The Importance of Advancing SARS-CoV-2 Vaccines in Children

Carol M Kao[1], MD, Walter A Orenstein[2,3], MD, Evan J Anderson[1,2], MD

[1] Department of Pediatrics, Emory University School of Medicine, Emory + Children's Pediatric Institute, Atlanta, GA, USA. [2]Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA. [3]Emory Vaccine Center, Atlanta, GA, USA.

Corresponding Author:
Evan J. Anderson, MD
Division of Pediatric Infectious Diseases
Associate Professor of Pediatrics and Medicine
Emory University School of Medicine
Emory + Children's Pediatric Institute
2015 Uppergate Drive NE
Atlanta, Georgia 30322, USA
Phone number: 404-727-1746
Fax: 404-727-9223
Email: evanderson@emory.edu

Summary: Children likely play an important role in the transmission of SARS-CoV-2. There is potential direct and indirect benefit through community protection or 'herd immunity' of a SARS-CoV-2 vaccine in children, thus they should be included in future vaccine clinical trials.

Abstract: While the role of children in the chain of transmission of SARS-CoV-2 remains to be fully defined, they likely play an important role based on our knowledge of other respiratory viruses. Children are more likely to be asymptomatic or have milder symptoms and less likely to present for healthcare and be tested for SARS-CoV-2; thus, our current estimates are likely under-representative of the true burden of SARS-CoV-2 in children. Given the potential direct benefit of a SARS-CoV-2 vaccine in children and the substantial indirect benefit through community protection or 'herd immunity', we argue that planning and implementation of SARS-CoV-2 vaccines should include children. Furthermore, community protection occurred after widespread implementation of prior childhood vaccines against *Streptococcus pneumoniae,* rubella and rotavirus. We detail considerations for vaccine clinical trials, potential barriers to the implementation of widespread vaccination and argue why children would be an ideal target population for vaccination.

Keywords: Immunization, SARS-CoV-2, pediatrics, community protection

Since SARS-CoV-2, the novel coronavirus that causes COVID-19 disease, first emerged in Wuhan, China, there have been over 5.5 million cases of SARS-CoV-2 worldwide including over 1.6 million in the United States (US) [1]. SARS-CoV-2 is highly transmissible between humans and once community distancing measures are relaxed, recrudescence of SARS-CoV-2 can be expected until infection rates induce population immunity levels in excess of herd immunity thresholds, probably more than 2/3 of the population infected based on the estimated basic reproduction number (R_0) [2-4]. This underscores the urgent need for a safe and effective SARS-CoV-2 vaccine. An astounding number of vaccine candidates are in various stages of development [5]. As of May 22, there are 114 vaccines in development and ten vaccines in Phase 1 or 2 clinical trials, including an mRNA-based SARS-CoV-2 vaccine (ClinicalTrials.gov Identifier NCT04283461) that went into clinical trials less than 10 weeks after the genetic sequence of the virus was released and is enrolling adults of any age [6].

Given the epidemiology of severe cases and deaths from COVID-19, it is tempting to focus vaccine development and implementation strategies on high-risk populations (e.g., elderly, immunocompromised). There is a lack of discussion about moving vaccine clinical trials into children. We believe that this approach is shortsighted and fails to consider the critical importance of children in contributing to adult infectious diseases.

Ill-defined burden of SARS-CoV-2 in Children

Although pediatric cases were not reported initially during the SARS-CoV-2 pandemic, retrospective data demonstrate that children were indeed infected early on [7]. As of May 26, 2020, children <18 years comprised 3.5% (42,810 of 1,211,030) of all laboratory-confirmed COVID-19 cases in the US [8] and 5.2% of COVID-19 associated hospitalizations [9]. Data from COVID-NET show that children <4 years of age account for the highest percentage of hospitalizations among pediatric patients and the majority have at least one underlying medical condition [9]. Thus, similar to other respiratory pathogens (e.g., influenza, respiratory syncytial virus), SARS-CoV-2 disproportionately affects the very young and old.

In general, children with COVID-19 are asymptomatic or have mild to moderate symptoms, although recently an increasing number of children worldwide have presented with a severe inflammatory syndrome with Kawasaki Disease-like features now termed Multisystem Inflammatory Syndrome in Children (MIS-C) in the setting of recent or past infection [10-14]. The full clinical spectrum of SARS-CoV-2 disease in children continues to evolve as more information becomes available. In a retrospective cohort study, children <10 years of age were as likely to be infected (7.4%) as the population average (6.6%), but less likely to have fever or severe symptoms [15]. Thus, children are less likely to be seen by a healthcare provider [10] and less likely to be tested. In addition, early school and daycare closures may have temporarily mitigated the disease burden in children. Until large-scale population studies are completed, the true burden of SARS-CoV-2 in children will remain unknown. As schools are considering re-opening, data regarding SARS-CoV-2 seroprevalence

and transmission in children are urgently needed to further the understanding of the role of children in the chain of transmission [15].

The Role of Children in Community Transmission and Community Protection

Although the SARS-CoV-2 symptomatic burden is limited in children, there is likely direct benefit of a vaccine in children and substantial indirect benefit through community protection as observed with other respiratory and gastrointestinal pathogens [16]. Epidemiologic studies of other common community human coronaviruses (HCoV) (e.g., HKU1, NL63, 229E, OC43) and novel coronaviruses (Severe acute respiratory syndrome (SARS-CoV-1), Middle East respiratory syndrome (MERS)-CoV) may inform our understanding of SARS-CoV-2 in children. Similar to the current pandemic, children were less affected and had lower mortality during the SARS-CoV-1 and MERS-CoV outbreaks [17-19]. The BIG-LoVE study, conducted prior to emergence of SARS-CoV-2 looking at weekly viral surveillance in Utah households found that young children had the highest number of positive total viral episodes and longest duration of viral shedding with an average of 2 weeks [20]. Children have also been shown to have higher rates of HCoV compared to adults, and there is a higher likelihood of HCoV viral detection in households containing young children [20, 21]. In addition, HCoV is more often asymptomatic in children compared to other viruses like influenza and relying on hospitalization or testing rates alone underestimates the true community disease burden [20].

In addition to HCoV, children have been linked to the community spread of other respiratory and gastrointestinal pathogens. Community protection or 'herd immunity' has been clearly demonstrated after implementation of new childhood vaccines against *Streptococcus pneumoniae*, rubella, influenza, rotavirus, and Hepatitis A [16]. Dramatic

declines in invasive pneumococcal disease (IPD) and hospitalization for IPD occurred after the introduction of heptavalent pneumococcal conjugate vaccine (PCV7) in children in 2000 and again after the 13-valent pneumococcal conjugate vaccine (PCV13) in children in 2010, but before adult PCV13 vaccination [22]. Rubella and congenital rubella syndrome (CRS) were eliminated in the US following introduction of rubella-containing vaccines into the childhood immunization schedule for both girls and boys to interrupt transmission to pregnant women[16]. In comparison, ongoing cases of CRS occurred in the UK where pre-pubertal girls were initially prioritized for rubella vaccination until a universal pediatric vaccination policy was adopted. Targeted vaccination of schoolchildren in Tecumseh, Michigan during an influenza outbreak in 1968 resulted in substantial decreased community transmission compared to surrounding neighborhoods where similar strategies were not implemented [16]. Unvaccinated household contacts of influenza-vaccinated daycare children benefit, with less febrile respiratory illnesses, missed-school days, physician visits, missed work and physician-prescribed antibiotics [23]. After implementation of infant rotavirus vaccination in 2006, substantial decreases in both pediatric and adult hospitalizations for gastroenteritis occurred [16, 24] although unvaccinated children subsequently spread rotavirus to adults [25]. Similarly, marked declines in symptomatic adult hepatitis A infections and mortality occurred with widespread pediatric vaccination [16]. Importantly, the burden of disease and the critical role of children in transmitting each of these pathogens to adults was underappreciated until implementation of pediatric vaccination.

The impact of childhood vaccines is not surprising to those who care for children. Children are less able to control their secretions and maintain social distancing. Children

have prolonged viral shedding of HCoV up to 18 days and half of children with SARS-CoV-2 from Bambino Gesu Pediatric Hospital in Italy continued to have a positive SARS-CoV-2 nasopharyngeal swab at day 14, although whether this represents viable virus is unclear [20, 26, 27]. Importantly, detection of viral RNA in stool raises the possibility of SARS-CoV-2 fecal-oral transmission particularly to caregivers [27-29]. Obviously substantial risk exists for family and household members, but also is substantial for other critical adult members of society such as grocery workers, teachers, daycare providers, and healthcare providers who have frequent contact with children.

Considerations for SARS-CoV-2 Vaccine Clinical Trials in Children

We advocate that planning for SARS-CoV-2 vaccine clinical trials in children should begin now and studies implemented as soon as preliminary data is available about safety in adults from Phase II trials. Given the potential of direct benefit to children, we believe that a Phase II clinical trial in children would fall under a 46.405 designation by the Office for Human Research Protections. We would suggest an age de-escalation approach to pediatric vaccination to minimize safety concerns. Based on experience with prior FDA-approved vaccines, it is likely that children can receive the same dose established for adults. Multiple clinical trials are ongoing in adults and it is unknown at this time whether a single-dose or multiple doses will be needed to generate an immune response. Preliminary results from a Phase 1 study of a non-replicating Ad5 vectored COVID-19 vaccine found that a single-dose was immunogenic 28 days post-vaccination particularly in high-dose group individuals [30]. In children, this may differ between younger and older children. For example, children less than 9 years of age receiving seasonal influenza vaccine for the first time require a booster dose [31]. Finally, we would argue for the use of a placebo control, as there currently is no

standard vaccine for SARS-CoV-2 to be used as a comparator. Critical in such trials would be to determine not only whether children were protected from COVID-19 disease, but also protected from infection and shedding virus. For example, inactivated polio vaccine (IPV) is highly effective in protecting the central nervous system from paralytic disease but has very limited impact on fecal shedding following exposure to polio viruses, thus permitting transmission via that route in populations where fecal-oral transmission is common [32, 33].

In subsequent Phase 3 trials, long-term safety will need to be established in large cohorts of children. It may be necessary to expand to non-US sites given the large number of subjects required to meet study endpoints and also to increase the generalizability of findings to ethnically diverse populations. It may also be necessary to make the primary endpoint immunogenicity (e.g., seroconversion defined by 4-fold change in antibody titer from baseline to the vaccine structural protein target) rather than vaccine efficacy to facilitate FDA licensure, as it is unlikely any pediatric clinical trial can be powered to demonstrate protection against symptomatic COVID-19 or hospitalization. We are presuming that a correlate of protection will be identified from adult vaccination or natural history data allowing us the ability to determine the percentage of children who reach the "protective threshold" as a measure of protective immunity. Preliminary studies on COVID-19 hospitalized adults have shown universal antibody response within 2-3 weeks after infection and adults vaccinated with an Ad5 vectored COVID-19 vaccine developed SARS-CoV-2 specific humoral and T-cell responses [30, 34, 35]. A critical secondary endpoint would include determining whether children are protected from COVID-19 infections and viral shedding (e.g., microbiological detection of virus from the respiratory tract by PCR, immune response to non-targeted viral structural proteins), as these impact transmission.

SARS-CoV-2 Vaccine Implementation Challenges and the Importance of Pediatric Vaccination

Widespread implementation of a SARS-CoV-2 vaccine program will be challenging. Particularly early after licensure, there may be a limited supply of vaccine – begging the question which individuals to vaccinate first? Counter-intuitively, it may be wisest to focus initial vaccination efforts NOT on the highest risk adults (e.g., elderly, immunocompromised). In general, their responses to vaccines are impaired, sometimes relying upon adjuvants or higher doses of vaccine to improve efficacy (e.g., high dose influenza vaccine) [36, 37]. Additionally, due to impaired responses of the immunocompromised (e.g., leukemia patients, solid organ transplant and stem cell transplant recipients), studies have been complete and are underway in these populations to improve responses through use of higher doses of vaccines for *S. pneumoniae* and influenza (e.g., NCT01216332, NCT01525004, NCT02860039, NCT01215734, NCT03179761). In the setting of a very limited initial supply of vaccine, it may be better to focus vaccination efforts using a standard dose of vaccine on the close contacts of high-risk individuals assuming such contacts will make a more effective immune response to SARS-CoV-2 vaccines and particularly if further evidence supports the role of children in community transmission. These individuals may be better candidates for novel approaches such as long-acting monoclonal antibodies (if available).

Ultimately, post-licensure studies will be needed to understand the safety and effectiveness of a licensed vaccine. Multiple platforms can monitor vaccine safety post-licensure through passive and active surveillance systems such as Vaccine Adverse Events Reporting System (VAERS), World Health Organization Uppsala Monitoring Centre (WHO-

UMC), Vaccine Safety Datalink (VSD), Clinical Immunization Safety Assessment (CISA) Project and the New Vaccine Surveillance Network (NVSN). Although unlikely, should children suffer a vaccine-related adverse event after licensure they may be covered under the National Vaccine Injury Compensation Program.

Potential issues that need to be addressed about implementing COVID-19 vaccination in children

Prior to implementing a SARS-CoV-2 vaccine in children, outstanding obstacles will need to be addressed. Additional information regarding the current SARS-CoV-2 transmission is needed to optimize vaccine implementation strategies – it will be important to conduct serosurveys in communities impacted by COVID-19 to see what the true seroprevalence is in children. In addition, families can be surveyed to see which age groups are first affected to inform whether vaccination should first target the youngest children or school age children.

Despite these potential barriers, we believe that widespread vaccination in children will be feasible and likely successful. There already exists a 'medical home' for children to receive routine checkups (e.g., at least yearly checkups in all children and more frequent visits in those <2 years of age) [31]. In addition, pediatrician's offices have existing infrastructure for distributing and handling large quantities of vaccines (e.g., freezers, refrigerators for vaccine storage, experienced staff members). Any licensed and ACIP recommended vaccine would need to be available to all children regardless of insurance or socioeconomic status, which could be achieved through the US Vaccines for Children (VFC) program. Unfortunately, no similar structure exists in adults, particularly in the socioeconomic disadvantaged who are at highest risk for disease. And although

controversial, there is historical precedent to mandate vaccination in children as a precursor to school-attendance (e.g., measles vaccination) [38].

Conclusions

Children likely play an important role in the spread of SARS-CoV-2 based on available data and by our experience with other respiratory tract infections. Additional studies could establish this link and help guide future vaccination strategies, but the extent of this link will likely remain uncertain until after vaccine implementation. In addition to clear direct benefits to children, vaccinating children would likely provide community protection. Because of these features, children should be included early in SARS-CoV-2 vaccine clinical trials. If determined to be safe and immunogenic, such vaccines should be integrated into childhood immunization programs.

Disclosures: E.J.A has received personal fees from AbbVie and Pfizer 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, and Micron. C.M.K and W.A.O have no disclosures.

References

1. Johns Hopkins Coronavirus Resource Center. COVID-19 Map. Available at: https://coronavirus.jhu.edu/map.html. Accessed May 26 2020.
2. Fine PEM MK, Scott JA, Edmunds WJ. Community Protection In: Plotkin SA OW, Offit PA, Edwards KM. Vaccines: Elsevier, **2018**:1512-31.
3. Sanche S, Lin YT, Xu C, Romero-Severson E, Hengartner N, Ke R. High Contagiousness and Rapid Spread of Severe Acute Respiratory Syndrome Coronavirus 2. Emerg Infect Dis **2020**; 26(7).
4. Li Q, Guan X, Wu P, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med **2020**; 382(13): 1199-207.
5. Lurie N, Saville M, Hatchett R, Halton J. Developing Covid-19 Vaccines at Pandemic Speed. N Engl J Med **2020**; 382: 1969-73.
6. World Health Organization. Draft landscape of COVID 19 candidate vaccines. **2020**.
7. Liu W, Zhang Q, Chen J, et al. Detection of Covid-19 in Children in Early January 2020 in Wuhan, China. N Engl J Med **2020**; 382: 1370-1.
8. Centers for Disease Control and Prevention. Cases of Coronavirus Disease (COVID-19) in the U.S. Available at: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html. Accessed May 26 2020.
9. COVID-NET: COVID-19-Associated Hospitalization Surveillance Network, Centers for Disease Control and Prevention. https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html. Accessed May 26 2020.
10. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 Among Children in China. Pediatrics **2020**; 145(6):e20200702.
11. Shelley Riphagen XG, Carmen Gonzalez-Martinez, Nick Wilkinson, Paraskevi Theocharis. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet **2020**; 395(10237): 1607-8.
12. Verdoni L MA, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, Bonanomi E, D'Anitga L. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet **2020**.
13. CDC Health Alert Network. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). Available at: https://emergency.cdc.gov/han/2020/han00432.asp. Accessed May 26 2020.
14. Belhadjer Z, Meot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. Circulation **2020**.
15. Bi Q, Wu Y, Mei S, et al. Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study. Lancet Infect Dis **2020**.
16. Anderson EJ, Daugherty MA, Pickering LK, Orenstein WA, Yogev R. Protecting the Community Through Child Vaccination. Clin Infect Dis **2018**; 67(3): 464-71.
17. Denison MR. Severe acute respiratory syndrome coronavirus pathogenesis, disease and vaccines: an update. Pediatr Infect Dis J **2004**; 23(11 Suppl): S207-14.
18. Al-Tawfiq JA, Kattan RF, Memish ZA. Middle East respiratory syndrome coronavirus disease is rare in children: An update from Saudi Arabia. World J Clin Pediatr **2016**; 5(4): 391-6.
19. Memish ZA, Al-Tawfiq JA, Assiri A, et al. Middle East respiratory syndrome coronavirus disease in children. Pediatr Infect Dis J **2014**; 33(9): 904-6.
20. Byington CL, Ampofo K, Stockmann C, et al. Community Surveillance of Respiratory Viruses Among Families in the Utah Better Identification of Germs-Longitudinal Viral Epidemiology (BIG-LoVE) Study. Clin Infect Dis **2015**; 61(8): 1217-24.

21. Monto AS, Lim SK. The Tecumseh study of respiratory illness. VI. Frequency of and relationship between outbreaks of coronavirus infection. J Infect Dis **1974**; 129(3): 271-6.
22. Ahmed SS, Pondo T, Xing W, et al. Early Impact of 13-valent Pneumococcal Conjugate Vaccine Use on Invasive Pneumococcal Disease among Adults with and without Underlying Medical Conditions-United States. Clin Infect Dis **2019**.
23. Hurwitz ES, Haber M, Chang A, et al. Effectiveness of influenza vaccination of day care children in reducing influenza-related morbidity among household contacts. JAMA **2000**; 284(13): 1677-82.
24. Anderson EJ, Shippee DB, Weinrobe MH, et al. Indirect protection of adults from rotavirus by pediatric rotavirus vaccination. Clin Infect Dis **2013**; 56(6): 755-60.
25. Anderson EJ. Time to begin a new chapter and expand rotavirus immunization. Clin Infect Dis **2014**; 59(7): 982-6.
26. Martin ET, Fairchok MP, Stednick ZJ, Kuypers J, Englund JA. Epidemiology of multiple respiratory viruses in childcare attendees. J Infect Dis **2013**; 207(6): 982-9.
27. De Ioris MA, Scarselli A, Ciofi Degli Atti ML, et al. Dynamic viral SARS-CoV-2 RNA shedding in in children: preliminary data and clinical consideration of Italian regional center. J Pediatric Infect Dis Soc **2020**.
28. Xu Y, Li X, Zhu B, et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. Nat Med **2020**; 26(4): 502-5.
29. Xing YH, Ni W, Wu Q, et al. Prolonged viral shedding in feces of pediatric patients with coronavirus disease 2019. J Microbiol Immunol Infect **2020**.
30. Zhu FC, Li YH, Guan XH, et al. Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial. Lancet **2020**.
31. Centers for Disease Control and Prevention. Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger, United States, 2020. Available at: https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html. Accessed May 26 2020.
32. Poliomyelitis prevention in the United States: introduction of a sequential vaccination schedule of inactivated poliovirus vaccine followed by oral poliovirus vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep **1997**; 46(RR-3): 1-25.
33. Ogra PL, Karzon DT, Righthand F, MacGillivray M. Immunoglobulin response in serum and secretions after immunization with live and inactivated poliovaccine and natural infection. N Engl J Med **1968**; 279(17): 893-900.
34. Mehul S Suthar MZ, Robert Kauffman, et al. Rapid generation of neutralizing antibody responses in COVID-19 patients. medRxiv **2020**.
35. Long QX, Liu BZ, Deng HJ, et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. Nat Med **2020**.
36. DiazGranados CA, Dunning AJ, Jordanov E, Landolfi V, Denis M, Talbot HK. High-dose trivalent influenza vaccine compared to standard dose vaccine in elderly adults: safety, immunogenicity and relative efficacy during the 2009-2010 season. Vaccine **2013**; 31(6): 861-6.
37. Tsai TF. Fluad(R)-MF59(R)-Adjuvanted Influenza Vaccine in Older Adults. Infect Chemother **2013**; 45(2): 159-74.
38. Day E. Measles Outbreak Emergency Directive (2019). Available at: http://rocklandgov.com/files/2015/5362/9503/SOE_-_Measles_Directive_2019-03-26.pdf.