

# Proposals to Accelerate Novel Vaccine Development for Children

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The initial hallmark of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic was the virus' predilection for causing disease, hospitalization, and death among older adults and adults with comorbidities. Yet by September 2021, over six months after 3 highly effective and safe SARS-CoV-2 vaccines were first approved for use in adults, children comprised more than a quarter of all reported cases. In addition, pediatric hospital admissions for coronavirus disease 2019 (COVID-19) were the highest reported since the onset of the pandemic, largely because of the high case load associated with the highly transmissible delta variant of SARS-CoV-2.<sup>1</sup> Although most children continue to fare well after SARS-CoV-2 infection, children with underlying comorbidities carry a greater risk for severe disease. It was unfortunate that children returned to in-person school in summer 2021 with the youngest lacking access to the most powerful tool we have to protect them against SARS-CoV-2: vaccines.

Vaccines needed across the age spectrum are typically evaluated first in adults to ensure their safety and efficacy; once sufficient data are available, children enter clinical trials, often in a staged manner from oldest to youngest. Accordingly, SARS-CoV-2 messenger RNA (mRNA) vaccine trials for adolescents were initiated after release of the remarkable efficacy results of the phase 3 trials performed in individuals aged ages 16+ (Pfizer)<sup>2</sup> and 18+ (Moderna).<sup>3</sup> Pfizer and/or BioNTech enrolled children 12 to 15 years of age as part of an extension of their phase 3 clinical trial; these data led to expanded emergency authorization of the vaccine down to 12 years of age. Moderna conducted a similar trial; and together, these studies demonstrated that adolescents generate higher levels of antibody than seen in older individuals with comparable adverse event profiles.<sup>4,5</sup> Preclinical vaccine studies in nonhuman primates and ongoing trials with both mRNA vaccines in children <12 years of age (NCT04816643 and NCT04796896) have suggested that lower doses can achieve similar immunogenicity to that observed in adults, with potentially reduced reaction profiles. Pfizer/BioNTech has recently reported that its mRNA vaccine given at an optimized lower dose in children aged 5 to 11 years is safe and immunogenic. These data have been recently submitted to the US

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Food and Drug Administration and the European Medicines Agency, and other regulators will follow. Yet other SARS-CoV-2 vaccine manufacturers lag further behind in their pediatric vaccine trials.

Pediatric-specific studies are critical in vaccine development because both immune responses and adverse events after immunization may differ in children. For example, the US Food and Drug Administration issued calls to increase pediatric trial enrollment to detect rare side effects, including vaccine-associated myocarditis, an uncommon adverse event that occurs most commonly among young, male individuals after the second dose of mRNA vaccine (estimated 40 cases per million second doses in male individuals 12–29 years of age).<sup>6</sup> Although these increases in sample size will unlikely be large enough to observe cases of myocarditis, such efforts highlight the importance of conducting pediatric-specific vaccine trials as early as possible. The recent increase in pediatric COVID-19 cases, both mild and severe, has tipped the risk/benefit ratio even further in favor of broad SARS-CoV-2 vaccination of children. In the future, there will be distinct considerations for each new vaccine and pathogen as pediatric trials are planned, including both the risk/benefit ratio, the willingness of caregivers to enroll their children, and the challenges of addressing vaccine hesitancy.

We propose several recommendations to speed development, testing, and approval of vaccines for our youngest populations (Table 1). These recommendations could be applicable to novel vaccines for both ongoing infectious threats and future novel pandemics.

1. Use of preclinical pediatric animal models to inform pediatric vaccine trial design. Several animal models, such as nonhuman primates, have successfully been used to guide adult vaccine trials for other viruses. The infant nonhuman primate model has emerged as a highly relevant method for assessing early life vaccination with both current vaccines, such as influenza, pertussis, and meningococcus, and novel vaccines, such as HIV and malaria.<sup>7</sup> In fact, studies in infant nonhuman primates indicated the highly immunogenic nature of low doses of mRNA vaccine; however, these studies were limited in scope and not integrated with the overall SARS-CoV-2 vaccine development process. Such studies could be performed simultaneously with adult phase 1 trials to guide pediatric dosing ranges, as well as provide early safety signals.
2. Early introduction of dose-ranging and safety studies in children after initial adult phase 1 safety studies. In the setting of an emerging infectious disease that leads to morbidity in both adult and pediatric populations, studies in children and other special populations (eg, pregnant and lactating women, older adults, and immunocompromised individuals) should be cautiously introduced once early adult safety studies are complete and indicate no safety signals and robust immunogenicity. One practical approach is the development of pediatric-specific “shell protocols,” or generic pediatric clinical trial protocol templates that serve to accelerate trial-specific protocol development and harmonize clinical trials across vaccine candidates, such as study endpoints and adverse event reporting.
3. Simultaneous, multiage group trials, as opposed to age de-escalation. The norm in pediatric clinical trials has been a de-escalation approach, establishing dosing and safety profiles in older children before expanding enrollment to younger children. This strategy lacks efficiency and perhaps is unnecessary if preclinical dosing data from animal models are available. The design also may lack relevance because each age group has distinct immune responses and vaccine reactogenicity. For example, although low-grade fever is a manageable side effect in school-aged children, high vaccine-induced fevers in toddlers can precipitate febrile seizures and can generate the need for clinical sepsis evaluation in those <1 year of age. Characterizing reactogenicity in older teenagers before extending enrollment to infants may be unwarranted, particularly if different doses are used.
4. Weight-based and age-based vaccine dosing. Vaccine dosing has traditionally been established at a single dose or limited age-related dosing for premature children and older adults. This approach is in contrast to therapeutic pediatric dosing that is almost solely weight based. With SARS-CoV-2 mRNA vaccine trials, it is yet unknown if these distinct dose requirements are specific to the status of immune development or other physiology, or if perhaps they are related to weight. Obesity is known to have a negative impact on vaccine responses, and children with chronic diseases can vary considerably from typical weight for their age, leaving pediatricians with difficult questions regarding appropriate vaccine dosing for those children.

**TABLE 1** Recommendations for Speeding Pediatric Vaccine Development

Recommendation	Phase of Vaccine Development
Use of preclinical pediatric animal models to inform pediatric vaccine trial design	Preclinical/adult phase 1 <sup>a</sup>
Early introduction of dose-ranging and safety studies in children after initial adult phase 1 safety studies	Early phase pediatric/adult phase 2 <sup>b</sup>
Simultaneous, multiage group trials, as opposed to age de-escalation	Early phase pediatric
Weight-based versus age-based vaccine dosing	Early phase pediatric
Coordinated and mechanistic studies of adverse events across the age groups	Phase 3 <sup>c</sup> and postlicensure

<sup>a</sup> In phase 1 studies, researchers enroll limited numbers of normal healthy subjects, usually <100 individuals. Phase 1 studies also often involve dose-ranging studies, such that the first enrolled subjects are administered the lowest doses of vaccine and, if tolerated, the doses are increased.

<sup>b</sup> Phase 2 studies involve several hundred subjects and are often made up of a larger age range than subjects of earlier phase trials. With SARS-CoV-2 vaccines, phase 2 studies were used to expand the safety profile and to assess immune responses in larger numbers of subjects.

<sup>c</sup> Phase 3 trials are designed to determine if the vaccines will prevent a predefined endpoint, generally the prevention of laboratory-confirmed disease. Subjects enrolled in phase 3 studies are randomly assigned and blinded to receipt of either vaccine or a control, usually consisting of a placebo.

A more personalized approach based on weight and age should be investigated in both animal and human studies.

5. Coordinated and mechanistic studies of adverse events across the age groups. Rare adverse events are extremely difficult to study in clinical trials because of the challenge in enrolling adequate numbers of patients for robust analysis of the mechanisms and underlying risk factors for the outcome. Thus, when pediatric vaccines are approved, every effort should be made to leverage and connect the research and public

health infrastructures available in the United States for safety evaluations. Coordination among these established networks and clinical sites, such as those in the Centers for Disease Control and Prevention Immunization Safety Office and the National Institutes of Health, would aid in the future design of vaccines that might predict which individuals may be at highest risk for such rare events and how they might be reduced.

Reimagining the design and implementation of pediatric vaccine trials for both endemic and pandemic pathogens using the principles

described above could avoid leaving children without vaccine immunity while other age groups benefit and will protect them against severe disease and long-term complications from infectious pathogens.

#### ABBREVIATIONS

COVID-19: coronavirus disease 2019  
 mRNA: messenger RNA  
 SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

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