American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN®

90 Years of Caring for Children—1930–2020

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September 29, 2020

Alex Azar, JD
Secretary
U.S. Department of Health and Human Services
200 Independence Avenue, SW
Washington, DC 20201

Stephen M. Hahn, M.D.
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Secretary Azar and Commissioner Hahn:

On behalf of the American Academy of Pediatrics (AAP), a non-profit professional organization of more than 67,000 primary care pediatricians, pediatric medical subspecialists, and pediatric surgical specialists dedicated to the health, safety, and well-being of all infants, children, adolescents, and young adults, I write to express our support for the urgent work being done to develop a SARS-CoV-2 vaccine, as well as the importance of following the established vaccine and testing protocols that are essential to the manufacturing of safe and effective vaccines.

The coronavirus pandemic that is devastating our country has created an urgency to develop one or more safe and effective vaccines to begin controlling the spread of the SARS-CoV-2 virus throughout our communities. The scientific power that the United States is bringing to bear on this once-in-a-century crisis is inspiring and gives us hope that we ultimately will be successful in controlling this pandemic. Successful vaccination efforts in the United States will build upon 70 years of scientific collaborations and accomplishments that have resulted in safe and effective vaccines against polio, measles, diphtheria, tetanus, pertussis, pneumococcus, meningococcus, *Haemophilus influenzae*, human papillomavirus, and varicella, among others, as well as the global eradication of smallpox and two of the three wild poliovirus serotypes. We commend the focus and the intensity with which the Department of Health and Human Services (HHS) and the Food and Drug Administration (FDA) have brought this scientific juggernaut to bear as we face this new scourge.

Unfortunately, fear, mistrust, and misinformation about a potential SARS-CoV-2 vaccine is being spread from a vocal, well-established, and growing anti-vaccination movement. For a SARS-CoV-2 vaccine to be effective in controlling the pandemic, it must not only be safe and effective, but must also be embraced by medical providers and the public. For this to occur, Americans must have trust and confidence in the processes by which these vaccines are being tested for both safety and efficacy, and in the transparency of the scientific basis for licensure and recommendations for use. If that trust is jeopardized, mistrust of SARS-CoV-2 vaccines could become widespread and result not only in reduced uptake of SARS-CoV-2 vaccines but also in decreased confidence in all vaccines. If this were to happen, tens of millions of American lives would be at risk from the diseases prevented by our current vaccines.

The nation's pediatricians are critically important to the provision of pediatric vaccines, which prevent morbidity and mortality from vaccine preventable diseases. As such, the Academy strongly encourages HHS and FDA to ensure that the national approach to the coronavirus pandemic not compromise the trust that American parents have in our existing safe and effective approach to the vaccination of children. Any missteps in the approach to SARS-CoV-2 vaccine development programs would seriously jeopardize decades of trust and confidence in our pediatric providers and their ability to implement a pediatric immunization program that is globally recognized for its efficiency and effectiveness.

As pediatricians, we must also stress how crucial it is for children to be included in vaccine trials of SARS-CoV-2 vaccines. While some studies have shown that children under the age of 10 may be less likely to become infected and less likely to spread the virus to others, more recent data suggest children older than 10 years may spread SARS-CoV-2 as efficiently as adults. While the likelihood of spreading the disease may vary among different aged children, we know that children can and do spread the virus to household members, grandparents, teachers, and other children. In fact, in the United States alone, more than 587,000 COVID-19 cases have been reported in children, representing approximately 10 percent of all cases. Among the children who have acquired COVID-19, 109 have died from the virus, with more than two-thirds being Black and Latinx children.

Beyond the direct impact of the infection, children have been greatly affected by the pandemic, with large disruptions to in-person school and early learning, limited social interactions with peers and relatives, and curtailed access to playgrounds, sports activities, and other activity that helps develop social and emotional well-being. We know that lengthy time away from school and associated interruption of supportive services often results in social isolation, making it difficult for schools to identify and address important learning deficits as well as child and adolescent physical or sexual abuse, substance use, depression, and suicidal ideation.

As such, it is counter to the ethical principle of distributive justice to allow children to take on great burdens during this pandemic but not have the opportunity to benefit from a vaccine, or to delay that benefit for an extended period of time, because they have not been included in vaccine trials. Children must be included in vaccine trials to best understand any potential unique immune responses and/or unique safety concerns. Questions about unknown safety concerns will not be answered by posing questions, but only through carefully designed trials which include children. It would also be less than desirable to have one or more SARS-CoV-2 vaccines licensed or available under Emergency Use Authorization (EUA) at a time when no data have been collected on the safety, tolerability, dose, and regimen for children. For these reasons, we urge the inclusion of children in vaccine trials as we move forward in the development of a SARS-CoV-2 vaccine.

In addition, it is imperative that the same methodical steps utilized for the assessment of all other vaccine candidates be applied to the SARS-CoV-2 vaccines in development. It is important to note, however, that methodical does not mean slow; it means careful, and it requires transparency to the medical and scientific community as well as the general public. That transparent and deliberate approach should include a commitment to the following principles:

1. The most critical assessment of any vaccine candidate must include stringent and well-defined metrics for safety. Such assessment requires both adequate numbers of study subjects receiving the vaccine and appropriate time to determine whether a safety signal exists. We applaud Astra Zeneca for its decision on September 8 to halt the global Phase 3 ChAdOx1 vaccine while a thorough investigation was conducted of a serious safety event (SAE) in one United Kingdom (UK) participant. However, its reopening to UK enrollment without the public release of any information about the study subject's SAE is the opposite of the transparency that is needed in the SARS-CoV-2 vaccine studies. The attention to safety should follow both Dose 1 and Dose 2 of each study product. In addition, we believe that safety assessments should continue to be made for a period of time that leading vaccine scientists believe is necessary following Dose 2 of the vaccine before concluding that a given candidate vaccine is adequately safe for widespread, non-study use. Data now emerging suggest reinfection may occur three or four months following an initial infection, so there will need to be a sufficient period to continue studying the vaccines to ensure they are not being primed to develop a more severe infection through a T-cell or antibody-mediated enhanced response to wild-type virus.

2. Any SARS-CoV-2 vaccine studied for use in the United States should have publicly available, peer-reviewed data supporting its licensure based on efficacy in prevention of SARS-CoV-2 infection or COVID-19 disease. Such data are provided regularly through the existing FDA and Centers for Disease Control and Prevention (CDC) processes and are reviewed by the CDC's independent Advisory Committee on Immunization Practices (ACIP) and must be continued and well-publicized. Given the urgency of the pandemic, this may be in tension with the understandable desire to authorize a vaccine as rapidly as possible. We understand that vaccines directed against a number of other pathogens have in some cases been approved and recommended for use based only upon immunogenicity and safety data and without published data on clinical efficacy or effectiveness. However, in those cases, the incidence of the disease prevented is generally prohibitively low to prevent well powered efficacy trials, which is not the case during this coronavirus pandemic. Therefore, we support the publication of safety and immunogenicity data, in addition to rigorous and well powered efficacy data, followed by post-licensure surveillance of larger-scale assessments of safety and effectiveness.

3. Current SARS-CoV-2 vaccine candidates are based on immune responses directed against a variety of epitopes contained in the viral spike protein. Assessment of vaccine-induced immunogenicity must be based upon validation and measurement of neutralizing antibody titers directed against clearly described spike protein epitopes, including a comparison of relative epitope-specific neutralization titers. Short- and long-term assessment of duration of neutralizing antibodies should be conducted, as it is known that infections caused by other coronaviruses may result in incomplete or short-term immunity. Such an approach will provide a safe and reliable method to predict the degree and duration of the immunogenicity of any SARS-CoV-2 vaccine candidate and provide the basis for developing sound vaccination and possibly revaccination recommendations.

4. A priori sample sizes providing rigorously powered outcomes should be utilized in the assessment of safety, immunogenicity, and efficacy endpoints. If efficacy endpoints are met prior to the completion of a Phase 3 trial, these sample sizes must be the basis for determining the a priori efficacy endpoints. In order to determine valid efficacy outcomes, power determinations should not be determined after the trial has started or in post hoc analyses. The anonymized data used to calculate vaccine efficacy should be made available in an open source format. At a minimum, the protocol and statistical analysis plan for each Phase 3 study must be published online at the onset of the trial (and for those underway, must be posted now) so that the endpoints, interim analyses, and a priori statistical assumptions and calculations are available to the medical and scientific communities and the general public *before* they are acted upon by the study sponsor. Several vaccine developers have posted their protocols online, but their statistical analysis plans have not yet been made public.

5. Finally, the data serving as the basis for authorization or recommendations for use in Americans of any coronavirus vaccine must be based upon studies that include Americans subjects. In addition, the population studied *must reflect the racial and ethnic diversity* of the US population, and not exclude populations at risk that may greatly benefit from vaccinations, including children, pregnant women, and those with underlying comorbidities. As mentioned earlier, while infants and children do not appear to be at highest risk for serious complications, they and other at risk groups must be included in SARS-CoV-2 vaccine trials and data regarding safety, immunogenicity, and efficacy must be made available for licensed vaccines in these populations.

In summary, we understand that these undoubtedly are difficult times in which to conduct these historically important vaccine trials. We urge you to follow the principles outlined above, as they have been tested and designed to protect the lives of the Americans that the medical community serves.

Sincerely,

Sara H. Goza, MD, FAAP
President

SHG/pmj