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SARS-CoV-2 vaccine testing and trials in the pediatric population: biologic, ethical, research, and implementation challenges

As the nation implements SARS-CoV-2 vaccination in adults at an unprecedented scale, it is now essential to focus on the prospect of SARS-CoV-2 vaccinations in pediatric populations. To date, no children younger than 12 years have been enrolled in clinical trials. Key challenges and knowledge gaps that must be addressed include (1) rationale for vaccines in children, (2) possible effects of immune maturation during childhood, (3) ethical concerns, (4) unique needs of children with developmental disorders and chronic conditions, (5) health inequities, and (6) vaccine hesitancy. Because COVID-19 is minimally symptomatic in the vast majority of children, a higher acceptable risk threshold is required when evaluating pediatric clinical trials. Profound differences in innate and adaptive immunity during childhood and adolescence are known to affect vaccine responsiveness for a variety of childhood diseases. COVID-19 and the accompanying social disruption, such as the school shutdowns, has been disproportionately damaging to minority and low-income children. In this commentary, we briefly address each of these key issues, specify research gaps, and suggest a broader learning health system approach to accelerate testing and clinical trial development for an ethical and effective strategy to implement a pediatric SARS-CoV-2 vaccine as rapidly and safely as possible.

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INTRODUCTION

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RATIONALE FOR A PEDIATRIC SARS-COV-2 VACCINE

During the SARS-CoV-2 pandemic, the majority of children with confirmed infection have been asymptomatic or have had mild COVID-19 disease. For this reason, a higher acceptable risk threshold is required in children compared with adults. There are a number of compelling reasons to support pediatric COVID-19 vaccination as evidence accumulates that vaccines are safe and effective in adults.

1. In the USA, as of 7 January 2021, more than 2.3 million children have been infected with SARS-CoV-2. Hospitalization and mortality in children due to COVID-19 are lower than in adults. The hospitalization rate in children infected with COVID-19 is similar to that for influenza, and influenza vaccination reduces the risk of influenza-associated death by 50–66%. Moreover, pediatric COVID-19 hospitalization rates have increased dramatically in recent months in many states, raising concerns that medical resources suited for children may not be available as needed. Finally, new strains of SARS-CoV-2 are emerging which may be more infective for children and possibly more virulent.

2. Childhood vaccination not only protects young children and adolescents from disease but also protects adults. While evidence is accumulating that children are not “super-spreaders,” children can be a source of transmission of SARS-CoV-2 to each other and to adult family members.

3. Non-pharmaceutical interventions (NPI) are effective in children with evidence mounting from schools and summer camps. However, the NPI mitigation and prevention behaviors (face covering, physical distancing, hand hygiene, cohorting children in schools) are not natural behaviors, particularly in children and adolescents, who tend to be physically close in their social interactions.

4. Children are vulnerable members of our society and have suffered disproportionately from the disruption and shutdowns of the pandemic. Children have experienced loss of education, decreased well-child screening and routine vaccination visits, food insecurity, physical inactivity, and an increase in mental health needs. These adverse effects have impacted minority and low-income children disproportionately.

BIOLGIC AND MATURATIONAL CONSIDERATIONS

Efforts to implement SARS-CoV-2 vaccinations in children must consider two biological issues: (1) vaccines likely to be available are based on the novel platform using messenger ribonucleic acid (mRNA) to develop immunity; this class of vaccines is new and has only recently been tested in adults and in very small numbers of children (Pfizer product only), and (2) there are distinct differences in immunological function between infants, young children, and adolescents, which can influence response to vaccines.

More than 180 SARS-CoV-2 candidate vaccines are in development, of which 48 are in clinical evaluation as of 12 November 2020. These candidate vaccines use a variety of delivery platforms, from conventional protein-based delivery to novel vectors and RNA technology. Most capitalize on the fact that antibodies to the viral surface spike protein, in particular, antibodies to pre-fusion spike protein, effectively neutralize virus.

Each vaccine platform has advantages and disadvantages, but given the urgency of producing an effective, safe vaccine for SARS-CoV-2, the non-conventional platform of the mRNA vaccine provides several advantages, notably the rapid structure-based antigen design and scale-up of production. mRNA vaccines encoding viral antigens are delivered to host cells, where they are translated into protein that is processed and presented to induce humoral and cellular immune responses. The two candidate SARS-CoV-2 vaccines furthest along in development, both reporting >94% efficacy, utilize an mRNA platform. The candidate vaccines have been immunogenic and safe, although there have been frequent local and some systemic reactions, such as fever and malaise, but these reactions resolve quickly. There is strong evidence of protective immunity in animal experiments and the first human studies, and no evidence of disease enhancement.

The immune system of children differs from adults in many ways. Not surprisingly, the development of effective vaccines in newborns and young children for a variety of diseases (e.g., respiratory syncytial virus, diarrheal diseases, tuberculosis) has proved challenging. The mechanisms for these difficulties include the effect of maternally transferred immune factors and the immaturity of innate and adaptive immune cells. Vaccination early in life, as well as exposure to a variety of immunogens, can also affect response to pathogens and vaccines across the lifespan, sometimes in unpredictable ways. The emergence of the multisystem inflammatory syndrome in children associated with SARS-CoV-2 (ref. 24) is an example of how disease expression of COVID-19 is tied to maturational state.

Environmental factors in children and adolescents can also influence vaccine responsiveness. Childhood obesity is still at pandemic levels in the USA and globally. Obesity is associated with extensive changes in the serum levels of inflammatory and anti-inflammatory factors, as well as the number of immune cells and their function. This altered immunity has been associated with suboptimal (reduced) responses to vaccines, including Hepatitis B and tetanus, and increased susceptibility to influenza. Childhood obesity is linked to physical inactivity, which is increasing in children as a result of the pandemic shutdown and shelter-at-home policies. There is increasing evidence that obesity, irrespective of age, is associated with severe COVID-19, and may predispose to the disease. Tracking environmental factors like nutrition and physical activity may be useful in assessing the effectiveness of any COVID-19 vaccine given to children and adolescents.

ETHICAL ISSUES

Enrolling children in medical research involves a balance between access (to experimental but potentially life-saving therapeutics) and protection (from unsafe or ineffective therapeutics). As noted, children under the age of 12 years have yet to be enrolled in COVID-19 vaccine trials. This omission can be justified ethically by the need to ensure adequate safety data are obtained in adults who can give a voluntary and informed consent to participate in such trials, particularly since adults bear the major burden of disease. Even so, the long-term risks and benefits of a SARS-CoV-2 vaccine will take a long time to fully evaluate in adults while the public health needs of a vaccine are pressing. As phase 3 trials in adult volunteers continue to show safety and begin to show efficacy, it is critical that such research begin in older adolescents, then younger children, and then infants, so that minors can fully reintegrate into society, including a full return to in-person school learning without putting themselves, family members, or school personnel at risk.

CONSIDERATIONS FOR CHILDREN WITH SPECIAL NEEDS AND CHRONIC CONDITIONS OR DISEASES

Children with chronic disease or disabilities, especially those with low-incidence disabilities and the most significant support needs, illustrate the importance of comprehensive family outreach and education around vaccine testing and implementation for the pediatric population. For example, families of children with special needs may bring a history of fraught experiences in navigating recommendations for needed or suggested medical procedures, therapies, or parenting approaches throughout a child’s life. Vaccinations hold particular concern for many families of children identified with autism spectrum disorder (ASD). Although the
scientific community has demonstrated no link between receiving vaccines and ASD, questions about the safety of vaccines persist.56

Children with chronic diseases and conditions, particularly those that impact the immune system, are substantially under-immunized.57 Reasons for under-vaccination of special groups include awareness of the need for vaccination, fear of adverse outcomes or illness caused by the vaccine, and in some settings, cost. Healthcare providers can also contribute to attitudes through their own hesitancy to vaccinate children with special needs or chronic disease. Providing clear and comprehensive education regarding the purpose, goals, and risks of emerging pediatric COVID-19 vaccination from an explicitly trustworthy source is essential, and directly addressing the unique needs and risks posed for children with disabilities is especially important for empowering families to understand and weigh the potential and value of vaccine testing and implementation for these most vulnerable children.

HEALTH INEQUITIES

Health inequities continue to be evident as the COVID-19 pandemic persists. Minority children are more likely to be infected with SARS-CoV-2.58 Between March and July 2020, Hispanic and black children had the highest rates of COVID-19–associated hospitalization.59, 60 Previous studies demonstrate that race and ethnicity contribute to disparities in vaccine compliance in children and adolescents.41–46 There is also evidence that these factors may adversely influence enrollment in pediatric clinical trials.67 The development, testing, and implementation of pediatric COVID-19 vaccines must be accompanied by robust outreach and data monitoring to minimize health disparities.

PUBLIC ACCEPTANCE: LOGISTICS AND VACCINE HESITANCY

Even if SARS-CoV-2 vaccine trials in children show the vaccine to be safe and effective, the next challenge will be how to attain broad public acceptance. This will be complicated by the need for two doses for the current frontrunner vaccines, which must be given 21–28 days apart and the vaccines must be stored at low temperatures. Local and state governments may not have adequate funding to develop equitable distribution plans.66

Vaccine hesitancy has remained a long-term concern of pediatricians and public health workers.68 In a recent study that surveyed parental attitudes toward influenza vaccination, Santi-banez et al.69 noted “One in 5 children in the United States has a parent who is vaccine hesitant, and hesitancy is negatively associated with childhood influenza vaccination.” They also noted, “an 11.9 percentage point higher prevalence of ‘hesitant about childhood shots’ and 9.9 percentage point higher prevalence of concerns about serious, long-term side effects among parents of black compared with white children.” Low rates of vaccine compliance, particularly with the HPV vaccine,68 provide additional cautionary notes and highlight the challenges to be faced in overcoming potential vaccine hesitancy regarding SARS-CoV-2 vaccines in children. School mandated vaccination and exemptions from vaccination will surely emerge as contentious issues as pediatric COVID-19 vaccines become available.3, 49

These uncertainties will make it very challenging to develop either local or national policies and/or regulations regarding potential mandates for vaccination of children as a prerequisite for returning or remaining in school. Given that no children under the age of 12 years have been in vaccine trials thus far and the infection rate and hospitalization rate of adolescents over age 12 years is at least double that of younger children, age grouped introduction of vaccines into the pediatric population could be considered. A phased vaccination program for children that starts with 12–17 years and moves to younger children once we have clearer safety and efficacy data in young people might reduce vaccine resistance or hesitancy as well as being consistent with a limited vaccine supply and the need to prioritize its use.

**Table 1.** Pediatric COVID-19 vaccination development and distribution: examples of key knowledge gaps.

| Research area                                      | Unanswered questions and proposed focus                                                                 |
|---------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| Rationale for a pediatric vaccine                 | - Effectiveness of current non-pharmaceutical interventions: To what extent do current mitigation procedures (face coverings, physical distancing, hand hygiene) limit viral transmission, and how well are they adhered to in children and adolescents? |
| Maturational and environmental factors that influence vaccine responsiveness | - Is immunization of young children necessary to achieve SARS-CoV-2 herd immunity?                      |
|                                                   | - How may a maturing immune system influence the efficacy of the SARS-CoV-2 vaccines?                   |
|                                                   | - What are the possible long-term sequelae of COVID-19 disease and vaccination early in life?           |
|                                                   | - What is the effect of nutrition, psychosocial, and physical fitness factors on vaccine responsiveness?|
|                                                   | - What is the effect of preexisting conditions on vaccine responses (e.g. asthma, obesity, diabetes)? |
| Ethical issues in pediatric COVID-19 vaccine testing and implementation | - Are there lessons to be learned from the SARS-CoV-2-related Multisystem Inflammatory Syndrome in Children (MIS-C), particularly in relation to potential adverse events of a COVID-19 vaccine? |
|                                                   | - What would be needed to conclude that COVID-19 vaccine testing and/or widespread vaccination in the pediatric population is ethically justified? |
| Vaccination in children with special needs and/or disabilities | - What criteria/data need to be met that would justify mandating a SARS-CoV-2 vaccine for children? |
| Health disparities                                | - What special considerations need to be addressed before vaccinating children with chronic conditions, such as immunodeficiency, pediatric malignancy, sickle cell disease, and neurodevelopmental disorders? |
| Vaccine hesitancy regarding COVID-19              | - What mechanisms must be employed to ensure optimal COVID-19 outreach and acceptance among minority and low-income children and adolescents? |
|                                                   | - What factors represent true barriers to vaccination in various ethnic groups and what strategies can be developed to overcome them? |
|                                                   | - Is evidence for vaccine hesitancy from the influenza and HPV vaccines applicable to COVID-19?         |
|                                                   | - If so, how can this hesitancy be addressed?                                                         |
research necessary to ensure the most ethical, equitable, and effective development and implementation of pediatric SARS-CoV-2.

The nation begins the task of SARS-CoV-2 vaccination in adults and continuing testing and trials in children amidst a winter surge of COVID-19, which will inevitably impact essential components of comprehensive and thoughtful vaccine programs for pediatric populations. In response, we urge the establishment of regional and national “learning health systems (LHS)” for pediatric vaccine trials and implementation. The LHS model is well-suited for this challenge. Coalitions of community stakeholders (e.g., local healthcare agencies and school personnel), caregivers, parents, children, academic health centers, and data managers are the core elements of successful LHS. In this way, new knowledge and research relevant to pediatric SARS-CoV-2 can be rapidly distributed, discussed, and vetted to ensure continuous learning and timely improvements in outreach and implementation.

In the early months of the COVID-19 pandemic, a national working group convened and published a commentary outlining the challenges ahead that would inevitably need to be addressed as schools reopened. The commentary concluded with a message for school reopening that equally resonates with the immediate challenge of pediatric SARS-CoV-2 vaccine testing and clinical trials. This could be accomplished by building public health-focused collaboratives capable of continuous learning and rapid cycles of implementation, as COVID-19 information evolves at breakneck speed. Otherwise, we risk further compounding the incalculable damage already incurred by COVID-19 among children across our country and the world.

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D.M.C. conceptualized and outlined the commentary. B.A., C.K.C., L.F.R., K.D.L., C.T.L., S. edited and reviewed the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

ADDITIONAL INFORMATION
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REFERENCES
1. AAP: Include children in COVID-19 vaccine trials (American Academy of Pediatrics, 2020); https://www.aappublications.org/news/2020/11/17/covidvaccinetrials111720.
2. Leeb, R. T. et al. MMWR. COVID-19 trends among school-aged children—United States, 1 March–19 September 2020. https://www.cdc.gov/mmwr/volumes/69/mm6935e2.htm.
3. Opel, D. J., Diekema, D. S. & Ross L. F. Should we mandate a COVID-19 vaccine for children? JAMA Pediatr. 175, 125–126 (2021).
4. American Academy of Pediatrics. Children and COVID-19: State-level data report (accessed 15 Jan 2021); https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/.
5. Song, X. et al. Comparison of clinical features of COVID-19 vs seasonal influenza A and B in US children. JAMA Netw. Open 3, e200495 (2020).
6. Flannery, B. et al. Influenza vaccine effectiveness against pediatric deaths: 2010–2014. Pediatrics 139, 2010–2014 (2017).
7. Levin, Z., Choyke, K., Georgiou, A., Sen, S. & Karaca-Mandic, P. Trends in pediatric hospitalizations for coronavirus disease 2019. JAMA Pediatr. https://doi.org/10.1001/jamapediatrics.2020.5535 (2021).
8. Munro, A. P. S. & Faust, S. N. Children are not COVID-19 super spreaders: time to go back to school. Arch. Dis. Child. 105, 618–619 (2020).
9. Laxminarayan, R. et al. Epidemiology and transmission dynamics of COVID-19 in two Indian states. Science 370, 691–697 (2020).
10. Blaisdell, L. L., Cohn, W., Pavell, J. R., Rubin, D. S. & Vergales, J. E. Preventing and mitigating SARS-CoV-2 transmission—four overnight camps, Maine, June–August 2020. MMWR Morb. Mortal. Wkly Rep. 69, 1216–20 (2020).
11. Dorn, E., Hancock, B., Sarkeratannis, J. & Vinuileg. E. COVID-19 and Student Learning in the United States: The Hurt Could Last a Lifetime. McKinsey & Company (2020).
12. Bramer, C. A. et al. Decline in child vaccination coverage during the COVID-19 pandemic—Michigan Care Improvement Registry, May 2016–May 2020. Am. J. Transplant. 20, 1930–1931 (2020).
13. The Impact of Coronavirus on Food Insecurity. Feeding America (2020); https://www.feedingamerica.org/research/coronavirus-hunger-research.
14. Dunton, G. F., Do, B. & Wang, S. D. Early effects of the COVID-19 pandemic on physical activity and sedentary behavior in children living in the U.S. BMC Public Health. 20, 1351 (2020).
15. Loades, M. E. et al. Rapid systematic review: the impact of social isolation and loneliness on the mental health of children and adolescents in the context of COVID-19. J. Am. Acad. Child Adolesc. Psychiatry 59, 1218–1239.e3 (2020).
16. Dooley, D. G., Bindealy, A. & Tschudy, M. Low-income children and coronavirus disease 2019 (COVID-19) in the US. JAMA Pediatr. 174, 924–925 (2020).
17. World Health Organization. Draft landscape of COVID-19 candidate vaccines (accessed 19 Feb 2021); https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines.
18. Richards, S.E. Moderna edges Pfizer in COVID-19 vaccine effectiveness—and refrigeration. National Geographic (accessed 20 Nov 2020); https://www.nationalgeographic.com/science/2020/11/moderna-edges-pfizer-coronavirus-efficacy-and-refrigeration/.
19. Rossey, I., Saelens, X. Vaccines against human respiratory syncytial virus in clinical trials, where are we now? Expert Rev. Vaccines 18, 1053–1067 (2019).
20. Mokomane, M., Kasvoose, J., de Meo, E., Pernica, J. M. & Goldfarb, D. M. The global problem of childhood diarrhoeal diseases: emerging strategies in prevention and management. Ther. Adv. Infect. Dis. 5, 29–43 (2018).
21. Schrager, L. K., Yekemian, J., Drager, N., Levinsohn, D. M. & Olesen, O. F. The status of tuberculosis vaccine development. Lancet Infect. Dis. 20, e28–37 (2020).
22. Basha, S., Surendran, N. & Pichichero, M. Immune responses in neonates Expert Rev. Clin. Immunol. 10, 1171–1184 (2014).
23. Kollmann, T. R., Kampmann B., Mazmanian S. K., Marchant A. & Levy O. Protecting the newborn and young infant from infectious diseases: lessons from immune ontogeny. Immunity 46, 350–363 (2017).
24. Aronoff, S. C., Hall, A. & Del Vecchio, M. T. The natural history of severe acute respiratory syndrome coronavirus 2-related multisystem inflammatory syndrome in children: a systematic review. J. Pediatr. Infect. Dis. 9, 746–751 (2020).
25. Hemati, Z. et al. Association of sleep duration with metabolic syndrome and its components in children and adolescents; a propensity score-match-analysis: the CASPIAN-V study. Diabetol. Metab. Syndr. 10, 78 (2018).
26. Weber, D. J., Rutala, W. A., Samsa, G. P., Santimaw, J. E. & Lemon S. M. Obesity as a predictor of poor antibody response to hepatitis B vaccine. JAMA 254, 3187–3189 (1985).
27. Eliakim A., Swindt C., Zaldivar F., Casali P. & Cooper D. M. Reduced tetanus antibody titers in overweight children. Autoimmunity 39, 137–141 (2006).
28. Green, W. D. & Beck, M. A. Obesity impairs the adaptive immune response to influenza virus. Ann. Am. Thorac. Soc. 14, 5406–5409 (2017).
29. Hernández-Garduño, E. Obesity is the comorbidity more strongly associated for Covid-19 in Mexico: A case-control study. Obes. Res. Clin. Pract. 14, 375–379 (2020).
30. States National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Research involving Children (1977).
31. Pfizer Gets FDA Approval to Enroll Kids as Young As 12 in COVID-19 Vaccine Trial: Shots. Health News: NPR (2020); https://www.npr.org/sections/health-shots/2020/10/13/923248377/will-kids-get-a-covid-19-vaccine-pfizer-to-expand-trial-to-ages-12-and-up.
32. Kulkarni, P. Current topics in research ethics in vaccine studies. Persp. Clin. Res. 2013 4, 80–83 (2013).
33. Hodgson, S. H. et al. What defines an efficacious COVID-19 vaccine? A review of the challenges assessing the clinical efficacy of vaccines against SARS-CoV-2. Lancet Infect. Dis. 21, e26-e352020 (2021).
34. Boyle, P. We can’t defeat COVID-19 without vaccinating children. There aren’t even any kids’ clinical trials yet. AAMC (2020); https://www.aamc.org/news-insights/we-can’t-defeat-covid-19-without-vaccinating-children-there-aren’t-even-any-kids-clinical-trials-yet.
35. Geoghegan, S. O’Callaghan, K. P. & Oliff, P. A. Vaccine safety: myths and misinformation. Front. Microbiol. 11, 372 (2020).
36. Davidson, M. Vaccination as a cause of autism-myths and controversies. *Dialogues Clin. Neurosci.* 19, 403–407 (2017).
37. Doherty, M. et al. Vaccination of special populations: protecting the vulnerable. *Vaccine* 34, 6681–6690 (2016).
38. Goyal, M. K. et al. Racial and ethnic differences in emergency department pain management of children with fractures. *Pediatrics* 145, 1–11 (2020).
39. Moore, J. T. et al. Disparities in incidence of COVID-19 among underrepresented racial/ethnic groups in counties identified as hotspots during June 5–18, 2020—22 States, February–June 2020. *MMWR Morb. Mortal Wkly Rep.* 69, 1122–1126 (2020).
40. Kim, L. et al. Hospitalization Rates and Characteristics of Children Aged <18 Years Hospitalized with Laboratory-Confirmed COVID-19—COVID-NET, 14 States, March 1–July 25, 2020. *MMWR Morb. Mortal Wkly Rep.* 69, 1081–1088 (2020).
41. Anandappa, M. et al. Racial disparities in vaccination for seasonal influenza in early childhood. *Public Health* 158, 1–8 (2018).
42. Webb, N. S., Dowd-Arrow, B., Taylor, M. G. & Burdette, A. M. Racial/ethnic disparities in influenza vaccination coverage among US adolescents, 2010-2016. *Public Health Rep.* 133, 667–676 (2018).
43. Woinarowicz, M. & Howell, M. Comparing vaccination coverage of American Indian children with White children in North Dakota. *Public Health* 186, 78–82 (2020).
44. Santibanez, T. A. et al. Parental vaccine hesitancy and childhood influenza vaccination. *Pediatrics* 146, e2020007609 (2020).
45. Aristizabal, P. et al. Participation in pediatric oncology research protocols: racial/ethnic, language and age-based disparities. *Pediatr. Blood Cancer* 62, 1337–1344 (2015).
46. Missing from state plans to distribute the coronavirus vaccine: money to do it. *The New York Times* (2020); https://www.nytimes.com/2020/11/14/health/covid-vaccine-distribution-plans.html.
47. Edwards, K. M., et al. Countering vaccine hesitancy. *Pediatrics* 138, e20162146 (2016).
48. Karafiilakis, E. et al. HPV vaccination in a context of public mistrust and uncertainty: a systematic literature review of determinants of HPV vaccine hesitancy in Europe. *Hum. Vaccines Immunother.* 15, 1615–1627 (2019).
49. Simon, G. R. et al. Medical versus nonmedical immunization exemptions for child care and school attendance. *Pediatrics* 138, e20162145 (2016).
50. Friedman, C. et al. Toward a science of learning systems: a research agenda for the high-functioning learning health system. *J. Am. Med. Informatics Assoc.* 22, 43–50 (2014).
51. Cooper, D. M. et al. Reopening schools safely: the case for collaboration, constructive disruption of pre-coronavirus 2019 expectations, and creative solutions. *J. Pediatr.* 223, 183–185 (2020).