

Warp Speed for COVID-19 Vaccines: Why are Children Stuck in Neutral?

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Summary: While adult clinical trials of COVID-19 vaccines have moved quickly into Phase 3 clinical trials, clinical trials have not started in children in the US. Given the potential direct and indirect benefits of pediatric vaccination, implementation of Phase II clinical trials for COVID-19 vaccines should begin now.

Abstract: While adult clinical trials of COVID-19 vaccines have moved quickly into Phase 3 clinical trials, clinical trials have not started in children in the US. The direct COVID-19 impact upon children is greater than that observed for a number of other pathogens for which we now have effective pediatric vaccines. Additionally, the role of children in SARS-CoV-2 transmission has clearly been underappreciated. Carefully conducted Phase II clinical trials can adequately address potential COVID-19 vaccine safety concerns. Delaying Phase II vaccine clinical trials in children will delay our recovery from COVID-19 and unnecessarily prolong its impact upon children's education, health and emotional well-being, and equitable access to opportunities for development and social success. Given the potential direct and indirect benefits of pediatric vaccination, implementation of Phase II clinical trials for COVID-19 vaccines should begin now.

Keywords: SARS-CoV-2, pediatric, immunize, immunization, vaccination

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The US government has launched and invested billions of dollars in a massive effort to safely accelerate COVID-19 vaccine candidates toward licensure at ‘warp speed.’ Development of COVID-19 vaccines has been expedited partly by basic science and vaccine research conducted on related coronaviruses, Severe Acute Respiratory Syndrome (SARS) and Middle Eastern Respiratory Virus Syndrome (MERS) [1]. Conducting in parallel the multiple aspects of clinical trial development further accelerated vaccine development in adults while protecting subject safety. Phase I and II data are now available for a number of vaccine candidates [2-6], and Phase III clinical trials have begun.

Despite efforts to advance vaccines for adults at warp speed, COVID-19 vaccine clinical trials for children remain stuck in neutral. Children are infected with SARS-CoV-2, transmit the virus, and suffer COVID-19 complications. Safe and effective vaccines, when given to children, may provide both direct and indirect benefits. At the time that Phase III adult clinical trials are initiated, data support the initiation of careful pediatric Phase II clinical trials to evaluate safety and immunogenicity of advanced COVID-19 vaccine candidates. These initial pediatric studies should be conducted in parallel with adult efficacy trials, rather than delaying until adult efficacy is established. Additionally, it is incumbent upon us to begin these studies to address the economic, educational, and equity impact of COVID-19.

Potential Direct and Indirect Benefit in Vaccinating Children

Potential for Direct Benefit

Current estimates of US pediatric hospitalizations through August 29, 2020 are 15.8/100,000 in children 0 – 4 years of age and 9.2/100,000 in those 5-17 years of age [7]. Although the COVID-19 hospitalization burden is smaller in children than adults [8], hospitalizations rival the pre-vaccine era hospitalization burden of other now vaccine-preventable viruses (**Table 1**). Approximately one-third

of hospitalized SARS-CoV-2 PCR-positive children and up to 80% of those with Multisystem Inflammatory Syndrome in Children (MIS-C) are admitted to the ICU [8, 9]. The risk of serious COVID-19 in children (both hospitalizations and MIS-C) occurs with disproportionately higher rates in both Hispanics and Blacks as compared to Whites [8-10]. A pediatric COVID-19 vaccine could dramatically reduce hospitalization and racial disparities from COVID-19.

Children in the US are dying of COVID-19-related complications; in the first 5 months of the pandemic, 103 children have died in the US from COVID-19 through September 9, 2020 [11]. It is important to recognize that other vaccine-preventable diseases for which vaccination is recommended today, resulted in similar or fewer annual pediatric deaths before vaccines became widely utilized (e.g., hepatitis A, varicella, rubella, rotavirus) (**Table 1**) [12-15]. Additionally, pediatric COVID-19 deaths are rapidly approaching the 110-188 influenza-associated pediatric deaths per season from the past 4 seasons (2016 – 2020) [16]. The anticipated persistence of SARS-CoV-2 circulation and the burden of COVID-19 hospitalizations and deaths in children justify development of a pediatric indication for COVID-19 vaccines.

In addition to direct medical benefits, a COVID-19 vaccine could provide direct benefits on childhood education by allowing a safer return to school, a critical factor in children maximizing their potential. The intermittent or complete closure of schools to onsite education threatens to adversely impact that opportunity across all households that cannot provide direct educational oversight and is worse among households without adequate access to online learning – an issue disproportionately affecting racial minorities. In addition to the altered learning environment, social distancing and the lack of extracurricular activities (e.g., sports, drama, music, art, social events) impacts the emotional and psychological development of children. Thus, an approved COVID-19 vaccine for children could have far-reaching positive ramifications on health and educational equity.

Potential for Indirect Benefits from Pediatric COVID-19 Vaccination

Vaccinated children would receive potential direct impact from a COVID-19 vaccine, but substantial potential for indirect effects of implementing a vaccine in children should also be recognized, as has been observed with hepatitis A, rotavirus, pneumococcus, rubella, and potentially influenza [17-24]. Marked declines in adult pneumococcal disease occurred after implementation of 7-valent pediatric pneumococcal conjugate vaccine (PCV) [21]. Additional pronounced impact occurred after implementation of PCV-13 [20] such that routine PCV-13 vaccination is no longer routinely recommended in adults ≥ 65 years of age [25]. The potential for an indirect impact depends upon the ability of the vaccine to prevent transmission of a pathogen to unvaccinated populations. Although it is unknown whether this will be the case for COVID-19, recent nonhuman primate data in which animals received COVID-19 vaccination followed by SARS-CoV-2 challenge demonstrated declines in both disease and viral titers in the nose [26]. These nonhuman primate challenge data in conjunction with high neutralizing antibodies achieved in early human trials provide strong support for the potential of a direct and indirect impact of vaccination.

Vaccination of children against COVID-19 may mimic the indirect benefits previously identified with other vaccines [17, 18]. Data from a study of close contacts of SARS-CoV-2 infected patients suggest that while children were less likely to have severe symptoms, they were just as likely to be infected as adults (rate of about 7% in both) [27]. Several studies suggest that the viral titers in the respiratory tracts of children are greater than those of adults [28, 29]. A large contact tracing study of COVID-19 cases, conducted while schools were closed in South Korea, supports the concept that older children can transmit COVID-19, as the highest COVID-19 rate (18.6%) occurred in household contacts of those 10 – 19 years of age [30]. An outbreak at a summer camp reported an attack rate of 44%, demonstrating that children of all ages were susceptible for SARS-CoV-2 infection and that they may play a role in transmission [31]. Recent modeling demonstrated that US school closures were temporally associated with overall decreased COVID-19 incidence and mortality [32].

Approximately 3.8 million children are born in the US annually; all are naïve to COVID-19. Without a COVID-19 vaccine, children will likely serve as a reservoir, which would undermine efforts to end the pandemic. Until all children can more safely return to school and parents can return to fulltime work, it is difficult to imagine that the economy can completely recover.

Addressing Potential COVID-19 Vaccine Safety Concerns in Children

Ensuring the safety of potential vaccine candidates is paramount, particularly in children. Data in adults show that all COVID-19 vaccines evaluated thus far have local (e.g., pain, redness, swelling, induration) and systemic (e.g., fever, chills, myalgia) reactogenicity [2-4, 6, 33, 34]. Reactogenicity is self-limited, treatable, and reflects a typical innate immune response to antigen exposure. More important is vaccine safety. Uncommon, unexpected safety events can occur after vaccination, such as thrombocytopenia after the measles, mumps and rubella (MMR) vaccination; febrile seizures with certain vaccines; and intussusception associated with the original tetravalent rotavirus vaccine [35-37]. All vaccines have the potential for unknown and uncommon safety problems. The potential benefit and risks of new vaccines should be considered. A carefully designed clinical development plan can ensure that potential benefits outweigh risks. This approach has been successful in moving vaccines against RSV, CMV, and other pathogens into clinical trials. The vaccine safety network within the US includes several post-marketing surveillance systems for all vaccines to detect rare adverse events that were not detected pre-licensure [38]. Importantly, withdrawal for safety has only occurred once, with the tetravalent rotavirus vaccine [39]. Thus, the process of obtaining FDA licensure and post-licensure safety surveillance should remain rigorous and robust in ensuring safe vaccines. Statements by the FDA to date suggest that this will remain the case for COVID-19 vaccines [40].

Vaccine-associated immune-mediated enhanced disease (VAED), while a theoretical concern, is a process that is considered unlikely to occur with SARS-CoV-2. VAED may be associated with two different mechanisms of action [41]. Antibody-dependent enhancement (ADE), as has been observed with dengue, occurs when a vaccine-induced antibody paradoxically mediates increased viral entry [41], particularly with exposure to a different strain of virus. Although minor mutations have occurred in circulating SARS-CoV-2, including the D614G [42], available data do not suggest that major mutations have emerged. Vaccine-associated enhancement of respiratory disease (VAERD) occurred in association with use of a formalin-inactivated respiratory syncytial virus (RSV) vaccine in the 1960s. Investigations into the pathophysiology suggest that this was due to non-neutralizing antibodies and a predominantly Th2-biased response.[41] Importantly, all COVID-19 vaccines with available data induce high levels of neutralizing antibodies, and some also generate a Th1 response [2-4, 6, 34, 43].

The final safety issue that has been raised is the potential for induction of MIS-C associated with COVID-19. The timing of MIS-C (frequently weeks after infection) and the detection of neutralizing and receptor-binding-domain antibodies at the time of illness suggest that this might be an immune-mediated injury triggered by SARS-CoV-2 infection [9, 44]. Given the viremia that is known to occur with COVID-19 [45] and the response of most patients to brief courses of immunomodulators (e.g., steroids), it may be due to immunological recognition of viral antigens (or live virus) rather than triggering of an autoimmune condition. Although not powered to detect rare events, data from early clinical studies in humans have not yet identified any cases of ADE, or VAERD[2-4, 33, 34]. A vaccine that prevents infection could also prevent MIS-C; available data suggest that vaccines prevent COVID-19 in a nonhuman primate challenge model without enhancement of disease [26, 46, 47]. Large Phase III efficacy trials conducted in adults may provide additional insights into vaccine-elicited immunity and enhanced disease and such data would be anticipated to be available during the Phase II pediatric clinical trials. Given the rarity of MIS-C with natural infection, any risk is

unlikely to be resolved even with carefully conducted large pediatric clinical trials and ongoing surveillance for MIS-C will be necessary even after a vaccine approval.

Recommendations for Advancing COVID-19 Vaccines in Children

The current default position, waiting until data from adult efficacy studies are available, will unduly delay Phase II clinical trials of leading COVID-19 vaccines in children resulting in additional pediatric hospitalizations and deaths. Data are now available from early phase adult clinical trials [2-6]. Pediatric clinical trials of leading vaccine candidates can safely be initiated now. To establish safety, trials should start with adolescents and older children before expanding to younger children. The strategy of age de-escalating trials to bridge vaccines from adult studies to children is one that has been commonly used in the past to ensure early identification of safety signals while minimizing risks, establishing dosing, and evaluating immune responses. Similar to adult studies, it will take time to conduct these studies safely in children.

Moving forward now with pediatric COVID-19 vaccine trials will help prevent delays in obtaining a pediatric indication from the US Food and Drug Administration (FDA). The Pediatric Research Equity Act (PREA, section 505B of the FD&C Act (21 U.S.C. 355c)) requires manufacturers to conduct vaccine studies of safety and effectiveness in children. Although the timing of pediatric studies is not delineated in the Act, we believe the FDA, funding agencies, investigators, and manufacturers should join to initiate these studies now. The FDA clarified that to ensure compliance with 21 CFR Part 50 Subpart D, considerations of the prospect of direct benefit and acceptable risk to support initiation of pediatric studies and the appropriate design and endpoints for pediatric studies should be discussed in the context of specific vaccine development programs [48].

Despite FDA guidance and requirements of the law, to our knowledge no studies of COVID-19 vaccines in children have been developed or initiated in the US. It would be beneficial, in our

opinion, for the funders and overseers of US vaccine efforts (e.g., Operation Warp Speed, the US FDA, manufacturers) to ensure that pediatric studies of COVID-19 vaccines begin at the same time that vaccines move into Phase III adult clinical trials. To assist industry and government sponsors in moving forward with pediatric COVID-19 trials, the Infectious Diseases Clinical Research Consortium (IDCRC), in partnership with the Division of Microbiology and Infectious Diseases (DMID) of the National Institutes of Health, convened a panel of vaccine experts to develop a pediatric COVID-19 vaccine protocol template. The template is adaptable to multiple vaccines currently under evaluation in adults and could standardize the approach and endpoints across vaccine manufacturers. It features an age de-escalation strategy, incorporating multiple provisions that will allow these vaccines to be safely evaluated in adolescents, young children, and infants.

Conclusions

Children are at substantial risk of COVID-19. Delays in starting Phase II vaccine clinical trials in children will delay our recovery from COVID-19 and unnecessarily prolong its impact upon children's health and emotional well-being, their education, and equitable access to opportunities for development and social success, as well as the country's economy. Understanding the safety, immunogenicity, and efficacy of COVID-19 vaccines in children is critical to protect children and adults. For children, a vaccine has the added benefit of returning them safely to school and extracurricular activities, and allowing them to engage with their world face-to-face once again. Ensuring acceleration of vaccine clinical trials to warp speed for children will be critical in making this our future reality.

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Conflicts of Interest:

E.J.A has received personal fees from AbbVie, Pfizer, and Sanofi Pasteur for consulting, and his institution receives funds to conduct clinical research unrelated to this manuscript from MedImmune, Regeneron, PaxVax, Pfizer, GSK, Merck, Novavax, Sanofi-Pasteur, Janssen, and Micron. He also serves on a safety monitoring board for Kentucky BioProcessing, Inc.

JDC: his institution receives funds to conduct clinical research unrelated to this manuscript from Merck, GSK, Pfizer, and Sanofi. He is currently an investigator on federally-funded COVID-19 research with products manufactured by Moderna, Gilead, Eli Lilly, and EMD Serono. His institution receives grants from Moderna, outside the submitted work. He serves pro bono on a data and safety monitoring board for Sanaria.

CBC has received consulting fees from Karius, Horizon Pharma, Premier, and Astellas Pharmaceuticals. His institution has received funds to conduct clinical research unrelated to this manuscript from Merck Vaccines. He also serves on a data and safety monitoring board for Astellas Pharmaceuticals. Additionally, he has a patent for Staphylococcal Antibodies (16491271) pending.

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Table 1. Numbers of hospitalizations and deaths for COVID-19 in comparison to varicella, rubella, hepatitis A, and rotavirus in pre-vaccine era*

Virus	Hospitalizations/year	Deaths
COVID-19	15.4 per 100,000 ages 0-4 years 8.7 per 100,000 ages 5-17 years Through 8/22/2020[7]	103 children Age ≤18 years Through 08/26/2020 [11]
Varicella	4–31 per 100,000 Age <20 years Years 1988–1995[49]	50 children per year Age <15 years Years 1970–1994 [14]
Rubella	Not available‡	17 children per year All ages Years 1966–1968 [50]
Hepatitis A†	107 hospitalized children Age <15 years Year 2005[51]	3 children per year Age <20 years Years 1990–1995 [15]
Rotavirus	55,000–70,000 children Age <5 years Years 1993 – 2002[13, 52]	20–60 children per year Age <5 years Years 1999–2007 [13, 53]

*Data methods of collection and ages are variable across the pathogens, but are summarized by age and year(s) during which data were collected before widespread implementation of a vaccine. Data about the impact of other vaccines have previously been summarized [50].

†Hepatitis A hospitalization data after implementation of routine vaccination in those ≥2 years of age in 11 states with elevated rates of disease, but before routine hepatitis A vaccination was implemented in all children.

‡Data are not available, to our knowledge, about this outcome before vaccine implementation.

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