EDITORIALS

RSV Illness in the Young and the Old — The Beginning of the End?

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Respiratory syncytial virus (RSV) infection was reported 66 years ago among young children with lower respiratory tract illness who were hospitalized in Baltimore.[1] RSV infection has since emerged as the most frequent cause of hospitalization among infants in the United States and as the leading cause of pneumonia in young children worldwide. Among children younger than 5 years of age, RSV is associated with approximately 33 million cases of lower respiratory tract illness, 3.6 million hospital admissions, and more than 100,000 deaths each year.[2] Infants younger than 6 months of age are at greatest risk for RSV-associated illness and death, and more than 95% of RSV-associated deaths occur in low- and middle-income countries.[2] RSV infection also causes severe lower respiratory tract illness in older adults, particularly in those who are frail or have underlying cardiopulmonary disease. Approximately 60,000 to 160,000 RSV-associated hospitalizations and 6000 to 10,000 RSV-associated deaths occur each year in older adults in the United States.

A substantial research-and-development pipeline of prophylactic products against RSV (https://www.path.org/resources/rsv-vaccine-and-mab-snapshot/) includes vaccines and long-acting "vaccine-like" monoclonal antibodies that build on the success of palivizumab for prevention of severe RSV illness in the highest-risk infants. The overarching strategy has been to provide passive immunity to the youngest infants, either through maternal immunization or through direct administration of long-acting monoclonal antibodies, and to provide active immunity to older infants, children, and older adults through vaccination. These efforts have been made with care to avoid the tragic enhanced RSV illness that occurred in the 1960s in children who had not previously been infected with RSV and who received a formalin-inactivated RSV vaccine.[3] The development of many of these products that either directly provide or induce potent RSV neutralizing antibodies was made possible through elucidation of the structure of the RSV fusion (F) glycoprotein in its highly immunogenic prefusion and less immunogenic postfusion conformations.[4]

Walsh et al.[5] and Kampmann et al.[6] now report in the *Journal* the results of phase 3 trials of a vaccine containing RSV F in the prefusion conformation. RSVpreF, a bivalent vaccine containing RSV F from subtype A and B viruses, was evaluated in older adults in the RSV Vaccine Efficacy Study in Older Adults Immunized against RSV Disease (RENOIR) trial and in infants of women who received it in the Maternal Immunization Study for Safety and Efficacy (MATISSE) trial. The RENOIR trial enrolled 35,971 adults 60 years of age or older in seven countries, and the MATISSE trial enrolled 7392 pregnant women in 18 countries. Both trials were conducted during the coronavirus disease 2019 (Covid-19) pandemic. The trial sponsor, investigators, and participants persevered not only in the face of pandemic-associated logistic hurdles but also through RSV seasons that were tremendously altered, such that accrual of RSV cases was substantially impeded. Data from prespecified interim analyses were reported for

each trial, with additional reports anticipated at the end of the trial (after two RSV seasons in the RENOIR trial and when infant participants reach 12 or 24 months of age in the MATISSE trial).

The interim analysis of the RENOIR trial was conducted after 44 cases of RSV lower respiratory tract illness had accrued, before all the participants completed the first RSV season. Both primary end points were met, with 66.7% vaccine efficacy against RSV-associated lower respiratory tract illness with two or more signs or symptoms and 85.7% vaccine efficacy against RSV-associated lower respiratory tract illness with three or more signs or symptoms. Perhaps owing to the predominance of adults at the younger end of the age spectrum in the RENOIR trial (62.5% of the participants were 60 to 69 years of age), an insufficient number of cases of severe RSV-associated lower respiratory tract illness (hospitalization and illness warranting the use of oxygenation or mechanical ventilation) had accrued for evaluation. RSVpreF vaccine generally had acceptable safety and side-effect profiles, but one case of the Guillain–Barré syndrome and one case of the Miller–Fisher syndrome were reported at 7 and 8 days after vaccination, respectively.

The interim analysis of the MATISSE trial was conducted when 79% of the infants had completed 180 days of follow-up; 80 evaluable cases of medically attended RSV-associated lower respiratory tract illness had occurred within 90 days after birth and 174 cases had occurred within 180 days after birth. Although results with respect to a primary efficacy end point of medically attended RSV-associated lower respiratory tract illness within 90 days after birth did not meet the prespecified statistical success criterion, vaccine efficacy was 51.3% against this outcome within 180 days after birth. It is notable that the efficacy against severe RSV-associated lower respiratory tract illness was 81.8% within 90 days after birth (the coprimary end point) and 69.4% within 180 days after birth. RSVpreF vaccine did not prevent medically attended lower respiratory tract illness of any cause, perhaps because only 22% of the cases of medically attended lower respiratory tract illness were associated with RSV infection, an atypically low proportion that was probably related to the pandemic.

Along with the results of recent trials of other RSV prefusion F vaccines in older adults[7,8] and of nirsevimab (a monoclonal antibody to the RSV fusion protein) in infants,[9] the results of the RENOIR and MATISSE trials move us closer to prevention of RSV illness in the old and young. However, critical scientific questions about the RSVpreF vaccine and cross-cutting programmatic questions remain. In older populations, the greatest benefit of RSVpreF vaccine will be prevention of RSV-associated hospitalization and death, but the interim analysis of the RENOIR trial was not powered to address these outcomes. Data regarding protection through a second RSV season and concomitant administration of other vaccines, especially those for influenza and Covid-19, are also needed, as are postmarketing evaluations to assess whether the incidence of serious neurologic outcomes (observed in two recipients of the vaccine) is above the background incidence of these conditions.

In high-income countries, complex policy decisions about whether to offer maternal immunization with RSV preF vaccine or a long-acting RSV monoclonal antibody in infants will be required. In the United States, substantial efforts would be needed to increase the percentage of pregnant women who receive the RSVpreF vaccine above the 57 to 61% reported for influenza and tetanus–diphtheria–acellular pertussis vaccines.[10] If both the RSVpreF vaccine for pregnant women and RSV monoclonal antibodies for infants are available, enhanced communication between obstetrical and pediatric care providers will be necessary to ensure appropriate use of each product. Doubly protecting healthy term infants with the use of RSVpreF vaccine antenatally and an RSV monoclonal antibody postnatally while leaving many of the infants in the world unimmunized would waste valuable products and exacerbate worldwide inequities in child health.

For young infants in low- and middle-income countries, who are at the greatest risk for severe RSV-associated illness and death, additional information about the use of RSVpreF vaccine in low-resource settings, including the effect of the vaccine on lower respiratory tract illness of any cause, will help to ensure funding and guide decision making. Finally, protection of older infants and children is needed, and this can be

most safely accomplished by the development of other vaccines that induce humoral and cellular immune responses in populations that have not been previously infected with RSV.[3]

These two articles and previous articles[7-9] describe landmark accomplishments in the fight against RSV illness. This progress is remarkable, but substantial additional work to guide decision making and implementation is essential. We are only at the beginning of the end.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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Continued Progress in Therapy for Pulmonary Arterial Hypertension

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Pulmonary arterial hypertension is a devastating disorder characterized by precapillary pulmonary hypertension not caused by respiratory disease, obstruction of the pulmonary arteries, or certain less-common conditions. Idiopathic pulmonary arterial hypertension, heritable pulmonary arterial hypertension, and pulmonary arterial hypertension associated with a connective-tissue disease or exposure to drugs such as methamphetamine account for most cases in the developed world. For years, pulmonary arterial hypertension was considered to be an untreatable, progressive, and rapidly fatal condition.[1]

A new era of treatment for patients with pulmonary arterial hypertension began three decades ago. Investigations that were focused on imbalanced vasoconstriction and vasodilation produced groundbreaking demonstrations that survival might be improved with high-dose calcium-channel blockers in the small subgroup of patients with acute vasoreactivity on hemodynamic testing or with continuously infused prostacyclin regardless of acute vasoreactivity.[2,3] Subsequent trials of agents targeting the prostacyclin, endothelin, or nitric oxide signaling pathways led to our current armamentarium of 10 Food and Drug Administration–approved drugs used alone or in combination to improve exercise capacity and quality of life and delay disease progression.[4] Yet despite this era of remarkable progress, pulmonary arterial hypertension remains deadly for many patients, and available treatments provide insufficient functional and quality-of-life gains for many more.

The discovery of disrupted transforming growth factor β (TGF-β) signaling involving altered function of the bone morphogenetic protein receptor type 2 (BMPR2) in 70 to 80% of patients with heritable pulmonary arterial hypertension and 10 to 20% of those with idiopathic