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Continued Progress in the Development of Safe and Effective RSV Immunizations

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Before 2023, there were no immunizing tools to protect older adults and all infants from illness and death due to respiratory syncytial virus (RSV). In 2023, two RSV vaccines for older adults, one of which is also approved for use in pregnant persons, and a long-acting monoclonal antibody to protect infants and some toddlers up to 19 months of age were approved by the Food and Drug Administration and recommended by the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention.[1–3] These major developments occurred nearly 60 years after a formalin-inactivated RSV vaccine that had been administered to children in clinical trials resulted in enhanced respiratory disease in seronegative children who had been vaccinated, and hopes for a safe and effective RSV vaccine were dashed, or at least postponed. Investigation into why this vaccine failed ultimately led to identification of the stabilized prefusion conformation of the fusion (F) glycoprotein target, which propelled the scientific community to subsequently make remarkable progress in the development of RSV vaccines.[4]

Furthermore, the discovery of the RSV prefusion F protein as a stable antigen was foundational to the work on vaccine development for coronaviruses before the Covid-19 pandemic, and researchers were able to quickly pivot to targeting SARS-CoV-2 spike protein when it emerged.[5] In December 2020, the first mRNA vaccines against SARS-CoV-2 were authorized, 1 year after the disease and causative virus were first recognized. The development of these vaccines benefited from the head start provided by previous research on RSV vaccines and the mRNA platform that allows for fast production of large quantities of vaccine. Both factors were critical in controlling the Covid-19 pandemic, but they also show the immense potential for the rapid introduction of new vaccines worldwide.

The article by Wilson et al.[6] in this issue of the *Journal* presents the results of a phase 2–3 clinical trial of a vaccine that leverages both these important innovations in vaccine development. Vaccine efficacy was 83.7% (95.88% confidence interval [CI], 66.0 to 92.2) against RSV-associated lower respiratory tract disease with at least two signs or symptoms and 82.4% (96.36% CI, 34.8 to 95.3) against such disease with at least three signs or symptoms — findings consistent with trial estimates for the two currently approved vaccines

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in persons 60 years of age or older.[1] Efficacy was 68.4% (95% CI, 50.9 to 79.7) against RSV-associated acute respiratory disease (key secondary end point). Although the incidence of local and systemic reactions was higher among vaccine recipients than among placebo recipients, the incidence of serious adverse events was balanced between the two groups. In a finding consistent with those in trials of other single-antigen RSV vaccines derived from an RSV subtype A strain,[1] the vaccine showed lower efficacy against RSV B than against RSV A, and there was limited power to determine efficacy against RSV B in older age groups and with regard to disease with at least three signs or symptoms.

Although the trial population (median age, 67 years; 63.5% of the participants were 60 to 69 years of age) broadly reflects the age of adults hospitalized with RSV infection in the United States, some disparities exist.[7] For example, among persons hospitalized for RSV infection, a younger median age is observed among Black, Hispanic, and American Indian or Alaska Native persons than among White persons.[8] Moreover, 75.9% of the trial participants had a score indicating “fit” status on the frailty scale, and persons with immunocompromise were excluded from the trial. Thus, as in other clinical trials of RSV vaccine, the population that was studied was not representative of the population of older adults who would benefit the most from RSV protection — a situation that limits generalizability and highlights the ongoing need for greater inclusion of these populations in clinical trials.

As the authors acknowledge, the trial had limited follow-up and assessed efficacy to a median of only 112 days (range, 1 to 379), but the trial will continue to evaluate the immune response up to 24 months after vaccination. An important consideration will be how much protection an mRNA vaccine provides during subsequent RSV seasons and whether subsequent boosting will be appropriate. Such questions about duration of immunity, along with reactogenicity and cold-chain considerations, remain important areas for further evaluation in the implementation of mRNA vaccines.

The participants in this trial were enrolled in 22 countries, a factor that points to the global importance of the prevention of RSV infection. The burden of RSV disease in older adults in the United States and worldwide is substantial, and multiple RSV vaccines will provide an important intervention in this age group.[5] However, the effects of RSV infection are most profound in infants, with at least 100,000 potentially preventable deaths each year, 97% of which occur in low- and middle-income countries. The vaccination of pregnant persons with RSV vaccines can protect their young infants by means of the placental transfer of antibodies.

As often happens with lifesaving immunizations, RSV vaccines are being initially produced and approved for use in high-income countries, although efforts are under way by the Bill and Melinda Gates Foundation and others to help ensure access to RSV vaccines for pregnant persons in lower-income countries.[9] There are also phase 1 clinical trials planned or under way to evaluate mRNA RSV vaccines in pregnant persons and in children,[10] which may provide more tools for preventing RSV infection in the future. As the article by Wilson et al. exemplifies, the development of safe and effective vaccines against RSV has been a long and tortuous journey marked by setback and discovery but that now stands poised to have substantial effects on public health.

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