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DOI: 10.1542/peds.2021-050531

Journal: Pediatrics

Article Type: Pediatrics Perspectives


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Potential Conflict of Interest (includes financial disclosures): Dr. Plotkin has consulted for Moderna, Janssen, Pfizer, Sanofi, Merck, Codagenix, and Valneva. Dr. Levy is an inventor on pending vaccine adjuvant patent applications and served as a consultant for GSK in 2019.

Funding Support: No funds supported this article.

Contributor Statements
Dr. Plotkin and Dr. Levy conceptualized and designed the paper, drafted the initial manuscript and reviewed and revised the manuscript. Both authors approved the final manuscript.
Herculean efforts are on-going to develop vaccines against the SARS-2 new coronavirus that causes the disease known as COVID-19. WHO lists >100 candidate vaccines, with several already in clinical trials and at least two receiving Emergency Use Authorization (EUA) 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 17 DEC 2020 FDA Vaccines & Related Biologic Products Advisory Committee (VRBPAC) 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 SARS-CoV-2 infection. Nevertheless, protection against COVID-19 is evidently feasible if vaccines induce robust neutralizing antibodies and perhaps T cellular responses.\textsuperscript{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 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, i.e., our children. Pediatric coronavirus mRNA vaccine trials are enrolling children 12
to 15 years of age (Pfizer) and 12 to 17 years old (Moderna). Further age de-escalation will await analysis of the safety and efficacy data from these older children.

While widespread adult vaccination has a good chance of controlling the epidemic and reducing risk of infection, there will be 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 non-live vaccines like inactivated polio and influenza often do not. 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 the 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. 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 sub-
optimal. Such ongoing viral reservoirs may potentially enable reintroduction of virus into the United States.

Clearly, some vaccines will be successful in preventing disease, but the crucial related question is whether or not any of them will prevent or diminish excretion of virus, thereby reducing transmission from infected vaccinees 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 demonstrated 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 multi-system inflammatory syndrome of children (MIS-C), and death have been described underscoring the importance of pediatric vaccination. High viral load in young children, including viral replication in the GI tract, further suggests that vaccination of children should help protect adults. An important additional argument in favor of vaccinating children would be to decrease the circulation of the virus in order to protect adults. Mandating vaccination of adults would help, but that is likely to be unacceptable in our society, requiring new laws, while mandatory pediatric vaccination has been accepted by most Americans. If the vaccines are highly effective in children they will protect parents, teachers and others in contact with them. As 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 showed a hospitalization rate of 17.2 per 100,000 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 under 5 years of age, a greater proportion of severe infections have been documented in children 12 to 17 years old.\(^10,11\) In addition, the Kawasaki disease-like multi-system inflammatory syndrome of children (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 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 U.S. 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 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 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 U.S. children aged 2 years receive 3 doses of hepatitis B vaccine and >90% receive polio and MMR vaccines. Provided that one or more vaccines demonstrate safety in children and lessen excretion of SARS-CoV-2, the severe burden of morbidity, mortality, and socio-economic 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.

References


17. New coronavirus variants could cause more reinfections, require updated vaccines | Science | AAAS (sciencemag.org)
### Table 1.

**Rationale for Eventual Mandatory Pediatric SARS-Coronavirus-2 Immunization**

1. Although uncommon, severe COVID does occur in children in the form of multi-system inflammatory syndrome in Children (MIS-C).

2. Children do become infected and excrete virus that could infect parents, teachers, and other children.

3. As 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 UK, 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.
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Pediatrics originally published online March 11, 2021; originally published online March 11, 2021;

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*Pediatrics* originally published online March 11, 2021; originally published online March 11, 2021;

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