Should children be vaccinated against COVID?

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What is known

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

What is new

- The balance of risks and benefits of COVID 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; other considerations include population-level factors
- The risks and benefits need continual reevaluation with the emergence of new variants of concern, and new data on effectiveness and adverse effects

Abstract

Whether all children less than 12 years of age should be vaccinated against COVID remains an ongoing debate. The relatively low risk posed by acute COVID 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 reevaluation of the risks and benefits. In this review, we do not argue for or against vaccinating children against COVID but rather outline the points to consider to highlight the complexity of policy decisions on COVID vaccination in this age group.

Introduction

Whether all children should be offered vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been controversial in 12 to 15 year olds and remains so for under 12s, partly because the balance of risk and benefit in this age group is more complex (see figure 1).

The risk of severe acute COVID in healthy children infected with SARS-CoV-2 is much lower than in adults.[1-11] 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 (MIS-C)', an immune-mediated disease that occurs in a small proportion of children two to six weeks after being infected with SARS-CoV-2.[12-21] The second is long COVID, the persistence of symptoms following SARS-CoV-2 infection, a heterogenous group of conditions.[22]

As well as potential long-term consequences, other considerations in deciding on COVID 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 but rather outline the points to consider to highlight the complexity of policy decisions on COVID vaccination in this age group.

Benefits and risks of vaccinating children against COVID

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 vaccines have been shown to be effective in children aged 12 to 17 years, and have been authorised for emergency use and subsequently recommended for this age group in many countries.[23-27] Both vaccines are currently being evaluated in children aged 6 months to 12 years and it is likely that emergency authorisation will be sought in this age group soon. Nevertheless, COVID vaccine trials in adolescents so far include less than 4000 participants and appropriately focus on efficacy, immunogenicity and rates of common reactions.[26,27] A phase 2/3 trial in children 5 to 12 years of age recently reported that an mRNA vaccine was safe, well-tolerated and induced robust neutralising antibodies.[28] Results from the same trial in children under 5 years of age are expected by the 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 US.[29] Arguments for and against vaccinating children against COVID are summarised in table 1.

Potential benefits of vaccinating children

1. Protection against COVID

COVID is generally a mild disease in children with less than 2% of infected children requiring hospital admission.[1-11] The rate of intensive care admission of hospitalised children ranges between 2 and 13%.[1,7,8,30,31] Higher rates (10-25%,[32,33] up to 33% in some studies[34,35]) are reported from the US. However, these number often include children who are hospitalised with COVID and not because of COVID, and therefore overestimate the severity. In children

and adolescents, the risk of death from SARS-CoV-2 infection is 0.005%,[36] and in those who are hospitalised with COVID it is 0-0.7%.[1,7,8,30,31,34,35] However, again, these numbers often include children who died with a SARS-CoV-2 infection and not because of it (a recent population-based study showed that only 41% of child deaths reported from SARS-CoV-2 infections were from COVID).[36] Therefore, the prevention of SARS-CoV-2 infection is not as strong an argument for vaccinating all healthy children as it is for adults. Nevertheless, this might change if new variants emerge which cause more severe disease in otherwise healthy children.

There is insufficient data to estimate the risk of myocarditis in children and adolescents with COVID, although one report from the US suggested a risk of 876 cases per million.[37] Another study reported an adjusted risk ratio for myocarditis from COVID compared with non-COVID patients of 36.8 in children less than 16 years of age and 7.4 in adolescents 16 to 24 years of age.[38] 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.[39] Information on the long-term outcome of myocarditis resulting from SARS-CoV-2 infection (e.g. progression to fibrosis) is currently lacking.

In the US, with the emergence of the more transmissibe Delta variant, a recent rise in infections in children has led to overcrowded hospital and intensive care units.[40] 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 in children since the Delta variant has become dominant. For hospitalised children, intensive care admission and mortality rates are currently stable at 23% and 0.4%[30] to 1.8%,[31] respectively.

At this time, COVID vaccines only have ‘emergency use authorisation’ in children between 12 to 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 for severe COVID 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.[41]

2. Protection against severe COVID

As, in their case, the risk of harm from vaccination is estimated to be lower than the risk of harm from COVID, 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, such as those with neuro-disabilities, Down’s syndrome, immunodeficiencies, malignancies, some cardiac, respiratory and renal diseases, obesity and poorly controlled diabetes.[42]

The low risk of hospitalisation and death from COVID might not be a good argument against vaccinating against this disease as the risk is similar or higher than that for other diseases for which vaccines are routinely given, such as varicella, rubella, hepatitis A, and influenza.[43] 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 and middle income countries (LMIC), the impact of COVID in children may be greater due to co-morbidities that impact immunity, including diarrhoea, dengue fever, tuberculosis, malnutrition, stunting and anaemia.[34] Similary, in high-income countries, children from deprived and ethnic minority groups are more frequently infected with SARS-CoV-2, which might be due to a greater

likelihood of living with unvaccinated adults or in multigenerational and overcrowded households.[44,45] These children have also been reported to have more severe COVID and to more frequently suffer from PIMS-TS.[46-48]

3. Protection against PIMS-TS

The risk of PIMS-TS is low, affecting less than 0.1% of SARS-CoV-2-infected children. Although up to 70% of children with PIMS-TS are admitted to intensive care units,[49,50] almost all patients recover without sequelae.[12-21,49,51,52] Between 79 and 100% of abnormal cardiac findings are reported to resolve within 14 to 30 days after hospital discharge.[49,53,54] Six months after discharge, 96% of children have a normal echocardiography, and renal, haematological, otolaryngological and neurological abnormalities have largely resolved.[46] However, the long-term consequences of PIMS-TS remain uncertain and the death rate from PIMS-TS is estimated to be 1-2%.[49,50] 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 vaccination could cause PIMS-TS, though there is no evidence of this to date.

4. Protection against long COVID

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 in children.[22] Studies to date report a prevalence ranging from 1.2 to 66%.[55-65] 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 nonresponder bias.[55-64,66-69] Of the five studies to date that have included controls,[56,60,62,66,70] two did not find a difference in the prevalence of persistent symptoms between infected and uninfected children.[62,66] This highlights the difficulty of separating COVID-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.[56,60,70]

5. *Prevention of community transmission*

Another advantage of vaccinating children is helping decrease transmission and thus reducing severe cases in adults and the risk of new virus variants emerging. As well as reducing disease, COVID vaccines also reduce infection. Initial studies reported that vaccinated individuals who become infected are less likely to transmit the virus due to decreased viral load and duration of virus shedding[71,72] and as a consequence, transmission from vaccinated individual to household contacts is significantly lower[73] (by 50% in one study[71]). However, more recent studies done since the Delta variant became dominant, show similar viral loads in vaccinated and unvaccinated individuals.[74-77]

Children, including young children, can transmit SARS-CoV-2.[78] Nonetheless, even though transmission in schools can contribute to the circulation of SARS-CoV-2,[79] the rate of transmission in educational settings is low and index cases are often adults.[80-83] The risk of infection in schools correlates strongly with local community infection rates, which can be reduced by vaccinating adults. 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 a shorter duration.[84,85] However, recent data from Australia reported a low risk of transmission in educational settings with protection measurements 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%).[86]

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.[6,87-89] However, one study suggests that children and adolescents are more likely to infect others.[90] Another study reported that household transmission was more common from children aged 0 to 3 than from children aged 14 to 17.[91] 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).[86] 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.

Another consideration is that, once SARS-CoV-2 becomes endemic, primary SARS-CoV-2 infection in early childhood, when COVID is mild, with subsequent boosting from ongoing exposure at older ages, may bring about population immunity, as seen with common circulating coronaviruses, more effectively than mass immunisation.[92]

6. 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

1. Risk of adverse effects

As with any vaccine, there are potential rare adverse effects of COVID vaccines. The development of myocarditis or pericarditis after mRNA vaccines has been a recent concern,[93,94] particularly in male adolescents (studies reporting 63 to 67 cases per million second vaccine doses in males aged 12 to 17 years,[93,95] and 150 cases per million second vaccine doses in males aged 16 to 19 years[96]). Another study reported the highest incidence of 10.7 cases per 100,000 persons in males aged 16 to 29 years.[97] Of these patients approximately 6% required intensive care admission.[98] However, most recovered without sequelae (86% had resolution of symptoms after a mean duration of 35 days).[99,100] Importantly, even in this age group, recent reports suggest the risk of myocarditis associated with COVID 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[101] and no cases have been reported to date in this age group. However, since the pathogenesis underlying thrombosis associated with COVID vaccines is thought to differ from that for clots from other causes, such as stasis and the oral 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 vaccines triggering PIMS-TS has been raised but there are no reports of this to date.[102]

2. 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 mycarditis.[99,103] 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.[104]

3. Vaccine supply

The currently limited global COVID vaccine supply is another factor to consider. To date, many LMIC 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 and death, including health care workers.[105] 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.[26] On the other hand, the infrastructure to upscale the production of COVID vaccines already exists and strategies for boosting global supply have been outlined.[106]

4. Cost

Since the risks of intensive care admission or death in children are so low, the cost-benefit ratio of COVID 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.[107] 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.

5. Other immunisation programmes

Routine immunisation programmes for children and adolescents have been disrupted by the pandemic.[108,109] Implementing a universal COVID 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 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 is more difficult than for adults as the balance of risks and benefits is more nuanced. If COVID remains a generally mild disease in children and in vaccinated adults, it may not be necessary to vaccinate all children.[92,110] 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 might need separate consideration to those 5 to 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.[92] In LMIC, where the burden of COVID is higher in the paediatric population as a result of co-morbidities, there may be a lower threshold for vaccinating children. A one-dose schedule (as now recommended in the UK and Norway)[111,112] 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 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 risk and benefits with caution and to proceed with care.

Competing interests

PZ, LP and NC declare that they have no competing interests.

AJP is Chair of UK Dept. Health and Social Care's (DHSC) Joint Committee on Vaccination & Immunisation (JCVI), but does not participate in policy decisions on COVID19 vaccine. He is a member of the WHO's SAGE. AJP is chief investigator on clinical trials of Oxford University's COVID19 vaccine funded by NIHR. Oxford University has entered a joint COVID19 vaccine development partnership with Astra Zeneca. The views expressed in this article do not necessarily represent the views of DHSC, JCVI, NIHR or WHO.

AF is an investigator in trials and studies of COVID19 vaccines manufactured by Pfizer-BioNTech, AstraZeneca, Janssen, Valneva and Sanofi but receives no personal remuneration or benefits for this work. He is a member of the UK Joint Committee on Vaccination and Immunisation and chairs the WHO Euro Regional Technical Advisory Group of Experts (ETAGE) on immunisation.

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Table Arguments for and against vaccinating children and adolescents against COVID

Argument	Arguments for COVID vaccination	Arguments against COVID vaccination
Benefits of vaccinating children		
(1) Protection against COVID	• Good justification if risk of SARS-CoV-2 infection is high • Risk of harm from vaccination lower than risk of harm from COVID[93] • Clear benefit for children with risk factors for severe COVID[42] • Risk of hospitalisation and death from COVID is commensurate with or higher than other diseases in routine immunisation programme[43] • Higher disease burden of COVID in children in LMIC with co-morbidities that impact immunity[34] • Higher immunogenicity of mRNA vaccines in children might mean one or lower dose sufficient[26] • Adolescents have a higher frequency of infection and disease burden than younger children	• Children are less likely to get infected after a SARS-CoV-2 exposure[79,113-116] • Most children have asymptomatic or mild COVID[1-4,6-8,11] • A large proportion of children might already be immune to SARS-CoV-2 in many regions of the world • Risk of COVID in children might be less if large proportion of adult population is vaccinated
(2) Protection against severe COVID	• Risk of severe COVID in children with underlying diseases is not negligible[1-4,6-8,11] • Risk of severe COVID in healthy children might be higher with SARS-CoV-2 current or future VOC	• Risk of severe COVID in healthy children is low[1-4,6-8,11] • At-risk children could be protected by targeted rather than universal vaccination
(3) Protection against PIMS-TS	• No long-term data on children with PIMS-TS; if sequelae are important the risk-benefit of COVID vaccination might change	• No data yet on whether vaccination prevents PIMS-TS • Risk of PIMS-TS is low, and children mainly recover without sequelae[12-20] • COVID vaccination might increase risk of PIMS-TS (no evidence to date)
(4) Protection against long COVID	• Long COVID can occur even after mild or asymptomatic infection[56,58,59,62,66,67,70] • Not well studied yet; could affect a large number of children	• The incidence of long COVID is still to be accurately determined[22] • Difficult to separate infection-associated from pandemic-associated symptoms[56,62,66]
(5) Prevention of community transmission	• Children, even young children, can transmit SARS-CoV-2[117] • Prevention of transmission to other children and older age groups • Prevention of transmission to high-risk household members • Herd immunity likely inachievable without vaccinating children and adolescents • Reduction in the risk of new VOC emerging • Risk of transmission might be changing with emergence of new VOC (e.g. delta)	• No data yet on whether vaccination prevents transmission in children • Transmission in educational settings is rare and index cases are often adults[80-83] • Index cases in households much more likely to be a parent or adolescent[6] • Community transmission will decrease if sufficient adults are vaccinated[71] • Subjecting children to potential risk of vaccine adverse effects to drive indirect effects with little or no direct benefit might be ethically questionable

	• Potential considerable indirect benefit (e.g. schools remaining open) to children even if no direct benefit (see (6)) • 'No one is safe until we are all safe'	• Effect of vaccination on transmission might decrease with waning immunity and emerge of VOC • Primary infection at young age when the disease is mild combined with boosting exposure from ongoing transmission at older age might be better strategy[92]
(6) Avoidance of indirect harms, including quarantine, school closure and other harms of lockdowns	• Transmission in school can contribute to the circulation of SARS-CoV-2[79] • Lockdowns and school closures have a major impact on physical and mental health of children[118] • Vaccinated children might be exempt from quarantine • COVID vaccination might become a requirement for international travel	• Might not be sufficient to prevent school closures and lockdowns (especially if a large proportion of adults are not vaccinated) • Might not be necessary to prevent school closures and lockdowns, especially if adult staff are all immunised

Risks of vaccinating children		
(1) Risk of adverse effects	• Myocarditis after mRNA vaccines is transient and usually without sequelae[93] • No reports of thrombosis after viral vector vaccines in children and adolescents to date[101] • No reports of PIMS-TS after vaccination to date	• Myocarditis after mRNA vaccines including need for intensive care[93,94,98,119] • Potential risk of thrombosis after viral vector vaccines • Potential trigger for PIMS-TS (no evidence to date)
(2) Long-term safety	• Adverse effects of vaccines usually occur early	• Long-term safety in children, including following myocarditis, unknown • If concerns arise this might lead to decrease in vaccine confidence and vaccine uptake, including against other diseases[104] • No studies to date have evaluated co-administration with other vaccines
(3) Vaccine supply	• One dose or a reduced dose might be sufficient in children	• Current limited vaccine supply should be prioritised for people at high risk for severe disease and death • Vaccine supply might be better used for adults in LMIC where <5% of population have been vaccinated[105]
(4) Cost	• Greater herd immunity likely better for returning to pre-pandemic economic stability	• Likely higher cost-benefit ratio in children
(5) Other immunisation programmes	• Could be combined with the administration of other routine vaccines	• Implementation of universal COVID vaccination programme in children could cause delays in the routine immunisation programmes by using up existing delivery resources and personnel

COVID – coronavirus disease
LMIC – low and middle income countries
mRNA – messenger ribonucleic acid
PIMS-TS – Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2
SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2
VOC – variants of concern

Figure 1 Summary of benefits and risk of vaccinating children against COVID (created by authors)