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Commentary

Children are the key to the Endgame: A case for routine pediatric COVID vaccination

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1. Commentary

The rapid development and deployment of effective vaccines against SARS-CoV-2 infection has been a historic achievement. Children, while not the primary age group affected by severe COVID-19 disease, have endured direct and indirect negative consequences of this pandemic that warranted vaccine testing in young age groups. In March 2021, Pfizer/BioNTech announced results from a controlled Phase 3 trial of its BNT162b2 COVID-19 vaccine in >2200 children and adolescents, age 12 to 15. The 18 symptomatic cases of COVID-19 reported during the trial were all in the placebo group – yielding a vaccine efficacy of 100% [1]. Vaccine-related symptoms were mild. These results were submitted to the FDA with a request to expand emergency use authorization (EUA) for children between ages 12 to 15, which was granted on 5-10-2021. Moderna vaccines has demonstrated similar safety and efficacy data for its COVID vaccine in children aged 12–17, and the European Medicines Agency has approved the vaccine for this age group, with a similar request for approval to the FDA currently pending. Both companies are conducting studies in younger children spanning ages 6 months through 12 years.

Given these encouraging immunogenicity and safety data, it is highly surprising that objections have been raised in some circles about deployment of COVID-19 vaccines in children. Indeed, a recently published opinion piece in the *British Medical Journal* (*BMJ Opinion*) raised concerns about the issuance of an EUA for adolescent COVID-19 vaccination [2]. The authors opined that such an EUA should require that an intervention would "address a serious or life-threatening condition", and that the "known and potential benefits of the intervention" should be balanced against "known and potential harms". These authors further posited that "the likelihood of severe outcomes or death associated with COVID-19 infection is very low for children". These comments evoke a hesitancy in embracing COVID-19 vaccination in children widely articulated in social media circles, and stems from the viewpoint that children are less likely to develop symptomatic COVID-19 disease than are adults [3]. The rationale of those who oppose pediatric SARS-CoV-2 vaccination is this: if children have mild, minimal COVID-19 disease, what is the point in immunizing them?

The fallacy in this argument, of course, is that infection with the SARS-CoV-2 virus does, in fact, induce *substantial morbidity and mortality in children*. Some of the comments from the Pegden *et al.* paper, and our responses, are noted in Table 1. Data from the American Academy of Pediatrics (AAP) and the Children's Hospital Association indicates, as of July 29, 2021, that there have been over 4.1 million cases of COVID-19 in children in the U.S. [4]. A total of 38,654 pediatric COVID-19 cases were reported during the week of July 22; by July 29, that number jumped 85 percent, to 71,726. The situation will only worsen as students go back to the classroom this fall. Since the pandemic began, children have accounted for ~14.0% of total cumulated cases, but more recently children have represented not only a steadily increasing absolute number, but also a higher relative percentage, of total cases. The consequences of COVID-19 infection in children are not trivial. For states and U.S. territories reporting data, since 5/21/2020 greater than 17,000 children have been hospitalized, and, as of 8/4/2021, 416 children have died, from COVID-19 [5]. As pediatric infectious diseases specialists, each of the authors of this article has taken care of multiple children severely ill with COVID-19. The effect on the children and their families is devastating, as are the financial and psychological costs of hospital COVID-19 precautions for all families who visit children's hospitals.

To put this into context, the deaths reported to date in the U.S. in children with COVID-19 are *more than double* the total average annual number of varicella-zoster virus (chicken pox) deaths that were reported prior to licensure of varicella vaccine [6]. Another instructive example comes from examination of the annual child mortality numbers that are attributable to seasonal influenza. According to the CDC, over the years since 2004–2005, annual influenza deaths in U.S. children have ranged from 37 to 188, with an average of 113 deaths per year; notably, 358 pediatric flu-related deaths were reported over two years (April 2009-September 2010) corresponding to the 2009-10 H1N1 pandemic. Approximately 80% of fatal cases occur in children not fully vaccinated against influenza [data available at: https://www.cdc.gov/flu/highrisk/children.htm]. As noted above, state-level reporting data collected since the advent of the COVID-19 pandemic has

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identified more pediatric deaths due to SARS-CoV-2 virus (416) *than in the H1N1 influenza pandemic years of 2009-10*. Thus, as with influenza, routine immunization of children against SARS-CoV-2 holds the promise of substantially reducing pediatric deaths. The COVID-19 vaccines tested to date in children have been highly effective (indeed, substantially moreso than any influenza vaccine) and safe. On the basis of available data, vaccination of children 12–15 years old is a slam dunk. If data acquired in the course of current, ongoing studies shows that COVID-19 vaccines are safe and effective in younger children (six months to 12 years), the same will be true for them.

We also note the importance of SARS-CoV-2-induced *Multisystem Inflammatory Syndrome of Childhood (MIS-C)* in gauging the value of pediatric COVID vaccination, and observe that protection against this syndrome would be provided by routine immunization. Surprisingly, this important syndrome was not even mentioned in the *BMJ Opinion* publication by Pegden *et al*., despite its emerging and well-recognized impact on pediatric practice that had already been well-described at the time of that paper's publication [2]. The omission of any discussion of MIS-C represents a serious shortcoming of this paper. This syndrome is characterized by a severe inflammatory response to infection that leads to multi-system organ damage. It has been suggested that the anti-spike (S) protein response induced by COVID-19 vaccination may induce MIS-C in some children, through some as-yet undefined genetic susceptibility [7]. We propose that there is no plausible biological basis to support such a speculation as a consequence of vaccination. MIS-C, though incompletely understood, is a known complication of SARS-CoV-2 *infection*, which provokes a post-viral immune response that has not been reported in the thousands of children receiving S protein RNA-based COVID-19 *vaccination*. Preventing SARS-CoV-2 infection through wide-spread pediatric vaccination should therefore decrease, *not* increase, MIS-C. As of June 29, 2021, there have been approximately 4200 cases of MIS-C reported in the U.S. [https://www.cdc.gov/mis/cases/index.html]. These children are often admitted to the intensive care unit, frequently require protracted hospital stays, and are at risk for substantial morbidity (including thrombosis, stroke, and myocardial dysfunction) and occasional mortality [8]. Prevention of this worrisome complication of SARS-CoV-2 provides *yet another compelling reason* to implement a program of COVID-19 vaccination in young children.

Another under-recognized benefit of COVID-19 vaccination in children is related to the potential for prevention of the residual, long-term central nervous system sequelae of infection. Unfortunately, the so-called "long COVID" syndrome – characterized by fatigue, alterations in taste and smell, and cognitive residua – is being increasingly recognized in children [9]. The duration of neurocognitive sequelae remains unknown, but could be prevented altogether by implementation of a routine COVID-19 immunization program. Finally, and most importantly, a critical component of the long-term impact of COVID-19 in pediatrics is its impact on the *mental health* of children. This takes into consideration the impact of the loss of parents, grandparents, uncles and aunts, and family friends. Many children have become orphaned and have been placed in foster care. The psychosocial impact of these losses and the disruption of family structure have each been devastating to children. Beyond these concerns, the loss or perpetual interruption of school, and the lost ability to socialize with peers and extended family, have also left an incalculable mental health toll, and will almost certainly result in long-term repercussions that will persist well into adulthood.

Pediatricians understand that the mental health of the growing child is a key component of overall health. For this reason, pediatricians have been at the forefront of evaluating the role that pediatric immunization against COVID-19 can play in short-term disease control in communities and schools, and in long-term psychosocial well-being in families. Moreover, children are increasingly playing a critical role as vectors in SARS-CoV-2 dissemination in the community. Increased rates of pediatric transmission due to the more transmissible variants, including the B.1.617.2 (Delta) variant, are now also being described. In addition to enhanced transmissibility, preliminary evidence suggests that the Delta variant may elicit more severe disease in children. Transmission of this strain has exploded in children, and in many states children ages 10–19 now represent the source of the majority of all new COVID-19 cases (increasingly the Delta variant), driven by exposures in youth sports, classrooms, and daycare centers. Children in turn spread virus to susceptible adults, and – depending upon emerging patterns of strain variants such as Delta or the newly emerging C.37 or "Lambda" variant – even *previously immunized* adults can become infected with new strain variants, and are at risk for hospitalization and even mortality. Thus, *the rationale for pediatric immunization is compelling from multiple standpoints*: to protect children from disease, hospitalization, MIS-C, and death; to protect their psychological and social well-being; to protect

Table 1
Response to Pegden et al. [2] regarding the issuance of an EUA for pediatric COVID-19 vaccination.

Responses to Criticisms of the EUA for Pediatric COVID Vaccination and Proposals to Implement Vaccine Programs for Children	
Concern	Response
Lack of safety data for COVID vaccines in children	• Over 2000 doses in pediatric Phase III studies administered [1]; excellent safety profile
Uncertainty about effectiveness in children	• Vaccine efficacy of 100% in Phase III study
Lack of knowledge about role children play in transmission	• Children now account for up to 20% of new COVID cases and are increasingly being shown to play central role in transmission, including the B.1.617.2 (Delta) variant [4]
Lack of symptomatic disease or attributable mortality in pediatric COVID cases	• As of July 29, 2021 over 17,000 hospitalizations and over 400 pediatric deaths due to COVID-19 [4] • > 4100 cases of MIS-C to date, with 37 deaths • Greater mortality in children is attributable to COVID-19 than to either pandemic influenza or varicella
Lack of impact of COVID-19 on pediatric health	• Vaccination should protect against MIS-C and "long COVID" syndrome in children • Vaccination will enable enhanced social and emotional well-being for children
Demonstration of myocarditis in adolescents and young men receiving BioNTech vaccine	• Very rare (rate of 16 cases per million second doses in people ages 16–39) • Self-limited, uneventful recovery in vaccine-associated cases observed to date; additional studies needed in girls and young women to understand if vaccine-associated myocarditis is unique to men • Myocarditis substantially more common in otherwise healthy young men and women recovering from COVID-19 disease (2.3%); vaccine therefore predicted to *protect* against COVID myocarditis

their families and community contacts; and to allow for safe in-person schooling – vital for a child's education, well-being and mental health (Table 2). Thus, we submit that the time has come, pending completion of currently active pediatric studies, to begin planning for an urgent implementation of a program of widespread immunization of children, including children as young as six months of age, against COVID-19. As previously noted, a summary of our responses to Pegden *et al.* is provided in Table 1.

Looking to the future, a number of issues need to be considered as we move toward a goal of universal pediatric COVID-19 immunization. The recent identification of mycocarditis in a case series of seven young men (age range, 14–19) who received the BNT162b2 vaccine was a significant event, and this association requires continued scrutiny [10]. Reassuringly, no patient in this case series was critically ill, each recovered, and the authors noted that there was no definitive causal relationship established between these episodes of myocarditis and vaccine administration. As of this writing, there have been 475 total cases of myocarditis in individuals under 30 years of age reported to the Vaccine Adverse Event Reporting System. It has been estimated that the incidence of myocarditis after a second dose of a COVID-19 mRNA vaccine is 16 per million second doses (https://www.aappublications.org/news/2021/06/10/covid-vaccine-myocarditis-rates-061021). On the other hand, in one study the prevalence of subclinical and/or clinical myocarditis in young athletes (27 men and 10 women) recovering from COVID-19 *infection* was found to be 2.3%, or 23,000 per million cases of COVID-19 [11]. Thus, to put these cases of vaccine-associated myocarditis into perspective, we propose that routine immunization with a COVID-19 vaccine would actually *prevent* most cases of SARS-CoV-2 myocarditis.

Another key issue that needs to be addressed in this discussion is that of global *vaccine equity*. There have been concerns raised about expanding pediatric vaccine programs in the U.S. and Europe in an age group where the morbidity and mortality are lower than in older adults, even as the vaccine needs of higher-risk individuals, particularly those in the developing world, are ignored. We assert that this a false dichotomy. We are at a stage where the infrastructure and technology for SARS-CoV-2 vaccination can support significant upscaling of production. Multiple practical strategies have been outlined for boosting the global supply of COVID-19 vaccines [12]. The U.S. and other high-income countries have the capacity to address the global needs of vaccination in children *and* adults, and we must find the political will to do so. This issue must not be used as an argument against rapid deployment of COVID-19 vaccines in children.

Finally, as more data emerges on the safety of COVID-19 vaccines in children, and if the health equity issues that currently limit access to vaccines in the developing world are resolved, we believe COVID immunization should be considered a *necessary prerequisite for school attendance*. Already there are mandates in place for COVID-19 vaccination at many colleges and universities in the U.S. Some legal scholars have questioned if immunizations recommended in the context of an EUA can be mandated, and individuals with an anti-vaccine agenda post protests on social media complaining that, because COVID-19 vaccines do not yet have formal FDA approval, they should still be considered "experimental". This argument is absurd, and full FDA approval will be rapidly forthcoming – both for adults and children. We propose that when COVID-19 vaccines become authorized and approved for children, vaccination should be mandated for school attendance at *all educational levels*, and not just colleges and universities. There is clearly a precedent on this issue for other vaccine-preventable diseases. Schools have, for decades, mandated that children be immunized against dangerous communicable diseases, such as whooping cough, measles, and polio prior to school attendance. There is also an acknowledgement of the need to immunize against diseases that may be minimally symptomatic in a child but may lead to devastating consequences if transmitted to a susceptible adult (such as transmission of rubella infection to a pregnant women). Such school immunization mandates have been an unmitigated success [13,14]. It is also important to note that for most vaccine-preventable diseases, universal immunization of healthy school-age children is essential in order to protect their immunocompromised classmates, who may not respond well to vaccines. This is certainly a critical issue for COVID-19, since we know that immune compromised individuals respond suboptimally to the current vaccines, and are at much greater risk for adverse outcomes should SARS-CoV-2 infection be acquired. Some authors have argued that there are insufficient data to mandate pediatric COVID immunization at this time, asserting that it would be ‘‘a mistake to consider making a COVID-19 vaccine mandatory" without additional data that they acknowledge "often requires years of research" [15]. We believe that there is a greater urgency at play here, unprecedented in scope, that makes comparisons to other vaccine programs very challenging. In the midst of a pandemic, we cannot afford to wait for the years of additional research that some authors have called for. We have, or will soon have, the necessary and reassuring safety and efficacy data we need to commence routine early childhood vaccination. Reducing disease in children, both symptomatic and asymptomatic, is urgent, and will be critical in reducing the overall incidence of COVID-19 – and, ultimately, in ending the pandemic, given the clear role that children play as vectors/reservoirs of infection and disease. We assert that, given the demonstrable morbidity and mortality of COVID-19 in children and the emerging evidence of the central role that children play in SARS-CoV-2 transmission, *that the time has come to act boldly*. Lives are in the balance. Pediatric COVID vaccination will save lives and protect both children and adults. We urge the Advisory Council on Immunization Practices and the Red Book Committee of the AAP to move forward expeditiously with incorporation of COVID-19 vaccines into the routine Child and Adolescent Immunization Schedule once safety and effectiveness are confirmed in all pediatric age groups. Ultimately the control of SARS-CoV-2 infection in children will not only protect their health, but will represent the ‘‘endgame” in enabling long-term control of the COVID-19 pandemic for all age groups.

Table 2
Proposed Benefits of Universal Childhood COVID-19 Vaccination.

Proposed Benefits of Routine Childhood COVID-19 Immunization
• Prevention of COVID-associated hospitalizations and mortality in children
• Prevention of post-infection syndromes including MIS-C and long COVID
• Eliminate/minimize routes of spread to high-risk individuals
• Children with immunodeficiencies, cancer, chronic illnesses
• Protection of high-risk adults
• Allow for social re-integration
• Schools
• Youth Sports
• Group Activities
• Decrease mask requirements for vaccinated individuals

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Mark R. Schleiss reports a relationship with Moderna Vaccines that includes: consulting or advisory. Dr. Schleiss is a consultant for Moderna Vaccines. Dr. Permar is a consultant for Pfizer, Moderna, and Merck Vaccines.

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