CHEST

Respiratory Syncytial Virus Vaccination in the Adult Pulmonary Patient

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TOPIC IMPORTANCE: Since its discovery in 1957, respiratory syncytial virus (RSV) has been widely recognized as a common and deadly pathogen. Although early studies focused on the impact of RSV on the health of children, more recent data show that RSV imposes a significant burden on individuals aged ≥ 70 years. RSV also substantially harms the health of individuals with cardiopulmonary diseases.

REVIEW FINDINGS: Early efforts to develop an RSV vaccine were hampered by toxicity due to antibody-enhanced viral pneumonia and a lack of efficacy in vaccines that targeted the postfusion configuration of the F fusion protein, which is crucial to the pathogenesis of RSV-mediated injury. A newer wave of vaccines has targeted a stabilized prefusion F protein, generating effective neutralizing antibodies and reducing the burden of mild and severe RSV lower respiratory tract injury. This review focuses on the burden of RSV in patients with pulmonary diseases, highlights the tumultuous path from the early days of RSV vaccine development to the modern era, and offers insights into key gaps in knowledge that must be addressed to adequately protect the vulnerable population of patients with severe pulmonary diseases.

SUMMARY: RSV vaccination with bivalent RSVPreF or RSVPreF3OA, which target the stabilized prefusion F protein, can be broadly recommended to adults aged ≥ 60 years with pulmonary diseases. However, more data are needed to understand how these vaccinations affect key clinical outcomes in individuals with pulmonary disease. CHEST 2024; 166(5):963-974

KEY WORDS: pulmonary disease; respiratory syncytial virus; RSV; prophylaxis; vaccine

Respiratory syncytial virus (RSV) is a single-stranded RNA virus that causes primarily respiratory disease in vulnerable populations, including infants,[1] older individuals,[2] and immunocompromised hosts.[3] Since its discovery in 1957 as a common human pathogen,[4] RSV has been increasingly recognized as a major cause of morbidity and mortality; it has an estimated cost of $6.6 billion annually in the United States, with the majority of direct costs being in those hospitalized due to RSV infection.[5] With the recent US Food and Drug Administration (FDA) approvals of vaccines in adults aged ≥ 60 years[6] and, more recently, in pregnant women for the protection of infants,[7] a targeted public health effort to prevent disease due to RSV infection is within reach.

ABBREVIATIONS: AE = adverse event; CHF = congestive heart failure; FDA = US Food and Drug Administration; FI = formalin-inactivated; GBS = Guillain-Barré syndrome; ILD = interstitial lung disease; LMIC = low- and middle-income country; LRTD = lower respiratory tract disease; LRTI = lower respiratory tract infection; mRNA = messenger RNA; RSV = respiratory syncytial virus; Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis

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The aim of the current review was to examine the history of RSV vaccine development, guide clinicians on which individuals should be eligible for RSV vaccination, highlight areas of uncertainty regarding high-risk groups that may potentially benefit from RSV vaccination but are not addressed in current FDA indications, and consider RSV vaccines that might undergo review for FDA approval in the near future.

Literature Search

An initial literature search was performed on PubMed/MEDLINE for peer-reviewed reports of randomized clinical trials of RSV vaccines through February 15, 2024, by using the search terms ("respiratory syncytial virus" OR "RSV") AND "vaccine" and further filtering by randomized clinical trials. We further focused on phase II and phase III studies of RSV vaccines with a trial outcome of vaccine efficacy[8-13] and excluded studies that focused only on children or those studying the efficacy of passive immunity through the administration of monoclonal antibodies. Additional peer-reviewed published studies were included at the discretion of the authors to highlight relevant background information, focusing on RSV infections in adults.

Evidence Review

Global Epidemiology of RSV Infection in Individuals With Lung Disease

Globally, RSV causes > 25 million annual infections resulting in lower respiratory tract disease (LRTD), contributing to > 76,000 annual deaths.[14] Because surveillance is not widespread or systematic, as was often the case during the SARS-CoV-2 pandemic, these figures are likely to be underestimates. The majority of deaths occur in children aged ≤ 5 years, followed by older individuals aged ≥ 70 years. RSV infection is the second leading cause of death due to documented lower respiratory tract infection (LRTI) after pneumococcal pneumonia and accounts for > 50% of deaths due to LRTI in children aged ≤ 5 years. RSV infections have historically occurred with a predictable temporality, with a typical season starting in October or November and ending as late as May[15]; however, the SARS-CoV-2 pandemic has affected the typical seasonality of RSV infections, with recent seasons starting in early summer and with infections occurring "off-season."[16] If the loss of the historical temporal patterns persists, an optimal timing of vaccine administration may be difficult to pinpoint.

RSV infection imposes a significant burden in individuals with chronic lung diseases. RSV infection was evident in > 11% of hospitalizations in individuals with COPD and > 7% of hospitalizations in individuals with asthma, although it is not clear whether hospitalizations were due to exacerbations of airway disease.[2] Conversely, hospitalization due to RSV infection is more common in patients who have COPD or asthma.[17] In addition, RSV is more commonly identified in adults with COPD who develop an acute respiratory illness compared with influenza.[18] A recent study of 377 patients with COPD observed for three consecutive RSV seasons found that 27 (9%) of 310 exacerbations were attributed to RSV.[19] Crucially, nearly 60% of RSV-associated exacerbations were only detected using serologic methods, suggesting that surveillance using nucleic acid amplification testing from nasal specimens may also underestimate the degree to which RSV contributes to COPD exacerbations.

RSV has a bidirectional relationship to asthma, with RSV infection increasing the risk for subsequent asthma in children and asthma increasing the risk for hospitalization due to RSV.[20] However, a meta-analysis of 42 studies examining viral infections as a cause of asthma exacerbation found that RSV is identified in only 2% of asthma exacerbations in adult patients,[21] compared with nearly 10% of asthma exacerbations in children. In general, the evidence implicating RSV as a major pathogen in adults with asthma is weaker than in children.

RSV infection may result in more acute exacerbations of COPD than other respiratory viruses such as influenza.[22] A systematic review of 19 studies involving > 1,700 individuals with COPD found that RSV infections were implicated in 10% of acute exacerbations of COPD.[23] Individuals with COPD and comorbid congestive heart failure (CHF) may be associated with a higher probability of requiring medical attention for RSV infection.[24] In a study of patients with Global Obstructive Lung Disease stage III or IV COPD or American Heart Association class III or IV CHF, RSV was identified in 22% of individuals during a single respiratory virus season; about one-half of participants with evidence of RSV infection required medical attention as specified by the study protocol,[25] although most infections were mild.

RSV infection may accelerate the rate of decline in pulmonary function over time in those with COPD.[26] Individuals with COPD who actively smoke may also

have impaired antiviral responses, which delay clearance of acute RSV infection[27]; this may compound the existing innate immune defects in the lung epithelium of individuals with chronic inflammatory airway diseases (eg, COPD, asthma).[28] Notably, although CHF, advanced age, and LRTI increase the risk for mortality following RSV infection, it is unclear if the presence of COPD does[29] or whether the severity of COPD modifies the risk for mortality after RSV infection.

Although it is established that severe viral infections can result in pulmonary fibrosis,[30,31] less is known about the effect of viral infections in individuals with interstitial lung disease (ILD). Viral infections, including RSV, are detected in a minority of individuals with exacerbations of ILD,[32,33] but it is not clear whether RSV infection is sufficient to induce exacerbation of ILD. Other viruses, particularly human herpesviruses, are associated with an increased risk for the development of ILD but not exacerbation of existing ILD.[34] The role of RSV in the pathogenesis or deterioration of ILD remains unknown.

Structure of RSV

RSV is part of the Paramyxoviridae family of single-stranded negative-sense RNA viruses, along with other human pathogens such as human parainfluenza virus, measles virus, and mumps virus.[35] The RSV genome encodes 11 structural and nonstructural proteins, and an understanding of the function of these proteins is crucial to understanding the rationale for the development of various RSV vaccines (Fig 1).[36] These include the nucleoprotein (N), phosphoprotein (P), and RNA-dependent RNA polymerase (L) proteins that are crucial to viral replication, as well as the receptor attachment glycoprotein (G), fusion protein (F), and short hydrophobic protein (SH), which are located on the viral membrane.[37] The G protein is involved in viral attachment to host cells, whereas the F protein is involved in fusion of RSV to host cells; it also contributes to the syncytia that give RSV its name.[38]

The process of RSV infection and replication starts with G protein attachment to human ciliated epithelial cells.[36] Subsequently, the F protein (F0 prior to fusion) is proteolytically cleaved by furin to generate an F2 and an F1 protein that are covalently linked.[39] A fusion peptide located at the N-terminus of the F1 subunit mediates viral fusion and subsequently the release of RSV RNA genetic material into the cytoplasm,[40] after which replication occurs using host cellular machinery. Because the fusion of the RSV particle with human epithelial cells is a crucial step for further replication, the F protein has been the primary target of monoclonal antibody and vaccine development. Interestingly, although not a paramyxovirus, human metapneumovirus shares substantial homology with the structure of the RSV virion,[41] and the efficacy of RSV vaccines of human metapneumovirus has been studied as a secondary objective.[10]

Early Efforts to Develop an RSV Vaccine

The first human trials of RSV vaccines evaluated formalin-inactivated (FI) RSV given as an intramuscular injection to infants.[42] The vaccine series involved two doses given 1 month apart, followed by a third dose given 3 months later. RSV was isolated from a throat washing and subsequently grown in vervet monkey kidney tissue cultures. Forty-three percent of vaccinated infants developed neutralizing antibodies after three doses of the FI-RSV vaccine, but the vaccine was ineffective in preventing RSV infection; 65% of infants who received the FI-RSV vaccine developed serologic evidence of RSV infection, compared with 53% of infants who received one of the control parainfluenza vaccines. Furthermore, 80% of infants who received the FI-RSV vaccine developed symptoms requiring hospitalization, compared with 5% of infants in the control arm who received a parainfluenza vaccine. Among the infants who were hospitalized, the severity of hospitalization was greater in infants receiving the FI-RSV vaccine. Two infants who received the FI-RSV vaccine died of RSV infection. Three other studies found similar results, with FI-RSV failing to protect against RSV infection, and further increasing the risk for enhanced RSV infection among vaccinated infants.[43-45]

Later work revealed that antibodies induced by the FI-RSV vaccine did not prevent viral fusion[46] due to a lack of antibodies directed against the prefusion F protein.[47] In addition, the generation of unprotective antibodies resulted in a skewing toward a type 2 inflammatory response and a diminished cytotoxic T-lymphocyte response; this may have resulted in additional injury to the lung from eosinophilic inflammation[48] and immune complex deposition,[49] leading to enhanced RSV disease. In short, the initial trials of RSV vaccination using FI-RSV were a failure due to lack of efficacy and a worsening of RSV illness among those who received the vaccine. Subsequent studies focused on passive immunoprophylaxis showed that RSV immunoglobulin[50] and the anti-F glycoprotein monoclonal antibody palivizumab[51] were effective at preventing severe RSV disease; other attempts at RSV

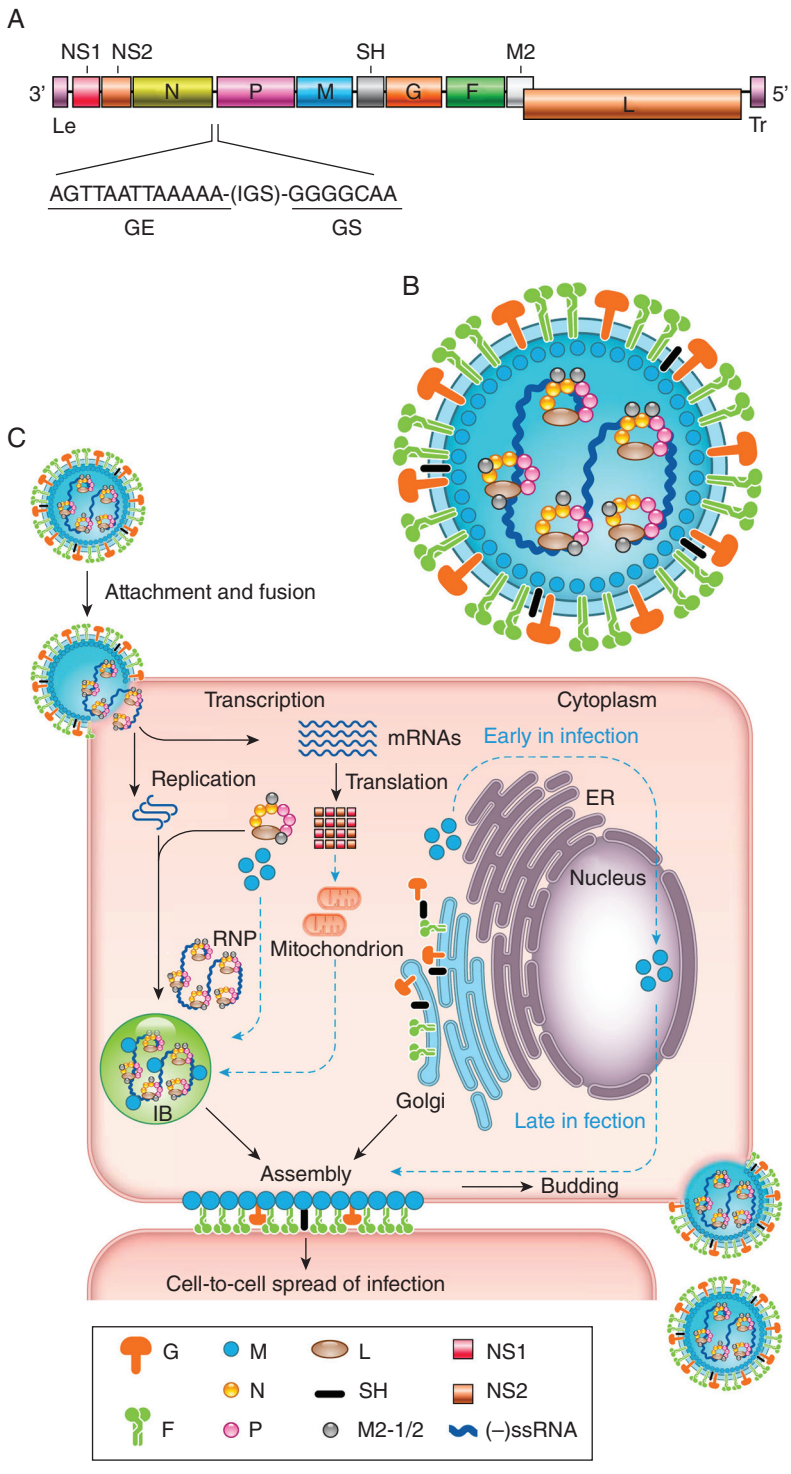

Figure 1 – *A-C, Respiratory syncytial virus (RSV) genome, virion structure, and infectious cycle. A, RSV genomic RNA structure. B, Diagram of the RSV virion and key structural proteins. C, Key events in the RSV life cycle; RSV binds to the target cell membrane via the attachment of the G protein, followed by viral fusion mediated by the F protein, and then release of genomic RNA into the cytoplasm. Host cellular machinery translates the genome into viral proteins, which are assembled into new viral particles. RSV can spread to contiguous cells via F-mediated fusion of neighboring plasma membranes leading to the formation of large syncytia. ER = endoplasmic reticulum; F = fusion; G = attachment; L = large polymerase; M = matrix; M2 = encodes anti-termination factor M2-1 and RNA regulatory factor M2-2; mRNA = messenger RNA; N = nucleoprotein; NS = nonstructural protein; P = phosphoprotein; RNP = ribonucleoprotein; SH = small hydrophobic; ssRNA = single-stranded RNA. (Figure reproduced and legend adapted with permission from Hu et al.*[36]*)*

vaccine development, including vaccines directed toward the G protein[52] and a live attenuated RSV vaccine,[53] were halted due to a lack of efficacy or safety concerns.

A phase II study of RSV F protein nanoparticle vaccination suggested that the vaccination of healthy pregnant women might protect both mother and child.[54] A phase III study involving 4,636 healthy pregnant women studied the effect of an RSV F protein nanoparticle vaccine to prevent medically significant RSV LRTI in infants[8]; however, the trial did not meet prespecified definitions of vaccine efficacy.

Modern RSV Vaccines Targeting Prefusion F Protein: Development and Early-Phase Trial Data

Given the reported efficacy of palivizumab, investigators focused on developing vaccines targeting the F protein.[55] Palivizumab has activity against both the prefusion F protein, which is relatively labile, and the postfusion F protein (Fig. 2),[56] which is relatively stable, but antibodies against the prefusion F protein are believed to be most responsible for the neutralization of RSV.[57,58] In particular, antibodies against the Ø site of the prefusion F protein trimer were 10 to 100 times more potent than palivizumab,[56] although this site may vary substantially between strains.[59] Stabilization of the Ø site was possible through the use of an antibody (D25) that binds to the RSV prefusion F protein but also contained structural elements that could fill in hydrophobic cavities within the RSV F protein, maintaining the prefusion structure while exposing the Ø site.[55] Other alternative methods to stabilize the prefusion F protein were also successful, opening the path for the new generation of RSV prefusion F protein vaccines (Table 1).[60-64]

RSVPreF3 OA: In the first phase I/II study of an RSVPreF3 vaccine (GlaxoSmithKline), 502 healthy nonpregnant women underwent vaccination with 30, 60, or 120 µg of lyophilized RSVPreF3 antigen or placebo.[65] Headache was the most common adverse event (AE), but the vaccine was otherwise well tolerated. All three dose levels induced a satisfactory humoral response compared with placebo. In a second phase I/II study, the RSVPreF3 antigen was tested with a liposome-based adjuvant (AS01) in 48 young adults aged 18 to 40 years and 1,005 older adults aged 60 to 80 years to examine safety and immunogenicity.[66] This second study involved a factorial design, examining the same three antigen doses as in the first study in combination with either no adjuvant, $AS01_E$ adjuvant, or $AS01_B$ adjuvant. AEs were more common in participants receiving vaccine, in particular adjuvanted vaccine; the most common AE was pain at the site of administration, but no serious AEs were attributed to the vaccine. Increasing vaccine doses linearly increased the antibody titers, but neither adjuvant increased the antibody titers. However, cell-mediated immunity was boosted with the $AS01_E$ adjuvant, and therefore the phase III study used a 120 µg dose of RSVPreF3 vaccine combined with the $AS01_E$ adjuvant (RSVPreF3 OA), which was better tolerated than the $AS01_B$ adjuvant.

However, a subsequent pivotal phase III double-blind, randomized, placebo-controlled trial comparing a maternal formulation of the RSVPreF3 vaccine (RSVPreF3-Mat) vs placebo was halted due to a higher

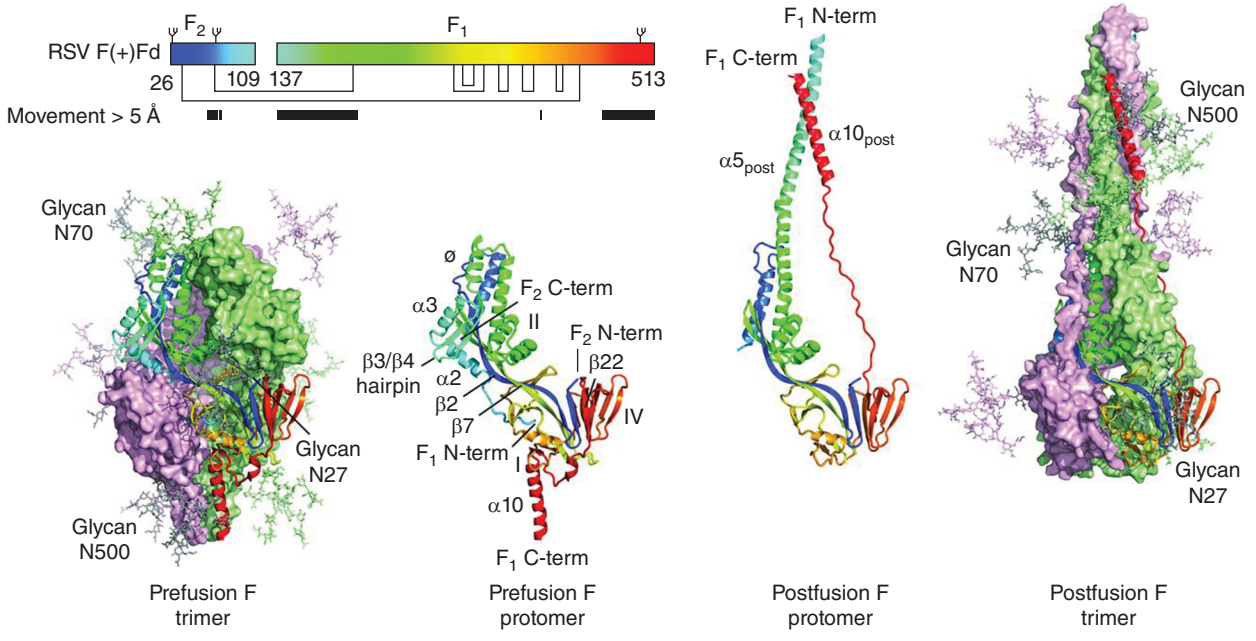

Figure 2 – *Structural images of prefusion (left) and postfusion (right) trimeric structures. Inner images display a single respiratory syncytial virus (RSV) F protomer in ribbon representation, colored as a rainbow from blue to red, N-terminus of F2 to C-terminus of F1, respectively. Inset: Rainbow coloring of the boxes representing the F2 and F1 subunits matching that in the structures. Glycans are shown as branches on top of the boxes, and disulfide bonds are shown as black lines under the boxes. Black bars indicate regions with high motion between prefusion and postfusion conformations. (Figure reproduced and legend adapted with permission from McLellan et al.[56])*

TABLE 1] Summary of Selected RSV Vaccines for Use in Adults With Pulmonary Diseases

Vaccine	Key Trials	Population	Vaccine Efficacy	Considerations for Pulmonary Disease	FDA Approval Date
RSVPreFOA3 (Arexvy, GlaxoSmithKline)	AReSVi-006 (NCT04886596)[61]	Adults ≥ 60 years of age	83% for LRTI; 94% for severe disease[a]	Data lacking for patients with pulmonary disease	May 3, 2023
Bivalent RSVPreF (Pfizer)	RENOIR (NCT05035212)[62]	Adults ≥ 60 years of age	67% for 2 signs or symptoms[b]; 86% for 3 signs or symptoms[b]	33% vaccine efficacy in patients with cardiopulmonary disease[c]	May 31, 2023
	NCT04032093[63]	Healthy pregnant women	Not reported in adults		August 21, 2023
mRNA-1345 (Moderna)[b]	ConquerRSV (NCT05127434)[64]	Adults ≥ 60 years of age	68% for 1 sign or symptom[d]; 84% for 2 signs or symptoms[d]; 82% for 3 signs or symptoms[d]	Vaccine efficacy similar in patients with COPD	Pending approval

FDA = US Food and Drug Administration; LRTI = lower respiratory tract infection; RSV = respiratory syncytial virus.

[a]Severe disease defined as presence of two or more lower respiratory symptoms, including new or increased wheezing, new or increased crackles/rhonchi, respirations ≥ 20 respirations/min, oxygen saturation < 95% or ≤ 90% if baseline < 95%, or need for oxygen supplementation.

[b]Signs or symptoms include cough, wheezing, sputum production, shortness of breath, or tachypnea.

[c]Cardiopulmonary disease defined as asthma, COPD, or congestive heart failure.

[d]Not approved for use by the FDA. Efficacy estimates vary based on presence of two or three key symptoms, which include cough, shortness of breath, fever (≥ 37.8 °C), wheezing and/or rales and/or rhonchi, sputum production, tachypnea (≥ 20 breaths per minute or ≥ 2 breaths per minute increase from baseline), hypoxemia (new oxygen saturation ≤ 93% or new or increasing use of supplemental oxygen), and pleuritic chest pain for at least 24 h.

rate of preterm birth in those receiving vaccine compared with those receiving placebo (7.6% vs 5.0%; relative risk, 1.5; 95% CI, 1.1-2.0).[67] The trial was designed to enroll 10,000 women aged 18 to 49 years who were pregnant with a singleton fetus at 24 to 34 weeks' gestation and randomized women in a 2:1 ratio to receive vaccine or placebo; however, the trial was halted after enrolling 5,328 women. Vaccine efficacy was estimated at 65.5% for RSV LRTD and 69% for severe RSV LRTD (oxygen saturation < 93%, chest retractions, inability to feed, or loss of consciousness). The mechanism for the increase in preterm births remains unknown.

Bivalent RSVPreF Vaccine

Concurrently, another bivalent RSVPreF vaccine was developed for use in adults targeting the RSV-A Ontario strain and the RSV-B Buenos Aires strain (Pfizer). In the first phase I/II study involving 618 adults 18 to 49 years of age, participants were randomized in a 1:3:3 ratio to receive placebo, RSVPreF without aluminum hydroxide, or RSVPreF with aluminum hydroxide at doses of 60, 120, or 240 μg.[68] The most common AEs were local reactions, headache, and fatigue; no fatal events were reported. All three doses were found to be safe and immunogenic. A second phase I/II study used an identical randomization strategy in 617 participants aged 50 to 85 years[69] but also included concurrent influenza vaccination; the investigators reported similar results, with no serious vaccine-related AEs and a satisfactory humoral response with all three doses. Based on these two studies, a 120 μg dose with an aluminum hydroxide adjuvant was chosen to proceed to phase II/III studies.

In a phase IIa viral challenge study, adults 18 to 50 years of age were randomized to receive either RSVPreF or placebo prior to a viral challenge.[11] Seventy participants received either vaccine or placebo, and 62 subsequently underwent intranasal inoculation with RSV (Memphis 37b strain); 60 completed the study. RSV inoculation occurred 28 days after administration of vaccine or placebo, and participants were monitored in a quarantine unit. Vaccine efficacy was estimated at 86.7% (95% CI, 53.8%-96.5%); 6% of vaccinated participants developed symptomatic RSV infection, compared with 48% who received placebo vaccine. RSV viral load was substantially lower in vaccinated participants. The vaccine was well tolerated, and no severe AEs were observed in either group. Notably, participants with any significant medical condition and those with a smoking history of ≥ 10 pack-years were excluded from the study.

In a phase IIb randomized controlled trial, 713 nonpregnant women were randomized 1:1:1:1:1 to receive placebo, and 120 μg RSVPreF with either placebo or concurrent tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine, 240 μg RSVPreF with aluminum hydroxide and either concurrent placebo or Tdap, or placebo vaccine with concurrent Tdap.[70] A serious vaccine-related AE occurred in one participant receiving 120 μg RSVPreF with placebo (constipation) and in one participant receiving 120 μg RSVPreF with Tdap (lymphadenopathy). No deaths occurred, but one spontaneous abortion occurred in a participant receiving 240 μg RSVPreF with aluminum hydroxide with placebo; this was not considered to be vaccine related. Concurrent RSVPreF with Tdap vaccination, regardless of dose, was found to be noninferior to RSVPreF alone when considering anti-RSV neutralizing antibody titers. However, antibodies directed toward pertussis were not noninferior in participants receiving both RSVPreF and Tdap compared with those receiving placebo with Tdap, raising concerns about the efficacy of multiple concurrent vaccinations. Similarly, antibody responses to the influenza vaccine were also lower with concurrent RSVPreF and influenza vaccination.[69]

Ad26.RSV.preF

Ad26.RSV.preF is a recombination adenovirus serotype 26 vector that encodes a stable RSV prefusion F protein (Janssen). In a viral challenge study, Ad26.RSV.preF vaccination generated RSV neutralizing antibodies and reduced the severity of RSV infection.[71] A subsequent study confirmed the safety and immunogenicity of Ad26.RSV.preF.[72] In a randomized, double-blind, placebo-controlled phase IIb trial of 5,782 adults aged ≥ 65 years comparing Ad26.RSV.preF vaccination vs placebo (A Study of an Ad26.RSV.preF-based Regimen in the Prevention of Reverse Transcriptase Polymerase Chain Reaction [RT-PCR]-Confirmed Respiratory Syncytial Virus [RSV]-Mediated Lower Respiratory Tract Disease in Adults Aged 65 Years and Older [CYPRESS]), the vaccine efficacy of Ad26.RSV.preF was estimated at 70% to 80% depending on the case definition of RSV LRTD,[73] and severe AEs occurred with similar frequency in both groups. Overall, 29% of the cohort had COPD, and efficacy was lower in the combined subgroup with chronic cardiac or pulmonary comorbidities, including COPD and asthma

(58%-60%). However, a pivotal phase III trial (A Study of an Adenovirus Serotype 26 Pre-fusion Conformation-stabilized F Protein [Ad26. RSV. preF] Based Respiratory Syncytial Virus [RSV] Vaccine in the Prevention of Lower Respiratory Tract Disease in Adults Aged 60 Years and Older [EVERGREEN])[74] was discontinued in 2023 when the sponsor shuttered their adult RSV vaccination program.

Late-Phase and Pivotal Phase III Trial Data for RSV Prefusion F Protein Vaccines

In a placebo-controlled phase III trial (AReSVi-006), 24,966 participants aged ≥ 60 years were randomized to receive either RSVPreF3OA or placebo prior to a single RSV season.[10] Enrollment included participants with chronic medical conditions, including 2,496 participants with cardiopulmonary conditions who received vaccine and 2,422 participants with cardiopulmonary conditions who received placebo. Notable exclusion criteria included the use of immunosuppressive medications or patients with other immunocompromise and any life-threatening illness. In all participants, the vaccine efficacy was 82.6% (95% CI, 57.9%-94.1%), meeting the primary objective for efficacy (lower limit of CI > 20%). Efficacy against severe RSV LRTI (ie, preventing normal activity) in all participants was 94.1% (95% CI, 62.4%-99.9%), whereas vaccine efficacy against any LRTI was 71.7% (95% CI, 56.2%-82.3%). No patients died of RSV. Vaccine efficacy was similar regardless of age, RSV subtype, or the presence of coexisting conditions. The vaccine was well tolerated, although three deaths occurred in each group that were attributed to vaccine or placebo. No data on safety efficacy were reported specifically for the subgroup of individuals with cardiopulmonary disease. This pivotal phase III trial resulted in FDA approval in individuals aged ≥ 60 years for the prevention of RSV LRTI.

A phase IIb randomized controlled trial enrolled 406 healthy pregnant women without pulmonary disease.[12] The study found neutralizing antibody responses in mothers who received either 120 or 240 μg of bivalent RSVPreF, with or without aluminum hydroxide, compared with placebo, in addition to transplacental transfer of antibodies to neonates. There was a numerical but not statistically significant increase in premature deliveries in women who received either vaccine dose compared with those who received placebo (4.2% vs 3.7%).

In a pivotal phase III study (Study to Evaluate the Efficacy, Immunogenicity, and Safety of RSVpreF in Adults [RENOIR]), 34,284 participants were randomized to receive either bivalent RSVPreF or placebo vaccine.[9] Participants with stable cardiopulmonary disease were considered eligible; 1,956 participants who received RSVPreF and 2,040 who received placebo were considered to have lung disease. Among those who received RSVPreF, 1,541 (9%) had asthma and 1,012 (6%) had COPD, similar to those who received placebo vaccine (1,508 with asthma [8%] and 1,080 with COPD [6%]). Notable exclusion criteria included COPD requiring > 10 mg/d of prednisone, immunocompromise or immunodeficiency, and cancer. Eleven cases of RSV LRTI with ≥ 2 signs or symptoms of cough, wheezing, sputum production, shortness of breath, or tachypnea were noted among vaccinated participants, compared with 33 cases in those receiving placebo vaccine; the result was a vaccine efficacy of 66.7% (95% CI, 28.8% to 85.8%), which met the prespecified criteria for success (lower CI boundary > 20%). The most common symptom was cough, followed by sputum production. Only two cases of RSV LRTI with ≥ 3 signs or symptoms were seen in vaccinated participants, compared with 14 cases in those receiving placebo vaccine, resulting in a vaccine efficacy of 85.7% (95% CI, 32.0% to 98.7%). Point estimates for vaccine efficacy were similar among age groups and in patients with or without coexisting medical conditions. However, patients with more than one cardiopulmonary disease, including asthma, COPD, or CHF, seemed to have lower vaccine efficacy (33.3% for ≥ 2 signs or symptoms [95% CI, –213.7% to 87.9%]; 50% for ≥ 3 signs or symptoms [95% CI, –302.1% to 96.4%]).

Together, these results led to FDA approval for a single dose of 120 μg of bivalent RSVPreF to be given to individuals ≥ 60 years of age to prevent RSV LRTI or to pregnant individuals at 32 to 36 weeks of gestational age to prevent severe RSV infection in infants.

RSV Vaccines on the Horizon

In a phase II/III randomized, double-blind, placebo-controlled study (A Study to Evaluate the Safety and Efficacy of mRNA-1345 Vaccine Targeting Respiratory Syncytial Virus [RSV] in Adults ≥ 60 Years of Age [ConquerRSV]), participants aged ≥ 60 years were randomized to either receive an RSV messenger RNA (mRNA) vaccine or placebo.[13] The mRNA-1345 vaccine (Moderna) uses a stabilized RSV prefusion F protein derived from an RSV A strain to generate an immune response. Participants with stable COPD and CHF were included, and those with uncontrolled cardiopulmonary

disease were excluded. In addition, participants with immunocompromise or immunodeficiency were excluded. Vaccine efficacy for the total cohort was estimated at 83.7% for RSV LRTD with at least two pulmonary signs or symptoms (eg, cough, shortness of breath) and 82.4% for RSV with at least three signs or symptoms. In total, 960 participants with COPD (5.4%) received vaccine, and 978 received placebo (5.5%). Vaccine efficacy was similar in participants with COPD or CHF compared vs those without these diseases. Exacerbations of COPD occurred in four vaccinated participants and in six receiving placebo within 28 days of vaccination. The mRNA-1345 vaccine was granted a breakthrough exemption by the FDA in January 2023 and will be considered for approval in 2024. Numerous other vaccines are in various stages of development but are beyond the scope of the current review.[75]

Areas of Uncertainty

Immunocompromised hosts were excluded from all major late-phase trials of RSV vaccination. Immunocompromised hosts bear unique considerations regarding vaccination against respiratory pathogens[76] because they have a higher risk of dying of viral pneumonias,[77] but they may also have inferior responses to vaccination. The 2013 guidelines from the Infectious Diseases Society of America highlight unique considerations, including optimal timing of vaccination, concerns over live virus vaccination, the need to vaccinate close contacts and household members, and others.[78] Unique scenarios, such as RSV vaccination in the setting of hematopoietic cell transplantation and chimeric antigen receptor T-cell therapy, are deserving of special attention.[79,80] However, in the absence of primary data, the efficacy of RSV vaccination in immunocompromised hosts remains unknown.

Vaccine efficacy in patients with pulmonary diseases was not equal in late-phase trials of RSVPreF3OA, bivalent RSVPreF, and mRNA-1345.[9,10,13] mRNA-1345 vaccine efficacy was similar in patients with and without pulmonary disease but was notably lower with the use of bivalent RSVPreF. Subgroup data were not available for patients with pulmonary diseases with RSVPreF3OA. Therefore, it is possible that these three vaccines may not be equally beneficial in patients with pulmonary diseases, necessitating studies that directly compare vaccine efficacy according to vaccine type. Specific complications, such as exacerbations of COPD, were only reported with mRNA-1345 and were not meaningfully lowered by vaccination; however, this analysis is limited by the low number of exacerbations and the length of observation in the study. The pulmonary community will need to dedicate effort to fully understand the benefits of RSV vaccination in patients with pulmonary diseases and to affect specific pulmonary outcomes. Nevertheless, vaccination can be recommended within the indications set forth by the FDA and the Centers for Disease Control and Prevention.

Given recent variations in RSV seasonality and concerns for efficacy with co-administration of RSV vaccine in conjunction with other annual vaccines such as influenza, the optimal timing of RSV vaccination remains unknown. However, because protection lasts at least two seasons based on emerging top-line data,[81,82] it is possible that RSV vaccination may be scheduled in such a way that other vaccinations, such as influenza or pneumococcal vaccines, do not interfere with the generation of RSV neutralizing antibodies; further data may be needed to confirm the optimal timing of RSV vaccination in relation to other recommended vaccinations.

A follow-up study of AReSVi-006 participants found that signs and symptoms associated with breakthrough RSV infection, measured by using the InFLUenza Patient-Reported Outcome (FLU-PRO) instrument, were less severe in vaccinated participants compared with those who received placebo.[83] To date, similar data are not available for individuals vaccinated with RSVPreF or mRNA-1345, and therefore it is not clear whether all vaccines reduce symptom burden in patients who develop postvaccination breakthrough RSV infection.

Emerging data from the Centers for Medicare & Medicaid Services suggest that first vaccination with RSVPreF between May and December 2023 increased the risk for Guillain-Barré syndrome (GBS) by about sevenfold among Medicare beneficiaries aged $\geq$ 65 years who were enrolled in Medicare Parts A and B and Part D.[84] However, during the same period of observation, RSVPreF3OA was not associated with a significant increase in GBS risk. In this particular analysis, GBS was expected to occur in 25 cases per 1 million vaccinated with RSVPreF3, about five times higher than the background rate of five cases of GBS per 1 million individuals. Further postmarketing surveillance data will be needed to determine the exact risk of GBS in individuals from the general population who are eligible for RSVPreF vaccination.

Finally, low- and middle-income countries (LMICs) shoulder an outsized burden due to RSV infection, both in terms of overall incidence and RSV-attributed mortality.[85] Historically, access to new vaccines in LMICs has lagged behind that in high-income countries, as was clearly evident during the SARS-CoV-2 pandemic.[86] Ensuring access to RSV vaccines in LMICs would reduce the substantial global disparities in RSV-associated disease.

Summary

RSV vaccines targeting the prefusion F protein are poised to curtail the devastating annual impact of RSV LRTI in adults. Studies focused on patients with immune compromise and those with pulmonary diseases are necessary to understand whether vaccine efficacy is maintained and whether key secondary end points, such as exacerbation of pulmonary diseases, are affected by vaccination. Nevertheless, RSV vaccination can be broadly recommended to adults with pulmonary diseases who are aged ≥ 60 years.

Financial/Nonfinancial Disclosures

None declared.

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