COVID-19 vaccines for children younger than 12 years: are we ready?

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On May 5, 2021, Canada became the first country in the world to approve COVID-19 vaccine for emergency use in children aged 12–15 years; later the same month, the US Food and Drug Administration and European Medicines Agency also gave the green light to the Pfizer-BioNTech COVID-19 vaccine for adolescents.[1] Children younger than 12 years are the next population who need a safe and efficient COVID-19 vaccine. In *The Lancet Infectious Diseases*, Bihua Han and colleagues reported the results of a double-blind, randomised, controlled, phase 1/2 clinical trial, which showed that the inactivated COVID-19 vaccine (CoronaVac) had good safety, tolerability, and immunogenicity in youths aged 3–17 years.[2] This promising result should inspire the ongoing trial of other COVID-19 vaccines in children younger than 12 years.

Children contributed 14·1% of the total COVID-19 cases in the USA.[3] In children, COVID-19 is usually mild and often asymptomatic. However, in rare cases, children can become seriously ill and need hospitalisation and intensive care. One of the possible adverse outcomes has been termed multisystem inflammatory syndrome in children (MIS-C);[4] children with MIS-C have fever and become severely inflamed, and develop multisystem disorders involving the heart, lungs, kidneys, brain, skin, eyes, and gastrointestinal tract. The overall mortality of MIS-C is approximately 1–2%.[5] Evidence has shown an association between COVID-19 and MIS-C occurrence.[6] These adverse outcomes of COVID-19 in children justified the necessity to vaccinate children against COVID-19, as the BNT162b2 vaccine has shown 100% efficacy in children aged 12–15 years.

Herd immunity against COVID-19 is the prerequisite to end this pandemic, either through vaccinations or natural infection. Most estimates placed the threshold at 65–70% of the population gaining immunity, mainly by vaccination. However, widely circulating virus variants and persistent vaccine hesitancy make this threshold difficult to reach. A worldwide survey showed only 54% of respondents reported that they would definitely have a COVID-19 vaccination if it were available.[7] In addition, novel variants with increased transmissibility and enhanced immune-evasion changed the herd-immunity equation.[8] Thus, the calculation has to be revised upwards and children must be covered in the immunisation campaign. Moreover, from an epidemiological perspective, if we leave children unvaccinated when adults achieve immune protection, we cannot exclude the possibility that unvaccinated children become the virus shelter, given that most COVID-19 cases in children are mild and asymptomatic.

The inactivated vaccine in Han's trial induced higher titres of neutralising antibodies compared with adults aged 18–59 years who received the same vaccine;[2] the Pfizer-BioNTech vaccine showed a similar trend: vaccinees developed higher titres of neutralising antibodies in children aged 12–15 years than in those aged 16–25-years.[9] Children's strong response means that they are more likely to develop immune overactions than adults, such as fever and allergy, so COVID-19 vaccine for children should balance a protective immune response and side-effects. For the inactivated vaccine, CoronaVac, the 3 μg dose induced higher titres of neutralising antibodies than the 1·5 μg dose, whereas it showed no significant difference in side-effects between the two doses, so 3 μg doses were used for phase 3 trials in children. But for other vaccines, such as the mRNA and viral vector vaccines, lowering the vaccination dose used in adults should be considered in the clinical trial for children.

The safety and efficacy of COVID-19 vaccine in adults cannot guarantee the same performance in children. COVID-19 illness in adults post-vaccination was identified by onset of symptoms of acute respiratory illness; whereas in children, most COVID-19 cases are mild and asymptomatic, and parents might not be aware of the infection since children get sick more frequently than adults (such as with common colds), which would make the infection rate underestimated and efficacy overestimated. Moreover, children younger than 12 years are at their key stage of growth and development; caution should be taken to evaluate the long-term effect of vaccine on children's development. Although vaccinating children is essential to reach herd immunity and limit the severity of COVID-19, safety should be the paramount factor to be considered

before COVID-19 vaccine can be rolled out in younger children. Given the distinct immunogenicity profile and development stage of children, post-marketing surveillance of the vaccine safety should be done and maintained for a longer period than that in adults.

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How reliable are COVID-19 burden estimates for India?

With nearly 31 million reported COVID-19 cases and 410 000 deaths,[1] India is one of the countries with the heaviest burden of COVID-19 cases and deaths. There is near-universal consensus that the country's reported morbidity and mortality data are substantial underestimates. The majority of the morbidity and mortality in India are a consequence of the second wave, which started in March, 2021,[1] and which is attributable largely to the delta SARS-CoV-2 variant. There is some suggestion that India was largely spared from the COVID-19 disease burden in the first wave of the pandemic that began in June, 2020.[1] In the absence of good vital registration data and electronic health records that are available in more well resourced countries, good-quality surveillance data are relied upon to estimate disease burden. In this context, the study by Ramanan Laxminarayan and colleagues[2] in *The Lancet Infectious Diseases* makes a valuable contribution by reporting results from a large-scale active SARS-CoV-2 surveillance programme in Madurai, Tamil Nadu, during the first wave of the pandemic. In this study, prospective testing through RT-PCR was done from May 20, 2020, to Oct 31, 2020, for individuals with fever or acute respiratory symptoms as well as selected groups of individuals at high risk of COVID-19, including returning travellers, frontline workers, contacts of laboratory-confirmed COVID-19 cases, residents of containment zones, and patients having medical procedures. The authors also report data from a cross-sectional serosurvey done from Oct 19, 2020, to Nov 5, 2020.

On the basis of this surveillance, Laxminarayan and colleagues[2] report that the proportion of individuals who tested positive after RT-PCR was 3·6% overall (5·4% among symptomatic individuals and 2·5% among asymptomatic individuals). Although the number of males and females who received RT-PCR tests was broadly similar among symptomatic individuals, more males were tested than females among asymptomatic individuals. Adjusted odds of symptomatic SARS-CoV-2 infection were 21% higher among males than females, although this difference was reversed for asymptomatic infection. The case-fatality ratio among RT-PCR-confirmed cases was 2·4%. Although these findings are important for understanding the risk profile of symptomatic and asymptomatic infections at the population level, interpretation of these findings should be made in the context of several potential


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