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Considerations for vaccinating children against COVID-19

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SUMMARY

COVID-19 vaccines have been introduced in children and adolescents in many countries. However, high levels of community transmission and infection-derived immunity make the decision to introduce COVID-19 vaccination of children in countries yet to do so particularly challenging. For example, other vaccine preventable diseases, including measles and polio, generally have far higher childhood morbidity and mortality in low-income and middle-income countries (LMICs) than COVID-19, and coverage with these vaccines has declined during the pandemic. Many countries are yet to introduce pneumococcal conjugate and rotavirus vaccines for children, which prevent common causes of childhood death, or human papillomavirus vaccine for adolescents. The Pfizer and Moderna COVID-19 vaccines that have been widely tested in children and adolescents had a positive risk-benefit profile at the time they were tested. However, the benefit is less compared with other life-saving vaccines in this age group, particularly in LMICs and settings with widespread infection-derived immunity. The resources required for rollout may also pose a considerable challenge in LMICs. In this paper, we describe COVID-19 in children, with a focus on LMICs, and summarise the published literature on safety, efficacy and effectiveness of COVID-19 vaccination in children and adolescents. We highlight the complexity of decision-making regarding COVID-19 vaccination of children now that most of this low-risk population benefit from infection-derived immunity. We emphasise that at-risk groups should be prioritised for COVID-19 vaccination; and that if COVID-19 vaccines are introduced for children, the opportunity should be taken to improve coverage of routine childhood vaccines and preventative healthcare. Additionally, we highlight the paucity of epidemiological data in LMICs, and that for future epidemics, measures need to be taken to ensure equitable access to safe and efficacious vaccines before exposure to infection.

KEY MESSAGES

⇒ COVID-19 vaccines are effective against severe COVID-19 in children and adolescents, although there is limited additional benefit in healthy children in the context of widespread infection-derived immunity.
⇒ There is a paucity of epidemiological data in children and adolescents from low-income and middle-income countries (LMICs). Using high-income data may potentially underestimate the severity of COVID-19 in LMICs, and thus the importance of vaccination.
⇒ However, the risk of severe COVID-19 in healthy children and adolescents is very low in all settings, although deaths do occasionally occur and serious illness may require supportive care.
⇒ Where finances are limited, COVID-19 vaccination should prioritise those at high risk and the elderly based on the risk-benefit of vaccination.
⇒ Where routine immunisation coverage is below target, prioritisation should be given to improving the uptake of existing routine vaccines, which prevent diseases with a higher burden, to minimise competing demands on immunisation providers.
⇒ If implementing COVID-19 vaccination for healthy children, consideration should be given to improving supply and delivery systems for routine childhood vaccines that have a greater impact on morbidity and mortality, particularly measles, pneumococcal conjugate vaccine, rotavirus, polio and human papillomavirus.

INTRODUCTION

Although the SARS-CoV-2 virus has become more transmissible, it causes relatively less severe disease, especially in populations that are highly vaccinated or have previously been exposed to the virus.[1] The WHO has recently updated its guidance for COVID-19 vaccination in children and adolescents and has suggested that countries consider vaccination of this age group based on contextual factors, such as the disease burden, cost-effectiveness, opportunity costs and other health or programmatic priorities.[2] In this opinion piece, we discuss the decision to vaccinate children against COVID-19, particularly in low-income and middle-income countries (LMICs) which is a complex decision due to the existing protection offered by infection-derived immunity; an age group with the lowest risk of severe COVID-19 outcomes; and a higher risk of poor health outcomes from other vaccine preventable diseases. As data on many aspects of COVID-19 in children from LMICs are severely limited, we present relevant data on the disease from high-income settings, as appropriate.

Table 1 Case fatality rates of COVID-19 and other vaccine-preventable diseases in children and adolescents

Disease or pathogen	Age group	Case fatality rate (per 1000)
COVID-19[3]*	<1 year	0.017
	1–4 years	0.003
	5–11 years	0.003
	12–15 years	0.009
	15–19 years	0.015
Invasive pneumococcal disease[104]	<5 years	450 (210–620)†‡
Pertussis[105]	<6 months	72.0 (36.0–118)§
	All ages (including adults)	55.0 (33.0–61.0)§
Influenza[106]	<5 years	29.6 (7.9–51.3)§ (LMICs)
		1.7 (0.8–2.6)§ (HICs)
Respiratory syncytial virus[107]	<1 year	6.6 (1.9–16.9)‡
	<1 year, preterm	1.0 (0.2–12.1)‡
	2 years	4.7 (1.2–14.7)‡
	<5 years	6.2 (2.6–13.7)‡

*Due to the relatively low proportion of COVID-19 cases in children that are tested in all settings, limited data from low-income and middle-income countries, and higher case fatality rates reported early in the pandemic, mortality estimates are presented from a national study in England.
†Severe disease only.
‡Credible interval.
§Confidence interval.
HICs, high-income countries; LIMCs, low-income and middle-income countries.

Acute COVID-19 ranges from asymptomatic to life-threatening, although deaths are extremely rare in children and adolescents.[3] Estimates of case fatality rates for major diseases of childhood in comparison to COVID-19 mortality are shown in table 1. Over the first year of the pandemic, the under-18 COVID-19 case fatality rate was 2 per million in the UK and this decreased with the Omicron variant.[4] While these data cannot be directly extrapolated to LMICs, from which data are lacking, case fatality rates are considerably lower than for the main vaccine preventable diseases in childhood. Measles case fatality rates vary from approximately 1 in 2000 in high-income settings to 1 in 20 or higher in settings with high rates of malnutrition.[5] The risk of severe COVID-19 among children and adolescents follows a U-shaped distribution, with the greatest risk in younger infants and older adolescents and lowest risk in primary school aged children.[6 7] The Omicron subvariants more commonly infect the upper airways so the common clinical manifestations, croup and bronchiolitis, are similar to other common respiratory viruses in young children, with some requiring treatment for upper airway obstruction, rehydration and observation in intensive care.[8 9] Children with comorbidities, including diabetes, severe asthma, pulmonary and cardiovascular diseases, epilepsy, learning and physical disabilities, immunocompromising conditions and obesity, are at greater risk.[10]

Although less severe, the increased transmissibility of the Omicron subvariants and greater case numbers have resulted in an increase in child and adolescent hospitalisations.[11–13] Globally, 16 100 COVID-19 deaths have been reported in those aged 0–19 years, approximately 0.4% of total reported COVID-19 deaths.[14] Of these reported deaths, 53% occurred among adolescents aged 10–19 years, and 47% were among children aged 0–9 years.[14] However, there are few data for LMICs. In the USA with a population of more than 70 million aged <18 years, there have been 1489 child deaths with COVID-19, many associated with immunosuppressive conditions and other comorbidities, shown in comparison to other countries in table 2.[15] South Africa has reported 927 deaths in children aged 0–19 years.[16]

Multisystem inflammatory syndrome in children (MIS-C) is a serious but treatable complication of SARS-CoV-2 infection in children involving inflammation of multiple organs. MIS-C occurred in fewer than 1 in 10 000 Omicron cases, 2–6 weeks after acute infection.[17] It is most common in children aged 8–9 years.[18] Early diagnosis and treatment, including immunomodulatory therapies, has improved outcomes since 2020 and those with MIS-C usually make a full recovery.[19] Despite low vaccination uptake in children, in England, MIS-C case numbers did not increase with Omicron despite a large proportion of children being infected over a 4-week period in January 2022 (the percentage of children aged 8–11 years old with prior infection increased from 55% to 97%).[20 21] Overall, there have been 9333 reported cases in the USA, peaking at 262 cases per week in January 2021. Similar to England, since the Omicron subvariant BA.1 wave in early 2022, there has been a dramatic decline in MIS-C in the USA and Australia, with fewer than 10 reported cases per week since August 2022 in the USA.[22 23] The reasons for this are unknown but may be related to changed properties of both the virus and the host (immunity from prior infection and vaccination). Vaccination was more than 90% effective against MIS-C following infection with Delta.[24–26]

Table 2 Number of reported COVID-19 deaths in children and adolescents

Country	Age group (years)	Deaths (n)	Timeframe	Population*	Incidence risk† (per million)
Australia[108]	0–19	12	To 15 January 2023	6 287 000	1.9
Canada[109]	0–11	47	To 26 January 2023	4 736 060	9.92
	12–19	25		3 289 705	7.60
Denmark[110]	0–9	4	To 8 February 2023	617 585	6.48
	10–19	4		677 796	5.90
England and Wales, UK[111]	<1	43	To 30 January 2023	607 324	70.8
	1–4	28		2 624 712	10.7
	5–9	38		3 524 627	10.8
	10–14	55		3 596 029	15.3
	15–19	130		3 394 665	38.3
Finland[112]	0–19	0	To 16 February 2023	1 762 993	0
Scotland, UK[113]	<1	2	To 6 February 2023	46 782	42.8
	1–14	4		806 948	4.96
South Africa[16]	0–9	481	To 30 December 2022	11 298 392	42.6
	10–19	446		10 816 052	41.2
USA[15]	0–17	1489	To 15 February 2023	73 106 000	20.4

*Population figures from government census data.
†To date in the pandemic.

Post-acute COVID-19 syndrome, or long COVID, is uncommon in children and difficult to distinguish from other effects of the pandemic as well as symptoms that occur frequently in children regardless of whether or not they have had COVID-19.[27] Delayed recovery following an acute infection may occur but is less common than in adults and the majority of children make a full recovery.[28–30]

Severity of clinical outcomes of COVID-19 in children in LMICs may be exacerbated by multiple factors, including limitations in healthcare systems, delayed presentation due to hesitancy to access services and lockdowns, and high prevalence of comorbidities.[31 32] In South Africa, hospitalisations of children increased rapidly with the first Omicron wave, particularly in children aged 0–4 years.[33] In six countries in sub-Saharan Africa, mortality was 8.3% in hospitalised children and adolescents with COVID-19, substantially higher than in high-income settings.[34] Another assessment of COVID-19 incidence and deaths in 17 African countries in 2020 showed that paediatric cases comprised 9% of all cases and 2.4% of deaths, reflecting a much higher paediatric mortality than in high-income settings.[35] Reports from India, Indonesia and Nepal also suggest that child mortality may be substantial, although these studies may be affected by reporting bias and no studies of mortality rates in LMICs have been published to date.[36 37]

COVID-19 vaccines for children and adolescents

With the development of mRNA COVID-19 vaccines for children, most high-income countries (HICs) introduced these vaccines for adolescents and many for younger children. The WHO has authorised the Pfizer-BioNTech and Moderna vaccines for use in children aged 6 months and older. Both vaccines are approved for use in this age group in the USA. In the UK, Pfizer-BioNTech is also authorised in those aged 6 months and older and Moderna in those aged 6 years and older. The Novavax vaccine has been authorised for use in adolescents aged 12–17 years by the WHO and many countries, including the USA, the UK and Australia. The WHO recently authorised the Sinovac vaccine for use in children aged 3–17 years, making it the only inactivated vaccine authorised for children. The WHO recommends that children and adolescents who are at high risk should be offered COVID-19 vaccination, but that the priority remains to fully vaccinate older people, those with chronic health conditions and healthcare workers.[38] As children have the lowest risk of severe disease, the vaccination of children and adolescents should always account for prioritisation of the elderly and other high priority groups and not affect supply chains or programmes for the administration of primary series and boosters in these groups.

Vaccine safety

The Moderna and Pfizer-BioNTech vaccines have been shown to be safe in children and adolescents, with a positive risk-benefit profile, particularly in those at high risk of severe COVID-19 disease.[39] This includes a satisfactory safety profile in the lower antigen mRNA formulations for children 6 months to 5 years of age.[40] Few data are available on the safety profile of the inactivated vaccines, Sinovac and Sinopharm, although the reactogenicity of inactivated vaccines has generally been shown to be lower

Box 1 Literature search strategy and selection criteria

⇒ A literature search of PubMed was conducted for articles published between 1 January 2020 and 30 September 2022 and related to COVID-19 vaccine efficacy and effectiveness in children and adolescents
⇒ The following search terms were used: ('COVID-19 vaccine' or 'COVID-19 vaccination'), ('efficacy' or 'effectiveness') and ('children' or 'child' or 'adolescent' or 'adolescents')
⇒ Inclusion criteria were original research articles with efficacy or effectiveness data on COVID-19 vaccination of children and adolescents
⇒ From the final list of 510 considered studies, all those describing original efficacy or effectiveness data were included

than other vaccines.[41] The mRNA vaccines pose a low risk of myocarditis and pericarditis that is highest in males aged 16–17 years following the second dose—around 100 cases per million second doses.[42] Post-vaccination myocarditis cases are generally mild, with brief hospitalisations or ambulatory management and recover with conservative management.[43] Myocarditis cases have been reported much more rarely following booster doses, including Omicron-adapted bivalent vaccines. There is ongoing longer term follow-up of post-vaccination myocarditis cases to see if there are any sequelae.[44] Of note, there is a higher risk of myocarditis from COVID-19 than from vaccination in most age groups.[45] The risk of myocarditis following mRNA vaccines is very low in children aged 5–11 years—around one case per million second doses, which is likely related to the lower background rate of myocarditis (from all causes) in this age group.[39] The vaccination dose interval has been increased to 8 weeks in many countries, which has been shown to both improve immunogenicity and reduce the risk of myocarditis.[46]

COVID-19 vaccine efficacy and effectiveness

We conducted a systematic search (strategy outlined in box 1) for COVID-19 vaccine efficacy and effectiveness studies in children and adolescents. The results are summarised in table 3.

The mRNA vaccines have been shown to be effective against severe disease and MIS-C in children and adolescents, with most of the available data in older paediatric populations. The Pfizer-BioNTech and Moderna paediatric vaccines have a lower mRNA content than the adult vaccines, 3 µg Pfizer-BioNTech (one-tenth of the adult dose) and 25 µg Moderna (one-quarter of the adult dose). In clinical trials, the three-dose paediatric Pfizer-BioNTech schedule showed 80% efficacy against symptomatic Omicron infection in children aged 6 months to 4 years.[47] The two-dose Moderna schedule showed 51% efficacy against infection in children aged 6 months to under 2 years, and 37% in those aged 2–5 years.[48] A recent systematic review of the efficacy, effectiveness and safety of COVID-19 mRNA vaccines in children aged 5–11 years found that they were associated with lower risk of infection (OR 0.53; 95% CI 0.41 to 0.70), hospitalisation (OR 0.32; 95% CI 0.15 to 0.68) and MIS-C (OR 0.05; 95% CI 0.02 to 0.10); the risk of adverse events that prevented normal daily activities was 8.8% (95% CI 5.4% to 14.2%).[49]

Two doses of the inactivated Sinovac and Sinopharm vaccines are approved for use in children aged 3 years and older in many countries, although phase III trial data are not yet available in children and adolescents. Vaccine effectiveness of Sinovac has been reported as 40% and 59% against symptomatic infection and hospitalisation, respectively, in children aged 6–11 years in Brazil; and 38% and 65% against the same outcomes in those aged 3–5 years in Chile.[50 51] A study of national data from Argentina showed effectiveness of any of the Pfizer-BioNTech, Moderna or Sinopharm vaccines was 67% against death in children aged 3–11 years and 98% effective against death in those aged 12–17 years.[52] The Sinovac and Sinopharm vaccines have been shown to be effective in adults in Thailand if boosted with an mRNA vaccine or AstraZeneca.[53] A study of heterologous schedule vaccination using Sinovac prime-Pfizer-BioNTech boost has also been conducted in children in Thailand. The results are similar to those in adults, showing high neutralising antibody titres between the heterologous regimen and the homologous two-dose Pfizer-BioNTech regimen (Chokephaibulkit K, personal communication, 2023). The heterologous approach may be an alternative schedule to minimise the adverse reactions from mRNA vaccines. Two doses of the Cuban FINLAY-FR-2 vaccine followed by a third dose of FINLAY-FR-1A, targeting a different protein of the receptor-binding domain, has been shown to produce a similar antibody response in children aged 3–18 years compared with vaccinated young adults.[54] Cuba has a higher quality primary healthcare system and from September 2021, proceeded to vaccinate all children aged 2 years and older, who mostly would have been naïve to SARS-CoV-2. This rollout was conducted in younger age groups before widespread Omicron infection and before many HICs began vaccinating this age group. High-quality epidemiological data early in the pandemic, plus the ability to produce a vaccine, resulted in a lower number of reported COVID-19 deaths in Cuba than other countries in the region.[55] By enhancing epidemiological capacity, LMICs would be better equipped to respond to potential future pandemics.

For newborns and younger infants, maternal vaccination has been shown to protect the infant up to 6 months of age. Effectiveness of two doses of mRNA vaccines during pregnancy against COVID-19 hospitalisation among infants aged under 6 months was 61%.[56] Maternal vaccination during lactation, particularly with mRNA vaccines, also produces antibody responses in human milk that might protect the infant.[57] Vaccination of pregnant women should be maintained in all settings as, in addition to the benefits to the infant, there is a higher risk of COVID-19 adverse outcomes during pregnancy despite this decreasing with Omicron.[58]

Table 3 Efficacy and effectiveness of COVID-19 vaccine primary series against symptomatic infection and severe outcomes by variant in children

Vaccine type	Vaccine efficacy and effectiveness	
	<12 years (except where specified 3–17 years)	**12–17 years**
Moderna (mRNA)	**Omicron** efficacy against ► Symptomatic infection: 55% (6 months to <2 years) and 38% (2–6 years)[48] **Omicron** effectiveness against ► Any infection: 18% (3–17 years)[52]	**Pre-Omicron** efficacy against ► Symptomatic infection: 93% (12–17 years)[114]
Pfizer-BioNTech (mRNA)	**Pre-Omicron**: efficacy against ► Symptomatic infection: 91% (5 to <12 years)[115] **Delta and Omicron** effectiveness against ► Any infection 0–13 days post-vaccination: 65% (5–11 years)[116] ► Any infection 28–34 days post-vaccination: 12% (5–11 years)[116] ► Hospitalisation 14–67 days post-vaccination: 74% (5–11 years)[117] ► MIS-C: 94% in Denmark (5–17 years)[25] **Omicron** effectiveness against ► Any infection 0–14 days post-vaccination: 39% (5–11 years)[118] ► Any infection 43–84 days post-vaccination: 21% (5–11 years)[118] ► Any infection: 28% (3–17 years)[52] ► Symptomatic infection 2 months post-vaccination: 29% (5–11 years)[119] ► Symptomatic infection: 80.4% (6 months–4 years)[47]	**Alpha and Delta** efficacy against ► Symptomatic infection: 100% (12–15 years)[120] **Delta** effectiveness against ► Symptomatic infection 7–21 days post-vaccination: 93% (12–18 years)[121] ► Symptomatic infection 14–27 days post-vaccination: 86% in Brazil and 91% in Scotland (12–17 years)[122] ► Hospitalisation: 94% (12–18 years)[123] ► MIS-C: 91% in France and USA (12–18 years)[24 26] **Delta and Omicron** effectiveness against ► Any infection 0–13 days post-vaccination: 76% (12–17 years)[116]; 80% (16–17 years) and 79% (12–15 years)[124] ► Any infection 14–29 days post-vaccination: 83% (16–17 years) and 77% (12–15 years)[124] ► Any infection 28–34 days post-vaccination: 56% (12–17 years)[116] ► Any infection 30–59 days post-vaccination: 61% (16–17 years) and 50% (12–15 years)[124] ► Hospitalisation 14–149 days post-vaccination: 92% (12–15 years) and 94% (16–17 years)[117] **Omicron** effectiveness against ► Symptomatic infection 14–27 days post-vaccination: 63% in Brazil and 78% in Scotland (12–17 years)[122] ► Symptomatic infection 7–34 days post-vaccination: 53% (16–17 years)[125] ► Symptomatic infection ≥63 days post-vaccination: 23% (16–17 years)[125] ► Symptomatic infection 2 months post-vaccination: 17% (12–15 years)[119] ► Symptomatic infection ≥98 days post-vaccination: 14% in Brazil and 31% in Scotland (12–17 years)[122] ► Hospitalisation: 81% (12–17 years)[126] ► Hospitalisation or death ≥98 days post-vaccination: 85% (12–17 years)[122]
Novavax (protein subunit)		**Delta** efficacy against ► Symptomatic infection: 80% (12–17 years)[127]
Sinovac (inactivated virus)	**Delta and Omicron** effectiveness against ► Symptomatic infection: 76% (6–11 years)[128] ► Hospitalisation: 78% (6–11 years)[128] **Omicron** effectiveness against ► Symptomatic infection: 40% (6–11 years)[50] ► Hospitalisation: 59% (6–11 years)[50] ► Any infection: 38% (3–5 years)[51] ► Hospitalisation: 65% (3–5 years)[51]	
Sinopharm (inactivated virus)	**Omicron** effectiveness against ► Any infection: 28% (3–17 years)[52]	
AstraZeneca (viral vector)	Trials suspended when evidence emerged of the higher risk of thrombosis with thrombocytopaenia syndrome in adults	

MIS-C, multisystem inflammatory syndrome in children.

Table 4 Duration of protection from COVID-19 vaccine primary series against infection and hospitalisation in children and adolescents

Vaccine type	Vaccine efficacy and effectiveness	
	<12 years	12–17 years
Pfizer-BioNTech (mRNA)	**Omicron (BA.1)** effectiveness against ► Symptomatic infection in Singapore (5–11 years) – 7–14 days post-vaccination: 49% – 15–29 days post-vaccination: 38% – 30–59 days post-vaccination: 29% – ≥60 days post-vaccination: 26%[129] ► Hospitalisation in Singapore (5–11 years) – 83% without evidence of waning up to 2 months[129] ► Hospitalisation in the USA (5–11 years) – Median 34 days post-vaccination: 68%[130]	**Delta** effectiveness against ► Hospitalisation in the USA (12–18 years) – 2–22 weeks post-vaccination: 93% – 23–44 weeks post-vaccination: 92%[130] **Delta or Omicron** effectiveness against ► Hospitalisation in the USA (12–15 years) – <5 months post-vaccination: 92% – ≥5 months post-vaccination: 73%[117] ► Hospitalisation in the USA (16–17 years) – <5 months post-vaccination: 94% – ≥5 months post-vaccination: 88%[117] **Omicron** effectiveness against ► Symptomatic infection in the UK (12–17 years) – ≥70 days post-vaccination: 23%[131] ► Hospitalisation in the USA (12–18 years) – 2–22 weeks post-vaccination: 43% – 23–44 weeks post-vaccination: 38%[130]

Determining the duration of protection for all outcomes in children is ongoing. Studies in adults indicate effectiveness against symptomatic infection with Omicron wanes rapidly after two doses of Pfizer-BioNTech, Moderna or AstraZeneca to less than 50% by 3 months and little or no effect by 6 months.[59 60] Available data on duration of protection in children and adolescents are presented in table 4. The USA recommends booster and second booster doses, now with bivalent vaccines, for everyone aged 5 years and older, although 77% of children aged 5–11 years had been infected with SARS-CoV-2 by February 2022.[61] The duration of protection is unclear in this age group, and the risk of severe disease is very low, especially following the primary series in children without comorbidities. Vaccine effectiveness against MIS-C in the context of Omicron also remains unclear, especially as infection is only temporarily reduced following vaccination and MIS-C has greatly decreased in the USA and other high-income settings despite low vaccination coverage in children.[23 62] A study in Thai adolescents showed that those with impaired immunity had a poor response to two doses of Pfizer-BioNTech vaccine but those with chronic diseases had a good initial response with immunity waning after 3 months, suggesting a booster dose may be required as in healthy populations.[63] Additional immunogenicity studies in high-risk paediatric groups, that are priority for vaccination, are warranted.

The role of infection-derived and hybrid immunity to SARS-CoV-2

An important consideration in the context of high global transmission of Omicron is infection-derived immunity post SARS-CoV-2 infection and hybrid immunity from prior infection plus vaccination. A study in children aged 5–11 years in North Carolina, USA, reported effectiveness of Omicron infection against reinfection among unvaccinated children of 91%, and among vaccinated children of 94%.[64] Although certainty was low due to small numbers, effectiveness against hospitalisation was higher following previous infection than after vaccination, and waned more slowly. In England, protection against Omicron infection in a national test-negative study, comparing groups with different vaccination and infection status, was highest among adolescents with previous Omicron infection and vaccination, reaching 96% 15–24 weeks after the second dose of vaccine.[65]

The impact of prior SARS-CoV-2 infection on immunological responses to COVID-19 vaccination is still being determined but so far shows no evidence of immunological 'blunting'. A study in UK children aged 6–14 years found primary Omicron infection elicited a weak antibody response, with only 53% developing detectable neutralising antibodies.[66] Children with secondary Omicron infection following prior infection with a pre-Omicron variant developed a greater immune response and vaccination was strongly immunogenic following prior infection with Omicron. Cellular responses against Omicron were strong and similar in all groups.

For countries that have not introduced COVID-19 vaccination for children but have high levels of prior infection, the risk of severe disease may be reduced, as has been seen with MIS-C declining over time irrespective of vaccination.[21 22] Studies suggest that hybrid immunity may be superior to infection-induced or vaccine-induced immunity alone.[67] Immunogenicity studies in Thailand found that a single dose of Pfizer-BioNTech or AstraZeneca, but not Sinovac, following natural infection, provided similar protection against Delta and Omicron compared

with three doses of vaccine.[68] A single dose of the Cuban-developed FINLAY-FR-1A vaccine has also been shown to efficiently boost pre-existing natural immunity.[69]

Determining the prevalence of prior infection requires seroprevalence studies as the high transmissibility of Omicron and testing limitations lead to underestimates of infection rates. In the UK, seroprevalence surveys showed that 97.6% of children aged 8–11 years had evidence of prior infection with SARS-CoV-2 by the third week of February 2022 during the Omicron BA.1 wave. In communities with high seroprevalence, vaccines have augmented natural immunity by boosting antibody titres and broadening immunity.[70] Whether one or two doses administered to children with prior infection has similar vaccine efficacy is currently unknown and will depend on the choice of vaccine and immune evasiveness of the predominant SARS-CoV-2 variant. High-risk children and adolescents, irrespective of their prior infection status, are likely to require at least two doses of vaccine. Indeed, as more evidence becomes available, annual vaccination may be considered for high-risk children, as currently for some adults in HICs, similar to influenza vaccine recommendations.[71] It is important to note from a vaccine policy perspective that individuals should not seek out natural infection to optimise protection, as each individual's response to current and future variants will be multifactorial. However, where community seroprevalence data have been undertaken over time at regional and country level, it has been helpful in making evidence-based COVID-19 vaccine recommendations. At the end of 2021, seroprevalence studies showed approximately 50%–70% of children globally were still susceptible to SARS-CoV-2 infection.[72] However, since the spread of Omicron, seroprevalence is likely to be high in most populations and undertaking seroprevalence surveys at this point in the pandemic seems unjustified.[67]

In the context of widespread natural immunity following Omicron infection, the additional benefits of vaccinating otherwise healthy children seem to be marginal.[73] As such, some countries have revised their child and adolescent schedules and are only targeting high-risk children. In the UK, The Netherlands and Sweden, healthy children aged 5–11 years are no longer vaccinated.[74–76] In Norway, vaccination is only offered on request for children aged under 18 years.[77] Few countries recommend vaccination of children under 5 years of age, with the USA being a notable exception, recommending vaccination of all healthy children as young as 6 months and booster doses to all aged 5 years and older.[78]

COVID-19 vaccine equity and opportunity costs

Distribution of COVID-19 vaccines globally has been highly inequitable, with many HICs securing several doses of vaccine per head of population in the early stages of vaccine rollout.[79] HICs subsequently progressed to vaccinate younger age groups and children before LMICs had vaccinated their elderly and most at-risk groups. This meant that most people in LMICs were infected before they were offered a vaccination and therefore now have infection-derived immunity. Furthermore, there are barriers to vaccination in LMICs that particularly affect those at greatest risk (those living in marginalised communities and those with disabilities), who should be prioritised for vaccination.[80 81]

A major difference with COVID-19 vaccination is the age group targeted and policymakers will have to expand the Expanded Programme on Immunisation (EPI) structure and take a systematic and collaborative approach to introduce and sustain the programme.[82] A considerable amount of research, conducted by WHO, UNICEF and many other partners, is exploring how best to overcome the additional barriers to rollout in LMICs compared with HICs. This includes adaptation of EPI programmes to include adults, training and recruiting of more health providers and volunteers, and exploring financing options among stakeholders.[83] However, the cost to deliver programmes has opportunity costs and in the context of limited workforce capacity, health workforce burnout and other competing priorities, countries need to rationalise how best to spend their time and money.

There have been considerable interruptions to the EPI in many countries during the pandemic, leading to declining routine vaccination coverage as countries' health systems have pivoted to focus on the COVID-19 response.[84] Measles outbreaks have increased and polio cases have occurred due to low vaccine coverage even in non-endemic countries.[85 86] In addition, increasing malnutrition due to the pandemic is a poor prognostic indicator for measles and other infectious disease severity.[87 88] Where vaccine coverage has declined, high priority should be placed on supplementary immunisation programmes before diverting efforts to COVID-19 vaccination in children, as the diseases covered by routine EPI have higher morbidity and mortality in children than COVID-19. However, supplementary immunisations activities could consider adding other antigens, including COVID-19 vaccine, to maximise harmonisation of programme activities. More research is required on reactogenicity and immunogenicity of COVID-19 vaccines co-administered with other vaccines. There may be potential in the future for use of combined respiratory virus vaccines that are currently in development against combinations of COVID-19, influenza and respiratory syncytial virus.

As there are no longer constraints on COVID-19 vaccine supply, and uptake is high in adults in many settings, it may be that children are offered a COVID-19 vaccine before essential life-saving vaccines are included in national immunisation programmes. It is estimated that pneumococcal pneumonia is responsible for about 300 000 deaths in children each year.[89] Pneumococcal conjugate vaccine (PCV) has been shown to reduce pneumonia hospitalisations by more than 50%, yet 46 countries, mostly LMICs, have not introduced the vaccine.[90 91] Similarly, 80 countries have not introduced rotavirus vaccine despite more than 128 000 deaths each

Box 2 Considerations on the prioritisation of COVID-19 vaccination for otherwise healthy children and adolescents

⇒ Current EPI coverage, especially measles and polio vaccines
⇒ Whether PCV, rotavirus and HPV vaccines have been introduced into the national immunisation schedule
⇒ COVID-19 burden and outcomes in children and adolescents
⇒ COVID-19 vaccine coverage in older age groups and high-risk groups
⇒ Levels of vaccine hesitancy
⇒ Other health system priorities

Box 3 Research priorities for COVID-19 vaccination in children and adolescents

⇒ Immunogenicity and duration of protection in high-risk populations
⇒ Understanding the burden of disease and severity with each variant of concern, including in LMICs
⇒ The role of hybrid immunity with new variants and response to vaccination and reinfections
⇒ Clinical trials of the safety and immunogenicity of co-administration of other childhood vaccines with COVID-19 vaccines
⇒ Vaccination dosage requirements in the context of lower disease burden and high levels of infection-derived immunity
⇒ Vaccine hesitancy and barriers to uptake

LMIC, low-income and middle-income countries

year. Eighty-six countries have not introduced human papillomavirus (HPV) vaccination of adolescents despite more than 300 000 women dying of cervical cancer each year, mostly in LMICs.[90 92] Co-infection with SARS-CoV-2 and other vaccine preventable diseases, such as influenza and pneumococcal pneumonia, increases disease severity. It is important that COVID-19 vaccine does not compete with routine EPI vaccination, but rather COVID-19 vaccine may be considered as an addition to the routine EPI vaccines. Considering the remarkable gains with COVID-19 vaccine rollout, with more than 50% of the world's population being fully vaccinated in a little over 1 year,[93] affordable delivery of all EPI vaccines should be a priority. Considerations for countries on the prioritisation of COVID-19 vaccines in children and adolescents are outlined in box 2.

Despite low EPI vaccine coverage in some settings, acceptance of routine childhood immunisations is generally high in LMICs.[94] However, studies on COVID-19 vaccine acceptance in LMICs have found substantial variation.[95] The most common reason for vaccine refusal in adults is concern about side effects. Although little is known about COVID-19 vaccine acceptance among parents of children in LMICs, hesitancy towards COVID-19 vaccines could potentially jeopardise uptake of routine vaccines and increase potential for a subsequent surge in vaccine preventable diseases. Each setting may need to carefully consider the timing of routine immunisation catch up in relation to offering COVID-19 vaccine if this is to be offered, to avoid any inadvertent harms to routine immunisation programmes. Depending on local circumstances, adding COVID-19 vaccination to the EPI programme may provide confidence to parents. Understanding vaccine hesitancy is one of several research priority areas related to COVID-19 vaccination in children and adolescents that are highlighted in box 3.

Lockdowns and school closures have had a disproportionate impact in LMICs, not least because of the much higher relative proportion of children in the population compared with HICs. In addition, in LMICs, the young often live in multigenerational households and therefore in closer proximity to the frail. In such settings, COVID-19 vaccination is most important in the high-risk elderly population. Vaccinating children may have helped prevent infections if they were available for this age group early on in the pandemic, when they were more effective against infection prior to the emergence of the Omicron variant.[96] However, when Omicron emerged, the uptake of vaccines in high-risk groups in LMICs was still suboptimal and a priority. Additionally, vaccinating children would have greater benefits if the vaccines were able to prevent infection more robustly, thereby limiting community transmission.[97 98] As the current COVID-19 vaccines were not available to children and adolescents until mid-2021 and they are non-sterilising, they did not contribute greatly to keeping schools open.[96]

The newer bivalent vaccines have slightly improved effectiveness against infection with Omicron but are far from being sterilising.[99] Intranasal vaccines, many of which are in development, including candidates from AstraZeneca, Bharat Biotech, CanSinoBIO and the Gamaleya Center, have greater potential to prevent infection. Intranasally administered live attenuated influenza vaccines provide broader protection and are better at preventing influenza infection in children than inactivated influenza vaccines due to the production of mucosal antibodies that protect at the point of entry of the virus.[100] Intranasal influenza vaccines have boosted vaccine efficacy to more than 87% in children, compared with rates of 30%–60% with injectable vaccines, although waning of effectiveness still occurs.[101 102] Intranasal influenza vaccines are not used by many countries so development of scalable and affordable delivery platforms will be crucial. Disappointingly at this stage, the intranasal AstraZeneca COVID-19 vaccine has not been shown to induce a consistent mucosal antibody response or a strong systemic immunological response.[103]

CONCLUSION

In LMICs, most people were infected by the time vaccines became available, which highlights the profound inequity in global vaccine distribution. More needs to be done to prevent this from happening again, including the consideration of children earlier in the clinical trial development process. By the time vaccines became available for low-risk populations of otherwise healthy children, infection-derived immunity

provided similar protection to vaccine-derived immunity and therefore countries who have not vaccinated children now need to consider whether to vaccinate based on their own context. The COVID-19 pandemic will, however, continue to have a significant impact on the paediatric population until high-risk children globally are also offered vaccination. Further studies are required to understand the immunogenicity and duration of protection in these high-risk groups, and the number of doses required in those who have been previously infected. The speed with which COVID-19 vaccination has been implemented highlights the scale of programmes that is possible if the required support is available, while noting that some of the reasons behind successful COVID-19 vaccination in LMICs had a negative impact on routine immunisation, such as the repurposing of EPI staff and other healthcare workers. Clinical trials of the safety and immunogenicity of co-administration of measles containing vaccine and other childhood vaccines would support countries opting to use COVID-19 vaccine rollouts as an opportunity to improve supply and delivery systems of all childhood vaccines. Countries may consider strategies for co-implementation of EPI and COVID-19 vaccines based on local or regional epidemiology, as available, and local circumstances, informed by surveys to determine the level of acceptance and barriers to vaccination in children.

Given the very high prevalence of risk factors for severe COVID-19 in LMICs, vaccination against COVID-19 is an important consideration in all age groups, including children. However, decisions should be made considering the direct benefits to the individual child, not broader benefits to the household, educational setting or community, particularly as the effectiveness against infection is transient.[73] The WHO has recently emphasised that LMICs should prioritise providing COVID-19 booster doses to people at high risk, including pregnant women. Countries may then consider vaccinating adolescents followed by younger children, in accordance with the age-based risk-benefit of vaccination and in the context of other health priorities.[2] Importantly, if COVID-19 vaccines are made available to children, the opportunity should be taken to increase coverage of routine childhood vaccines and opportunistically provide preventative healthcare and treatment at each encounter with the health system. This will help to address the indirect adverse effects of the pandemic on children.

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