

Should we be vaccinating children against COVID-19 in high-income countries?

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High income countries are now considering vaccination of children as part of their COVID-19 control strategy, but this poses several scientific, practical and ethical questions, which are still to be resolved. There are 4 key issues; the benefits for children of being vaccinated to defend their health and well-being, the potential for impact on transmission and benefit to wider society, the risks of vaccination for the individual, and the consequences of redirection of supply to children rather than to local adults or those elsewhere in the world who would benefit more from the doses.

Benefits of vaccination to individual children include prevention of acute infection as well as prevention of long-term sequelae associated with COVID-19 disease. Older adults and those with co-morbidities comprise the majority of hospitalisations due to SARS-CoV-2 infection and a very small proportion of children are severely affected and admitted to hospital. The estimated proportion of SARS-CoV-2 infections in children who are asymptomatic varies widely between 30-95% depending on the case-selection criteria used but is generally acknowledged to be higher than in adults [1]. Seroprevalence rates in UK children under 18 (representing approximately 20% of the total population the UK) were estimated to be between 5-10% during the first wave of the pandemic, [2] during which 651 admissions to hospital were recorded of which 118 were admitted critical care. [3] In a cross-sectional analysis of 12,306 American children testing positive for SARS CoV-2 (age 9.4 years +/-5.6 years) [4] approximately 5% were hospitalised but only 4.1% of these children required ventilation. In children with no comorbidities, hospitalisation was 3.5% (of whom 0.4% required critical care and 0.3% required ventilation). Policy makers need to be able to identify the small number of children who are at high-risk of severe disease and offer them targeted vaccination.

Hospitalisation rates are difficult to estimate given the uncertainty about the denominator and the fact that, in many cases, a positive PCR test may be a coincidental finding, but these data are necessary to inform vaccination policy.

Post-COVID syndrome (also referred to as Long COVID) is defined as signs and symptoms that develop during or following an infection consistent with COVID-19 which continue for more than 12 weeks and are not explained by an alternative diagnosis. Whilst initially reported in adults, there are also cases described in children. Retrospective analysis of 129 Italian children with positive SARS-CoV-2 testing suggests that almost half of children reported being troubled by symptoms more than 120 days after onset of SARS CoV2 infection. However, as with adult studies, objective outcome measures remain to be identified [5,6] and form an area of active research which requires more data, particularly from controlled studies, to make an accurate assessment of disease burden and causality. However, particularly when considering fatigue as a main symptom, the condition appears to be less common in children than adults based on current evidence [7]. Nonetheless, the incomplete epidemiology adds to the difficulty in making informed policy decisions around vaccination.

Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PIMS-TS), also known as multisystem inflammatory syndrome in children (MIS-C) is a multisystem disorder associated with SARS-CoV-2 infection in children in the preceding 6-8 weeks. A small proportion of these children become critically ill with shock and multi-organ failure requiring intensive care. Early clinical characterisation suggests that fever and non-specific symptoms (such as vomiting in 45%, abdominal pain in 53% and diarrhoea in 52%) are associated with laboratory markers of

inflammation (elevated CRP and ferritin), shock requiring fluid resuscitation and inotropic support, and coronary artery dilatation or aneurysm in 14%. 268 cases of PIMS-TS meeting British Paediatric Surveillance Unit case definition criteria were identified between 1st March and 24th July 2020 with median age at presentation of 8.2 years (interquartile range 4.0 - 12.1 years), [8] 44% of whom required intensive care admission. 16% required invasive mechanical ventilation, however, the median paediatric intensive care stay was 3 days with an overall mortality rate of 1.1%. Similarly, in surveillance data from the US, 4018 cases meeting the CDC case definition of MIS-C were reported, with 36 associated deaths. [9] The pathogenesis of PIMS-TS is not understood and so neither safety nor efficacy of vaccines in its causation and prevention, respectively, are known. Indeed, even if COVID-19 vaccination were shown to prevent the development of PIMS-TS, the majority of affected children would be too young to receive vaccines under current guidance in those countries which are introducing adolescent vaccination.

The role of children in transmission of coronavirus in the wider community is not understood clearly and there are few well-designed epidemiological studies using individual-level data to examine transmission from children to adults. Although parents and older children are more often index cases for families, parents and younger children (aged 0-6 years) are still capable of within-family transmission. [10,11] The effect of the widespread school closures implemented in many countries on transmission has been difficult to evaluate with confounding due to other non-pharmaceutical interventions being implemented at the same time [12] and in different geographic and demographic settings. Initial studies show that vaccination can reduce transmission of SARS CoV-2 by 40-50% in adults, [13] and may become important if it is shown that novel variants are shown to spread more easily or are more virulent in children. While vaccination of children may reduce transmission, the size of any potential impact is unclear with few outbreaks reported in the school setting [14]. There is little evidence to suggest that incidence is any higher than the background community rates, further data collection is needed to see whether this relationship changes as transmission amongst immune adults decreases and children, being unvaccinated and so more susceptible to infection, represent a larger proportion of residual infections in the community.

School closures may impact upon transmission but also have wide-ranging consequences for education and mental health. Thus the potential educational, social and psychological benefits to children of being vaccinated need to be considered in decisions about vaccine policy. Repeated and prolonged school closures perpetuate educational inequalities and disproportionately affect the most vulnerable children. [15] The true mental health and educational costs to children of the COVID-19 pandemic will probably take some time to quantify as these children return to school and mental health services resume normal capacity. [16] It remains to be seen whether SARS-CoV-2 infection poses a greater health risk to school children beyond other seasonal respiratory virus infections and whether it can be treated as such once the adult population has been adequately vaccinated. It is uncertain how much of the benefit which could be obtained by vaccinating children, might also be delivered through vaccinating adults and adjusting school exclusion and shielding policies as data emerge.

While there should be some benefits of vaccination even if the magnitude is likely to be modest, these need to be balanced against the risks and costs of vaccination for children and society. The BNT162b2 (Pfizer/BioNTech) mRNA vaccine was approved for use in 12-15 year olds under Emergency Use Authorisation in the US on 10th May 2021. It was subsequently approved for use in the same age group in the UK and by the European Medicines Agency on 5th June 2021 based on safety and immunogenicity data from a study in 2260 adolescents aged 12-15 years of age half of whom received 2 doses of the vaccine [17]. Several countries have since announced plans to extend their programs to include either all adolescents from age 12 or those considered to be at high risk of severe disease. In the absence of pediatric data, the association of rare cases of thrombosis and thrombocytopenia with the AstraZeneca and Johnson & Johnson vaccines in adults would need to be considered if these vaccines were to be used in children. Although the Pfizer/BioNTech vaccine is authorised, it is relatively reactogenic in teenagers and young adults and there could be a net negative impact on schooling in terms of school-days lost to side-effects, since few of these children are expected to become clinically unwell if they acquire SARS-CoV-2 infection. Anxiety-related adverse events following immunisation (AEFIs) may cluster, as seen in the case of mass HPV vaccination rollout in Denmark [18]. Currently, there is limited available information about unexpected or rare side-effects. Since roll out began, two case series have described a temporal association between receipt of the Pfizer/BioNTech vaccine and cardiac side effects. Myocarditis was reported in 7 Israeli teenagers aged 16-18 years who initially presented with chest pain after vaccination (mean 2.1 days) [19] however all were mild and none required cardiac or respiratory support. 6 out of 7 cases occurred after a second dose. Similarly, a US report describes 7 healthy male adolescents aged 14-19 years who presented with symptomatic pericarditis or perimyocarditis on average 4 days after receiving a Pfizer/BioNTech vaccination. [20] Elevated cardiac enzymes were noted and symptoms resolved rapidly, although four patients received treatment with intravenous immunoglobulin and steroids and three with non-steroidal anti-inflammatory drugs. Further surveillance is needed to confirm the association and for policymakers to evaluate the balance of these and any other risks against the benefits of vaccination.

For maximum and fastest impact, national programmes need to prioritise high two-dose coverage in adults, especially the elderly and those with co-morbidities over administration of vaccines to younger age cohorts. More broadly, global health leaders [21,22] have emphasised the need to prioritise vulnerable adults in low and middle-income countries over children in high-income countries. COVID-19 vaccination rollout has again highlighted global inequality in access to medicines; as of June 5, only 1.6% of global vaccine doses have been administered in Africa (35 million of a total of 2 billion doses given so far), with Europe and the US accounting for 36% of doses administered to date whilst representing 17% of the global population. There is a moral argument that vulnerable adults in low- and middle-income countries who are at greater risk of dying from COVID-19 disease should be prioritised for vaccination over children in high-income countries, while global supply of vaccine is constrained. Aside from considerations of equity, failure to minimise viral replication and large epidemic waves around the world will hasten viral evolution and the spread of variants that are either more transmissible, better able to evade naturally-acquired and/or vaccine-induced immunity or both – as has recently occurred with the delta variant now rapidly proliferating in many countries. Unless available vaccine doses are used strategically to maximum effect around the world, everyone will suffer, not just the inhabitants of poorer countries.

At this present time, there is an urgent need for more evidence to allow an accurate assessment of the arguments for and against widespread paediatric vaccination against SARS CoV-2. Local circumstances including the effectiveness of health care delivery systems, current SARS CoV-2 burden and variant epidemiology and acceptance and coverage of COVID19 vaccines in the adult population also influence policy formulation, all of which will change over time [23]. As the pandemic is brought under control in the adult population, it is likely that children will form a greater proportion of the overall infection and disease burden, and better data will be available to inform decisions. But for now, we should protect those at high risk of serious disease and death from covid19 wherever they live in the world (such as healthcare workers, older adults, and those with comorbidities) before widespread use of doses among low-risk children in high income countries.

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