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Review

Crossing the Rubicon: A fine line between waiting and vaccinating adolescents against COVID-19

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SUMMARY

Several countries with advanced adult COVID-19 immunisation programmes have already started vaccinating adolescents with an mRNA vaccine that recently received emergency use authorisation for 12–15 year-olds. The decision to vaccinate adolescents remains highly divisive among parents, clinicians, politicians and policy makers. There are very few downsides to immunising adolescents with a safe and effective COVID-19 vaccine because that would significantly reduce their risk of COVID-19 and all its complications. Based on current evidence, however, adolescents have a very low risk of severe or fatal COVID-19, even among those with comorbidities, or rare complications such as long COVID or Paediatric Multisystem Inflammatory Syndrome (PIMS-TS), a hyperinflammatory syndrome temporally associated with SARS-CoV-2. Additionally, currently authorised vaccines are very reactogenic and have limited post-marketing population-level safety data in adolescents and young adults, but these are emerging from countries that have forged ahead with vaccinating adolescents. Countries that have yet to make a recommendation can afford to wait until there is sufficient information to make informed decisions on the risk-benefits of vaccinating adolescents with current and future COVID-19 vaccines. Alternatives to two-dose vaccination in adolescents may include a single dose or a reduced dose schedule as is currently being trialled in younger children.

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Introduction

Eighteen months into the coronavirus disease 2019 (COVID-19) pandemic, nearly 200 million confirmed cases and 4 million deaths have already been recorded worldwide.¹ Age remains by far the most important risk factor for death due to COVID-19, with case fatality rates increasing rapidly after 70 years of age, while specific comorbidities also contribute to an increased risk of death in adults.^{2,3} A number of COVID-19 vaccines successfully completed clinical trials after demonstrating acceptable safety, immunogenicity and reactogenicity profiles,⁴ and 2.7 billion doses have already been administered to 22.0% of the world's population by mid-June 2021.⁵ Emerging real-world data continue to demonstrate high vaccine effectiveness against severe disease, hospitalisations and death

due to COVID-19, including against variants of concern, even after a single dose of COVID-19 vaccine but more so after two doses.⁶

Compared to adults, children have been relatively spared by SARS-CoV-2, the virus responsible for COVID-19, with significantly lower risks of symptomatic disease, severe disease, hospitalisation, intensive care admission or death due to COVID-19.⁷ When exposed to SARS-CoV-2, most children remain asymptomatic or develop a mild, transient upper respiratory tract illness that usually lasts a few days.⁸ COVID-19 case fatality rates in children have remained extremely low, and restricted mainly to adolescents with severe life-limiting conditions, especially neurodisabilities.⁹ In May 2021, North American, European and other regulatory authorities extended the emergency use authorization for the BNT162b2 (Comirnaty, Pfizer-BioNTech) mRNA COVID-19 vaccine to include children aged 12–15 years (referred to as adolescents hereafter) after clinical trials demonstrated immunogenicity, acceptable reactogenicity and protection against SARS-CoV-2 infection in this age-group.¹⁰ It is likely that other COVID-19 vaccines will soon receive similar authorisation for adolescents,¹¹ and clinical trials on COVID-19 vaccines in younger childhood age-groups are already underway.¹² Consequently, several high-income countries with established adult COVID-19 immunisation programmes

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have already started vaccinating adolescents, including the United States, Canada, Israel and several European, middle-Eastern and Asia-Pacific countries.¹³ Whilst many countries, including the UK, are still deliberating on the decision to vaccinate adolescents, the World Health Organization (WHO) and some countries initially recommended against vaccinating adolescents against COVID-19 until more evidence became available, but this was subsequently updated on 22 June 2021 to include considerations for offering the vaccine to children at high risk of COVID-19 alongside other priority groups for vaccination.¹⁴ Here, we discuss the pros and cons of vaccinating adolescents against COVID-19 and options for countries that have yet to make a decision about vaccinating adolescents.

The pros of vaccination

There are many arguments for vaccinating adolescents against COVID-19, for whom an immunogenic and effective vaccine is already available. First and foremost is the direct protection afforded by vaccination. Most countries with established COVID-19 immunisation programmes are vaccinating adults from 18 years of age and some from 16 years of age. The arguments for vaccinating adolescents are essentially the same as those for vaccinating young adults in that the risk of COVID-19 and severe disease do not stop below a certain age. Likewise, most of the comorbidities defined within the priority risk-groups for vaccinating adults are also likely to apply to adolescents. Although their overall risk remains very low, adolescents can still develop severe COVID-19 and require hospitalisation, especially if they have underlying comorbidities,¹⁵ and nearly all childhood deaths in high-income countries have occurred in adolescents rather than younger children.¹⁶ Of those who recover from their acute infection, too, a small proportion may develop persistent and prolonged symptoms,⁸ including Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), just like with other respiratory viruses.¹⁷ Whilst significantly less common in adolescents and young children than in adults,⁸ the condition commonly termed 'Long COVID', 'long haulers', 'Post-acute COVID Syndrome' has yet to have a consensus case definition, making the risk, burden and outcomes difficult to define in any age-group.¹⁸

Additionally, an unexpected complication of SARS-CoV-2 infection in children was the emergence of Paediatric Multisystem Inflammatory Syndrome (PIMS-TS), a hyperinflammatory syndrome temporally associated with SARS-CoV-2, with features of Kawasaki disease and toxic shock syndrome, and also known as Multisystem Inflammatory Syndrome in Children (MIS-C).¹⁹ PIMS-TS occurs 2–4 weeks after exposure to SARS-CoV-2,¹⁹ and one study using cases in the United States estimate an incidence of 316 per million SARS-CoV-2 infections (3/10,000 or 0.03%) in 0–20 year-olds, including 197 per million SARS-CoV-2 infections (2/10,000 or 0.02%) among 11–15 year-olds²⁰. Children with PIMS-TS typically present with fever and features of circulatory shock with cardiac involvement, gastrointestinal symptoms and elevated markers of inflammation.^{19,21} Complications include cardiac dysfunction, shock, myocarditis, coronary artery dilatation or aneurysm, and acute kidney injury, with more than half the children requiring paediatric intensive care admission, and an overall case fatality rate of 1–2%.^{19,21} Vaccinating adolescents would, therefore, potentially reduce the risk of COVID-19 and PIMS-TS, resulting in fewer hospitalisations, intensive care admissions, long COVID cases and death, although the numbers needed to vaccinate to prevent these rare outcomes in adolescents would likely be very large and assumes that those who are most at risk of disease will have the vaccine when offered.

In addition to direct protection, there are additional indirect benefits of vaccinating adolescents. There is increasing evidence that both the mRNA and virus-vector COVID-19 vaccines not only protect against severe disease but also prevent asymptomatic in-

fections. A recent UK study, for example, found that adults who become infected 3 weeks after receiving one dose of the Pfizer-BioNTech or AstraZeneca vaccine were between 38 and 49% less likely to pass the virus on to their household contacts than those who were unvaccinated.²² Vaccinating adolescents would, therefore, make them less likely to transmit the virus to those around them, in school, in the household and in the wider community, including unvaccinated children and adults as well as clinically extremely vulnerable individuals who may not be adequately protected by vaccination, such as the immunocompromised. Vaccinating adolescents would also reduce disruption to their education, by protecting them individually against illness and their classmates from becoming infected, thus reducing the risk of school outbreaks and eliminating the need for bubbles, classes and year groups to self-isolate. This strategy would also provide parents with reassurance that their children are safe to attend school and allow them to plan their work without concerns about having to take time off work when their child has to self-isolate due to COVID-19 or because they were in contact with a case inside or outside school.

Given that most countries with established COVID-19 immunisation programmes have already acquired large volumes of COVID-19 vaccines, adding adolescents to an on-going rolling programme would likely to be easily achieved too. Many countries, including the UK, have established school-based immunisation programmes which could easily be adapted to vaccinate adolescents in school, which would also achieve higher vaccine uptake than primary care-based immunisation programmes.²³

The cons against vaccination

There are, however, several reasons for not rushing into extending COVID-19 vaccination for adolescents – at least, not for now. First and foremost is to allow time for formal evaluation of post-marketing safety of available vaccines after mass implementation in younger adults and, where implemented, in adolescents. The ChAdOx1-S/nCoV-19 adenoviral-vector (AstraZeneca) COVID-19 vaccine, for example, was recently found to be associated with a rare but severe vaccine-induced thrombosis and thrombocytopenia (VITT) syndrome in younger adults after their first dose,²⁴ which led to halting of clinical trials with the same vaccine in adolescents.²⁵ Similar safety concerns have also been raised with another adenoviral vector vaccine, Ad26.COV.2.S (Janssen/Johnson & Johnson).²⁶ More recently, both mRNA vaccines (Pfizer and Moderna) have been reported to cause acute myocarditis after the second dose, and mainly in young adults and adolescents which, in some cases, was severe enough to warrant hospitalisation and, rarely, admission to an intensive care unit.²⁷

Given the very low risk of severe disease or death due to COVID-19 in adolescents, it is necessary to consider that rare but potentially severe adverse events following COVID-19 vaccination could outweigh the risk-benefits of vaccinating adolescents, even in those with comorbidities, who also invariably recover uneventfully after developing COVID-19.²⁸ In a recent US study of adolescents hospitalised primarily for COVID-19 during the first 3 months of 2021, the weekly hospitalisation rate was only 0.6–2.1 per 100,000 adolescents- 70% had an underlying comorbidity and, while 31% were admitted to an intensive care unit, only 5% required mechanical ventilation and none died.¹⁵ Similarly, unlike many of the earlier studies with serious methodological flaws that reported high rates of long COVID,¹⁸ more recent studies with inclusion of appropriate control groups have indicated that the outcomes of COVID-19 in children are similar to other respiratory viral illnesses, with only a small minority reporting persistent symptoms beyond eight weeks.⁸ Additionally, whilst the epidemiological link between SARS-CoV-2 infection and PIMS-TS in children

continues to strengthen, the risk of this rare complication is estimated to be extremely low,²⁰ and, with better recognition of the condition, its clinical course and availability of effective treatments, the prognosis for PIMS-TS remains very favourable.²⁹

Another important consideration before recommending vaccination of adolescents is the potential indirect impact of the current adult COVID-19 immunisation programme on cases in children. In Israel, for example, the rapid and successful rollout of the Pfizer-BioNTech vaccine in adults led to a rapid reduction in cases, initially among adults but soon followed by equivalent declines among children aged < 16 years, indicating that adults are likely the main drivers of SARS-CoV-2 transmission in the community, including spreading the virus to children.³⁰ Israel is no longer in lockdown and children have now returned to full in-person education,³¹ although some cases and occasional outbreaks continue to occur, mainly in unvaccinated groups including children.³² Similar, as yet unsubstantiated, data are emerging from Brazil and parts of the US showing that adult vaccination is associated with declines in childhood cases.³³

If the Israel experience is confirmed in other regions with high adult vaccine uptake then vaccinating children – including adolescents – may not be needed to achieve herd immunity.³³ Also known as indirect or population protection, herd immunity is often misinterpreted as a threshold proportion of a population that would need to be immune to protect the rest of the (unvaccinated) population. If a vaccine can prevent transmission, then herd immunity can be achieved by targeting vaccination towards the major transmitters in the population. For example, immunising infants and toddlers, who are the main nasopharyngeal carriers of *S. pneumoniae*, with pneumococcal conjugate vaccines, results in large reductions in invasive pneumococcal disease across all age groups because of interruption of transmission from vaccinated young children to unvaccinated older children and adults.³⁴ Similar population reductions have been observed after immunising teenagers, who are the main nasopharyngeal carriers of *N. meningitidis*, with meningococcal conjugate vaccines.³⁵ In the current pandemic, the data indicate that young adults are driving SARS-CoV-2 transmission,³⁶ and, therefore, high vaccine uptake in young adults would indirectly protect unvaccinated individuals across all age groups, including children. In the UK, COVID-19 vaccination was prioritised for those at highest risk of severe disease and death. This included older adults, health and care workers and those underlying at-risk medical conditions. The rollout was extended gradually to younger adults and, since June 2021, is now offered to all adults from 18 years of age. If sufficient vaccine uptake is achieved in young adults, then, like Israel, significant reductions would be expected in all age groups, including children, through herd protection. On-going UK surveillance will help answer this important question in the coming months.

The decision not to vaccinate adolescents, however, would mean that infection in children and outbreaks in schools will continue to occur, even in populations with high adult vaccine uptake.³² As a consequence, SARS-CoV-2 would circulate in children and, like other respiratory viruses, would provide natural immunity over time, fortunately with very little risk of severe or fatal COVID-19. In England, since with the emergence of more transmissible alpha (B.1.1.7) since December 2020 and delta (B.1.6.1.7.2) variants since April 2021,³⁷ it is likely that a substantial proportion of children are already naturally immune to SARS-CoV-2. Virus circulation would also provide natural boosting of immunity in vaccinated adults, potentially avoiding the need for booster vaccinations at least in the short- to medium-term. Additionally, since nearly all adults would be vaccinated in the population, the risk of children infecting education staff or household members would reassuringly be limited.

Currently available options

Over the recent months, several million adolescents have already been immunised with an mRNA vaccine as part of national COVID-19 vaccination programmes in many countries. This provides countries such as the UK that have yet to make a decision on immunising adolescents an opportunity to wait for additional data on post-marketing safety and effectiveness before making their recommendations. In particular, data on the risk of adverse events such as myocarditis/pericarditis after mRNA vaccination and, perhaps more importantly, the outcomes of children who developed myocarditis/pericarditis following vaccination are only just emerging, and some of these cases have been very severe. Estimating the absolute risk of such rare but potentially severe adverse events takes time, and it is critical to balance this risk (which is restricted to a few days immediately after vaccination) against the benefits of many months to years of protection against severe and fatal COVID-19, long COVID and PIMS-TS afforded by vaccination.

Perhaps as importantly, as emerging data from Israel and elsewhere indicate, if young adults appear to be the primary drivers of transmission, then cases in children may fall once adults are vaccinated. Another possible option would be to vaccinate specific cohorts of children, such as those with underlying comorbidities that increases their risk of COVID-19. Data from the first wave of the pandemic indicated very low hospitalisation and case fatality rates even in children with co-morbidities, but older children with severe neurodisability were over-represented among severe and fatal cases.³⁸ Consequently, the UK recommended COVID-19 vaccines for adolescents with severe neurodisability as soon as a vaccine was authorised in adults (and prior to authorisation in adolescents) in order to protect this vulnerable group as quickly as possible.³⁸ Now that an authorised vaccine is available for adolescents, current recommendations could be widened to include more risk groups in children, but we need robust data on both the relative and absolute risks of severe COVID-19 in children with specific comorbidities. At the same time, however, it is not possible to identify children who might be at increased risk of PIMS-TS or long COVID and, therefore, vaccination cannot be targeted specifically towards children at risk for these complications. Whether vaccination should be recommended based on factors such as non-white ethnicity, obesity, or lower socio-economic status, which have all been associated with an increased risk of COVID-19,¹⁵ is debatable and certainly challenging to implement as part of a national immunisation programme, as would recommending vaccination for younger children with comorbidities that have been associated with an increased risk of severe COVID-19 in adolescents and adult.

If countries wish to recommend a national adolescent immunisation programme against COVID-19, one potentially attractive option would be to offer a single dose of mRNA vaccine which has been shown to be highly protective against SARS-CoV-2 infection in healthy adults,³⁹ especially given that adolescents mount even higher immune responses after mRNA vaccines than young adults.¹⁰ A single-dose option is made more attractive by the fact that nearly all cases of myocarditis and pericarditis in adolescents and young adults have been reported after the second dose of vaccine. Such a schedule would certainly be sufficient for protection in those with previous COVID-19, which is likely to be a significant proportion of the childhood population since with the emergence of more transmissible SARS-CoV-2 variant.³⁷ Given the very high immune responses following mRNA vaccination in adolescents, there is also an argument to use lower doses of COVID-19 vaccines, as is currently being trialled in younger children.¹²

As well as mRNA and viral-vector based vaccines, there are several other effective COVID-19 vaccines with different mechanisms of action used globally, including protein subunit and inactivated-virus vaccines, and many others are in late-phase clinical trials.⁴

Some of these vaccines, such as the protein subunit and inactivated virus vaccines, appear to be less reactogenic in adults and may, therefore, have better safety profiles than mRNA or viral-vector vaccines, but will need to undergo appropriate clinical trials and regulatory authorisation before they can be recommended for adolescents.^{40,41}

Conclusions

The decision to vaccinate adolescents against COVID-19 remains highly divisive among parents, clinicians, politicians and policy makers. Whilst current evidence indicates a very low risk of severe or fatal COVID-19, even among those with comorbidities, or rare complications such as long COVID or PIMS-TS, there are very few downsides to immunising this group with a safe and effective COVID-19 vaccine. Currently authorised vaccines, however, are highly reactogenic and have limited post-marketing population-level safety data in adolescents and young adults, but these are emerging from countries that have forged ahead with vaccinating adolescents. Countries that have yet to make a recommendation can afford to wait until there is sufficient information to make informed decisions on the risk-benefits of vaccinating adolescents with current and future COVID-19 vaccines.

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