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Pediatric RESEARCH

SPECIAL ARTICLE

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

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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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IMPACT:

- As the US begins an unprecedented implementation of SARS-CoV-2 vaccination, substantial knowledge gaps have yet to be addressed regarding vaccinations in the pediatric population.
- Maturational changes in the immune system during childhood have influenced the effectiveness of pediatric vaccines for other diseases and conditions, and could affect SARS-CoV-2 vaccine responsiveness in children.
- Given that COVID-19 disease is far milder in the majority of children than in adults, the risk–benefit of a pediatric SARS-CoV-2 vaccine must be carefully weighed.
- The needs of children with developmental disabilities and with chronic disease must be addressed.
- Minority and low-income children have been disproportionately adversely affected by the COVID-19 pandemic; care must be taken to address issues of health equity regarding pediatric SARS-CoV-2 vaccine trials and allocation.
- Research and strategies to address general vaccine hesitancy in communities must be addressed in the context of pediatric SARS-CoV-2 vaccines.

INTRODUCTION

As pediatric providers, physician scientists, and advocates for children, we aim to identify key challenges associated with COVID-19 vaccinations in children and to propose a means to overcome them. The National Academy of Medicine recently published an algorithm for vaccine distribution consisting of four phases. Phase 3 (40–45% of the US population) includes all children and young adults in the United States 30 years of age or younger, but it is noted that, "children are not currently included in any major vaccine trials for COVID-19 and would need to be included in these trials before mass vaccination of children could take place." The American Academy of Pediatrics has also advocated for the inclusion of children in pediatric SARS-CoV-2 vaccine testing.[1] We brought together a group of frontline healthcare providers, ethicists, community representatives, and translational researchers to explore essential issues surrounding pediatric COVID-19 vaccination, including (1) rationale for pediatric vaccination, (2) possible effects of immune maturation during childhood, (3) ethical issues related to vaccine testing and vaccination in children, (4) unique considerations for children with special needs, (5) diversity and disparity in the context of pediatric vaccination, (6) vaccine hesitancy in children and parents, and (7) strategies for research, outreach, and community involvement.

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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.[2] For this reason, a higher acceptable risk threshold is required in children compared with adults.[3] 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.[4] 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,[5] and influenza vaccination reduces the risk of influenza-associated death by 50–66%.[6] 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.[7] 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,"[8] children can be a source of transmission of SARS-CoV-2 to each other and to adult family members.[9]
3. Non-pharmaceutical interventions (NPI) are effective in children with evidence mounting from schools and summer camps.[10] 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 shut-downs of the pandemic. Children have experienced loss of education,[11] decreased well-child screening and routine vaccination visits,[12] food insecurity,[13] physical inactivity,[14] and an increase in mental health needs.[15] These adverse effects have impacted minority and low-income children disproportionately.[16]

BIOLOGIC 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,[1] of which 48 are in clinical evaluation as of 12 November 2020.[17] 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,[18] 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,[19] diarrheal diseases,[20] tuberculosis[21]] 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.[22] 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.[23] 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.[25] This altered immunity has been associated with suboptimal (reduced) responses to vaccines, including Hepatitis B[26] and tetanus,[27] and increased susceptibility to influenza.[28] Childhood obesity is linked to physical inactivity, which is increasing in children as a result of the pandemic shutdown and shelter-at-home policies.[14] There is increasing evidence that obesity, irrespective of age, is associated with severe COVID-19, and may predispose to the disease.[29] 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).[30] As noted, children under the age of 12 years have yet to be enrolled in COVID-19 vaccine trials.[31] 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.[32] Even so, the long-term risks and benefits of a SARS-CoV-2 vaccine will take a long time to fully evaluate in adults[33] 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.[34]

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.[35] 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.[36]

Children with chronic diseases and conditions, particularly those that impact the immune system, are substantially under-immunized.[37] 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 comprehensible 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.[38] Between March and July 2020, Hispanic and black children had the highest rates of COVID-19–associated hospitalization.[39, 40]. Previous studies demonstrate that race and ethnicity contribute to disparities in vaccine compliance in children and adolescents.[41–44] There is also evidence that these factors may adversely influence enrollment in pediatric clinical trials.[45] 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.[46]

Vaccine hesitancy has remained a long-term concern of pediatricians and public health workers.[47] In a recent study that surveyed parental attitudes toward influenza vaccination, Santibanez et al.[44] 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,[48] 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.

SUMMARY AND ACTION ITEMS

Federal, state, and local authorities are now gearing up for the daunting task of distributing the vaccine to adults. Many fundamental knowledge gaps exist that will affect the testing and implementation of SARS-CoV-2 vaccines for children (Table 1). We encourage public and private partnerships to support the

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?
	• Is immunization of young children necessary to achieve SARS-CoV-2 herd immunity?
Maturational and environmental factors that influence vaccine responsiveness	• 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)?
	• 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?
Ethical issues in pediatric COVID-19 vaccine testing and implementation	• What would be needed to conclude that COVID-19 vaccine testing and/or widespread vaccination in the pediatric population is ethically justified?
	• What criteria/data need to be met that would justify mandating a SARS-CoV-2 vaccine for children?
Vaccination in children with special needs and/or disabilities	• What special considerations need to be addressed before vaccinating children with chronic conditions, such as immunodeficiency, pediatric malignancy, sickle cell disease, and neurodevelopmental disorders?
Health disparities	• 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?
Vaccine hesitancy regarding COVID-19	• 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[50] 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.[51] 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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AUTHOR CONTRIBUTIONS

D.M.C. conceptualized and outlined the commentary. B.A., C.K.C., L.F.R., K.D.L., C.T.L., S. R.-A., W.E.S., J.T., E.R.U., and F.Z. contributed sections and paragraphs. C.L.B. and J.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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