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EDITORIAL COMMENTARY

Vaccine Prevention of Respiratory Syncytial Virus Infection in Older Adults: The Work Continues

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(See the major article by Falloon et al, on pages 1362–70.)

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The worldwide population >60 years of age, termed "older adults," is at its largest in human history and is expected to reach 2.1 billion by 2050 [1]. Lower respiratory tract infection (LRTI) is a common cause of illness in this population, and routine vaccination to prevent *Streptococcus pneumoniae* and influenza virus infections, with their attendant morbidities, is recommended in some countries. Respiratory syncytial virus (RSV), the well-known cause of annual winter epidemics of bronchiolitis and pneumonia in young children, is increasingly recognized as a significant cause of respiratory illness in older adults [2-4]. The recently initiated World Health Organization Global RSV Surveillance Pilot project is one effort aimed at further characterizing the age and risk groups for severe disease across all ages so that an evidence base to inform RSV vaccination policy will be available [5]. Some 17 RSV vaccines are currently in clinical phase evaluation, with 7 candidate vaccines for the older adult age group and many more at the preclinical stage of evaluation [6].

Development of an RSV vaccine for older adults must address several challenges posed by the host and the virus. Older adults' ability to respond to immunogens is compromised by natural immunosenescence [7], and potent antigens, use of adjuvants, higher doses, and multiple vaccine doses may be needed to increase the quality and quantity of their immune responses. These needs must be balanced by the practical considerations of immunization delivery programs and their costs. If duration of protection is limited, then annual revaccination may be required, which would need to be coordinated with annual influenza vaccination. Older adults can be assumed to have previously been exposed to wild RSV throughout life, and these exposures may shape their response to an RSV vaccine. Immune control of RSV is not completely understood, and a correlate of immunity to RSV is not established [8], although there is evidence that neutralizing activity in serum and nasal immunoglobulin A correlate with protection in adults [9]. The virus encodes 10 proteins, 3 of which (F, G, and SH) are present on the viral envelope. The most commonly used RSV vaccine antigen is the F (fusion) protein, which mediates viral entry into the host cell and to which serum neutralizing activity has been found [8]. Further, prophylactic anti-F monoclonal antibody given to infants reduces the incidence of RSV-associated LRTI hospitalization [10]. RSV vaccines studied in older adults include protein-based subunit vaccines [6, 6–11], particle-based vaccines [13], and gene-based vector vaccines [6]. To date, there are no published studies of an RSV vaccine in older adults demonstrating robust vaccine efficacy.

The article by Falloon et al in this issue of *The Journal of Infectious Diseases* advances our understanding of the road ahead for RSV vaccine development in older adults. The antigen presented was an RSV (antigenic group A)[14] F protein in the postfusion configuration with glucopyranosyl lipid adjuvant, a synthetic mimic of the lipid A component of endotoxin, in an oil-in-water solution. The prefusion and postfusion conformations of the RSV F protein have been proposed as key determinants of immunogenicity following the observation that most neutralization by human sera is directed at the prefusion F (pre-F) form, in which a highly sensitive neutralizing epitope (Ø) is exposed [15]. The adjuvant was chosen to promote a T-helper type 1–biased response, which had been shown in their earlier studies to increase humoral and cellular immunity [16].

Falloon et al conducted a randomized, double-blinded, placebo-controlled study in a medically stable population ≥60 years of age to determine the efficacy of a single dose of the adjuvanted RSV F vaccine in reducing laboratory-confirmed (by real-time polymerase chain reaction analysis), RSV-associated illness. Seasonal standard-dose influenza vaccine was given concurrently at a separate site. Conducted in the northern and southern hemisphere winters of 2015–2016, the incidence of any respiratory illness, defined as at least 1 respiratory symptom

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for 1 day, was 28.9%. Of these illness episodes, only 33 of 539 (6.1%) were confirmed to be due to RSV, with a 1.7% incidence of RSV-associated acute respiratory illness (ARI) in the vaccine arm and a 1.6% incidence in the placebo arm. Vaccine efficacy was estimated at −7.1% (90% confidence interval [CI], −106.9%–44.3%), and, thus, the trial did not meet its efficacy end point. In further prespecified analyses, efficacy was not demonstrated when different ARI definitions were used, when analysis was conducted according to various subgroups, or by baseline clinical condition. By contrast, the RSV vaccine was clearly immunogenic, based on anti-F RSV immunoglobulin G antibody at day 29 after vaccine, with significantly higher responses than observed in control recipients at the end of the RSV season, despite waning over time. Assessments of microneutralization, palivizumab-competing antibodies, and cell-mediated responses (by enzyme-linked immunospot analysis) were only done in a subset of participants, but levels were increased as compared to those on day 0. No safety signal was associated with the novel adjuvant in this study.

When an efficacy trial does not meet its primary end point, several possibilities can be considered. As the investigators note in their discussion, there were no deficits identified in manufacture of the candidate vaccine or in study execution. The incidence of the primary end point, laboratory-confirmed RSV illness, was lower than the 2% estimate used to plan the sample size, and, therefore, the "negative" result of the study could be due to an inability to detect a vaccine effect that is truly present but smaller than estimated (type II error); in such a case, the study results can be considered inconclusive [17, 4]. Year-to-year variation in RSV attack rates makes predicting this outcome measure particularly vexing. Protection might have been easier to detect in a different population, such as those with risk factors for severe RSV disease. Indeed, when Falloon et al examined the 802 participants considered medically stable but high risk at baseline, vaccine efficacy was 51.2%, albeit with a wide CI crossing 0% (90% CI, −33.3%–83.9%). A future trial might focus on higher-risk persons. Finally, it is biologically plausible that efficacy was not demonstrated because the quantitatively high immune responses generated were directed at the postfusion conformation of RSV, rather than the potentially more immunogenic prefusion conformation, and thus were not neutralizing.

Vaccine development is an expensive and time-consuming endeavor, with long time lines between promising preclinical studies and the ultimate test of human studies to determine safety and efficacy. Each well-done research endeavor adds to the body of knowledge and helps shapes the next research question. The study by Falloon et al provides evidence of a well-tolerated adjuvanted RSV vaccine that is highly immunogenic but not, in this study, associated with clinical protection. The evaluation of other RSV antigens and of RSV-F vaccines with the stabilized pre-F configuration is urgently needed to protect this vulnerable population.

Notes

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