

Considering Mandatory Vaccination of Children for COVID-19

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Herculean efforts are ongoing to develop vaccines against the severe acute respiratory syndrome 2 new coronavirus that causes the disease known as coronavirus disease 2019 (COVID-19). The World Health Organization lists >100 candidate vaccines, with several already in clinical trials and at least 3 receiving Emergency Use Authorization in the United States. We already know that some vaccines can protect against illness caused by the virus (Pfizer, Moderna, and AstraZeneca). However, we do not yet know whether these vaccines induce immune responses at the nasopharyngeal mucosa such that protection against nasopharyngeal infection and carriage of the virus is achieved. The publicly available briefing document for the December 17, 2020, Food and Drug Administration Vaccines and Related Biologic Products Advisory Committee meeting suggested such an effect in the Moderna vaccine study, but much remains to be learned regarding magnitude and durability of any such effect against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Nevertheless, protection against COVID-19 is evidently feasible if vaccines induce robust neutralizing antibodies and, perhaps, T-cellular responses.^{1,2} Although immune memory has not yet been extensively studied, vaccines that induce those responses usually induce persistent memory and therefore immunity.

Vaccines against COVID-19 are being administered to adult populations. The National Academy of Medicine and the Centers for Disease Control and Prevention recommend that vaccination begin with those at high risk of exposure, such as medical personnel, patients in long-term care facilities, and first responders, followed by those with high risk of severe coronavirus disease (COVID), such as the elderly and those with comorbidities. Vaccination of other adults will follow, with previously healthy adolescents and children being the lowest priority. Herein, we argue that in formulating our national SARS-CoV-2 immunization strategy, we would do well to remember the future (ie, our children). Pediatric coronavirus messenger RNA vaccine trials are enrolling children aged 12 to 15 years (Pfizer) and 12 to 17 years (Moderna). Further age de-escalation will await analysis of the safety and efficacy data from these older children.

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Although widespread adult vaccination has a good chance of controlling the epidemic and reducing risk of infection, there will be persistent COVID-19, for at least two reasons. First, eradication would entail prevention of replication in the nasopharynx. Live attenuated vaccines are capable of inducing mucosal responses, as is the case with vaccines such as measles, rubella, and oral polio, but nonlive vaccines like inactivated polio and influenza often do not.³ Much will therefore depend on the ability of a COVID-19 vaccine to induce antibodies locally or systemically that mobilize to the mucosae. Although SARS-CoV-2 may not be eradicated, prevention of mucosal replication will at least reduce spread of the virus.

Second, control and possible eradication of SARS-CoV-2 will depend on nearly all people accepting vaccination. However, history and recent survey data suggest that fear, opposition, and skepticism about vaccination may render vaccine coverage less than ideal for vaccines recommended for adults.⁴ Thus, vaccine coverage in adults will be incomplete, particularly if periodic boosters are needed to maintain immunity. A reservoir of virus in children will likely lead to repeated exposure of unprotected adults. The need for two injections of most candidate vaccines will also limit coverage rates in the adult population. If booster doses are necessary to maintain immunity, that will also lessen protection of adults.

The effect of the above difficulties in vaccination may well be that despite reduction in COVID-19 and absence of major epidemics, the virus will persist in the form of sporadic cases and occasional outbreaks. Recent observations of reinfections also suggest continued virus circulation. Moreover, as with other infectious diseases, there will be many unvaccinated people in geographic regions wherein vaccine delivery

infrastructure and/or vaccine acceptance are suboptimal. Such ongoing viral reservoirs may potentially enable reintroduction of the virus into the United States.

Clearly, some vaccines will be successful in preventing disease, but the crucial related question is whether any of them will prevent or diminish excretion of the virus, thereby reducing transmission from infected vaccine recipients to others. If licensed vaccines do reduce viral excretion, we will be in a position to reduce viral circulation to protect our entire population. Provided such a vaccine were revealed to be safe in pediatric trials, the key step then would be to mandate vaccination of children. Although symptomatic COVID-19 is less common in children, pediatric COVID in the form of multisystem inflammatory syndrome of children (MIS-C) and death have been described, underscoring the importance of pediatric vaccination.⁵ High viral load in young children, including viral replication in the gastrointestinal tract, further suggests that vaccination of children should help protect adults.⁶ An important additional argument in favor of vaccinating children would be to decrease the circulation of the virus to protect adults. Mandating vaccination of adults would help, but that is likely to be unacceptable in our society, requiring new laws, although mandatory pediatric vaccination has been accepted by most Americans.⁷ If the vaccines are highly effective in children, they will protect parents, teachers, and others in contact with them. Because immune responses in children after infancy are typically stronger than in adults, persistence of immunity is more likely. Furthermore, if a pediatric vaccine resulted in a long duration of immunity, it would eventually produce a population resistant to virus introduction and circulation.

The American Academy of Pediatrics noted in December 2020 that >2

million cases of COVID-19 have already occurred in children. A review of prevalence in children living in 22 states revealed a hospitalization rate of 17.2 per 100 000,⁸ and in Canada, children accounted for 1.9% of confirmed cases of clinical illness, with ~7% of those cases resulting in intensive care.⁹ Whereas COVID-19 can be severe in children aged <5 years, a greater proportion of severe infections have been documented in children aged 12 to 17 years.^{10,11} In addition, the Kawasaki disease-like MIS-C occurs most often in school-aged children, with a mean age of 8 years.

Emerging evidence on viral transmission further bolsters the case for pediatric immunization. Although the rate of severe COVID is much lower in the young, it does appear that SARS-CoV-2 infections are more prevalent in adolescents than in the elderly.¹² There is an estimated 9% rate of transfer to others within the household.¹³ Although secondary transmission to adults from children was less frequent than from other adults,¹⁴ transmission from children to other family members is common.¹⁵ Moreover, children may excrete the virus in stool.¹⁶

Thus, there are practical, immunologic, ethical, and social reasons that further bolster the rationale for vaccinating children against SARS-CoV-2, as listed in Table 1. A pediatric SARS-CoV-2 immunization strategy could mimic the success of the rubella vaccine, which is mandated for all children in the United States and some other countries and is recommended for children across the globe. The rubella vaccine is also given to seronegative adults in an effort to reduce infection of women during pregnancy, but it is vaccination of children that serves the main epidemiological purpose: to protect pregnant women. Similarly, a vaccine against COVID-19 given to children could also help protect

TABLE 1 Rationale for Eventual Mandatory Pediatric SARS-CoV-2 Immunization

1. Although uncommon, severe COVID does occur in children in the form of MIS-C and pulmonary disease.
2. Children do become infected and excrete virus that could infect parents, teachers, and other children.
3. Because childhood infection is often asymptomatic, other precautions will not suffice.
4. If strain change decreases long-lasting immunity, children will at least be primed for an accelerated response to infection or revaccination.
5. Vaccination of children will be needed to reach high coverage and, potentially, herd immunity.
6. Viral mutations are generating variants, such as the one from the United Kingdom, that are spreading more readily to children.
7. Pediatric vaccination programs have a highly successful international track record in making major advances in reducing infectious diseases.
8. There is a well-developed international infrastructure for pediatric immunization that will be a practical path to ensure global immunization against SARS-CoV-2.
9. After immunizing teachers, pediatric vaccination will further accelerate opening of schools and normalizing children's activities key to their well-being and parental work productivity.
10. As is the case for other vaccines, mandatory vaccination of children guarantees high coverage, as opposed to strictly voluntary vaccination.

adults in contact with them and, together with direct vaccination of young adults, would serve to protect the elderly from infection. Depending on the durability of vaccine-induced protection, booster vaccination against COVID-19 could also be recommended later in life.

Childhood vaccination is accomplished in many countries through voluntary acceptance by parents concerned about infectious disease in the community. The high vaccine coverage rates in American children in the absence of the once endemic infections prevented by those vaccines are the result of the general acceptability of pediatric immunization, as well as mandates that require immunization for school entry. For example, ~90% of US children aged 2 years receive 3 doses of hepatitis B vaccine and >90% receive polio and measles-mumps-rubella vaccines. Provided that ≥ 1 vaccine reveals safety in children and lessens excretion of SARS-CoV-2, the severe burden of morbidity, mortality, and socioeconomic distress due to this pandemic would merit eventually making pediatric vaccination mandatory. By decreasing virus circulation in children, pediatric immunization may be our best hope to control COVID-19 and to return to normal social, educational, and

economic activity. SARS-CoV-2 strain changes portend a need for continuous large-scale vaccination with updated vaccines, further underscoring the potential importance of pediatric immunization campaigns.¹⁷

ABBREVIATIONS

COVID: coronavirus disease
COVID-19: coronavirus disease 2019
MIS-C: multisystem inflammatory syndrome of children
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

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