RSV vaccination during pregnancy: Finally ready for prime time

FDA approved in August of this year, the new bivalent RSV prefusion F vaccine represents a major and welcomed breakthrough, as an effective vaccine for women during pregnancy and for infant protection has eluded scientists and clinicians for 50 years

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DON'T MISS

Breakthroughs in the prevention of RSV disease among infants by Robert L. Barbieri, MD, **on page 4**

CASE Pregnant woman asks about the RSV vaccine

A 28-year-old primigravid woman at 30 weeks' gestation inquires about the new vaccine to protect her newborn baby against respiratory syncytial virus infection (RSV). Her neighbor's daughter recently was hospitalized for the treatment of RSV, and she is understandably concerned about her own newborn. The patient is healthy, and she has never had any serious respiratory infection. She is taking no medications other than prenatal vitamins.

- What advice should you give her?
- If you decide to administer this vaccine, what is the appropriate timing of administration?
- Are there any maternal or fetal safety concerns related to use of this vaccine in pregnancy?

Respiratory syncytial virus (RSV) is a member of the *Paramyxoviridae* family. It is an enveloped, single-stranded RNA virus that is 150-300 nm in size. The virus codes for 10 virus-specific proteins. The 2 most important are the G protein, which enables the virus to attach to host cells, and the F protein, which facilitates the entry of the virus into the host cell by fusing the host and viral membranes. Two distinct subtypes exist: A and B. There is genetic variation within each subtype and between subtypes. These subtle genetic variations create the potential for reinfections, and hence, research has focused on development of a vaccine that covers both subtypes.[1]

RSV is the most common cause of acute lower respiratory tract infection in infants younger than 6 months of age. In these children, RSV is one of the most prominent causes of death, with mortality particularly marked in low- and middle-resource countries as well as in children who were born premature and/or who are immunocompromised. RSV has its greatest impact during winter epidemics in temperate climates and during the rainy seasons in tropical climates. The virus rarely is encountered in the summer.[1] Among young children, RSV primarily is transmitted via close contact with contaminated fingers or fomites and by self-inoculation of the conjunctiva or anterior nares. The incubation period of the infection is 4 to 6 days, and viral shedding may persist for 2 weeks or longer. Most patients gradually recover within 1 to 2 weeks.[1] Adults who contract RSV usually have symptoms suggestive

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The author reports no financial relationships relevant to this article.

doi: 10.12788/obgm.0321

of a common cold; however, in older adults or those who have comorbidities, serious and potentially life-threatening lower respiratory tract infections may develop.

Recently, there have been 2 main approaches to the prevention and treatment of RSV in infants. One has been the development of monoclonal antibodies such as motavizumab, palivizumab, and nirsevimab. The other has been the development of a vaccine that could be administered to pregnant women and which could provide protection for the neonate in the early months of life.[2,3]

In late August 2023, the US Food and Drug Administration (FDA) announced the approval of a new bivalent RSV prefusion F vaccine (ABRYSVO, Pfizer) intended for administration to pregnant women.[4] Of note, previous efforts to develop whole-virus vaccines either have been ineffective or have potentiated the disease in infants who became infected; development of an effective vaccine had eluded scientists and clinicians for nearly 50 years.[2] Thus, the new vaccine that targets the F protein of the virus represents a major and welcomed breakthrough.

This article reviews the 3 most recent investigations that preceded the ultimate approval of this vaccine and discusses specific logistical issues related to vaccine administration.

KEY POINTS

- RSV is the most common cause of acute lower respiratory tract infection in infants younger than 6 months of age.
- In low- and middle-resource countries, RSV is a leading cause of infant death.
- In late August 2023, the FDA approved the first RSV vaccine that can be administered to pregnant women to provide protection for the infant in the first few months of life.
- The vaccine specifically targets the F protein of the virus, a protein which is essential for facilitating fusion between the viral and host cell membranes, resulting in penetration of the virus into the host cell.
- The vaccine should be administered as a single intramuscular injection at 32 to 36 weeks' gestation.
- The vaccine is approximately 82% effective in preventing severe lower respiratory tract infection in infants within the first 6 months of life.
- To exercise an abundance of caution, because of a *possible* association between administration of the vaccine and an increased risk for preterm delivery, vaccination should be delayed until 36 weeks in patients clearly identified as at-risk for preterm delivery.

First step toward vaccine approval

Madhi and colleagues[5] were among the first to conduct a large well-designed study to evaluate the effectiveness of maternal vaccination in preventing neonatal infection in the first few months of life. The authors enrolled more than 4,500 healthy pregnant women at 28 to 36 weeks of gestation and assigned them to receive either a single intramuscular dose of an RSV fusion (F) protein vaccine or placebo in a ratio of 2:1. The primary end point was a "medically significant lower respiratory tract infection" within the first 90 days of life. The percentage of infants who met the primary end point was low in both groups: 1.5% in the vaccine group and 2.4% in the placebo group (efficacy 39.4%). The efficacy of the vaccine in preventing lower respiratory tract infection with severe hypoxemia was 48.3% and 44.4% in preventing hospitalization. Although there were differences between the 2 groups, they did not meet the prespecified success criterion for efficacy. Vaccine recipients had more local injection site reactions (40.7% vs 9.9%); however, there was no difference in the frequency of other adverse effects.

FAST TRACK

An initial study evaluating a single dose of RSV fusion (F) protein vaccine to prevent "medically significant lower respiratory tract infection" within an infant's first 90 days found the vaccine to be 39.4% effective

Intermediate step: Continued assessment of vaccine safety and immunogenicity

The next important step in the development of the RSV vaccine was a study by Simoes et al,[6] who conducted a phase 2b trial to determine the safety and immunogenicity of the RSVpreF vaccine. The authors randomly

FAST TRACK

The most convincing data for FDA approval of the RSV vaccine was a phase 3 prospective, randomized, double-blind trial conducted in 18 countries over 4 RSV seasons; vaccine efficacy to prevent lower respiratory tract illness within 90 days of delivery was 81.8%

assigned pregnant women at 24 to 36 weeks of gestation to receive either 120 or 240 µg of RSVpreF vaccine or placebo. The key endpoints were the following: maternal and infant safety; the maternal-to-infant transplacental transfer ratio; and the presence of RSV A, B, and combined A/B neutralizing antibody in maternal serum and umbilical cord blood at delivery. The authors conducted a planned interim analysis that included 327 mothers who received the vaccine. The incidence of adverse effects was similar in mothers and infants in the vaccine compared with the placebo group. None of the adverse effects were judged to be serious. The transplacental neutralizing antibody transfer ratios ranged from 1.4 to 2.1 across a range of gestational ages. The vaccine elicited meaningful neutralizing titers of antibody in maternal serum even up to 7 weeks after immunization. The levels of neutralizing antibodies in umbilical cord blood did not vary substantially with respect to gestational age. A post hoc analysis showed that the transferred antibodies prevented medically-attended RSV-associated lower respiratory tract illnesses in the infants.

Final step: Convincing proof of efficacy

The most recent of the 3 studies, and the one that had the greatest impact in convincing the FDA to approve the vaccine, was the report by Kampmann and colleagues.[7] The authors conducted a phase 3 prospective, randomized, double-blind trial in 18 different countries over 4 RSV seasons: 2 in the northern hemisphere and 2 in the southern hemisphere. They enrolled healthy pregnant women with singleton gestations at 24 to 36 weeks of gestation and assigned them in a 1:1 ratio to a single intramuscular injection of 120 µg of a bivalent RSV prefusion F protein-based (RSVpreF) vaccine or placebo. They excluded patients with any recognized risk factor for an adverse pregnancy outcome, including preterm labor. The 2 primary efficacy endpoints were a medically-attended severe RSV–lower respiratory tract infection and any medically attended RSV-associated lower respiratory tract illness in infants within 90, 120, 150, and 180 days after birth.

The efficacy of the vaccine in preventing severe lower respiratory tract illness within 90 days of delivery was 81.8% (99.5% confidence interval [CI], 40.6–96.3). The efficacy within 180 days of delivery was 69.4% (97.58% CI, 44.3–84.1). These differences reached the study's pre-established statistical criteria for success. The overall rate of lower respiratory tract infections was not significantly different. The frequencies of adverse effects in mothers and infants were similar in the vaccine and placebo groups. In particular, the frequency

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of preterm delivery in the vaccine group was 0.8%, compared with 0.6% in the placebo group (P = NS).

In previous reports to the FDA,[4] the frequency rate of preterm delivery in RSV vaccine recipients was slightly increased in vaccine recipients compared with patients who received placebo. The difference among the groups was too small to infer a causal relationship; however, as a condition of vaccine approval, the FDA has required Pfizer to conduct a postmarketing study to be certain that administration of the vaccine does not increase the risk for preterm delivery.

Practical details

The new vaccine is a bivalent recombinant vaccine that elicits a robust antibody response against the F (fusion) protein of the virus. In addition to the F antigen, the vaccine contains the following buffer ingredients: tromethamine, sucrose, mannitol, polysorbate, and sodium chloride.[8] There are no preservatives in the vaccine.

The vaccine should be administered in a single, 0.5 mL, intramuscular injection at 32 to 36 weeks of gestation. Patients who are allergic to any of the components of the vaccine should not be vaccinated. Patients with a mild upper respiratory tract infection may receive the vaccine. Administration should be delayed in patients who are moderately to severely ill. The vaccine may be administered at the same time as other vaccines, such as influenza or Tdap.

The most common side effects of the vaccine are local injection site reactions, such as pain, redness, or swelling. Some patients may experience mild systemic manifestations, including fatigue, fever, headache, nausea, diarrhea, arthralgias, and myalgias. According to the Centers for Disease Control and Prevention, the approximate wholesale acquisition cost of the vaccine is $320 for 1 injection.

CASE Resolution

This patient is healthy and has no contraindication to the new RSV vaccine. According to the FDA, the optimal time for administration of the vaccine is 32 to 36 weeks of gestation. The patient should anticipate very few side effects following the vaccination, and the vaccine has approximately 80% efficacy in preventing severe lower respiratory tract infection in her neonate. ●

FAST TRACK

As a condition of vaccine approval, the FDA has required a postmarketing study ensuring that vaccine administration during pregnancy does not increase preterm birth risk

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