children and adolescents infected with SARS-CoV-2 are also reported in similar frequencies in those without evidence of infection highlights that one of the major challenges remains to distinguish long-term SARS-CoV-2 infection-associated symptoms from pandemic-related symptoms. It is worrisome that more than half of children and adolescents, even when they have not had COVID-19, report physical and psychologic symptoms, highlighting how much children and adolescents have suffered from the pandemic.

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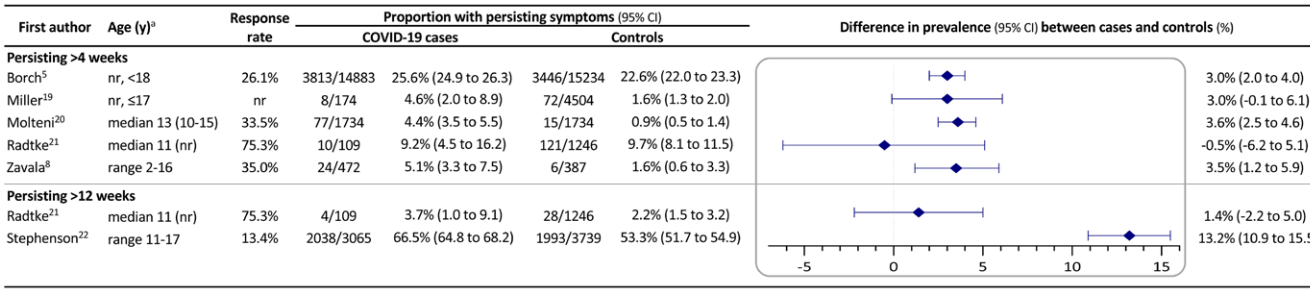

[a] mean (SD), median (interquartile range), or range; CI: confidence interval; nr: not reported.

FIGURE 1. Prevalence of persistent symptoms after COVID-19 in children and adolescents and in non-COVID-19 controls. full color online

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Current Abstracts

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Typhoid Fever in the US Pediatric Population, 1999-2015: Opportunities for Improvement

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Typhoid fever is caused by *Salmonella enterica* serotype Typhi (Typhi) and transmitted via the fecal-oral route. An estimated 10.9 million cases occur globally each year, causing approximately 117,000 deaths, primarily among populations with limited access to safe water and sanitation. Children are especially susceptible to infection, particularly in endemic settings. Despite the significant illness burden, with prompt appropriate antimicrobial therapy, mortality rates have declined from 10-20% to below 1%. Approximately 300 culture-confirmed cases of typhoid fever are reported to the Centers for Disease Control and Prevention (CDC) each year, although an estimated 5,750 cases occur. Most cases occur in persons who had not received typhoid vaccination and who traveled internationally within 30 days of illness onset. The CDC recommends typhoid vaccination for travelers to 167 countries or territories with recognized exposure risks.

Two typhoid vaccines are available in the United States, a parenteral Vi capsular polysaccharide vaccine (ViCPS) and an oral live attenuated vaccine (Ty21a). Both are 50-80% effective, ViCPS is not licensed for use in children younger than 2 years, and the Ty21a vaccine is not licensed for children younger than 6 years old. Newer typhoid conjugate vaccines (TCVs), which combine the ViCPS with a protein carrier, have demonstrated higher efficacy (82.0-91.5%) and induce a robust immune response in young children. In October 2017, the World Health Organization (WHO) Strategic Advisory Group of Experts on Immunization updated recommendations to introduce TCV as a single dose for infants and children 6 months of age or older in endemic countries. To explore the implications of updated vaccination strategies targeting younger at-risk children in the United States, the epidemiologic, clinical, and antimicrobial resistance (AMR) characteristics of pediatric typhoid fever infections diagnosed in the United States are presented.

During 1999-2015, 5,390 typhoid fever cases were reported to CDC's National Typhoid and Paratyphoid Fever Surveillance (NTPFS). Four duplicate reports were removed and 255 cases did not meet the case definition, leaving 5,131 (95.2%) cases. Of these, 1,992 (38.8%) occurred in persons younger than 18 years old, including 210 in those 6-23 months old. The overall proportion of cases younger than 18 years was stable over time. California reported the most pediatric cases (n=363), followed by New York (n=340) and New Jersey (n=175). Pediatric cases were more likely to be U.S. citizens (79.5% vs 53.4%, $P < .001$) than adults. Among the 1,941 (97.4%) of 1,992 pediatric persons with available travel history data, 1,616 (83.3%) of 1,941 reported international travel or living outside the United States within 30 days of illness onset. Eighty-one per cent were hospitalized and none died. Most, 1,435 (88.8%) of 1,616, pediatric travel-associated cases were vaccine-eligible. Travel to Asia represented 84.5% (1,365/ 1,616) of all pediatric single-continent travel destinations.

During the study interval, 5,243 Typhi isolates were tested by CDC's National Antimicrobial Resistance Monitoring System (NARMS). Patient age was available for 5,004 (95%) isolates; 2,003 were pediatric cases. Isolates from children were less likely to be fully susceptible to relevant antimicrobials compared with those from adults. No isolates from pediatric cases were resistant to azithromycin or ceftriaxone. Isolates from pediatric patients with known travel to Asia only were more likely to be fluoroquinolone-non-susceptible than isolates from patients who traveled to other continents (727 (79.3%) of 917 vs 5 (4.8%) of 125. Fluoroquinolone-non-susceptibility was common among those reporting travel to South Asia, including India (465 (89.3%) of 521), Bangladesh (139 (82.7%) of 168), and Pakistan (98 (62.0%) of 158).

Comment: In the U.S., given the clustering of imported cases among children traveling to and from South Asia, parts of Africa, and Latin America, TCVs should be made available within the traveler vaccination strategies in addition to reinforcement of other stringent preventive measures and advice. Investment in safe water and foods as well as personal hygiene have played an important role in the control of typhoid, and it is imperative that future strategies for typhoid control and mitigation of the spread of antimicrobial-resistant strains of the pathogen include all potential public health control measures including the use of effective vaccines (Bhutta ZA. *Clin Infect Dis* 2021; 73:e4590-1).