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Prevention of Respiratory Syncytial Virus (RSV) Infection: New Products and Recommendations

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Respiratory syncytial virus (RSV) causes infections in the respiratory tract of people of all ages.[1] RSV is a seasonal infection that occurs most often between the months of November and April. The COVID-19 pandemic disrupted seasonal RSV infections; however data from the 2022-2023 RSV season suggests that patterns are returning toward pre-pandemic seasonality.[2] Infants, toddlers and those over the age of 65 years are most susceptible to severe infection. In children under the age of 5, RSV infections are responsible for 58,000-80,000 hospitalizations and 100-300 deaths annually.[2] In those 65 years and older RSV is implicated in approximately 60,000 to 120,000 hospitalizations and 6,000 to 10,000 deaths.[1]

Background

Symptoms of RSV are similar to other respiratory illnesses, such as cough, runny nose, sneezing, and fever. In most healthy individuals, RSV infection is self-limiting and does not cause serious sequelae. Individuals with certain underlying health conditions are most likely to experience complications from RSV including lower respiratory tract disease (LRTD) RSV infections may become serious, such as pneumonia, in adults aged 65 years and over, due to weakened immune systems associated with aging and comorbidities (e.g., diabetes and chronic cardiovascular disease). Children and infants may also suffer severe illness from RSV and develop complications such as bronchiolitis and pneumonia.[3] However, most children will have had an RSV infection by their second birthday without serious sequelae. Infants with certain conditions are at the greatest risk of developing complications, such has pneumonia and hospitalization, from RSV infection (**Figure 1**).

Figure 1. Risk Factors for Severe Illness from RSV in Children

- Premature infants
- Infants 12 months old and younger
- Children under the age of 2 with chronic lung disease or congenital heart disease
- Immunocompromised
- Neuromuscular disorders

RSV Preventative Therapies

Until recently there were no RSV vaccines. Palivizumab (SYNAGIS), a monoclonal antibody, was the only Food and Drug Administration (FDA) approved therapy for the prevention of RSV for use only in high risk infants and children. Within the last year, 3 new options for RSV prevention have been approved: BEYFORTUS, ABRYSVO and AREXVY. Indications and dosing intervals differ between the products and are described in **Table 1**.

Table 1. FDA Approved Products for Respiratory Syncytial Virus Prevention

Drug	Approved Populations*	Dosing∞
SYNAGIS[4] (Palivizumab)	- High risk pediatrics+	- Up to 5 monthly IM injections based on weight throughout RSV season
BEYFORTUS[5] (Nirsevimab)	- Neonates and infants born during or entering their first RSV season - Children up to 24 months who remain vulnerable to severe RSV disease during their second RSV season	- 50 mg IM if less than 5 kg in body weight - 100 mg IM if 5 kg or greater - Children in second RSV season: 200 mg IM
AREXVY[6] (RSVPreF3 vaccine)	- Adults 60 y and older	- 0.5 mL IM
ABRYSVO[7] (RSVpreF vaccine)	- Adults 60 y and older - Pregnant individuals at 32 through 36 weeks gestation	- 0.5 mL IM

Key: * See prescribing information for specific use; + Recommendation for use are based off of American Academy of Pediatric recommendations for high risk infants and children; ∞ Dosing recommendation is for one dose unless indicated
Abbreviations: IM = intramuscular; IV = intravenous; mL = milliliter; OTC = over the counter; PreF = perfusion conformation; SQ = subcutaneous; y = year.

SYNAGIS (Palivizumab)

SYNAGIS was shown to decrease hospitalizations in high risk infants and children.[3] SYNAGIS requires monthly dosing, based on weight, for 5 doses.[4] Palivizumab is approved for pediatric use for the following patients[3]:

- Premature birth (less than or equal to 35 weeks gestational age) and who are 6 months of age or younger at the beginning of RSV season
- Bronchopulmonary dysplasia (BPD) that required medical treatment within the previous 6 months and who are 24 months of age or younger at the beginning of RSV season
- Hemodynamically significant congenital heart disease (CHD) and who are 24 months of age or younger at the beginning of RSV season.

BEYFORTUS (Nirsevimab)

BEYFORTUS is a long-acting RSV F protein-directed fusion inhibitor. It was FDA-approved July 2023 for the prevention of RSV LRTD in all neonates and infants born during or entering their first RSV season, or in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.[5] Efficacy was based on 3 clinical trials in term and preterm infants; two phase 2 trials and one phase 3 trial.[5] Two studies were conducted in infants entering their first RSV season. The third trial was done in infants born at less than 35 weeks gestation and infants with chronic lung disease (CLD) or CHD entering their first RSV season and in those infants with CLD or CHD entering their second RSV season. In the phase 3 trial, term and late preterm infants with a gestational age greater than or equal to 35 weeks entering their first RSV season were enrolled. The primary endpoint was the incidence of Medically Attended Respiratory Syncytial Virus Lower Respiratory Tract Infection (MA RSV LRTI) characterized predominantly as bronchiolitis or pneumonia through 150 days after dosing and confirmed by a reverse transcription-polymerase chain reaction (RT-PCR). The number of MA RSV LRTI was 1.2% in the BEYFORTUS group compared to 5.0% in the placebo group (efficacy 74.9%; 95% CI, 50.6 to 87.3; p <0.001).[5] The most common adverse reaction was rash at the injection site.[5]

BEYFORTUS may be given in the second RSV season to those infants who are up to 24 months of age, who remain vulnerable, and received SYNAGIS or BEYFORTUS in their first RSV season.[5] SYNAGIS should not be given to infants who have already received BEYFORTUS in the same season.[5] BEYFORTUS may administered with other age-appropriate vaccines.[8]

ABRYSVO

ABRYSVO is a vaccine that works by facilitating an immune response against RSV pre F that protects against lower respiratory tract disease caused by RSV. Passive Immunization is accomplished by antibodies to RSV antigens from individuals vaccinated in pregnancy transfer transplacentally to protect infants younger than 6 months of age against RSV.[6] ABRYSVO is approved to prevent LRTD caused by RSV in people 60 years and older.[7] In August 2023, ABRYSVO received an additional indication for active immunization of pregnant individuals at 32 through 36 weeks gestation for the prevention of LRTD and severe LRTD caused by RSV in infants from birth through 6 months of age.[7]

ABRYSVO was studied in adults 60 years and older. The primary endpoint was relative risk reduction of first episode of RSV-LRTD. Interim analysis of an ongoing phase 3, double-blind, randomized, placebo-controlled trial in those 60 years and older found vaccine efficacy to be 66.7% (95% CI, 28.8 to 85.8) in those with 2 or more symptoms and 85.7% (95% CI, 32.0 to 98.7) in those with 3 or more symptoms who were followed out to 7 months.[7] The most common adverse reactions in those 60 years and older were fatigue, headache, pain at the injection site and muscle pain.

Evidence for the use of ABRYSVO in pregnant individuals was demonstrated in one phase 3, double-blind, randomized controlled trial.[8] RSV-associated LRTD in infants was defined as a medically attended visit with a RT-PCR confirmed RSV illness with one or more of the following respiratory symptoms: tachypnea based on age; SpO2 measured in room air <95%; chest wall indrawing. RSV-associated severe LRTD was a subset defined as meeting the LRTD RSV criteria plus at least one of the following: tachypnea based on protocol. (SpO2 measured in room air <93%; high-flow nasal cannula or mechanical ventilation (invasive or noninvasive), intensive care unit (ICU) admission for >4 hours and/or failure to respond/unconscious.[8] Six infants born to individuals who received ABRYSVO experienced severe LRTD caused by RSV within 90 days of birth compared to 33 infants who received placebo (vaccine efficacy 81.8%; 99.5% CI, 40.6 to 96.3%).[8] At 180 days from birth, 19 infants born to individuals who received ABRYSVO experienced severe LRTD caused by RSV compared to 62 infants who received placebo (vaccine efficacy 69.4%; 97.58% CI, 44.3 to 84.1%).[8] In pregnant individuals, the most common adverse events were pain at the injection site, headache, muscle pain and nausea. Low birth weight and jaundice was associated with the use of ABRYSO in infants born to pregnant individuals.[7]

There is no evidence to support use of SYNAGIS in infants born to individuals who received ABRYSVO. Additionally, the Centers for Disease Control (CDC) Advisory Committee on Immunization Practices (ACIP) advises that there is no evidence to support the use of BEYFORTUS in a baby born to an individual immunized against RSV during their pregnancy; however, BEYFORTUS may be appropriate in rare circumstances if the following occur: a pregnant person has an immunocompromising condition that prevents an adequate immune response or condition associated with a reduced transplacental antibody transfer, infants undergoing cardiopulmonary bypass causing loss of RSV antibodies and those infants at very high risk for severe RSV disease due to comorbidities (e.g., hemodynamically significant heart disease, ICU, requiring oxygen at discharge).[3]

Several clinical implications need to be taken into account when deciding which RSV protection is chosen for infants. **Table 2** presents the risks and benefits of RSV prevention via maternal vaccination (ABRYSVO) compared to infant injection with BEYFORTUS. Additionally, there is limited long-term efficacy and safety data on all the new RSV vaccines and preventative therapy. Evidence on hospitalization reduction and mortality benefits would also help to inform cost-effective evidence-based use.

Table 2. Risks versus Benefit of Maternal RSV vaccination Versus BEYFORTUS Infant Injection[4,6]

Preventative Therapy	Benefits	Risks
ABRYSVO (Maternal RSV vaccine)	- Protection is present upon birth - May be more resistant to virus mutations - Infant does not need to be injected	- Risk of preterm birth - Protection could be reduced due to fewer antibodies produced or are transferred from mother to baby
BEYFORTUS (Nirsevimab)	- Antibodies are given directly to the infant - Antibody levels may wane more slower - No risk of preterm birth	- Supply limitations - Requires infant receives injection

AREXVY

AREXVY (RSV vaccine) was approved in May of 2023 for the prevention of LRTD caused by RSV in those 60 years and older.[6] AREXVY mechanism of action works by eliciting an immune response against RSVpreF3 that protects against LRTD caused by RSV. AREXVY was approved based on a phase 3, randomized, placebo-controlled trial (n=24,960).[6] Results were based on an interim analysis at 6.7 months. The primary endpoint was the prevention of a first episode of confirmed RSV-A and/or B-associated LRTD during the first season. The incidence of infection was 1.0 per 1,000 person-years in those treated with AREXVY compared to 5.8 per 1,000 person-years in those treated with placebo (efficacy 82.6%; 95% CI, 57.9 to 94.1).[6] The most common adverse reactions reported with AREXVY are: injection site pain, fatigue, myalgia, headache and arthralgia.[6]

Guideline Recommendations

The American Academy of Pediatrics (AAP) and the CDC ACIP updated guidance released August 2023, recommended that a single dose of BEYFORTUS be used in all neonates and infants born during or entering their first RSV season, or in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. The AAP/ACIP also recommend SYNAGIS be used in those high-risk neonates, infants or children who are not able to access BEYFORTUS.[3,9] If those children who received SYNAGIS initially for the season and less than 5 doses were given, then one dose of BEYFORTUS could be given with no administration of additional doses of SYNAGIS.[9]

In October 2023 the CDC released updated guidance on the use of BEYFORTUS due to supply limitations. They are advising that the 100 mg doses be reserved for the infants that are most vulnerable: young infants (age <6 months) and infants with underlying conditions that place them at highest risk for severe RSV disease. There is no change to the 50 mg dose recommendation. For high-risk children 8-19 months for the 2023-2024 season, the CDC is recommending SYNAGIS, per AAP guidance, instead of BEYFORTUS to conserve supplies. BEYFORTUS is recommended for American Indian and Alaska Native children aged 8–19 months who are not SYNAGIS-eligible due to transporting children with severe RSV who require escalation of medical care since obtaining care is more challenging due to living in remote areas and high rates of RSV in infants and toddlers.

In July 2023 the CDC recommended the RSV vaccine may be given to adults ages 60 and over after discussion with their provider.[3] Such factors as the patient's risk for severe RSV disease and comorbidities (e.g., lung disease, cardiovascular disease, hematologic disorders) associated with an elevated risk should be taken into consideration. RSV vaccines may be given at the same time as other adult vaccines.[2]

Conclusion

There have been recent advances in the prevention of RSV in the most vulnerable populations, such as the very young and elderly. All infants should be protected by receiving an RSV preventative therapy in their first year if protection via maternal vaccination did not occur. However, supply constraints may limit availability to the highest risk infants. Adults 60 years and older should consider a RSV vaccination to protect against LTRD associated with RSV infection. Studies are ongoing to determine if additional doses of vaccines for RSV prevention in adults will be required for protection in subsequent seasons.

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