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COVID-19 vaccination for children aged 5–11 years

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COVID-19 vaccines have already prevented millions of deaths during the current pandemic.[1] Given the strong association between increasing age and severe COVID-19 outcomes, adults were prioritised for vaccination when the first COVID-19 vaccines were authorised at the end of 2020.[2] For children, BNT162b2 (Pfizer–BioNTech), an mRNA-based vaccine against SARS-CoV-2, was authorised in May, 2021, for adolescents aged 12–15 years and in December, 2021, for those aged 5–11 years. In *The Lancet*, Chiara Sacco and colleagues[3] report the effectiveness of BNT162b2 in children aged 5–11 years after the omicron variant (B.1.1.529) emerged in Italy. Their retrospective population-based analysis shows that between Jan 17 and April 13, 2022, 1 063 035 (35·8%) of 2 965 918 children included in their dataset (1 441 166 [48·6%] were female and 1 524 752 [51·4%] were male) had received two doses and 134 386 (4·5%) one dose, while 1 768 497 (59·6%) remained unvaccinated. Based on 766 756 confirmed cases of SARS-CoV-2 infection, the adjusted vaccine effectiveness against infection was 29·4% (95% CI 28·5–30·2) in fully vaccinated and 27·4% (26·4–28·4) in partially vaccinated children, with effectiveness decreasing from a peak of 38·7% (37·7–39·7) at 0–14 days after two doses to 21·2% (19·7–22·7) by 43–84 days. Similar findings were reported in a preprint article based on data from New York (NY, USA), in which vaccine effectiveness against infection in children aged 5–11 years decreased from 65% (95% CI 62–68) during the first 2 weeks after two doses to 12% (8–16) by 28–34 days.[4]

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In Sacco and colleagues' study,[3] the adjusted vaccine effectiveness against severe COVID-19 was 41·1% (95% CI 22·2–55·4) in fully vaccinated and 38·1% (20·9–51·5) in partially vaccinated children, based on 644 hospitalisations (including 15 admissions to intensive care units and two deaths), which translates to a risk of hospitalisation of 84 per 100 000 infections, risk of intensive care unit admission of 2 per 100 000 infections, and fatality risk of 0·3 per 100 000 infections in this cohort. A recent US study reported cumulative hospitalisation rates of 19·1 per 100 000 infections among unvaccinated children and 9·2 per 100 000 infections among vaccinated children aged 5–11 years during December, 2021, to February, 2022.[5] These studies highlight the low risk of severe outcomes irrespective of vaccination status in children aged 5–11 years.[3–5]

As with any intervention, we need to consider the benefits and risks of vaccinating 5–11-year-olds against COVID-19. Although increased protection against infection was observed with early variants of SARS-CoV-2, BNT162b2 has been found to offer limited, short-term protection against the omicron variant.[6,7] In May, 2022, the US Centers for Disease Control and Prevention recommended a third dose of BNT162b2 for children aged 5–11 years,[8] but real-world experience in adults indicates that protection against SARS-CoV-2 infection will also wane within a few weeks after the third dose.[7] Therefore, unless the plan is to revaccinate every few months, vaccination alone is unlikely to be an effective strategy for preventing SARS-CoV-2 infections. Reassuringly, reinfections in children have been found to be no more severe than primary infections.[9]

Studies have also shown that COVID-19 vaccines reduce, but do not prevent, transmission from vaccinated individuals infected with more recent variants, especially delta (B.1.617.2) and omicron.[10] Thus, any decision to vaccinate children aged 5–11 years should be made to protect the individual child and not others in the household, educational setting, or community. For this reason, children with underlying comorbidities should be prioritised for vaccination because of their increased risk of hospitalisation and death due to COVID-19.[11] Although Sacco and colleagues do not differentiate between those

with and without comorbidities, BNT162b2 will probably also help protect healthy children against their very low risk of severe COVID-19, as it does in adolescents and adults.[6,7] However, this protection is lower in children aged 5–11 years than in older age groups, possibly because of their lower vaccine dose (10 mg *vs* 30 mg).[12]

Another reason for vaccinating children aged 5–11 years, as has been shown in adolescents,[13] would be to protect against multisystem inflammatory syndrome in children (MIS-C), which is a rare but serious post-infectious, hyperinflammatory syndrome that typically occurs 2–6 weeks after SARS-CoV-2 infection. Interestingly, in England, for example, the incidence of MIS-C has been decreasing since the delta variant emerged, even in the absence of vaccination during the delta wave and low rates of adolescent vaccination during the omicron wave.[14] Additionally, there are also concerns about post-acute COVID syndrome (PACS), also known as long COVID. In adults, vaccination reduces the risk of PACS,[15] but this finding has not been reported in children. Reassuringly, paediatric studies with appropriate control groups conducted before COVID-19 vaccines became available for children identified low rates of persistent symptoms after SARS-CoV-2 infection.[16]

When considering risks, post-implementation studies have found BNT162b2 to be safe in children aged 5–11 years.[17] Importantly, the small but serious risk of vaccine-induced myocarditis appears to be much lower in children aged 5–11 years (reporting rate of 2·2 cases per million doses) than in adolescents or young adults.[17] Implementation of a large-scale immunisation programme, however, comes with both financial and opportunity costs—for example, diversion of health-care staff and resources could potentially affect the provision of other crucial health-care services, such as routine childhood immunisation programmes. Clinicians and parents must balance the relatively small risks of severe disease outcomes with the relatively small risks that accompany vaccination in children aged 5–11 years. Although many countries continue to actively recommend COVID-19 vaccination for children aged 5–11 years, some countries, such as Sweden, have advised against vaccinating healthy 5–11 year-olds,[18] whereas others, such as Norway, have made the vaccine available should parents wish to vaccinate their children.[19] With the US Food and Drug Administration authorisation of use of COVID-19 vaccines in children younger than 5 years,[20] the same dilemmas are likely to resurface, although with even more marginal risk–benefit ratios. In particular, considering that the global population has been living through the pandemic for more than 2 years and has been exposed to multiple waves of different SARS-CoV-2 variants, governments, policy makers, and clinicians need to urgently address the added value of vaccination—be it primary or boosters—for protection against severe disease outcomes in children who have already been infected by the virus. Above all, public messaging of the risks and benefits of vaccinating children against COVID-19 needs to be clear to encourage public confidence in vaccines and trust in those advocating for vaccination to prevent other, more serious diseases.

I am the clinical lead for surveillance of a number of vaccine-preventable infections, including paediatric COVID-19, at the UK Health Security Agency. The views and opinions expressed in this Comment belong solely to the author, and not necessarily to the author's employer, organisation, or committee.

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Intravenous thrombolysis before thrombectomy for acute ischaemic stroke

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Before endovascular therapy, patients with ischaemic stroke due to occlusion of large arteries were treated with only intravenous thrombolysis, specifically alteplase. Intravenous thrombolysis recanalised about 25% of occluded large arteries, resulting in fewer than 30% of patients achieving functional independence (modified Rankin Score [mRS] 0–2) at 90 days.[1] In 2015, second-generation thrombectomy devices, in combination with intravenous thrombolysis, were proven to recanalise about 70–80% of arteries and improve rates of functional independence by 20–30% compared with intravenous thrombolysis alone.[2] Some in the field began to ask if intravenous thrombolysis is even necessary for these patients. Intravenous thrombolysis can delay the more often definitive therapy of endovascular therapy. Moreover, intravenous thrombolysis could increase symptomatic intracerebral haemorrhage, or distal migration of thrombi, rendering them inaccessible to thrombectomy. Intravenous thrombolysis certainly incurs substantial cost.[3]

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Four previous trials have addressed this question of endovascular therapy versus intravenous thrombolysis and endovascular therapy. The SKIP trial in Japan and the MR CLEAN-NO IV trial in Europe did not show non-inferiority of endovascular therapy alone.[4,5] The DEVT and DIRECT-MT trials, both in China, showed non-inferiority but used wide margins inclusive of clinically meaningful effects.[6,7] DEVT allowed for up to a 10% reduced rate of functional independence, and DIRECT-MT allowed for an adjusted common odds ratio of as low as 0·80 for a favourable functional level, for direct endovascular therapy to be declared non-inferior. Both trials also had methodological issues that increased the risk of bias, including long arrival to intravenous thrombolysis start times and significant protocol deviations for DIRECT-MT.[8] Nevertheless, the results generated the hypothesis of differential treatment effects in Chinese patients, or perhaps Asian patients, compared with others.

In *The Lancet* two further trials by Urs Fischer and colleagues (SWIFT-DIRECT)[9] and Peter J Mitchell and colleagues (DIRECT-SAFE)[10] have each further tested the non-inferiority of bypassing intravenous thrombolysis. To address the question most ethically, as with the previous trials, these two trials exclusively enrolled the subset of endovascular therapy-eligible patients who arrived for medical care at thrombectomy-capable centres