



COVID-19 in children and the importance of COVID-19 vaccination

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As of August 30, 2021, COVID-19 has caused more than 216 million infections and 4.49 million deaths worldwide, with 0.58 million new cases [1]. Because the COVID-19 vaccine is distributed gradually and widely, the development of the global epidemic has been prevented to some extent, but the emergence of SARS-CoV-2 variants makes us worried. The alpha (B.1.1.7), beta (B.1.351), gamma (P.1) and delta (B.1.617) strains have been named variants of concern by the WHO [2]. The SARS-CoV-2 variants have increased in transmissibility and virulence, leading to higher morbidity and mortality. The delta variant has spread to at least 148 countries, territories and areas, as of August 2021, becoming the mainstream virus variant in the world [3]. Compared with the elderly, people with chronic diseases, and health care providers, children are seen as a low-priority age group for vaccination, making them become the largest unvaccinated population currently. We aimed to review the latest epidemiological evidence, and elucidate the importance of COVID-19 vaccination for children.

Epidemiological burden of COVID-19 in children

Increasing cases and incidence

Although few pediatric cases were reported initially during the COVID-19 pandemic, retrospective data demonstrate that children were indeed infected early on [4, 5]. In general, children with COVID-19 are asymptomatic or have mild to moderate symptoms and less likely to be tested. Therefore, relying on hospitalization or testing rates alone underestimates the true disease burden [6, 7]. Li et al. found that the

SARS-CoV-2 infection rate of children at the early stage of the epidemic in Wuhan was 2.4%–3.1%, with the overall infection rate of 4.4% [8]. Subsequent studies have shown consistently that children and adolescents are as likely to be infected as the adult population [9–11].

As of August 26, 2021, about 4.80 million children aged < 18 years were confirmed as COVID-19 in the United States, comprising more than 14% of all laboratory-confirmed COVID-19 cases. In the United States, more than 200,000 child COVID-19 cases were reported from August 19 to August 26, 2021, which was a continuing substantial increase than before [12]. Since the start of the vaccination roll-out in European Union or the European Economic Area (EU/EEA) countries, children have made up an increasing proportion of weekly case numbers with the most noticeable increase among those aged 5–11 years [13]. In addition, the round 13 of the Real-time Assessment of Community Transmission-1 (REACT-1) study in England reported that the average prevalence during 24 June–5 July 2021 was 0.59%, which was about four-fold higher compared with round 12 at 0.15%, and especially for younger ages. The highest prevalence was for those aged 13–17 years at 1.33% and increased by eight folds. Also, the prevalence was more than three times higher in the unvaccinated compared with those reporting receipt of two doses of vaccine [14].

Increasing hospitalization rate and cases

With the increasing cases and incidence, there are more children experiencing severe disease and requiring hospitalization, and some children even require admission to intensive care units or use of invasive mechanical ventilation. As of 26 August 2021, children aged < 18 years comprised 2.3% (19,082/812,130) of all COVID-19-associated hospitalizations in the United States [12]. From June to August in 2021, the number and rate of hospitalization in the United States have continued to rise, even exceeding the peak of the epidemic in January. According to the COVID Data Tracker conducted by US, the new admissions of children has reached 0.46 per 100,000 population on August

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27, an increase of more than four times than two months ago, with 338 new admissions on 7-day average [15]. Data from COVID-NET of US showed that [16] the weekly hospitalization rates for children under 5 and 5–17 years of age increased from 0.3 and 0.3 per 100,000 in June to 1.8 and 1.1 per 100,000 in August, respectively. Preston et al. found that nearly one-third of hospitalized pediatric patients with COVID-19 experienced severe COVID-19 and that 0.7% used invasive mechanical ventilation [17]. In England there were 6338 hospital admissions and 259 PICU admissions among children and young people with COVID-19 during the first pandemic year [18].

Half of pediatric hospitalizations with COVID-19 have at least one underlying medical condition [19]. Risk factors for severe COVID-19 cases in children included being younger than 1 year of age or having an underlying medical condition, such as congenital heart disease, asthma, obesity, diabetes, neurologic conditions, anxiety and fear-related disorders, and depressive disorders. Type 1 diabetes, obesity, and cardiac and circulatory congenital anomalies were the higher risk factors for hospitalization [18–21]. Nevertheless, children with severe COVID-19 are at risk for developing multisystem inflammatory syndrome in children (MIS-C), while the UK refer to it as pediatric inflammatory multi-system syndrome temporally associated with SARS-CoV-2 (PIMS-TS). MIS-C is typically a progressive illness, and patients can develop severe illness with multisystem organ involvement, including the gastrointestinal, cardiovascular, hematologic, mucocutaneous, and respiratory systems. Most patients had elevations in biomarkers indicating inflammation. Approximately two-thirds of patients in the US with MIS-C required admission to intensive care [22–24].

Deaths related to COVID-19 in children

While COVID-19 deaths in children are rare, they do occur. As of August 30, 2021, there have been 496 deaths among US children with COVID-19, much more than seen with influenza, and 37 deaths among 4404 children with MIS-C before July 25, 2021 [25, 26]. Deaths related to COVID-19 and MIS-C mainly occur in Hispanic or Non-Hispanic Black populations, and in males. During the first pandemic year, 25 children and young people in England died of SARS-CoV-2, including 22 with acute COVID-19 and three with PIMS-TS [27]. The European Centre for Disease Prevention and Control reported that among the 746,000 COVID-19 cases, 3998 were hospitalized and 48 died [13].

Indirect impact of COVID-19 on child health

Beyond morbidity and mortality, the COVID-19 pandemic carries unfavorable impacts on children and adolescents. For example, health care service and routine immunizations

programs were disrupted, and education was interrupted by school closures [28]. Causey et al. estimated that 30.0 million children missed doses of DTP3 (third-dose diphtheria-tetanus-pertussis vaccine) and 27.2 million children missed doses of MCV1 (first-dose measles-containing vaccine) due to the COVID-19 pandemic in 2020 globally [29]. In addition, the impact on the mental health of children and adolescents has increased, including anxiety, depression and disturbances in sleep and appetite [30]. In a global meta-analysis, the prevalence estimates of children and adolescent depression and anxiety were 25.2% and 20.5% during COVID-19, respectively [31]. Compared with pre-pandemic estimates, the prevalence of depression and anxiety symptoms during COVID-19 have doubled. School closures, isolation measures, increased family pressure, and decreased peer interactions are all potential adverse effects on the mental health of children and adolescents [32, 33]. Furthermore, orphanhood and caregiver deaths have been a hidden consequence of the pandemic owing to COVID-19-associated deaths. Globally, from March 1, 2020, to April 30, 2021, 1.56 million children are estimated to have experienced the death of caregivers [34]. Such children often face poverty, abuse, and institutionalization and have higher risks of experiencing mental health problems.

Role of children in SARS-CoV-2 transmission

Children could be important transmitters of SARS-CoV-2. Generally, children are less capable of controlling their respiratory secretions and maintaining social distance. A sick young child needs more care from parents and caregivers, which obviously will come with an increased risk of transmission to other family members. In addition, the detection of viral RNA in the feces and the prolonged fecal viral RNA shedding time among pediatrics increase the possibility of SARS-CoV-2 fecal–oral transmission [35, 36]. These transmission pathways may provide frequent and easy opportunities for viral transmission. Several studies of SARS-CoV-2 transmissibility have reported that viral loads in children are similar or higher than those in adults [37–39]. A study in Norway showed that young children and parents transmit the SARS-CoV-2 to the same extent within the family [40]. When the index case was a child aged 0–6 years, the secondary attack rates (24%) were higher than those of the index case for adolescents aged 13–16 years (14%) and 17–20 years (11%). Similarly, studies in Canada and Denmark have consistently found that younger children may have greater risk of transmitting SARS-CoV-2 to caregivers and siblings in the household than older children [38, 41].

Although SARS-CoV-2 transmission in school settings is not the primary determinant of community transmission, in a US population-based time series analysis [42], school

closure was associated with a significant decline in both incidence and mortality of COVID-19. Li et al. found that reopening schools was associated with increases in transmission [43]. Moreover, cases of children testing positive for SARS-CoV-2 have risen following the reopening of schools [44, 45]. In the 1 month ending 18 June, 2021, 181 SARS-CoV-2 outbreaks were confirmed in the UK related to primary and secondary schools [13]. Within the first two weeks of the new school year in the fall of 2021, at least 380,000 US children infected with SARS-CoV-2, which is more than twice than before [12]. Investigations of German childcare center outbreaks suggest that, both susceptibility and infectiousness of children aged between 1 and 6 years are substantially higher [10]. As the largest unvaccinated population, more SARS-CoV-2 transmission are expected to occur in children.

Safety and effectiveness of COVID-19 vaccine in children

It is reported that vaccines tested in young people over the age of 12 are safe and effective, including mRNA vaccines made by Moderna and Pfizer-BioNTech [46, 47]. The results of phase 1/2 clinical trial of two Chinese inactivated vaccines made by Sinovac and Sinopharm showed that vaccines were well tolerated and safe and induced humoral responses in children and adolescents aged 3–17 years [48, 49]. Several countries, including China, United States, Canada, Israel, and much of Europe and south Asia, are currently vaccinating over the age of 12 [50, 51]. China has authorized the emergency use of vaccine to extend the age to over 3 years old. To date, China has vaccinated more than 60 million children under the age of 18. In the US, at least one dose of vaccine has been administered to more than 11 million under 18 years of age, including 6.8 million aged 12–15 years [52]. Children under the age of 12 are the following population who need a safe and efficient COVID-19 vaccine; however, trials of Pfizer-BioNTech and Moderna vaccines in this age group are still in progress.

Owing to children's distinct immunogenicity profile and development stage, surveillance for COVID-19 vaccine safety among children should be conducted and maintained for longer periods than adults. By April 2021, a total of 31,434 cases reported adverse reactions in China, with an incidence of 11.86/100,000 doses, of which mild reactions accounted for 83%. The incidence of adverse reactions to COVID-19 vaccine of children and adolescents was not higher than that of adults [53]. Among the 8.9 million U.S. adolescents vaccinated with Pfizer-BioNTech, 9246 vaccine adverse events were reported, of which 90.7% were non-serious adverse events and 9.3% were serious adverse events

(including myocarditis) [54]. After reviewing the available evidence, cases of vaccine-attributable myocarditis in young people have been extremely rare, and the events are typically mild. These cases have recovered with no or minimal treatment [51, 55].

Summary

Compared to the pre-variants period of the epidemic, children currently account for a higher proportion of COVID-19 cases and a higher hospitalization rate. Considering that variants of concern show increased transmissibility, children, being the largest unvaccinated population, may be more likely to transmit and result in more COVID-19 cases in the future. Vaccination has benefits in terms of reduced community transmission and will help achieve herd immunity, which could considerably reduce morbidity, mortality, and pressure on health systems. It is also possible that it will help protect them from new variants. Furthermore, the available evidence confirms that the COVID-19 vaccines are safe and effective for children. Taking all these considerations into account, we should promote the vaccination against COVID-19 in children.

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Compliance with ethical standards

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