EDITORIAL

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Complexities of the COVID-19 vaccine and multisystem inflammatory syndrome in children

The 2019 novel coronavirus disease (COVID-19) is the most serious pandemic across all continents in over 100 years. With the number of people infected greater than 50 million, and deaths greater than 1.2 million at the time of publication,[1] rigorous study of viral replication and infectivity, the host immune response, and effective therapies and vaccines remains the top global health priority. Epidemiological evidence at this time would suggest that this virus will continue to be spread with ease and the global infection rate will continue to grow until one of two breakthroughs occur: 1) definitive evidence of a vaccine that is safe, effective, widely available and with good uptake by the population; or 2) immunity is achieved whereby the virus has infected a significant proportion of the population and thus the rate of infection falls. Both of these threshold events depend to some degree on durable or lasting immunity to the virus, but the duration of effective immunity—either from a vaccine or from the host immunologic response to natural infection—remains unknown at this time. Until the duration of immunity to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is known, the world-wide medical community will need to maintain careful and unrelenting scrutiny of the accumulating literature on all aspects of this disease.

Information regarding children and the COVID-19 pandemic has been widely variable and rapidly changing, and while a few excellent overviews of the pediatric worldwide exist[2,3] there will certainly be more breakthroughs in our understanding going forward. In particular, the global pediatric medical community awaits rigorous studies on a safe and effective vaccine for children. Investigation of vaccine effectiveness in children is appropriately staged to occur following large studies of vaccine candidate effectiveness in adult patients, the phase of development right now across the world.[4] Investigations of vaccine efficacy in the pediatric patient is complicated even further by the fact that children cannot consent, nor often even assent, to participate in these studies where the risk of serious harm is potentially significant. In addition, the fact that children as a whole are less severely affected by the virus necessities even higher enrollment in these pediatric, compared to adult vaccine effectiveness trials, in order to demonstrate statistical significance.

The medical community does not yet know exactly why children experience less severe disease from COVID-19.[5-7] Beyond the relative rarity of serious illness in children from acute infection from SARS-CoV-2, there has now emerged in children a different rare, but very serious, post-viral syndrome now termed multisystem inflammatory syndrome in children (MIS-C). Across the world, there are slight differences in the definition of MIS-C, but all generally include fever, elevated inflammatory markers, and rash or mucous membrane changes with or without myocardial dysfunction and shock that is not caused by another pathogen and with known exposure to or positivity for SARS-CoV-2 in the recent past.[8] This syndrome can be characterized by severe cardiovascular outcomes in pediatric patients, including significant coronary artery dilation in 17% and even nearly 30% of severely affected patients requiring extracorporeal membrane oxygenation support in a large Swiss and French cohort.[9] Children who have been diagnosed with severe MIS-C have been found to have higher levels of antibody response to SARS-CoV-2 including higher levels of receptor-binding domain, neutralization titers, and antibody levels against the spike protein and viral nucleocapsid.[10,11]

This kind of inflammatory risk makes vaccine development particularly challenging in the pediatric population. If the vaccine is able to induce this type of antibody response, then it would potentially place otherwise healthy children at risk of severe outcome following vaccination intended to prevent illness from SARS-CoV-2. Even in small numbers, this is highly concerning. It thus is critical to have a deeper understanding of the pathophysiology and mechanisms associated with those that develop MIS-C in order to effectively study vaccines in the pediatric

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population. Only by rigorously studying the vaccine candidates for links to potential MIS-C causes can we create the safety profile needed for large scale vaccination of the world's pediatric population.

Understanding the risk factors goes beyond the simple vaccine development as well. It is unlikely that there will be a risk-free vaccine. All interventions—including all known vaccines—incur some risk to those who receive them. Thus, the challenge before the global pediatric medical community is to effectively and transparently convey the small risk of adverse effect from vaccination with the much higher likelihood of significant and lasting benefit to the individual and the community. World-wide distribution of a safe and effective vaccine to mitigate the life-threatening effects of illness with COVID-19 will literally save millions of lives across the world over the next 18 months and reverse the world-wide decline in economic activity that is driving millions of families with children into poverty. However, if efforts to educate parents and others on the real benefits of vaccines for children is not effectively undertaken, then the inherent risks of pediatric illness from COVID-19, as well as measles and a host of other life-threatening infections will re-emerge around the world. Only deliberate and thoughtful education to vaccine eligible recipients and their parents will help to continue to grow the bond of trust between pediatricians and the patients we are trying to protect.

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CONFLICT OF INTEREST

None.

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