Should children be vaccinated against COVID-19?

Petra Zimmermann, Laure F Pittet, Andrew J Pollard, Adam Finn, Nigel Curtis

ABSTRACT

Whether all children under 12 years of age should be vaccinated against COVID-19 remains an ongoing debate. The relatively low risk posed by acute COVID-19 in children, and uncertainty about the relative harms from vaccination and disease mean that the balance of risk and benefit of vaccination in this age group is more complex. One of the key arguments for vaccinating healthy children is to protect them from long-term consequences. Other considerations include population-level factors, such as reducing community transmission, vaccine supply, cost, and the avoidance of quarantine, school closures and other lockdown measures. The emergence of new variants of concern necessitates continual re-evaluation of the risks and benefits. In this review, we do not argue for or against vaccinating children against COVID-19 but rather outline the points to consider and highlight the complexity of policy decisions on COVID-19 vaccination in this age group.

INTRODUCTION

Whether all children should be offered vaccination against SARS-CoV-2 has been controversial in children aged 12–15 years old, and remains so for those under 12 years of age, partly because the balance of risk and benefit in this age group is more complex (see figure 1).

The risk of severe acute COVID-19 in healthy children infected with SARS-CoV-2 is much lower than in adults.1–10 Two longer term consequences of SARS-CoV-2 infection might therefore be more of a concern in this age group. The first is ‘paediatric inflammatory multisystem syndrome-temporally associated with SARS-CoV-2 (PIMS-TS)’, also known as ‘multisystem inflammatory syndrome in children’, an immune-mediated disease that occurs in a small proportion of children 2–6 weeks after being infected with SARS-CoV-2.11–20 The second is long COVID-19, the persistence of symptoms following SARS-CoV-2 infection, a heterogeneous group of conditions.21

Aside from potential long-term consequences, other considerations in deciding on COVID-19 vaccine policy for children include safety (both common reactions and rare serious side effects), population-level factors, such as reducing community transmission, vaccine supply, cost of vaccination, the avoidance of quarantine, school closures and other lockdown measures, and the potential impact on routine immunisation programmes.

In this review, we do not argue for or against vaccinating children against COVID-19 but rather outline the points to consider to highlight the complexity of policy decisions on COVID-19 vaccination in this age group.

Benefits and risks of vaccinating children against COVID-19

The main question for implementing any vaccine is ‘do the benefits of the vaccine in preventing the harms of the disease outweigh any known or potential risks associated with vaccination?’ To date, two COVID-19 vaccines have been shown to be effective in children aged 12–17 years, and have been authorised for emergency use and subsequently recommended for this age group in many countries.22–24 Both vaccines are currently being evaluated in children aged 6 months–12 years and it is likely that emergency authorisation will be sought in this age group soon. Nevertheless, COVID-19 vaccine trials in adolescents so far include less than 4000 participants and appropriately focus on efficacy, immunogenicity and rates of common reactions.25 26 A phase 2/3 trial in children 5–12 years of age recently reported that a messenger RNA (mRNA) vaccine was safe, well tolerated and induced robust neutralising antibodies.27 Results from the same trial in children under 5 years of age are expected by the

What is already known on this topic?

- COVID-19 is generally asymptomatic or mild in children, but can be more severe in those with certain comorbidities.
- There is no consensus on whether all healthy children less than 12 years of age should be vaccinated against COVID-19.
- Data from COVID-19 vaccine use in this age group will become available in the near future.

What this study adds?

- The balance of risks and benefits of COVID-19 vaccination in children is more complex than in adults as the relative harms from vaccination and disease are less well established in this age group.
- One of the key arguments for vaccinating children less than 12 years of age, apart from reducing acute illness, is to protect them from long-term consequences of COVID-19; other considerations include population-level factors.
- The risks and benefits need continual re-evaluation with the emergence of new variants of concern, and new data on effectiveness and adverse effects.
end of 2021. Rare adverse effects are difficult to detect with such sample sizes, and are often seen only after large-scale use. Outside clinical trials, millions of adolescents between 12 and 18 years of age have been vaccinated, including 13 million in the USA. Arguments for and against vaccinating children against COVID-19 are summarised in table 1.

### Potential benefits of vaccinating children

#### Protection against COVID-19

COVID-19 is generally a mild disease in children with less than 2% of symptomatic children requiring hospital admission. The rate of intensive care admission of hospitalised children ranges between 2% and 13%, and higher rates (10% - 25%) are reported up to 33% in some studies. Higher rates than 2% of symptomatic children who are hospitalised with COVID-19 and not because of COVID-19, and therefore overestimate the severity. In children and adolescents, the risk of death from SARS-CoV-2 infection is 0.005%, and in those who are hospitalised with COVID-19 it is 0.0% - 0.7%. However, these numbers often include children who are hospitalised with COVID-19 and not because of COVID-19, and therefore overestimate the severity. In children and adolescents, the risk of death from SARS-CoV-2 infection is 0.005%, and in those who are hospitalised with COVID-19 it is 0.0% - 0.7%.

There are insufficient data to estimate the risk of myocarditis in children and adolescents with COVID-19, although one report from the USA suggested a risk of 876 cases per million. Another study reported an adjusted risk ratio for myocarditis from patients with COVID-19 compared with patients without COVID-19 of 36.8 in children less than 16 years of age and 7.4 in adolescents 16-24 years of age. A third study reported an 8.2-fold increase in myocarditis admissions during the pandemic, but no cases among the 1371 children and adolescents less than 18 years of age. Information on the long-term outcome of myocarditis resulting from SARS-CoV-2 infection (e.g., progression to fibrosis) is currently lacking.

In the USA, with the emergence of the more transmissible Delta variant, a recent rise in infections in children has led to overcrowded hospital and intensive care units. For hospitalised children, intensive care admission and mortality rates are currently stable at 23% and 0.4%-1.8% respectively. Of note, this has occurred in settings with low vaccine coverage in adults and suboptimal preventive measures in place. There are no reports indicating an increase in the severity of COVID-19 in children since the Delta variant has become dominant.

At this time, COVID-19 vaccines only have ‘emergency use authorisation’ in children between 12 and 16 years of age, which is for interventions that address a serious or life-threatening condition. It has been argued that, unless children are at high risk of severe COVID-19 because of an underlying condition, it is unclear whether the benefits to the individual outweigh the risks in this age group, and approval through the standard regulatory process should be awaited.

There are good reasons to consider offering vaccination to children and adolescents at higher risk of being hospitalised or becoming severely unwell from a SARS-CoV-2 infection, as, in their case, the risk of harm from vaccination is estimated to be lower than the risk of harm from COVID-19. This includes children with neurodisabilities, Down’s syndrome, immunodeficiencies, malignancies, some cardiac, respiratory and renal diseases, obesity and poorly controlled diabetes.

The low risk of hospitalisation and death from COVID-19 might not be a good argument against vaccinating against this disease as the risk is similar or even higher than that for other diseases for which vaccines are routinely given, such as varicella, rubella, hepatitis A and influenza. In addition, if a high proportion of children are infected, even a very low rate of severe illness might translate to a high absolute number of cases. Moreover, in low/middle-income countries (LMICs), the impact of COVID-19 in children may be greater due to comorbidities that impact immunity, including diarrhoea, dengue fever, tuberculosis, malnutrition, stunting and anaemia. Similarily, in high-income

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<tr>
<td>Protection against COVID-19</td>
<td>COVID-19 is generally mild in children</td>
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<td>Protection against severe COVID-19</td>
<td>Risk of adverse effects</td>
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<td>Impact of new variants uncertain</td>
<td>Long-term safety unknown</td>
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<tr>
<td>Protection against PIMS-TS</td>
<td>Efficacy against PIMS-TS unknown</td>
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<td>Protection against long COVID</td>
<td>Efficacy against long COVID unknown</td>
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<tr>
<td>Contribution to reducing community transmission</td>
<td>Impact on transmission uncertain</td>
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<td>Avoidance of isolation, quarantine, school closures and other indirect harms of lockdowns</td>
<td>Large proportion already immune</td>
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<td>Faster return to pre-pandemic activity and economic stability</td>
<td>Limited vaccine supply</td>
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<td>Impact on routine immunisations</td>
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<td>Cost</td>
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**Figure 1** Summary of benefits and risks of vaccinating children against COVID-19. PIMS-TS, paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2.
<table>
<thead>
<tr>
<th>Table 1 Arguments for and against vaccinating children against COVID-19</th>
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<td><strong>Arguments for COVID-19 vaccination</strong></td>
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<tr>
<td><strong>Benefits of vaccinating children</strong></td>
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<td>(1) Protection against COVID-19</td>
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<td>(2) Protection against severe COVID-19</td>
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<td>(3) Protection against PIMS-TS</td>
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<td>(4) Protection against long COVID-19</td>
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<td>(5) Prevention of community transmission</td>
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<td>(6) Avoidance of indirect harms, including quarantine, school closure and other harms of lockdowns</td>
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*Table 1: Arguments for and against vaccinating children against COVID-19.*
logical abnormalities have largely resolved. However, the after discharge, 96% of children have a normal echocardiogram and 100% of abnormal cardiac findings are reported to resolve with PIMS-CoV.

Protection against PIMS-TS
The risk of PIMS-TS is low, affecting less than 0.1% of children with PIMS-TS are admitted to intensive care units, almost all patients recover without sequelae. Between 79% and 100% of abnormal cardiac findings are reported to resolve within 14–30 days after hospital discharge. Six months after discharge, 96% of children have a normal echocardiography, and renal, haematological, otorhinolaryngological and neurological abnormalities have largely resolved. However, the long-term consequences of PIMS-TS remain uncertain and the death rate from PIMS-TS is estimated to be 1%–2%. There is no evidence to date on whether vaccination protects against PIMS-TS: although by protecting against SARS-CoV-2 infection it may well also protect against post-infectious sequelae; data are needed to confirm this. Since the pathogenesis of PIMS-TS remains unclear, there is also a theoretical risk that antibodies induced by COVID-19 vaccination could cause PIMS-TS, though there is no evidence of this to date.

Protection against long COVID-19
While vaccination prevents infection with SARS-CoV-2 to a degree and thus, presumably, persistent symptoms following the infection, more data are needed to determine accurately the incidence of long COVID-19 in children. Studies to date report a prevalence ranging from 1.2% to 66%. However, most of these studies have substantial limitations, including a lack of a clear case definition, the absence of a control group without infection, inclusion of children without laboratory-confirmed SARS-CoV-2 infection, follow-up at arbitrary time points and high non-responder bias. Of the five studies to date that have included controls, two did not find a difference in the prevalence of persistent symptoms between infected and uninfected children. This highlights the difficulty of separating COVID-19-related symptoms from those attributable to other factors associated with the pandemic, such as lockdowns and school closures. The three that did find a difference had significant limitations, including potential selection bias due to a high non-responder rate, that could lead to an overestimate of the risk of long COVID-19.

Prevention of community transmission
Another advantage of vaccinating children is helping decrease infectious transmission and thus reducing severe cases in adults and the risk of new virus variants emerging. As well as reducing disease, COVID-19 vaccines also reduce infection. Initial studies reported that vaccinated individuals who become infected are

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<tr>
<td>(1) Risk of adverse effects</td>
<td>Myocarditis after mRNA vaccines is transient and usually without sequelae</td>
<td>Myocarditis after mRNA vaccines including need for intensive care</td>
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<td>No reports of thrombosis after viral vector vaccines in children and adolescents</td>
<td>Potential risk of thrombosis after viral vector vaccines</td>
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<td>No reports of PIMS-TS after vaccination to date</td>
<td>Potential trigger for PIMS-TS (no evidence to date)</td>
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<td>(2) Long-term safety</td>
<td>Adverse effects of vaccines usually occur early</td>
<td>Long-term safety in children, including following myocarditis, unknown</td>
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<td>If concerns arise, this might lead to decrease in vaccine confidence and vaccine uptake, including against other diseases</td>
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<td>No studies to date have evaluated co-administration with other vaccines</td>
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<td>(3) Vaccine supply</td>
<td>One dose or a reduced dose might be sufficient in children</td>
<td>Current limited vaccine supply should be prioritised for people at high risk of severe disease and death</td>
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<td>Vaccine supply might be better used for adults in LMICs where &lt;5% of population have been vaccinated</td>
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<td>(4) Cost</td>
<td>Greater herd immunity likely better for returning to pre-pandemic economic stability</td>
<td>Likely higher cost-benefit ratio in children</td>
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<td>(5) Other immunisation programmes</td>
<td>Could be combined with the administration of other routine vaccines</td>
<td>Implementation of universal COVID-19 vaccination programme in children could cause delays in the routine immunisation programmes by using up existing delivery resources and personnel</td>
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LMICs, low/middle-income countries; mRNA, messenger RNA; PIMS-TS, paediatric inflammatory multisystem syndrome-temporarily associated with SARS-CoV-2.
less likely to transmit the virus due to decreased viral load and duration of virus shedding, and as a consequence, transmission from vaccinated individual to household contacts is significantly lower (by 50% in one study). However, more recent studies done since the Delta variant became dominant show similar viral loads in vaccinated and unvaccinated individuals.

Children, including young children, can transmit SARS-CoV-2. Nonetheless, even though transmission in schools can contribute to the circulation of SARS-CoV-2, the rate of transmission in educational settings is low and index cases are often adults. The risk of infection in schools correlates strongly with local community infection rates, which can be reduced by vaccinating older age groups. Nevertheless, the risk of transmission in different age groups and settings might change with the emergence of new virus variants of concern. For the Delta variant, it has been suggested that infected fully vaccinated individuals are as likely to transmit SARS-CoV-2 as infected unvaccinated individuals, although for shorter duration. Recent data from Australia reported a low risk of transmission in educational settings with protection measures in place, even with the Delta variant (the transmission rate from adults to children was 8%, from children to adults 1.3% and from children to other children 1.8%).

Earlier in the pandemic, it was reported that index cases in households were more likely to be a parent or adolescent than a young child. However, one study suggests that children and adolescents are more likely to infect others. Another study reported that household transmission was more common from children aged 0–3 years than from children aged 14–17 years. However, this might change with the Delta or other new variants. In a population with low numbers of vaccinated adults, infected children transmitted the Delta variant to 70% of households (in 57% of households all members became infected). Nevertheless, once a large proportion of the adult population is vaccinated, preventing transmission to them from unvaccinated children becomes less important. There is a stronger argument for vaccinating children and adolescents who live with immunosuppressed or other high-risk household members, not only for the protection of the latter but also to benefit the mental health of the former. Also, in LMICs children under 12 years of age form a larger proportion of the population and might therefore have a larger role in transmission.

Another consideration is that, once SARS-CoV-2 becomes endemic, primary SARS-CoV-2 infection in early childhood, when COVID-19 is mild, with subsequent boosting from ongoing exposure at older ages, may bring about population immunity, seen with common circulating coronaviruses, more effectively than mass immunisation.

Avoidance of indirect (population-level) harms
Vaccinating children and adolescents might help reduce the indirect harms caused by quarantine, lockdowns, repeat testing, school exclusion and closures, and other policies aimed at reducing community transmission, although the extent to which mass vaccination is necessary to achieve this remains unclear. Also, if the purpose of lockdowns and school closures is to protect adults, the incremental benefit of vaccinating children will be minimal once most adults are protected through vaccination. The possibility that vaccination might become a requirement for children for international travel is another consideration.

Potential risks of vaccinating children
Risk of adverse effects
As with any vaccine, there are potential rare adverse effects of COVID-19 vaccines. The development of myocarditis or pericarditis after mRNA vaccines has been a recent concern, particularly in male adolescents (studies reporting 6.3–6.7 cases per 100 000 second vaccine doses in males aged 12–17 years, and 15.1 cases per 100 000 second vaccine doses in males aged 16–19 years). Another study reported an incidence of 10.7 cases per 100 000 persons in males aged 16–29 years. Of these patients, approximately 6% required intensive care admission. However, most recovered without sequelae (86% had resolution of symptoms after mean duration of 35 days). Importantly, even in this age group, recent reports suggest the risk of myocarditis associated with COVID-19 is higher (see above).

The risk of thrombosis after viral vector vaccines observed rarely in adults also needs to be considered. The thrombotic risk in children or adolescents is less and no cases have been reported to date in this age group. However, since the pathogenesis underlying thrombosis associated with COVID-19 vaccines is thought to differ from that for clots from other causes, such as stasis and the contraceptive pill, further data from children are necessary. As thrombotic events have either not been observed or appear to be very rare in Asia, Africa and Latin America, some countries are considering these vaccines as an option. The theoretical risk of COVID-19 vaccines triggering PIMS-TS has been raised but there are no reports of this to date.

Long-term safety
The lack of long-term safety data is another consideration. Longer term follow-up of myocarditis cases is needed to exclude any possibility of myocardial fibrosis and associated dysfunction or arrhythmia risk. Two studies showed a high prevalence of late gadolinium enhancement in MRIs in patients suffering from post-vaccine myocarditis. Further studies are needed to establish whether this resolves or evolves into fibrosis. As discussed above, information on this risk is also needed for myocarditis resulting from SARS-CoV-2 infection.

Although the majority of adverse vaccine effects occur early after vaccination, any unforeseen adverse effects could undermine vaccine confidence and reduce vaccination rates against other diseases.

Vaccine supply
The currently limited global COVID-19 vaccine supply is another factor to consider. To date, many LMICs have only been able to vaccinate less than 5% of their population despite the COVAX programme. At this time, available supplies might be better prioritised for vaccinating adults with a higher risk of severe COVID-19 and death, including healthcare workers. Another consideration is the higher immunogenicity of mRNA vaccines in children, meaning that one dose or a reduced dose might be sufficient to protect this age group. On the other hand, the infrastructure to upscale the production of COVID-19 vaccines already exists and strategies for boosting global supply have been outlined.

Cost
Since the risks of intensive care admission or death in children are so low, the cost–benefit ratio of COVID-19 vaccination in children is higher. However, the emergence of new variants...
might change this if these variants cause more frequent or more severe disease in children. The cost of vaccination also needs to be balanced against the reduction in community transmission that might be achieved through vaccinating children, which would enable a faster return to pre-pandemic economic stability with associated benefits to children.

**Other immunisation programmes**

Routine immunisation programmes for children and adolescents have been disrupted by the pandemic. Implementing a universal COVID-19 vaccine programme for these age groups runs the risk of causing further delays by using up existing delivery resources and personnel. This in turn may harm children by resulting in more cases of vaccine-preventable infections and diseases such as cervical cancer, meningitis, measles and pertussis. However, if COVID-19 vaccination is combined with the administration of other routine vaccines, this problem might be reduced.

**CONCLUDING REMARKS**

In summary, the case for vaccinating all healthy children against COVID-19 is more difficult than for adults as the balance of risks and benefits is more nuanced. If COVID-19 remains a generally mild disease in children and in vaccinated adults, it may not be necessary to vaccinate all children. In addition, it is important to consider different age groups separately; the balance of risk and benefit of vaccination is likely to differ between infants, young children and adolescents. Children under 5 years of age are likely to need separate consideration to those 5–11 years of age. Continued monitoring of disease severity across all age groups is crucial. If a variant of concern emerges with increased severity in children (as is, for example, the case for Middle East respiratory syndrome-related coronavirus), this would alter the risk–benefit equation. In LMICs, where the burden of COVID-19 is higher in the paediatric population as a result of comorbidities, there may be a lower threshold for vaccinating children. A one-dose schedule (as now recommended in the UK and Norway) or a reduced-dose vaccine might be an option for this age group; this might also reduce the risk of myocarditis with the second dose of mRNA vaccines. Although mass COVID-19 vaccination of all ages, including children under 12 years of age, may become the general approach globally in the future, it seems wise at present to weigh up the risks and benefits with caution and to proceed with care.

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**REFERENCES**


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Review