Respiratory Syncytial Virus Vaccines

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Respiratory syncytial virus (RSV) infection is a common seasonal respiratory illness. Typically, RSV activity is high and peaks in December and January, but that pattern was disrupted during the COVID-19 pandemic.[1] Although it affects all ages, infants, older adults, and those who are immunocompromised are most likely to experience severe infection.

Nearly all children have been infected with RSV by age of 2 years, and it is the leading cause of hospitalization during the first year of life.[2,3] Infants with RSV infection frequently develop bronchiolitis and lower respiratory tract infection that leads to hospitalization. An estimated 50,000 to 80,000 hospitalizations and 100-300 deaths in infants are caused by RSV each year.[2]

The Centers for Disease Control and Prevention (CDC) estimate that 60,000 to 160,000 older adults are hospitalized for an RSV infection each year. Between 6000 and 10,000 people die of an RSV infection annually.[4] Known risk factors for severe RSV infection include advanced age, heart disease, lung disease, diabetes, immunocompromise, and other chronic medical conditions.[4,5]

RSV is an airborne-transmitted virus. Methods of transmission include coughing and sneezing. It can also be transmitted by direct contact. Transmission can occur two days prior to symptom onset and during clinical illness. RSV infection in infants is characterized by runny nose, decreased oral intake, and cough which may progress to wheezing and difficulty breathing. In adults, symptoms of RSV are those of other respiratory infections, including rhinorrhea, pharyngitis, cough, headache, fatigue, and fever. Symptoms typically resolve in 5 days.[6]

Protection from RSV infection is an important advance in medicine and public health. A long-acting monoclonal antibody, nirsevimab (Beyfortis™, Sanofi and Astra-Zeneca) has been licensed for children younger than 24 months of age.[7] For adults aged 60 years and older, two vaccines are available—recombinant RSVPreF3, adjuvanted (AS01E) (Arexvy®) from GlaxoSmithKline[8] and the recombinant RSVpreF vaccine (Abrysvo®) from Pfizer.[9] The RSVpreF vaccine is also licensed for immunization of pregnant individuals at weeks 32-36 gestation for the prevention of RSV infection in infants.[9]

Protection of Infants and Young Children From RSV

Two strategies are now available for RSV protection of infants and young children. Pregnant individuals can be immunized later in gestation to provide protection to their infants, or infants can receive a long-acting monoclonal antibody prior to or during RSV season. Both strategies provide protection against lower respiratory tract infection.

Nirsevimab

The Advisory Committee on Immunization Practices (ACIP) has recommended nirsevimab for all infants <8 months of age prior to or during RSV season which is October through March. Children who are at particularly high risk for complications of RSV infection aged 8-19 months should receive a dose prior to their second RSV season.[2] The second season dose is recommended for a small number of children who have pulmonary complications due to prematurity, severe immunocompromise, or cystic fibrosis with pulmonary manifestations. A second season dose is recommended for all American Indian and Alaskan Native children as

they experience high rates of severe RSV disease.[2] Nirsevimab is administered intramuscularly and can be administered with other childhood vaccines at the same clinic visit. The dose of nirsevimab is based on the child's weight and a higher dose for those who need it for a second RSV season (Table 1).

Compared to placebo, nirsevimab was 79.0% (95% confidence interval [CI] 68.5%–86.1%) effective in preventing medically-attended lower respiratory tract infection with RSV, 80% (95%CI 62.3%–90.1%) effective in prevention of hospitalization, and 90.0% 95%CI 16.4%–98.8%) for prevention of intensive care unit admission.[2] Nirsevimab is well-tolerated. The most common adverse reactions reported were injection site reactions and rash in fewer than 1%. Allergic reaction to nirsevimab or a component is the only contraindication.[7]

Passive Immunization Using RSVPreF Vaccine in Pregnant Individuals

Another strategy for protecting infants from severe RSV infection is through maternal immunization. The RSVPreF vaccine (Abrysvo®) was recently licensed for administration to pregnant individuals at 32 to 36 weeks gestation to prevent lower respiratory infection due to RSV in the infants.[9] This passive immunization strategy leads to infant protection that lasts from birth to age 6 months. At the time of this writing, the ACIP has not yet made a recommendation for the use of this vaccine.

Vaccine efficacy was measured from time of infant birth and was followed for at least 6 months. When administered at 32-36 weeks gestation, vaccine efficacy against severe lower respiratory tract infection at 90 days was 91.1% (95%CI 38,8-99.8) and at 180 days was 76.5% (95%CI 42.3-92.1). Vaccine efficacy against any lower respiratory tract infection due to RSV at 90 days was 34.7% (95%CI -34.6-69.3) and at 180 days was 57.3% (95%CI 29.8-74.7). The majority of solicited injection site and systemic reactions resolved in 2-3 days. Severe local reactions were reported by 0.3% of maternal participants and severe systemic reactions were reported by 2.3%. Preterm births were more frequent in the vaccine group (5.3%) compared to the placebo group (2.6%) in Study 1 (participants immunized 24-36.9 weeks gestation) and remained in Study 2 where vaccine was administered at 32 to 36 weeks gestation (vaccine group 4.2% vs placebo group 3.7%).[9]

TABLE 1. Nirsevimab Dosing Information

Child's Weight at Time of Dose Administration	*Nirsevimab Dose**
< 5kg	50 mg
> 5kg	100mg
Prior to second RSV season	200mg (as two 100mg/1ml injection)

**supplied as 50mg/0.5ml syringe and 100mg/1ml syringe that are color-coded*

Implementation Issues

A number of healthcare system issues will need to be addressed to implement the infant RSV immunization program. Nirsevimab is included in the Vaccines for Children Program. The ACIP cost effectiveness estimate for the use of nirsevimab for infants younger than 8 months of age was $102,000 per quality adjusted life year.[2] No similar information regarding maternal immunization is available at this time. The window for maternal RSV immunization is small (32-36 weeks gestation) which could present an obstacle. Also, a system must be developed to identify and recall infants younger than 8 months for nirsevimab prior to the season which has been identified as October. Infants born October to March could receive nirsevimab at the birth hospital prior to discharge. Because RSV immunization may be done at the birth hospital, pediatric clinic, obstetric clinic, and possibly public health clinic or pharmacy, coordination and information sharing through the immunization registry will be critical to avoid double immunization of the infant. Other system issues may be identified depending on the ACIP recommendation for maternal immunization.

Protection of Adults Aged 60 Years and Older From RSV

Two recombinant vaccines were recently licensed for the protection of adults aged 60 years and older. The ACIP recommended shared clinical decision making for the use of RSV vaccines in this population.[4] Rather than a routine recommendation for all members of the group, shared clinical decision making allows the clinician and the patient to choose the best strategy for the individual. That decision could be based on patient's underlying health and risk for severe RSV infection, the known risks and benefits of the vaccine, the clinician's discretion and the patient's values and preferences.[4,10]

RSVPreF Vaccine (Abrysvo®, Pfizer)

The RSVPreF vaccine uses recombinant bivalent pre-fusion protein antigens from the two subgroups, RSV A and RSV B. The clinical trial that led to licensure of this vaccine included just over 34,000 individuals aged 60 years and older who were randomized to vaccine or placebo and followed for approximately 12 months per participant.[11] That interval included one full and a second partial RSV season in the Northern Hemisphere. The primary endpoints of the study were incidence of RSV with at least two respiratory symptoms or incidence of RSV with at least three respiratory symptoms (Table 2). More local reactions were reported by vaccine recipients (12%) compared to placebo recipients (7%). The reactions were mild to moderate and median duration was 1 to 2 days.[11] Among study participants in phase 1, 2, and 3 trials, the relative risk of at least a grade 3 adverse event was 1.43 (95%CI 0.85-2.39) compared to placebo.[4] Grade 3 adverse events include those that prevent the individual from participating in usual daily activities. Three inflammatory neurologic events were reported among vaccine recipients while no such events were reported in the placebo group.[4]

The vaccine is supplied as a vial containing antigen and a syringe that is prefilled with sterile water as a diluent. To administer, place the plastic vial cap on the antigen vial and attach the syringe. Inject

the contents of the syringe and gently swirl the vial with the syringe attached and plunger depressed. When the antigen is reconstituted, draw up the contents of the vial into the attached syringe. After disconnecting the syringe from the vial adapter, attach a needle for vaccine administration. The vaccine is administered by intramuscular injection.[9]

RSVpreF3, Adjuvanted Vaccine (Arexvy®, GSK)

The RSVpreF3 vaccine contains a recombinant prefusion F glycoprotein and the AS01 adjuvant. This is the same adjuvant that is in the recombinant zoster vaccine, but the dose is smaller.[12] The pivotal clinical trial supporting licensure of the RSVpreF3 vaccine included almost 25,000 participants aged 60 years and older and followed them through two complete RSV seasons in the Northern Hemisphere.[13] The primary endpoint of this study was RSV associated lower respiratory tract disease with two or more respiratory symptoms (Table 2). Pain at the injection site was reported by 60.9% of those who received the vaccine compared to 9.3% who received placebo. The vaccine was well-tolerated but more reactogenic compared to placebo with symptom resolution in 1-2 days on average.[13] Grade 3 reactions from available studies were reported in 3.8% of vaccinees and 0.9% of controls (pooled relative risk 4.10; 05% CI 1.99-8.45). Three inflammatory neurologic events were reported in vaccinated individuals in trials without a placebo comparison.[4] No inflammatory neurologic events were identified in the phase 3 trial, and potential immune-mediated disease incidence was similar between vaccine and placebo recipients.[13]

The vaccine is supplied as two vials. The adjuvant-containing vial is the diluent that is transferred to the antigen vial using a syringe and needle. Gently swirl the vial until the antigen is dissolved with the

TABLE 2. Respiratory Syncytial Virus Vaccine Efficacy for Age 60 Years and Older[4,11,13]

	Vaccine Efficacy
Bivalent RSVpreF	
At least 2 respiratory symptoms	66.7% (95%CI 28.8-85.8)
At least 3 respiratory symptoms	85.7% (95CI 32.0-98.7)
Combined seasons 1 and 2 (>2 symptoms)	84.4% (59.6-95.2)
RSVpreF3	
Lower respiratory tract disease	82.6 (95%CI 57.9-94.1)
Combined seasons 1 and 2	74.5% (95%CI 60.0-84.5)
Participants with medical comorbidities	94.6% (65.9-99.9)

syringe and needle attached to the vial. Withdraw the reconstituted vaccine for intramuscular administration.[8]

RSV Vaccine Use

Both vaccines contain the pre-fusion (F) glycoprotein which induces potent neutralizing antibodies.[14] Both vaccines may be used for a single dose prior to RSV season.[4] No head-to-head comparisons are available. The populations enrolled and the endpoints of the studies were slightly different.

Data on and experience with coadministration of RSV vaccines with commonly used adult vaccines are lacking. Both RSV vaccine preparations have been administered with influenza. Influenza and RSV antibody concentrations following coadministration were generally lower but met noninferiority criteria. Only the influenza A H3N2 Darwin strain as an antigen in the adjuvanted influenza vaccine coadministered with the RSVpreF3 (GSK) vaccine was outside the noninferiority criteria.[4] The clinical significance of the lower antibody concentrations is unknown. The ACIP stops short of recommending coadminstration of RSV vaccines and other adults vaccines, such as COVID-19, tetanus-diphtheria-acellular pertussis, recombinant zoster (consider that the adjuvant is the same as the GSK RSVpreF3 vaccine), and pneumococcal vaccines. Clinicians are asked to consider the likelihood of the patient will return for additional immunization, the possibility that reactogenicity will be higher, the risk of acquiring the vaccine preventable disease, and patient preferences. However, the ACIP did state the coadministration of RSV vaccine and other adult vaccine is acceptable.[4]

The need for and timing of future doses of RSV vaccines is not yet known, but the clinical trials described above are ongoing to answer this question. Also, additional information about vaccine adverse effects will be sought, particularly the unresolved, but possible association of RSV vaccines with inflammatory neurologic conditions. Additional experience with administration of the RSV vaccines with other adult vaccines is urgently needed.

The RSV vaccines will be covered by Medicare Part D for enrolled individuals, typically those 65 years and older. For those aged 60-64 years, RSV vaccine will be covered by insurance. However, the timing of coverage may vary. Some may cover it already, but others may take time to add it to their formulary or will wait until the 2024 Adult Immunization Schedule is published.

As mentioned above the RSV vaccines are to be used with shared clinical decision making. The ACIP advises that clinicians and patients consider risk for severe RSV infection, including advanced age (though no specific age threshold for more strongly recommending RSV vaccine is made), frailty, residence in a long-term care facility, lung disease, cardiovascular disease, moderate or severe immunocompromise, diabetes, neurologic or neuromuscular conditions, kidney or liver disease, hematologic disorders, and other conditions that may increase the risk for severe RSV infection.[4]

Conclusion

The RSV monoclonal antibody and vaccines offer protection to segments of the population that are at high risk for hospitalization and mortality. These products were shown to be safe and efficacious is clinical trials. All infants 8 months of age and younger should receive nirsevimab. The use of the bivalent RSVpreF in pregnant individuals offers another option for passive immunization of vulnerable infants. The two RSV vaccine, bivalent RSVpreF and RSVpreF3, can be used to protect those aged 60 years and older. Clinicians can use shared clinical decision-making to determine which patients should receive these vaccines. Consider those that are at highest risk for severe infection, including advanced age and medical comorbidities.

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Disclosure: Mary Hayney has served as a speaker and consultant for GSK Vaccines and received research support from Takeda Pharmaceuticals and Dynavax.

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