Transformative Medicine (T-Med)

Volume 2 | Number 4 Article 6

December 2023

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Maley Zents
Reading Hospital - Tower Health

Emily Wagner
Reading Hospital - Tower Health

Mary Hoang
Reading Hospital - Tower Health

Christina Swiger
Reading Hospital - Tower Health

Recommended Citation

Zents M, Wagner E, Hoang M, Swiger C. Respiratory Syncytial Virus Vaccines for Adults. *Transformative Medicine (T-Med)*. 2023; 2(4):108-112. doi: https://doi.org/10.54299/tmed/zgke1217.

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Cover Page Footnote

We thank Dr. Matt Alspach, PharmD and Dr. Regine Ghoubrial-Waibel for precepting this project. We thank Dr. Adam Sigal, MD FACEP FAAEM for providing guidance on the article.

Respiratory Syncytial Virus Vaccines for Adults

Maley Zents[1], Emily Wagner[1], Mary Hoang[1], Christina Swiger[1]

1 Pharmacy Department, Reading Hospital, Tower Health, West Reading, PA

Published December 2023

ABSTRACT

Respiratory syncytial virus (RSV) is a virus that causes outbreaks of acute lower respiratory tract infections (LRTI) worldwide. The infections are associated with high rates of hospitalizations, which may lead to death, especially in older adults and young children. Due to the morbidity and mortality associated with RSV, pharmaceutical companies have dedicated research to create a vaccine since the 1960s. Despite setbacks after the failure of the first RSV vaccine, new developments in research have led to the approval of two new vaccines. Ensuring healthcare professionals and patients are well-informed about these vaccines is crucial for facilitating informed, collaborative clinical decision-making regarding their administration.

BACKGROUND

Respiratory syncytial virus (RSV) is a single-stranded ribonucleic acid (RNA) virus that causes acute lower respiratory tract infections (LRTI). The virus causes outbreaks worldwide, usually in seasonal patterns. In the United States, RSV is most common from late fall to spring, peaking around February.[1] Although the virus can infect those of any age, it causes more severe disease in older adults and young children. Each year, RSV leads to over two million outpatient visits, tens of thousands of hospitalizations, and hundreds of deaths in children less than five years old. Additionally, there are hundreds of thousands of hospitalizations and thousands of deaths in those over 65 years old.[2]

RSV transmission is initiated when an infected individual coughs or sneezes. The respiratory droplets may be directly inoculated in another person via the eyes, nose, or mouth when in close proximity. Additionally, one may become exposed through direct contact with contaminated skin or other surfaces.[3] Then, within the nasal epithelium, RSV becomes infectious. The RSV G protein is responsible for viral attachment to host cells. After attachment, the F protein promotes the fusion of the viral envelope and the plasma membrane, allowing RSV RNA insertion into the cell. From the upper respiratory tract, the virus migrates to the bronchiole, where it can replicate more efficiently.[4] Efforts to try and inhibit this process began over half a century ago with the first RSV vaccine.

In the 1960s, an RSV vaccine was developed as an intramuscular injection for babies. The vaccine was a formalin-inactivated RSV (FI-RSV) vaccine combined with alum. Unfortunately, the FI-RSV vaccine was unsuccessful. There were higher rates of more severe disease and hospitalizations in recipients compared to the unvaccinated population. The exact cause of enhanced respiratory disease (ERD) is unknown, but studies of vaccine immunopathology have suggested a couple of causes. First, the virus may have eliminated antibody-neutralizing determinants of the virus. By doing so, the FI-RSV antibodies may not have recognized the determinants of the native virus and did not respond to clear the virus upon initial exposure. Another proposed mechanism of the FI-RSV vaccine failure is due to the formalin component. The formalin may have altered surface antigens to block the signaling of the RSV F protein.[5] The FI-RSV vaccine induced pre-fusion and post-fusion changes in the F protein, which may have led to improper antibody formation. RSV-neutralizing antibodies are directed toward epitopes found on the pre-fusion form of the F protein. Therefore, antibodies may not have been able to form due to alteration of the pre-fusion F protein, leading to ERD.[6]

Many pharmaceutical companies have taken this information and dedicated years to RSV vaccine development. In May 2023, the Food and Drug Administration (FDA) approved two new RSV vaccines, Abrysvo® (Pfizer/New York) and Arex-

Correspondence to Maley Zents at maley.zents@towerhealth.org

Disclosure Statement: The authors have no conflicts of interest to declare.

Table 1. Comparison of FDA approved RSV vaccines [8, 9, 10]

Brand Name	Abrysvo® (RSVPreF)	Arexvy® (RSVPre3)
Pharmaceutical Company	Pfizer	GSK
Type of Vaccine	Inactivated Recombinant	Inactivated Adjuvanted Recombinant
Mechanism	Active immunization against RSV prefusion F glycoprotein (RSVPreF) Protect against RSV-A and/or B	Active immunization against RSV prefusion F3 glycoprotein (RSVPre3) Protect against RSV-A and/or B
Dosage Form	Solution reconstituted: 120 mcg/0.5 mL	Suspension reconstituted: 120 mcg/0.5 mL
Storage	Refrigerated at 36°F to 46°F in original package Discard if frozen	
Reconstituted Vials	Administer immediately or store at room temperature and use within 4 hours	
		Protect from light
Administration	IM: 0.5 mL as a single dose	
Indication	Adults ≥60 years of age	
	Pregnant patients 32 through 36 weeks gestation	
Contraindications	Severe hypersensitivity to RSV vaccine or any component of the formulation	
Adverse Reactions & Side Effects	• Hypersensitivity • Inflammatory neurologic events • Shoulder bursitis related to administration • Syncope • Injection site pain, joint pain, fatigue, headache, and muscle pain	
Price	$354.00 each	$336.00 each

IM = Intramuscularly

vy® (GlaxoSmithKline/Rixensart). Unlike the FI-RSV vaccine, Abrysvo® and Arexvy® do not induce changes in the F protein. They also specifically target the pre-fusion F protein, mimicking the body's normal physiological response to RSV exposure.[6]

VACCINE BASICS

The core differences between the two vaccinations include type of vaccine, mechanism, dosage form, and indication (*Table 1*).

Type of Vaccine

Abrysvo® and Arexvy® are both inactivated vaccines, which means that the killed version of the virus is used in production of the product. Therefore, inactivated vaccines cannot replicate to cause disease in people receiving the vaccination. The difference between the two products is that the GSK vaccine Arexvy® includes an adjuvant in the formulation. An adjuvant is used as an ingredient to create a stronger immune response in people receiving the vaccine.[7] This ensures that the body creates an adequate immune response to build lasting immunity against the virus.

Indication

Both vaccines are recommended for RSV associated lower respiratory tract disease prevention in adults 60 years of age and older. Unlike Arexvy®, Abrysvo® is also indicated for pregnant women who are 32 to 36 weeks gestation. [8,9]

https://scholarcommons.towerhealth.org/t-med/vol2/iss4/6
DOI: https://doi.org/10.54299/tmed/zgke1217

Table 2. Medically Attended Severe RSV-Associated Lower Respiratory Tract Illness

Time Interval	RSVPreF Vaccine (n=3495)	Placebo (n=3480)	Vaccine Efficacy
90 days after birth	6	33	81.8%
120 days after birth	12	46	73.9%
150 days after birth	16	55	70.9%
180 days after birth	19	62	69.4%

Table 3. Medically Attended RSV-Associated Lower Respiratory Tract Illness

Time Interval	RSVPreF Vaccine (n=3495)	Placebo (n=3480)	Vaccine Efficacy
90 days after birth	24	56	57.1%
120 days after birth	35	81	56.8%
150 days after birth	47	99	52.5%
180 days after birth	57	119	51.3%

ABRYSVO® STUDY SUMMARIES

RENOIR Clinical Study: RSV Vaccine Efficacy Study in Older Adults Immunized against RSV Disease[11]

This study is an ongoing, phase III, multicenter, double-blind, randomized, placebo-controlled trial with results from the interim analysis at the end of the 2022 RSV season. Healthy adults ≥ 60 years of age as determined by medical history, physical examination, and clinical judgement were included, while patients with history of severe adverse reaction associated with a vaccine and/or severe allergic reaction to any component of the study intervention or any related vaccine or conditions associated with prolonged bleeding were excluded. 35,971 participants were enrolled in the study with 17,215 participants receiving the RSVpreF vaccine and 17,069 participants receiving placebo.

RSV-associated lower respiratory tract illness with ≥ 2 signs or symptoms occurred in 11 participants in the vaccine group and 33 participants in the placebo group (vaccine efficacy, 66.7%). Two cases and fourteen cases, respectively, occurred with ≥ 3 signs or symptoms (vaccine efficacy, 85.7%). RSV-associated acute respiratory illness occurred in 22 participants in the vaccine group and 58 participants in the placebo group (vaccine efficacy, 62.1%). There were 12% of local injection site reactions in the vaccine group versus 7% in the placebo group and similar rates of systemic reactions among the vaccine and placebo groups. There were three severe adverse events within the vaccine group, with a case of a delayed allergic reaction, a case of Guillain-Bare syndrome, and a case of Miller Fisher syndrome.

MATISSE Clinical Study: Maternal Immunization for Safety and Efficacy[12]

This study was a phase III, double-blind, randomized, placebo-controlled trial over four RSV seasons (two in the Northern Hemisphere and two in the Southern Hemisphere). Healthy participants at 24 through 36 weeks' gestation, as determined by medical history, physical examination, and clinical judgement were included. Participants must have been receiving the prenatal standard of care based on their country's requirements and have a fetal anomaly ultrasound examination performed at ≥18 weeks of pregnancy with no significant abnormalities observed. Participants were excluded if they underwent in vitro fertilization, had pregnancy complications or abnormalities at the time of consent, had endocrine disorders, or had any signs of premature labor. 7,392 pregnant individuals underwent randomization, with 3,695 receiving the vaccine and 3,697 receiving the placebo. 7,128 infants were enrolled after delivery with 3,570 infants from the ma-

ternal RSVpreF vaccine group and 3,558 from the maternal placebo group.

Results

Forty-one percent of maternal recipients who received the RSVPreF vaccine reported local injection site reactions versus 10% who received placebo. There were similar rates of adverse events in infants from maternal recipients of both groups. There were serious adverse events in four of the RSVPreF vaccine recipients including pain in arm followed by bilateral lower extremities, premature labor, systemic lupus erythematous, and eclampsia.

AREXVY® STUDY SUMMARY

Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults[13]

This study is an ongoing, international, randomized, phase III, placebo-controlled trial. Older adults aged 60 or older who live in the community or in a long-term care facility who are medically stable were included. Participants were excluded if they had a history of severe adverse reaction associated with a vaccine and/or severe allergic reaction to any component of the study intervention or any related vaccine or if they had hypersensitivity to latex. 25,040 participants were enrolled in the study with 12,467 participants receiving the RSVPreF3 OA vaccine and 12,499 receiving the placebo.

Seven participants in the RSVPreF3 OA group and 40 participants in the placebo group reported an episode of RSV-associated lower respiratory tract disease within the median follow up period of 6.7 months, with a vaccine efficacy of 82.6%. One participant in the RSVPreF3 OA group and 17 participants in the placebo group reported an episode of severe RSV-associated lower respiratory tract disease, with a vaccine efficacy of 94.1%. Twenty seven participants in the RSVPreF3 OA group and 97 participants in the placebo group reported at least one episode of acute RSV-related lower respiratory tract infection, with a vaccine efficacy of 71.7%. 60.9% of RSVPreF3 OA vaccine recipients and 9.3% of placebo recipients had pain at the injection site following injection. There were similar rates of severe adverse reactions among both groups (~4.1%).

Both Abrysvo® and Arexvy® showed similar efficacy in preventing and lessening the severity of RSV-associated lower respiratory tract illness in older adults. Moreover, Abrysvo® showed effectiveness in preventing and lessening severity of RSV-associated lower respiratory tract illness in infants born to mothers who received the RSVPreF vaccine. With adverse events being mostly injection site reactions, both vaccines are safe and effective for prevention of RSV.

CONCLUSION

As it is currently RSV season, it is even more important now to take measures to prevent RSV infections, especially in the elderly population that is more likely to develop severe disease. Both new RSV vaccines Abrysvo® and Arexvy® can help reduce lower respiratory tract infections caused by RSV, therefore lowering rates of outpatient visits, hospitalization, and deaths.

Unlike the initial FI-RSV vaccine developed in the 1960s, the new RSV vaccines prove to be both efficacious and safe. Learning from the failed mechanisms of the old RSV vaccine, Pfizer and GSK have developed new RSV vaccines that target the F protein without inducing harmful changes in the protein. As demonstrated by the randomized, phase III, placebo-controlled clinical trials, these RSV vaccines reduce RSV-associated lower respiratory tract illness, including severe illness, in not only older adults and infants, but also in pregnant women. Abrysvo® and Arexvy® are also safe in all populations in which they were studied, with injection site reactions being the most common adverse effect.

Both Abrysvo® and Arexvy® are indicated for prevention of RSV disease in adults 60 years of age and older. Abrysvo® is also indicated in pregnant patients who are 32 through 36 weeks gestation. For healthcare providers, it is crucial that patients are educated on these vaccines. Because both vaccines are inactivated, patients can be assured that the vaccines will not cause RSV-associated disease. Like most influenza vaccines, the RSV vaccine consists of only one 0.5 mL dose given intramuscularly. Due to failure of the FI-RSV vaccine, patients may be hesitant to receive the new vaccines. Therefore, it may be beneficial to explain the differences in the vaccine mechanisms. With the recent approval of these new RSV vaccines, it is the responsibility of healthcare providers to be well-informed to help protect their patients from RSV-associated lower respiratory tract infection and its complications.

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