

Breakthroughs in the prevention of RSV disease among infants

RSV disease is a major public health problem among infants younger than age 8 months, causing 100 to 300 deaths annually. In 2023, two new treatments, nirsevimab and RSVPreF vaccine, have become available to prevent RSV



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Respiratory syncytial virus (RSV) is a negative-sense, single-stranded, ribonucleic acid (RNA) virus that is a member of Pneumoviridae family. Two subtypes, A and B, and multiple genotypes circulate during fall and winter seasonal outbreaks of RSV.¹ RSV can cause severe lower respiratory tract disease including bronchiolitis, pneumonia, respiratory failure, and death. Each year, RSV disease causes the hospitalization of 1.5% to 2% of children younger than 6 months of age, resulting in 100 to 300 deaths.² For infants younger than 1 year, RSV infection is the leading cause of hospitalization.³ In 2023, two new treatments have become available to prevent RSV disease: nirsevimab and RSVPreF vaccine.

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Nirsevimab

Nirsevimab is an antibody to an RSV antigen. It has a long half-life and is approved for administration to infants, providing passive immunization. In contrast, administration of the RSVPreF vaccine to pregnant persons elicits active maternal immunity, resulting in the production of anti-RSV antibodies that are transferred to the fetus, resulting in passive immunity in the infant. Seasonal administration of nirsevimab and the RSV vaccine maximizes benefit to the infant and conserves limited health care resources. In temperate regions in the United States, the RSV infection season typically begins in October and peaks in December through mid-February and ends in April or May.^{4,5} In southern Florida, the RSV season often begins in August to September, peaks in November through December, and ends in March.^{4,5}

This editorial reviews 3 strategies

for prevention of RSV infection in infants, including:

- universal treatment of newborns with nirsevimab
- immunization of pregnant persons with an RSVpreF vaccine in the third trimester appropriately timed to occur just before the beginning or during RSV infection season
- prioritizing universal maternal RSV vaccination with reflex administration of nirsevimab to newborns when the pregnant person was not vaccinated.⁶

Of note, there are no studies that have evaluated the effectiveness of combining RSVpreF vaccine and nirsevimab. The Centers for Disease Control and Prevention (CDC) does not recommend combining both RSV vaccination of pregnant persons plus nirsevimab treatment of the infant, except in limited circumstances, such as for immunocompromised pregnant people with limited antibody production or newborns who have

a massive transfusion, which dilutes antibody titres.⁶

RSV prevention strategy 1 **Universal treatment of newborns and infants with nirsevimab**

Nirsevimab (Beyfortus, Sanofi and AstraZeneca) is an IgG 1-kappa monoclonal antibody with a long half-life that targets the prefusion conformation of the RSV F-protein, resulting in passive immunity to infection.⁷ Passive immunization results in rapid protection against infection because it does not require activation of the immune system. Nirsevimab is long acting due to amino acid substitutions in the Fc region, increasing binding to the neonatal Fc receptor, which protects IgG antibodies from degradation, thereby extending the antibody half-life. The terminal half-life of nirsevimab is 71 days, and the duration of protection following a single dose is at least 5 months.

Nirsevimab is approved by the US Food and Drug Administration (FDA) for all neonates and infants born or entering their first RSV infection season and for children up to 24 months of age who are vulnerable to severe RSV during their second RSV infection season. For infants born outside the RSV infection season, nirsevimab should be administered once prior to the start of the next RSV infection season.⁷ Nirsevimab is administered as a single intramuscular injection at a dose of 50 mg for neonates and infants < 5 kg in weight and a dose of 100 mg for neonates and infants ≥ 5 kg in weight.⁷ The list average wholesale price for both doses is \$594.8. Nirsevimab is contraindicated for patients with a serious hypersensitivity reaction to nirsevimab or its excipients.⁷ In clinical trials, adverse



reactions including rash and injection site reaction were reported in 1.2% of participants.⁷ Some RSV variants may be resistant to neutralization with nirsevimab.^{7,9}

In a randomized clinical trial, 1,490 infants born ≥ 35 weeks' gestation, the rates of medically-attended RSV lower respiratory tract disease (MA RSV LRTD) through 150 days of follow-up in the placebo and nirsevimab groups were 5.0% and 1.2%, respectively ($P < .001$).^{7,10} Compared with placebo, nirsevimab reduced hospitalizations due to RSV LRTD by 60% through 150 days of follow up. In a randomized clinical trial enrolling 1,453 infants born between 29 weeks' and < 35 weeks' gestation, the rates of MA RSV LRTD through 150 days of follow up in the placebo and nirsevimab groups were 9.5% and 2.6%, respectively ($P < .001$). In this study of infants born preterm, compared with placebo, nirsevimab reduced hospitalization due to RSV LRTD by 70% through 150 days of follow up.⁷ Nirsevimab is thought to be cost-effective at the current price per dose, but more data are needed to precisely define the magnitude of the health

care savings associated with universal nirsevimab administration.¹¹⁻¹³ The CDC reports that the incremental cost-effectiveness ratio (ICER) per quality-adjusted life year (QALY) of nirsevimab administration to infants is approximately \$250,000, given an estimated cost of \$500 for one dose of vaccine.¹⁴

Universal passive vaccination of newborns is recommended by many state departments of public health, which can provide the vaccine without cost to clinicians and health care facilities participating in the children's vaccination program.

RSV prevention strategy 2 **Universal RSV vaccination of pregnant persons from September through January**

The RSVpreF vaccine (Abryvso, Pfizer) is approved by the FDA for the active immunization of pregnant persons between 32 through 36 weeks' gestation for the prevention of RSV LRTD in infants from birth through 6 months of age.¹⁵ Administration of the RSVpreF vaccine to pregnant people elicits the formation of anti-RSV antibodies that are transferred

transplacentally to the fetus, resulting in the protection of the infant from RSV during the first 6 months of life. The RSVpreF vaccine also is approved to prevent RSV LRTD in people aged ≥ 60 years.

The RSVpreF vaccine contains the prefusion form of the RSV fusion (F) protein responsible for viral entry into host cells. The vaccine contains 60 μg of both RSV preF A and preF B recombinant proteins. The vaccine is administered as a single intramuscular dose in a volume of 0.5 mL. The vaccine is provided in a vial in a lyophilized form and must be reconstituted prior to administration. The average wholesale price of RSVpreF vaccine is \$354.¹⁶ The vaccine is contraindicated for people who have had an allergic reaction to any component of the vaccine. The most commonly reported adverse reaction is injection site pain (41%).¹⁵ The FDA reports a “numerical imbalance in preterm births in Abrysvo recipients compared to placebo recipients” (5.7% vs 4.7%), and “available data are insufficient to establish or exclude a causal relationship between preterm birth and Abrysvo.”¹⁵ In rabbits there is no evidence of developmental toxicity and congenital anomalies associated with the RSVpreF vaccine. In human studies, no differences in the rate of congenital anomalies or fetal deaths were noted between RSVpreF vaccine and placebo.

In a clinical trial, 6,975 pregnant participants 24 through 36 weeks’ gestation were randomly assigned to receive a placebo or the RSVpreF vaccine.^{15,17} After birth, follow-up of infants at 180 days, showed that the rates of MA RSV LRTD among the infants in the placebo and RSVpreF vaccine groups were 3.4% and 1.6%, respectively. At 180 days, the reported rates of severe RSV LRTD in the placebo and

RSVpreF vaccine groups were 1.8% and 0.5%, respectively. In this study, among the subset of pregnant participants who received the RSVpreF vaccine ($n = 1,572$) or placebo ($n = 1,539$) at 32 through 36 weeks’ gestation, the rates of MA RSV LRTD among the infants in the placebo and RSVpreF vaccine groups were 3.6% and 1.5%, respectively. In the subset of pregnant participants vaccinated at 32 through 36 weeks’ gestation, at 180 days postvaccination, the reported rates of severe RSV LRTD in the placebo and RSVpreF vaccine groups were 1.6% and 0.4%, respectively.¹⁵

The CDC has recommended that the RSVpreF vaccine be administered to pregnant people 32 through 36 weeks’ gestation from September through the end of January in most of the continental United States to reduce the rate of RSV LRTD in infants.⁶ September was selected because it is 1 to 2 months before the start of the RSV season, and it takes at least 14 days for maternal vaccination to result in transplacental transfer of protective antibodies to the fetus. January was selected because it is 2 to 3 months before the anticipated end of the RSV season.⁶ The CDC also noted that, for regions with a different pattern of RSV seasonality, clinicians should follow the guidance of local public health officials. This applies to the states of Alaska, southern Florida, Hawaii, and Puerto Rico.⁶ The CDC recommended that infants born < 34 weeks’ gestation should receive nirsevimab.⁶

Maternal RSV vaccination is thought to be cost-effective for reducing RSV LRTD in infants. However, the cost-effectiveness analyses are sensitive to the pricing of the two main options: maternal RSV vaccination and nirsevimab.

It is estimated that nirsevimab may provide greater protection than maternal RSV vaccination from RSV LRTD, but the maternal RSVpreF vaccine is priced lower than nirsevimab.¹⁸ Focusing administration of RSVpreF vaccine from September through January of the RSV infection season is thought to maximize benefits to infants and reduce total cost of the vaccination program.¹⁹ With year-round RSVpreF vaccine dosing, the estimated ICER per quality-adjusted life-year (QALY) is approximately \$400,000, whereas seasonal dosing reduces the cost to approximately \$170,000.¹⁹

RSV prevention strategy 3 **Vaccinate pregnant persons;** **reflex to newborn treatment** **with nirsevimab if maternal** **RSV vaccination did not occur**

RSVpreF vaccination to all pregnant persons 32 through 36 weeks’ gestation during RSV infection season is not likely to result in 100% adherence. For instance, in a CDC-conducted survey only 47% of pregnant persons received an influenza vaccine.² Newborns whose mothers did not receive an RSVpreF vaccine will need to be considered for treatment with nirsevimab. Collaboration and communication among obstetricians and pediatricians will be needed to avoid miscommunication and missed opportunities to treat newborns during the birth hospitalization. Enhancements in electronic health records, linking the mother’s vaccination record with the newborn’s medical record plus an added feature of electronic alerts when the mother did not receive an appropriately timed RSVpreF vaccine would improve the communication of important clinical information to the pediatrician.

Next steps for the upcoming peak RSV season

We are currently in the 2023–2024 RSV infection season and can expect a peak in cases of RSV between December 2023 and February 2024. The CDC recommends protecting all infants against RSV-associated LRTD. The options are to adminis-

ter the maternal RSVpreF vaccine to pregnant persons or treating the infant with nirsevimab. The vaccine is just now becoming available for administration in regional pharmacies, physician practices, and health systems. Obstetrician-gynecologists should follow the recommendation of their state department of public health. As noted above, many state

departments of public health are recommending that all newborns receive nirsevimab. For clinicians in those states, RSVpreF vaccination of pregnant persons is not a priority. ●



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