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Editorial

One Year of COVID-19 mRNA Vaccines: Incredible Progress and Unfinished Business

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As we approach the end of the calendar year 2021, it is incredible to reflect on the progress made in the last 12 months. In December 2020, the SARS-CoV-2 mRNA vaccines were granted emergency use authorizations (EUAs) to allow for widespread vaccination of the general population, with prioritization of those most vulnerable to infection while supplies were still limited.[1] According to Centers for Disease Control and Prevention data available at the time of this writing, in the last year almost 200 million people in the United States are fully vaccinated and >500 million doses have been administered.[2] According to the Johns Hopkins Coronavirus Resource Center, globally >7 billion doses have been administered and 3 billion people are fully vaccinated.[3] The world's 2 most populous countries, China and India, have delivered half of those doses to their citizens. The focus of this editorial is on 2 topics that have received significant attention in the United States during the last few months: the need for booster doses and expansion of the EUA to include children 5 to 11 years of age.

The need for booster doses is well established for virtually every vaccine in use today. Booster doses help address the natural waning of immunity that occurs over time, and the timing of booster doses depends on the magnitude of the early vaccine response, the speed with which antibody responses decline over time, and the threshold for vaccine-induced immunity to provide protection after exposure to the pathogen. For smallpox vaccine, the response to one dose was so robust and the threshold for protection so low that no booster was ever needed. For pertussis, the response to vaccine is more fleeting and the threshold for protection against infection is much higher, so booster doses are recommended every 5 to 10 years. When vaccination for SARS-CoV-2 was initiated, most of these variables were still unknown. With active monitoring of real-world vaccine effectiveness and surveillance for breakthrough cases, public health agencies have been able to define which populations would benefit from booster doses of SARS-CoV-2 vaccines. After initial estimates of vaccine efficacy of 95% in the Phase II/III trials and >90% in real-world effectiveness studies, several large observational studies found that vaccine effectiveness began to decrease at approximately 5 to 6 months after the primary series.[1,4–7] Although the estimates hovered around 60% to 70%, there is nuance to these figures that must be considered. These estimates define infection as any polymerase chain reaction detection regardless of symptoms. When hospitalization is used as the outcome for vaccine effectiveness, the estimates remain >90%. Studies also found considerable differences in age subgroups, with decreases being more rapid and pronounced in those >65 years of age. It is well known that older adults respond with lower antibody levels and less robust cellular responses to all vaccines, so this finding is consistent with existing data from other pathogens. As a result of these findings and because the Delta variant was still actively circulating in many regions of the United States, public health advisory groups made a recommendation for booster doses to all adults >65 years of age as well as those younger patients who had risk factors for severe diseases or more frequent, intense exposure. The specific recommendation to include all health care workers for booster dosing generated some controversy because advisory panels were split on whether to offer it. Ultimately, Centers for Disease Control and Prevention Director Rochelle Wolensky, MD, MPH, was the arbiter of this "scientific close call" and chose to issue the recommendation in favor of inclusion.[8,9] From the global health and equity perspective, the decision to recommend booster doses in the United States only fueled the criticism of how affluent countries such as the United States were "hoarding" vaccine supplies for their populations, whereas many poor countries still had little to no access to the SARS-CoV-2 vaccine.[10]

The inclusion of children with the SARS-CoV-2 vaccination campaign began in May 2021 with an EUA of the Pfizer/BioNTech mRNA vaccine for adolescents 12 to 17 years of age.[11] The same 30-mg dose and 3-week interval as adults was used in the Phase II/III studies and led to similar estimates of vaccine efficacy (95%) and

neutralizing antibody levels that were almost twice as high as those seen in young adults.[12] Real-world estimates of vaccine effectiveness have been very close to those observed in the preclinical trials, and virtually no breakthrough cases are being seen in adolescents, likely because of the exceptionally robust immune responses already mentioned. However, within several weeks of initiating adolescent vaccination came reports of sporadic cases of perimyocarditis that seemed to be temporally associated with the second dose of the vaccine.[13,14] After review of the reported case information, public health agencies and most medical specialty societies all endorsed universal immunization as offering tremendous potential benefits compared with the very rare risk of a potential adverse effect.[15,16] There are those who advocate for some modification of the current regimen to use only 1 dose or to expand the interval between doses, but data are lacking to support making any significant changes to the currently recommended schedule. As a result of concerns about potential adverse effects and because an efficacious lower dose needed to be defined, vaccination of children 5 to 11 years of age with the Pfizer/BioNTech mRNA vaccine was not authorized until November 2021.[17,18] The dose used in the Phase II/III study was 10 mg, one-third of the adult dose with the same 3-week dosing interval, but recipients developed neutralizing antibodies at levels comparable to young adults receiving the 30-mg dose.[19] The estimated vaccine efficacy in the study performed in July to September 2021 was approximately 91%. This rate is comparable to the 95% seen in the adolescent trial but is also notable because this efficacy estimate was generated during the surge of Delta variant cases.[12,19] This very high efficacy supports the assertion that current formulations of SARS-CoV-2 mRNA vaccine offer excellent protection against the Delta variant. Similar to what was seen when adolescent vaccination was first authorized, the early weeks have seen a surge in those families who have been eagerly waiting to get vaccinated. However, surveys have documented that many parents are apprehensive or downright oppose having their children vaccinated, so there will still be major segments of the pediatric population who will be unimmunized and who could serve as vectors for future transmission.[20] The pediatric preclinical studies with the Moderna vaccine are partially complete, so it is likely that an EUA will be issued at some point in the coming year.[21]

Where does all this information leave us as we look toward a possible end to the global pandemic? As cases continue to occur in the United States and Western Europe, it is clear that the largest remaining obstacle will be convincing those who have not yet been vaccinated to receive the vaccine. Vaccine mandates have generated public outcries of encroachment on personal freedoms, but they have been very effective in increasing vaccination rates.[22,23] Additional formulations of vaccine covered in a prior commentary may offer those apprehensive of mRNA vaccines a reason to finally get vaccinated.[24] With more children being included in the EUA for vaccination, cases in schools and day care centers will decrease, and fewer adults will be exposed as a result. Ultimately, the pandemic can only end when we achieve truly global vaccine coverage, which would prevent the future emergence of variants that could escape vaccine protection. Although progress in the past year has been staggering, it is also a stark reminder that there is still much hard work to be done.

In this December issue, we extend our thanks to all members of our editorial team for helping us bring you the best content possible. We thank the reviewers who have helped us maintain the integrity and quality of *Clinical Therapeutics*. Finally, we thank you our readers and extend to all of you best wishes for a healthy and fulfilling 2022.

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