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## Review

# A systematic review of current status and challenges of vaccinating children against SARS-CoV-2



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## ABSTRACT

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has inflicted immense damage to countries, economies and societies worldwide. Authorized COVID-19 vaccines based on different platforms have been widely inoculated in adults, showing up to 100% immunogenicity with significant efficacy in preventing SARS-CoV-2 infections and the occurrence of severe COVID-19. It has also greatly slowed the evolution of SARS-CoV-2 variants, as shown in clinical trials and real-world evidence. However, the total dosage of COVID-19 vaccines for children is much smaller than that for adults due to limitations from parental concern of vaccine safety, presenting a potential obstacle in ending the COVID-19 pandemic. SARS-CoV-2 not only increases the risk of severe multisystem inflammatory syndrome (MIS-C) in children, but also negatively affects children's psychology and academics, indirectly hindering the maintenance and progress of normal social order. Therefore, this article examines the clinical manifestations of children infected with SARS-CoV-2, the status of vaccination against COVID-19 in children, vaccination-related adverse events, and the unique immune mechanisms of children. In particular, the necessity and challenges of vaccinating children against SARS-CoV-2 were highlighted from the perspectives of society and family. In summary, parental hesitancy is unnecessary as adverse events after COVID-19 vaccination have been proven to be infrequent, comprise of mild symptoms, and have a good prognosis.

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## 1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first emerged at the end of 2019, causing the coronavirus disease

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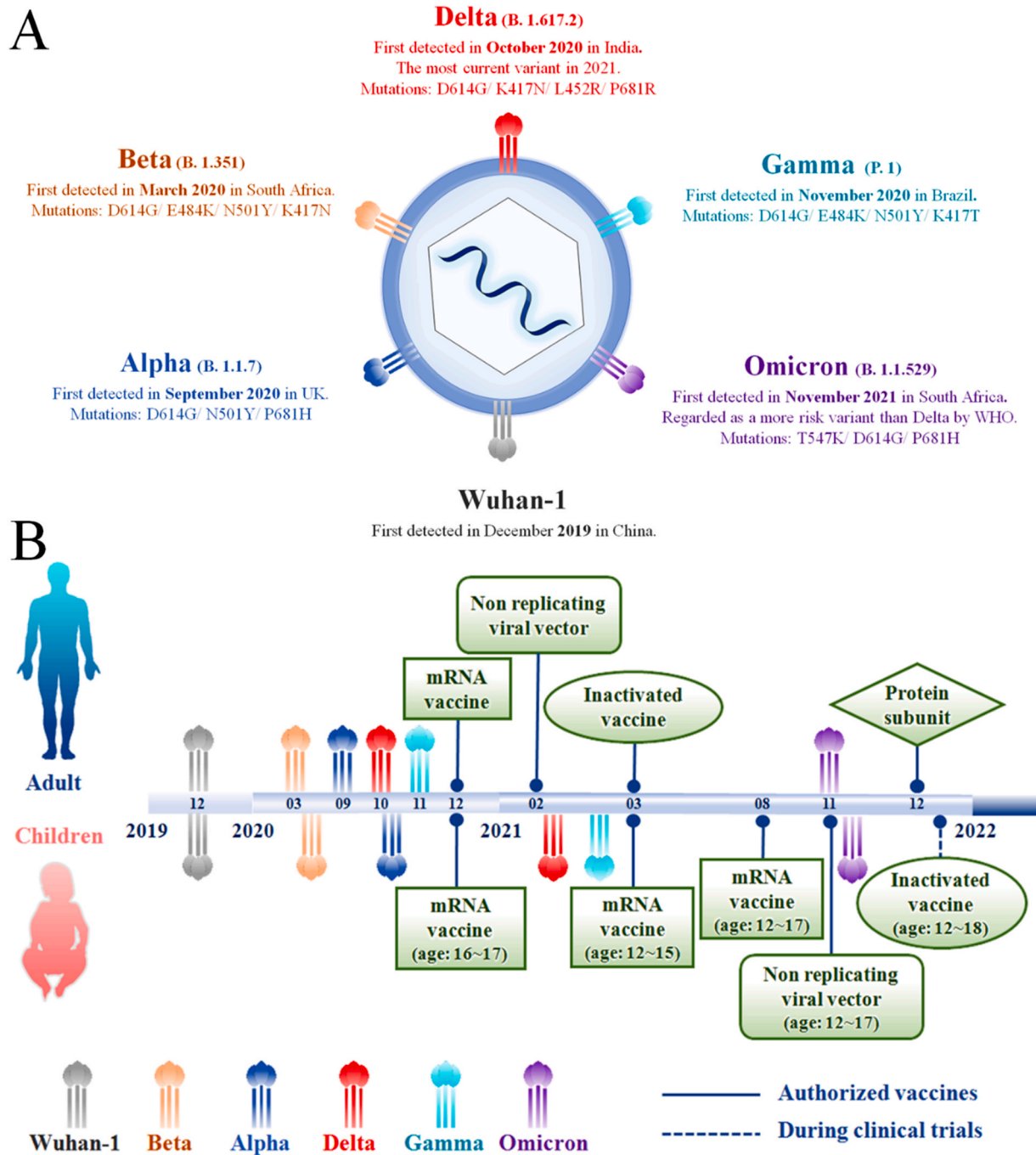


Fig. 1. (A) The current variants of SARS-CoV-2; (B) A timeline depicting the distinction of SARS-CoV-2 variants and vaccines between adults and children.

2019 (COVID-19) which has resulted in more than 406 million infected cases and nearly 5.8 million deaths worldwide as of February 10, 2022 [1–4]. Since the first outbreak of the COVID-19 pandemic, SARS-CoV-2 has evolved into thirteen variants from the original D614G lineage (Wuhan-1), including five variants of concern (VOCs) (Fig. 1A) and eight variants of interest (VOIs), namely Epsilon (B.1.427 and B.1.429), Zeta (P.2), Eta (B.1.525), Theta (P.3), Iota (B.1.526), Kappa (B.1.617.1), Lambda (C.37) and Mu (B.1.621) [5–8].

Successively, Wuhan-1, Beta (B.1.351), Delta (B.1.617.2), and Omicron (B.1.1.529) have led four waves of global pandemics, and have displayed increasing transmissibility and reduced sensitivity to immune mechanisms [9–16]. Therefore, the emergence of SARS-CoV-2 VOCs presents a challenge in controlling the spread of SARS-CoV-2 infection and in establishing immunity among the community.

Since the first wave of pandemic, a total of ten vaccines based on different platforms were authorized by the World Health

Organization (WHO) listed under emergency use listing (EUL), including protein subunit vaccines (Novavax, COVOVAX), RNA vaccines (Pfizer-BioNTech, Moderna), non-replicating viral vectors (Janssen, Oxford/AstraZeneca, Covishield), and inactivated vaccines (Covaxin, Covilo, CoronaVac). The vaccines listed under EUL provide the fundamental impetus for the control of COVID-19 epidemic [17–20]. Currently, 197 countries and regions have conducted widespread vaccinations, and the cumulative global dose has exceeded 10.32 billion doses, of which about 61.7% of the world population has received at least one dose (up to February 12, 2022) [21]. Vaccination against COVID-19 in adults showed considerable safety, high level of neutralizing antibody titers, and a strong immune effect against new variants of SARS-CoV-2, as shown by clinical trials and real-world evidence, such as achieving nearly 100% effectiveness in preventing the occurrence of severe cases and deaths [22–25]. Therefore, COVID-19 vaccines have played an important role in controlling the spread of COVID-19 in adults in practical application.

However, the vaccination rate of children was much lower than that of adults, which may be closely related to the hesitancy of parents [26,27]. The COVID-19 vaccine is worrying for some parents who have not vaccinated their children, and this concern stems from three main sources: (1) the lack of severe symptoms of COVID-19 in children [28–30]; (2) the adverse events after vaccination, such as fatigue, dizziness, injection pain and even myocarditis [31–36]; (3) insufficient clinical data on the efficacy of each vaccine [37]. In fact, this hesitancy of parents is unnecessary, because more than 65% of the side effects caused by the COVID-19 vaccine in children is relieved or ceases within 1–3 days [38–41]. Furthermore, clinical data proves that vaccines authorized for children have significantly shown strong efficacy in preventing infection and reducing the risk of morbidity of COVID-19 in children [42–45] [46–48]. In addition, the innate immunity of children is not strong enough to block the invasion of new SARS-CoV-2 variants, which may be a key reason for the increase in the infection rate of children during the third and fourth waves of the COVID-19 pandemic [49–53]. Therefore, as an integral aspect of the societal transmission of SARS-CoV-2, children should be vaccinated as soon as possible to prevent a wider and more severe COVID-19 pandemic.

Children infected with SARS-CoV-2 display a series of unique characteristics in symptomatology, epidemiology and immune response mechanism compared to adults. Thus, deriving a set of exclusive vaccination strategies for children is necessary. In addition to establishing a systematic review of the efficacy of existing COVID-19 vaccines for children, the clinical manifestations of children infected with SARS-CoV-2, the status of vaccination against COVID-19 in children, vaccination-related adverse events, and the unique immune mechanisms of children are discussed in this article. Furthermore, the necessity and challenges of vaccinating children against SARS-CoV-2 from a social perspective is reviewed in order to provide a direction towards prevention strategies and effective countermeasures for children in the global post-pandemic era.

## 2. The clinical manifestation of SARS-CoV-2 infected children

The incidence of COVID-19 in children is lower than that in adults, which is related to the lower expression of angiotensin converting enzyme-2 (ACE2) in children [51,54]. Pathophysiological analysis shows that ACE2, the primary target receptor for SARS-CoV-2, is less present in children and may be responsible for the low number of infections, mild symptoms, and low viral load in children

with COVID-19 [55–60]. However, children with stronger innate immunity than adults, are more susceptible to SARS-CoV-2-related severe multisystem inflammatory syndrome in children (MIS-C), an immune overexpression disease characterized by diarrhea, dizziness, arrhythmia and other multisystem symptoms [27,59,61–71]. Severe MIS-C increases the risk of hospitalization and is the most common cause of death among children with COVID-19 [65,72,73]. Thus, the severe consequences for children infected with SARS-CoV-2 cannot be underestimated.

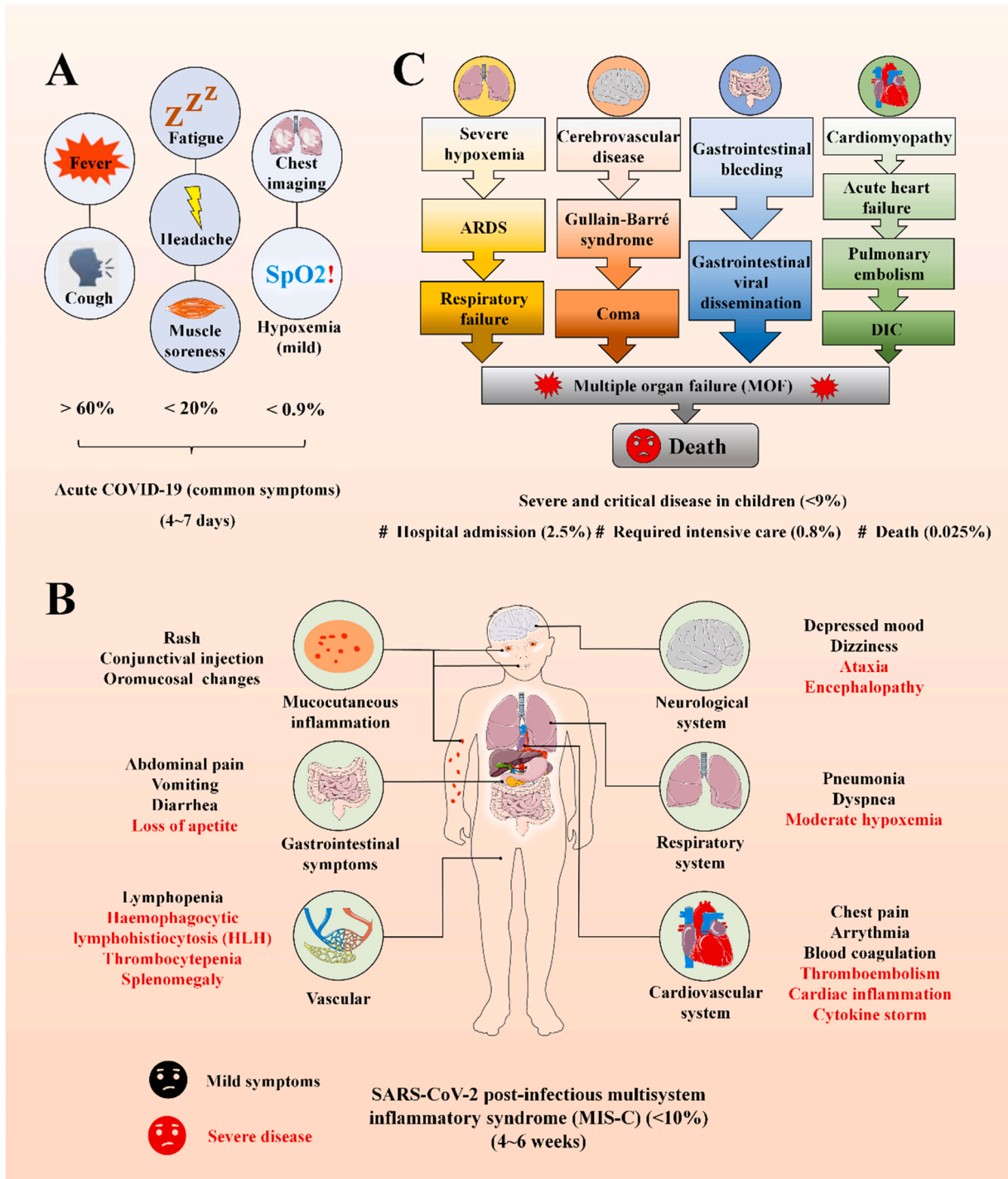
Anna Mania et al. (2021) evaluated clinical findings, laboratory parameters, and outcomes of a total of 332 children with COVID-19 who were split into three groups based on the severity of clinical symptoms, which includes mild to moderate COVID-19 (267 children), COVID-19 related pneumonia and those with oxygen therapy (OT) (60 children), and COVID-19 related pneumonia with intensive care required (ICU) (5 children) [74]. Combining the results of this study and observational studies in various countries, the infection of children with SARS-CoV-2 can be divided into three stages as follows (Fig. 2) [62,75]. Firstly, more than 80% of infections consisted of acute COVID-19 with mild or asymptomatic presentations, mainly occurring 4–6 days after infection, which indirectly suggests that the prevalence in children may be higher than reported (Fig. 2A) [76–78]. Secondly, less than 9% developed mild or moderate SARS-CoV-2 post-infectious MIS-C within 4–6 weeks of infection and inflammatory dysfunction of various degrees in multiple systems, such as mucocutaneous, gastrointestinal and cardiovascular, throughout the body (Fig. 2B) [72,79–82]. Thirdly, a small amount of patients with severe underlying diseases or moderate MIS-C without timely intervention, deteriorated and eventually progress to severe and critical disease, which included multiple organ failure (MOF) or death. Among all the above, about 2.5% were admitted to hospital, 0.8% required intensive care and the mortality rate was around 0.025% (Fig. 2C) [73,83–87].

## 3. Why children should be vaccinated against COVID-19?

With the frequent evolution of SARS-CoV-2, SARS-CoV-2 can also pose as an increasing threat to children. Vaccination, even with challenges including serious adverse events and uneven distribution of vaccines, is currently considered one of the most effective ways in mitigating the COVID-19 global pandemic. The need for children to be vaccinated against COVID-19 can be summarized as follows.

Firstly, the impact of SARS-CoV-2 on children is a key link in a series of chain reactions. Although children with COVID-19 have mild symptoms and low transmissibility, they are the nexus of SARS-CoV-2 transmission between families, schools and societies, with a ‘shadow pandemic’ on the economics and politics in adult society (Fig. 5A) [66,88–94]. The ‘shadow pandemic’ has spawned school closures and mandatory home isolation policies around the world. As a result, children are facing more psychological problems from schools and families than in previous years [95–105]. Therefore, children’s COVID-19 vaccine is related to the progress of the epidemic worldwide, so completion of children’s vaccination requires the participation of the global society.

Secondly, fully vaccinated populations have a greater advantage in controlling the incidence of COVID-19 over unvaccinated populations [45–48,106,107]. Children aged 3–17 years vaccinated with inactivated SARS-CoV-2 vaccine (CoronaVac) displayed low severity of post-vaccination adverse events and a high safety profile, supported by data from a phase 1/2 clinical trial [106] (Fig. 5B). Available



**Fig. 2.** (A) Schematic represent the acute COVID-19 (common symptoms) caused by SARS-CoV-2. (B) Schematic represent the multisystem inflammatory syndrome (MIS-C) caused by SARS-CoV-2. (C) Schematic represent the severe critical disease in children.

data indicates that the RNA vaccine (BNT162b2) is 95% immunogenic in 16–25 years old and 100% immunogenic in 12–15 years old, confirming the absolute superiority of RNA vaccines in preventing SARS-CoV-2 infection [48]. Other studies have shown that full

vaccination of two or three doses of RNA vaccine can significantly increase the level of neutralizing antibodies in the recipients, preventing the occurrence of a global pandemic amid the frequent emergence of new variants of SARS-CoV-2 both in adults and



**Table 1**  
Vaccination status of the current authorized COVID-19 vaccines for children (ages 0–17 years) around the world.

Platform types	Vaccine	Authorized events			Number of authorized countries	Ages indication for children (year)	Vaccine effectiveness in children (95% CI)	Booster dose	Ref
		Approval institution	Date	Approval institution					
mRNA Vaccines	mRNA-BNT162b2	*WHO EUL; *CRS EUR	12/ 31/ 2020		134	12–17 (WHO); 5–17 (CDC)	100% (immunogenicity) (USA, China, and South Africa)	FDA: administration of a third primary series dose for children aged over 12 years and immunocompromise individuals aged 5–11 years Intervals: at least 5 months Age: 18 years and older Intervals: 5 months	[48,110,112,140,148,149]
	Other names: Pfizer-BioNTech; COMIRNATY								
Viral vector	mRNA-1273	*WHO EUL; *CRS EUR	04/ 30/ 2021		85	12–17 (WHO)	98.8% (serologic response) (USA)	Age: 18 years and older Intervals: 5 months	[46,149,150]
	Other names: Moderna; Spikevax								
	ChAdOx1 nCoV-19	*WHO EUL; *CRS EUR	02/ 15/ 2021		137	Pause	76% (one dose) 81.3% (two doses) for adult (ages 18–55 years) 83.5% (two doses) for adult (ages over 65 years)	Age: 18–70 years old Intervals: at least 28 days	[123,151–154]
	Other names: Oxford/AstraZeneca; Vaxzevria; AZD1222	*ART Endorsed							
Inactivated vaccine	A426. COV 2. SOther names: Janssen (Johnson & Johnson); Ad26COVS1	*WHO EUL; *CRS EUR *ART Endorsed	12/ 03/ 2021		106	Pause	66.9% (prevention of severe COVID-19); 76.7% (severe-critical COVID-19) for adult (USA, Brazil, and South Africa)	Age: 18 years and older Intervals: 2 months	[154–158]
	BBIBP-CorV Other names: Sinopharm (Beijing); Covilo	*WHO EUL; *CRS EUR *ART Endorsed	05/ 07/ 2021		88	3–17 (Phase 3 clinical trial)	100% (neutralization activity) (China)	Age: 3 years and older Intervals: at least 28 days (two or three doses)	[113,142,159,160]
Inactivated vaccine	CoronaVac Other names: Sinovac	*WHO EUL; *CRS EUR *ART Endorsed	06/ 01/ 2021		52	6 months and more (Phase 3 clinical trial)	100% (neutralization antibody activity) 100% (immunogenicity) (China)	Age: 3 years and older Intervals: 28 days (second dose) 6 months (third dose)	[106,141,161]

\*WHO EUL: World Health Organization Emergency Use Listing  
\*CRS EUR: Caribbean Regulatory System Emergency Use Recommendation  
\*ART: Africa Regulatory Taskforce (ART) Endorsed

children [45,48,108–113]. Robust clinical data also confirmed that the COVID-19 vaccine is safe in children with specific diseases, including congenital immunodeficiency, congenital heart disease, pediatric inflammatory bowel disease and allergy [114–122]. Given that some parents are still hesitant about vaccine safety, reducing the single-dose volume of vaccines for children and extending the vaccination interval has been proven to reduce the occurrence of adverse events, which is expected to become the vaccination strategy for children in the future [111,123,124]. Thus, aside from those who are severely allergic to vaccine ingredients, children should be vaccinated against COVID-19 to slow the evolution of SARS-CoV-2 and the progression of the global pandemic.

Lastly, the current COVID-19 pandemic is extremely severe, which requires comprehensive vaccination around the world. Post-vaccination breakthrough infections caused by the SARS-CoV-2 variant, like the Delta and Omicron variant, is a common phenomenon, indicating that the SARS-CoV-2 variants have evolved the capability for immune evasion [10,108,125,126]. In addition, it can be seen that physical barrier alone is not enough to fend off the COVID-19 pandemic for people of different ages, races and genders, so it is necessary to establish an immune barrier for all members through vaccination. In particular, children as a special group face some unique challenges, such as difficulty in strictly implementing physical protection, often being outside the scope of public health strategies, and lack of awareness of self-protection, making children one of the most vulnerable groups to be susceptible to new variants of SARS-CoV-2 [49,52,127,128]. Moreover, the uneven distribution of vaccines in various countries and regions has become an obstacle in delaying the vaccination of children [129–132]. It is reassuring that this issue is being effectively alleviated through the development of vaccines that are gradually maturing around the world, and it cannot be an obstacle from prioritizing vaccinating children [133–137]. Consequently, to accelerate the process of fully vaccinating all human beings against COVID-19, more clinical data related to vaccines for children are needed to dispel the concerns of parents regarding vaccine safety.

#### 4. The status of vaccination against COVID-19 and related side effects in children

Due to the widespread vaccination of adults against COVID-19, a strong immune barrier against severe COVID-19 has been established in the population, which cannot be broken even by multiple evolutions of SARS-CoV-2 [10,14]. Conversely, children are not widely vaccinated against COVID-19, which exposes them to SARS-CoV-2 without the protection of vaccines, increasing the risk of infection [53,88,138]. According to available data, as of December 31, 2021, nearly 9.17 billion doses of COVID-19 vaccine have been administered globally, of which 86.4%–90.4% have been administered to adults, whereas only 9.6%–13.6% have been administered to children [21,139]. WHO approved the application of mRNA vaccines to children aged 16–17 as early as December 2020, and then expanded the authorized age to 12–17 years old in August 2021 (Fig. 1B) [48,140]. Following, the non-replicating viral vector and inactivated vaccines were successively authorized by WHO for children over 12 years old [106,141,142]. Table 1 lists the status and immune efficacy of authorized COVID-19 vaccines for children, including mRNA vaccines (Pfizer-BioNTech, Moderna), non-replicating

viral vector (Oxford/AstraZeneca, Ad26COVS1) and inactivated vaccines (Sinopharm, Sinovac). In particular, the Pfizer-BioNTech vaccine was considered one of the most effective vaccines, showing 100% immunogenicity and significant safety, which has been recommended by the Center for Disease Control and Prevention (CDC) as a booster for children vaccinators [143–145]. Moreover, Sinovac, which has a vaccination count of more than 2.3 billion doses (as of January 29, 2022) in 52 countries, shows 100% neutralizing antibody activity in children under 3 years old in international multicenter phase III clinical trials [146,147]. However, despite the high safety and immunogenicity of vaccines authorized for children by WHO, this age group represents a low proportion of the total number of vaccinated populations. For example, results of a survey conducted in Spain between January 8, 2021 and January 21, 2022, showed significant differences in the proportion of age groups who were fully vaccinated. More than 90.49% of the population over 50 years old were fully vaccinated, whereas this group accounted for less than 44.41% in children under 14 years old. Moreover, less than 0.05% of children under 9 were fully vaccinated [45,139]. Therefore, it is evident that the number of vaccinated children is far less than that of adults.

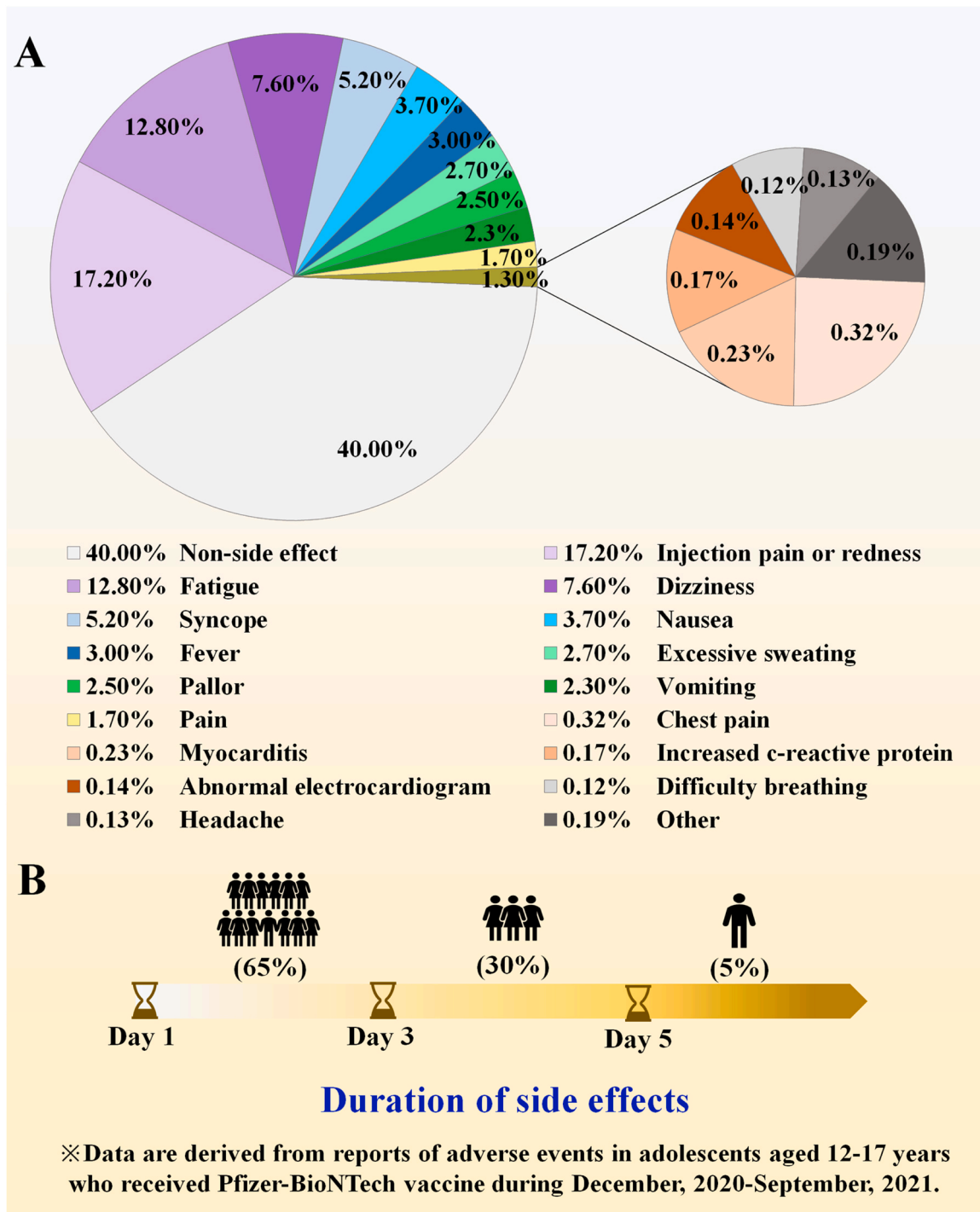
Part of the data come from official reports of individual countries or regions and do not represent global average.

The evaluation of efficacy and adverse effects of various vaccines is based on a comprehensive assessment of infection rates, mortality, doses, post-vaccination infections, occurrence and duration of post-vaccination adverse events.

Findings from global surveys on the acceptance of vaccinating children against COVID-19 reveals that parental concerns mostly consist of side effects and doubts about incomplete clinical data describing vaccine efficacy [26,31,32,43,44,154,162–164]. Yet, the incidence of adverse events after vaccinating children was below 3%, among which the most common side effects were injection site discomfort, fatigue, dizziness, and in rare cases, myocarditis due to MIS-C (Fig. 3A) [69,71,158,165–169]. These symptoms were generally mild, 65% of which disappeared within 1–3 days after onset, and only 5% required hospitalization for further treatment (Fig. 3B) [165,170–172]. In addition, serious adverse events with COVID-19 vaccines were rare, with fewer than 0.01% of deaths which were related to underlying diseases rather than the vaccine itself [38,45,47,145]. For example, AstraZeneca and J&J adenoviral vector vaccines have been suspended in children for causing vaccine-induced fatal prothrombotic immune thrombocytopenia (VIPIT), although this side effect was found to occur only in women between the ages of 30 and 65 [67,68,173–182]. Side effects were also shown to be related to the type of vaccine. Sinopharm vaccines, for instance, were found to be safe and showed a lower prevalence of adverse events compared with other vaccines [183,184]. As COVID-19 vaccines related adverse events appear to have negligible impact on vaccinated children, it follows that vaccinating children remains a safe option in preventing the COVID-19 epidemic from further developing.

#### 5. The COVID-19 vaccine mechanism in children

COVID-19 vaccines have strong immune efficacy and safety in stopping the global COVID-19 pandemic [110,111]. Therefore, understanding the mechanism of SARS-CoV-2 infection and the COVID-



**Fig. 3.** (A) The types and proportions of adverse events reported from children who vaccinated with COVID-19 vaccines. (B) The duration of post-vaccination adverse events of COVID-19 vaccine in children.

19 vaccine immunization process in children is a preferential method in designing the appropriate vaccine formulation. Design of the vaccine starts from understanding the basic structure of the Spike (S) protein, which is the characteristic structure for SARS-CoV-

2 to enter host cells. The S protein is contained by a receptor binding domain (RBD) and an N-terminal domain (NTD). The mutations on RBD and NTD determine the type of SARS-CoV-2 variant and the severity of COVID-19 [185–189]. SARS-CoV-2 can bind to the ACE2



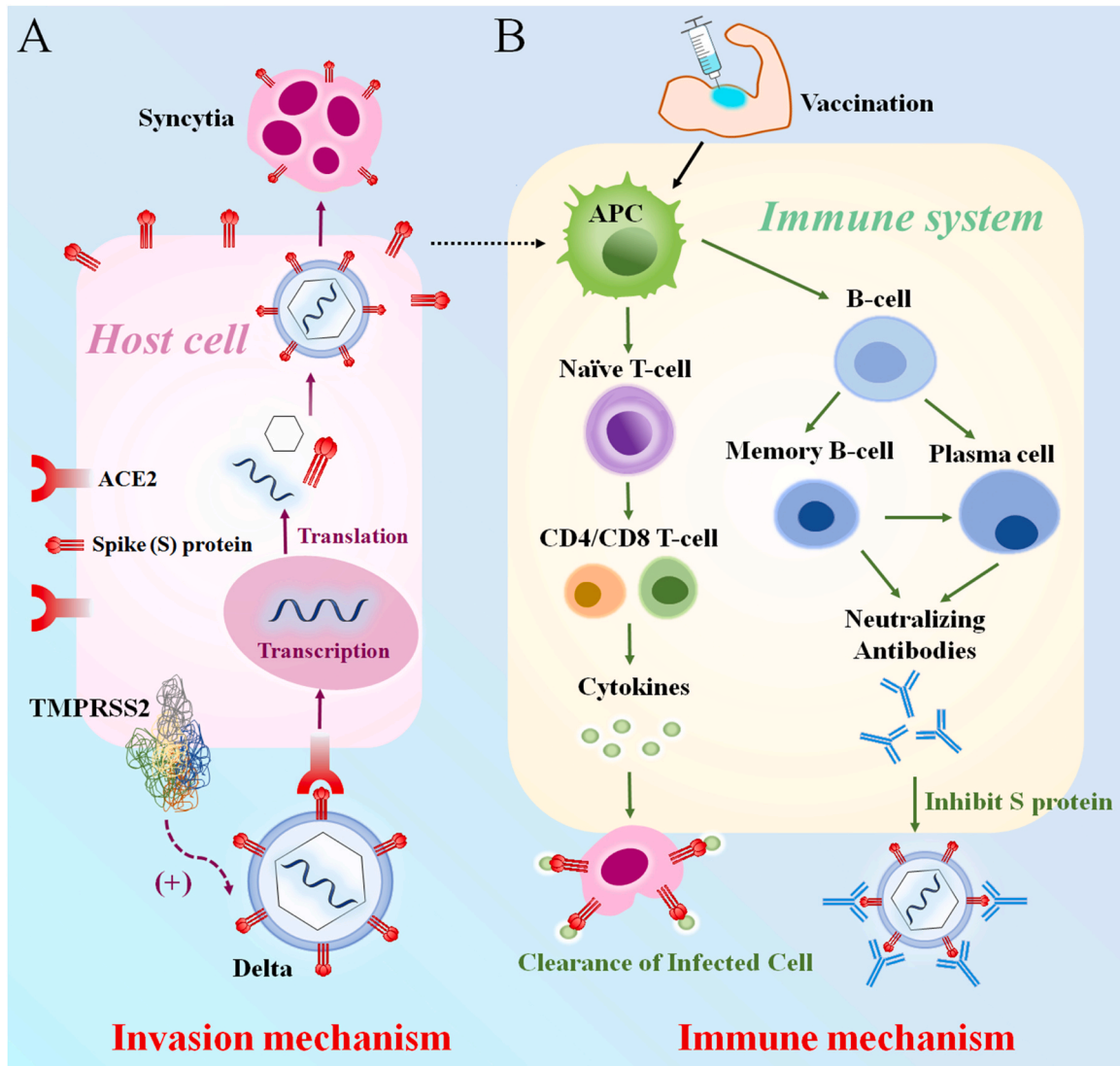
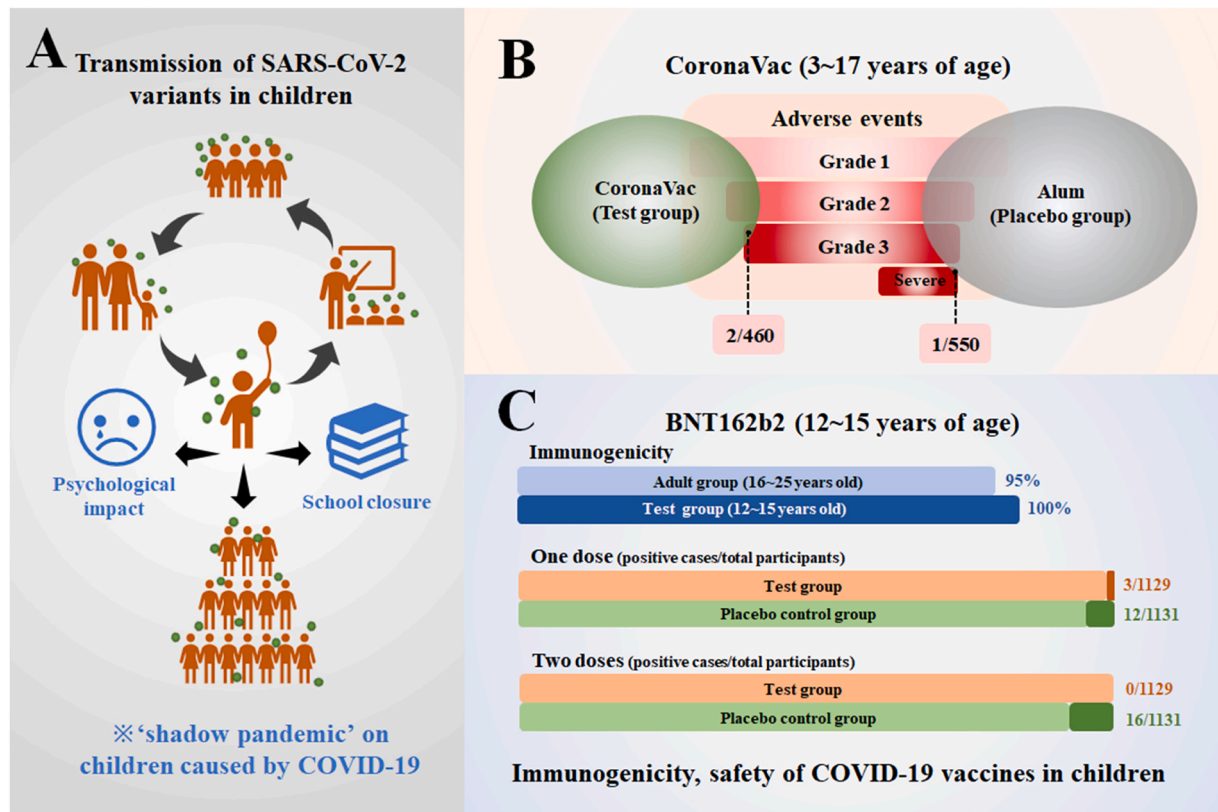


Fig. 4. (A) The mechanism of SARS-CoV-2 invasion in children and (B) immune mechanism of children vaccinated against COVID-19.

receptor under the mediation of transmembrane serine protease 2 (TMPRSS2), and sends RNA into the host cell for intracellular transcription and translation [185,190,191]. More ACE2 receptors subside in the lung, heart and kidney, which tends to promote membrane fusion, leading to more syncytia than other organs (Fig. 4A) [189,192–199]. The vaccines developed according to the above process can activate humoral and cellular immunity by inducing the antigen presenting cells (APC) of children, wherein humoral immunity produces neutralizing antibodies that can bind to the ACE2 receptor, preventing the invasion of SARS-CoV-2 [200–204]. On the other hand, cytokines produced by the cellular immune system, such as IL-6, can rapidly label and eliminate infected host cells [205–207]. These two immune pathways are the strongest barriers to ensuring

that children are not infected with SARS-CoV-2 (Fig. 4B). The above processes in children are not fundamentally different from those in adults. Due to the special immune characteristics of children, however, children with COVID-19 have milder symptoms and lower viral loads. Furthermore, children can induce similar or higher levels of neutralizing antibodies compared to adults [28,51,208]. In essence, children have stronger innate immunity compared to adults, which leads to early control of infection at the site of entry and a lower chance of transmission between children, but it also makes children more susceptible to MIS-C [50,54,200,209]. In addition, it is theorized that the low expression of ACE2 in children, the weak affinity of SARS-CoV-2 with ACE2 in children, and the strong regeneration ability of the pediatric lung epithelium are all protective factors for



**Fig. 5.** (A) The transmission of SARS-CoV-2 variants in children and the shadow pandemic on children caused by COVID-19; the immunogenicity, safety of (B) CoronaVac and (C) BNT162b2 in clinical trials.

children suffering from COVID-19 [210–213]. Even so, the infection of SARS-CoV-2 is a common phenomenon in children. Therefore, the decisive role of vaccines in fighting SARS-CoV-2 infection in children cannot be ignored, and it is imperative to widely vaccinate children. Fig. 5.

## 6. Conclusion

The COVID-19 pandemic has ravaged the world, which has affected children both physically and mentally. It is one of the most threatening diseases that children are facing this century. Since children play an essential role in the evolution and transmission chain of SARS-CoV-2, vaccinating children under strict physical protection is necessary. Currently, widely authorized vaccines have demonstrated about 100% superiority in both efficacy and safety against SARS-CoV-2 infections between the age of 12–17 years. Although a few worrisome adverse events have caused parental hesitation, it is worth mentioning that those post-vaccination side effects were almost exclusively mild, such as injection site discomfort, fatigue and dizziness, which relieved or resolve within 5 days in 95% of cases. Upon examining clinical trials and the evolution of the virus, we note that children are key factors in ending the pandemic and the vaccination of children can effectively help reduce societal harm and prevent the intensification of the pandemic. More clinical data is required for the various types of vaccines for children to provide a safer and more effective solution in ending COVID-19.

## Conflict of Interest

The authors declared that they have no conflicts of interest to this work.

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