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Society for Maternal-Fetal Medicine Statement: Clinical considerations for the prevention of respiratory syncytial virus disease in infants

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Respiratory syncytial virus is a leading cause of lower respiratory tract illness globally in children aged <5 years. Each year, approximately 58,000 hospitalizations in the United States are attributed to respiratory syncytial virus. Infants aged ≤6 months experience the most severe morbidity and mortality. Until recently, prevention with the monoclonal antibody, palivizumab, was only offered to infants with high-risk conditions, and treatment primarily consisted of supportive care. Currently, 2 products are approved for the prevention of respiratory syncytial virus in infants. These include the Pfizer bivalent recombinant respiratory syncytial virus prefusion F protein subunit vaccine, administered seasonally to the pregnant person between 32 0/7 and 36 6/7 weeks of gestation, and the monoclonal antibody, nirsevimab, administered to infants aged up to 8 months entering their first respiratory syncytial virus season. With few exceptions, administering both the vaccine to the pregnant person and the monoclonal antibody to the infant is not recommended. All infants should be protected against respiratory syncytial virus using one of these strategies. Key considerations for pregnant individuals include examining available safety and efficacy data, weighing accessibility and availability, and patient preferences for maternal vaccination vs infant monoclonal antibody treatment. It will be critical for maternal–fetal medicine physicians to provide effective and balanced counseling to aid patients in deciding on a personalized approach to the prevention of respiratory syncytial virus in their infants.

Key words: lower respiratory tract infection, monoclonal antibody, patient counseling, pregnancy, prevention, respiratory syncytial virus, vaccine

Introduction

Despite the global impact of respiratory syncytial virus (RSV) infection on infant and childhood morbidity and mortality, preventive strategies have been limited. The US Food and Drug Administration (FDA) recently approved 2 new immunization products. The RSV vaccine approved for use in pregnancy, marketed as Abrysvo and developed by Pfizer (New York, NY), is a bivalent recombinant protein subunit vaccine, administered seasonally as a single 120-μg dose to pregnant individuals at 32 through 36 weeks of gestation.[1]

Nirsevimab, marketed as Beyfortus and jointly developed by Sanofi (Paris, France) and AstraZeneca (Cambridge, United Kingdom), is a monoclonal antibody that inhibits the RSV F protein, and is administered to neonates and infants aged <8 months who are either born during or entering their first RSV season.[2] It has also been licensed for use in children aged up to 24 months who remain at risk for severe RSV infections during their second RSV season due to underlying conditions.

Current guidance emphasizes that either maternal vaccination or infant monoclonal antibody therapy should be administered for the prevention of RSV-associated lower respiratory tract infection (LRTI), with some exceptions.[3] It is important to note that both products have distinct efficacy and safety profiles and unique considerations related to implementation and equity, which may influence patient preferences for either vaccination or antibody treatment. This guidance aims to summarize current knowledge regarding RSV disease in infants, available strategies for primary prevention, and recommendations for counseling pregnant people in choosing vaccination during pregnancy versus RSV preventive antibody in their infant.

Burden of respiratory syncytial virus in infants

RSV is a leading cause of respiratory disease and hospitalization in infants and children. Global estimates from

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2019 indicated that 33 million RSV-associated LRTI episodes occur annually in children aged 0 to 60 months, with 1 in 5 episodes occurring in infants aged 0 to 6 months (6.6 million; range, 4.6–9.7 million), contributing to 1.4 million medically attended (MA) outpatient visits or hospitalizations in this age group. In 2019, RSV contributed to 1 in every 28 deaths among infants aged 28 days to 6 months.[4]

In the United States, RSV contributes to 80,000 annual hospitalizations and 100 to 300 annual deaths in children aged <5 years.[5,6] Morbidity and mortality are heightened in infants aged <6 months, preterm infants, and those with congenital heart disease or chronic lung disease. However, 66% of affected infants have no underlying high-risk condition.[7,8] Thus, the incentive to develop passive immunization programs targeting infants in their first 6 months of life is important for achieving the most significant reduction in the burden of RSV-related disease.

Respiratory syncytial virus transmission

Human RSV is a filamentous enveloped, negative-sense, single-stranded RNA virus of the *Pneumoviridae* family.[9] The 2 major subgroups of RSV (A and B) have antigenic differences in their glycoproteins G and F. The prefusion form of the RSV glycoprotein F (preF) is the major target of potent virus-neutralizing antibodies and a key vaccine antigen.[10] Both subgroups circulate each season.

RSV is primarily transmitted through close contact with respiratory droplets from an infected person (e.g., coughing, sneezing, kissing), touching contaminated surfaces, and, rarely, through aerosolized droplets. RSV replicates exclusively in the respiratory epithelium. The disease is caused by viral replication and inflammation in the small bronchioles and alveoli of the lower respiratory tract. Host immune responses lead to increased mucus production, inflammation, and airway narrowing and trapping, which clinically manifests as bronchiolitis.

RSV season usually begins in mid-September and peaks in winter months, with offset during late April to mid-May. Tropical climates (e.g., southern Florida, Hawaii, Guam, Puerto Rico, the United States Virgin Islands, and US-Affiliated Pacific Islands) and Alaska may have RSV circulation patterns that are unpredictable and differ from those found in most of the continental United States.

Respiratory syncytial virus clinical manifestations

Symptoms are usually consistent with a respiratory tract infection and include rhinorrhea, pharyngitis, cough, headache, fever, and anorexia. In very young infants, the only symptoms may be irritability, decreased activity, or difficulty breathing. The contagious period usually lasts 3 to 8 days, with recovery occurring in 1 to 2 weeks. However, those with weakened immunity may remain contagious for as long as 4 weeks.[11] Treatment is supportive.

Rationale for respiratory syncytial virus immunization during pregnancy

Immunization of pregnant people is a known strategy for reducing infant disease severity, hospitalization, and death following infection. It is well established that vaccination during pregnancy confers protection against influenza, tetanus, pertussis, and COVID-19 in neonates and infants aged up to 6 months.[12–15]

Maternal transfer of RSV antibodies following infection-induced immunity is associated with reduced incidence of RSV hospitalizations in neonates, suggesting a benefit of passive immunization against RSV in infants. Passive immunity is also associated with reduced RSV-associated secondary complications such as otitis media, antibiotic use for respiratory tract infections, and childhood wheezing.[16] However, data suggest that the protective thresholds achieved following natural immunity are insufficient to protect infants from hospitalization, and are likely best achieved following vaccination.[17]

In the 1960s, immunization with a formalin-inactivated, whole-virus vaccine led to more severe disease in vaccinated infants aged <6 months (68% hospitalization and 6.7% mortality) after subsequent infection,[18] thus driving the need for passive immunization strategies.

Efficacy and safety of the respiratory syncytial virus prefusion F vaccine and then respiratory syncytial virus monoclonal antibody against infant disease

Immunization of birthing persons against respiratory syncytial virus

The safety and efficacy of the Pfizer RSVpreF vaccine was evaluated in the Maternal Immunization Study for Safety and Efficacy (MATISSE) trial.[19] This was a phase 3, randomized, double-blind, multicenter, placebo-controlled study to investigate the efficacy and safety of vaccination administered to pregnant individuals to prevent RSV disease in infants. Participants were aged ≤49 years, between ≥24 and ≤36 weeks of gestation, with uncomplicated, singleton pregnancies. Pregnant individuals with high-risk pregnancies were excluded from the study. Exclusion criteria included body mass index >40 kg/m^2 before pregnancy, pregnancies resulting after in vitro fertilization, preeclampsia, eclampsia, uncontrolled hypertension, placental abnormalities, polyhydramnios or oligohydramnios, significant bleeding or blood clotting disorder, and unstable endocrine disorders including poorly controlled diabetes or thyroid disease. The primary efficacy objective was the prevention of MA RSV LRTI or MA severe LRTI within 180 days after birth. MA RSV LRTI was defined as an MA visit (e.g., physician's office, urgent care visit, emergency room, or hospitalization) and ≥1 of the following: tachypnea, pulse oximetry reading (peripheral oxygen saturation [SpO_2]) <95%, and chest wall excursions. MA severe RSV LRTI was defined as MA visit and ≥1 of the following: tachypnea,

SpO_2 <93%, need for high-flow nasal cannula or other assisted ventilation, intensive care unit (ICU) admission >4 hours, and altered mental status.

The final analytical cohort included 3568 infants born in the vaccine group and 3558 infants born in the placebo group. Regarding the primary efficacy objective, vaccine efficacy was 69.4% against severe LRTI (97.58% confidence interval [CI], 44.3–84.1; 19 [0.5%] in vaccine and 62 [1.8%] in placebo group) and 56.8% against hospitalization at 180 days (97.58% CI, 10.1–80.7; 19 [0.5%] in vaccine and 44 [1.3%] in placebo). Efficacy against severe LRTI at 180 days was 76.5% (95% CI, 41.3–92.1) among trial participants enrolled within the approved dosing interval.

At 90 days, vaccine efficacy was 81.8% against severe LRTI (99.5% CI, 40.6–90.3; 6 [0.2%] in vaccine and 33 [0.9%] in placebo) and 67.7% against RSV-related hospitalizations (99.5% CI, 15.9–89.5; 10 [0.3%] in vaccine and 31 [0.9%] in placebo). Approved dosing interval efficacy against severe LRTI at 90 days was 91.1% (95% CI, 38.8–99.8).

The most commonly observed local and systemic adverse reactions in pregnant individuals included pain at the injection site (40.6%), headache (31.0%), muscle pain (26.5%), and nausea (20.0%). Zero cases of inflammatory neuropathy occurred. However, inflammatory neuropathy was observed in 2/26,000 vaccine recipients in the age >60 years RSV trial.

Imbalances were observed in absolute numbers of preterm birth (5.7% in vaccine vs 4.7% in control group), stillbirth (0.3% vs 0.2%), and preeclampsia (1.8% vs 1.4%); however, none of these were statistically significant. Newborn outcomes, specifically respiratory distress, jaundice, hypoglycemia, and sepsis did not differ between groups.

A developmental toxicity study in female rabbits revealed no evidence of impaired female fertility after administration of a vaccine formulation containing 2 times the antigen content of a single human dose of the RSV preF vaccine.[1]

Preexposure prophylaxis with monoclonal antibodies in infants

Palivizumab (Synagis; Swedish Orphan Biovitrum AB, Stockholm, Sweden) was licensed in 1988 for the prevention of RSV illness in infants at high risk for RSV disease. It is an intramuscular injection administered to eligible infants monthly for a maximum of 5 doses, initiated before the start of RSV season. High-risk infants include preterm infants born before 29 weeks of gestation who are aged <12 months at the start of the RSV season, preterm infants with chronic lung disease, infants aged ≤12 months with hemodynamically significant congenital heart disease, and infants from high-burden communities (e.g., American Indian and Alaskan Native).[20] It is not indicated for the treatment of RSV in infants. Although palivizumab is efficacious at reducing RSV burden in infants, its impact has been limited by burden of administration (monthly injection throughout RSV season) and cost.[21]

The efficacy of nirsevimab has been supported in multiple clinical trials. The phase 2B MELODY trial included 1453 preterm infants born between 29+0 and 34+6 weeks[22] of gestation during or entering their first RSV season. Infants were randomized 2:1 to nirsevimab vs placebo. Among those who were treated, 25 (2.6%) experienced MA RSV LRTI, as opposed to 46 (9.5%) infants in the placebo group. Nirsevimab was associated with a 70.1% (95% CI, 52.3–81.2; $P<.001$) reduction in MA RSV-associated LRTI and a 78.4% (95% CI, 51.9–90.3; $P>.001$) reduction in infant hospitalization. The phase 3 MELODY trial[23] included 1490 infants, born at least after 35+0 weeks of gestation, 994 of whom received nirsevimab and 496 received placebo. Among treated infants, 12 (1.2%) experienced MA RSV LRTI, as opposed to 25 (5.0%) of those who received placebo, corresponding to an efficacy of 74.5% against MA LRTI (95% CI, 49.6–87.1; $P<.001$) and 62.1% against hospitalization (95% CI, 8.6 to 86.8; $P=.07$). Subsequently, a pooled analysis demonstrated that nirsevimab reduced MA RSV-associated LRTI by 79.5% (95% CI, 65.9–87.7; 51 [6%] in placebo vs 19 [1%] in treatment group), hospitalization by 77.3% (95% CI, 50.3–89.7; 21 [3%] in placebo vs 9 [1%] in treatment), and ICU admission by 86.0% (95% CI, 62.5%–94.8%; 18 [2%] in placebo vs 5 [<1%] in treatment).[24] In comparison, the 150-day vaccine efficacy against severe LRTI observed in the RSV preF vaccine trial was 70.9% (97.58% CI, 44.5–85.9; 16 [0.5%] in vaccine vs 55 [1.6%] in placebo). Adverse reactions were reported in 1.2% of participants and included rash (0.3%) and injection site pain (0.9%).[2]

Current recommendations for infant protection using the Pfizer maternal prefusion form of the respiratory syncytial virus glycoprotein F vaccine or nirsevimab

Active immunization of the birthing parent or passive immunization to the infant is recommended for the prevention of severe RSV disease; with few exceptions, both products are not needed. Pregnant people should be made aware of both options.

The RSV preF vaccine is recommended in pregnant individuals between 32 0/7 and 36 6/7 weeks of gestation, using seasonal administration (September to January in the continental United States), for the prevention of LRTI and severe LRTI caused by RSV in infants from birth through 6 months of age.[1] It is contraindicated in individuals with a history of anaphylaxis against its components, which include the following buffer ingredients: 0.11-mg tromethamine, 1.04-mg tromethamine hydrochloride, 11.3-mg sucrose, 22.5-mg mannitol, 0.08-mg polysorbate 80, and 1.1-mg sodium chloride per 0.5 mL. The vaccine does not contain preservatives. The RSV preF vaccine may be coadministered with other recommended vaccines during pregnancy, although patients may opt to delay receipt of the vaccine (Box 1).

Nirsevimab is recommended in the following scenarios:

- Infants whose pregnant parent either did not receive the RSV preF vaccine or whose vaccine history is not known.

BOX 1
Key points for counseling pregnant persons regarding respiratory syncytial virus vaccination

- Burden of RSV in infants, including increased risk for hospitalization of infants before 6 mo
- Data demonstrating efficacy of maternal RSV vaccine in protecting infants from severe illness
- Data demonstrating no increased risk of adverse maternal or infant outcomes, but uncertainty regarding the risk of preterm birth
- Low rate of vaccine reactogenicity
- Seasonal administration (Sept. to Jan. in the continental United States) between 32 0/7 and 36 6/7 weeks of gestation for pregnant people
- Coadministration with other vaccines based on patient preferences. If delaying, Tdap should be administered at 27–30 wk of gestation
- Option of nirsevimab, yet availability and acceptability will vary by pediatric practice and birthing hospital

RSV, respiratory syncytial virus.
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- Pregnant patient vaccinated within 14 days of delivery.
- Infants and children aged 8 to 19 months at increased risk for severe RSV disease and entering their second RSV season, irrespective of vaccine status of the pregnant person.

Nirsevimab may also be considered for infants when there is potential incremental benefit despite vaccination. This includes:

- Maternal conditions resulting in inadequate immune response and/or decrease in transplacental transfer (i.e., infants born to pregnant people with chronic immunosuppression with anticipated diminished immune responses to vaccination [e.g., those with organ transplant or chronic steroid use])
- Infants with loss of maternal antibodies (i.e., those who have undergone cardiopulmonary bypass or extracorporeal membrane oxygenation)
- Infants with substantially increased risk for severe RSV disease (i.e., hemodynamically significant congenital heart disease)

Nirsevimab is contraindicated in infants and children with a history of serious hypersensitivity reactions, including anaphylaxis, to nirsevimab-alip or to any of the ingredients, which include arginine hydrochloride (8 mg), histidine (1.1 mg), L-histidine hydrochloride monohydrate (1.6 mg), polysorbate 80 (0.1 mg), sucrose (21 mg), and water.

What issues should be considered regarding prefusion form of the respiratory syncytial virus glycoprotein F vaccination during pregnancy?

Vaccine hesitancy and reduced immunization among birthing persons

Although vaccination is a core component of pregnancy care that has improved maternal and infant outcomes, coverage among pregnant people has declined, and is lowest in racial and ethnic minorities. During the 2022–2023 influenza season, only 47.2% of pregnant people had received an influenza vaccine either during or before pregnancy, 27.3% had received a COVID-19 booster during or before pregnancy, and 55.4% had received tetanus-diphtheria-acellular pertussis (Tdap) vaccination during pregnancy, with lowest coverage among non-Hispanic Black women and Hispanic or Latino women.[25]

Vaccine hesitancy among pregnant patients is increasing and stems from concerns related to safety for their pregnancy and unknown long-term adverse effects of vaccines perceived to be new, and limited access. However, prenatal care providers' recommendations are among the most important factors affecting vaccine decision-making. Maternal–fetal medicine specialists should be prepared to counsel patients regarding RSV preF vaccination in the context of other routinely recommended vaccines in pregnancy and emphasize the role of vaccines in improving outcomes in patients and their infants.

Uncertainty regarding the risk of vaccination on preterm birth

The first concern is regarding a potential signal of preterm birth associated with vaccination. The data demonstrate a nonsignificant difference in preterm births between the vaccine and the placebo group. Preterm events occurred in 5.7% (95% CI, 4.9–6.5; 202/3568) in the vaccine group, as opposed to 4.7% (95% CI, 4.1–5.5; 169/3558) in the placebo group, correlated with a relative risk (RR) of 1.19 (0.97–1.45). When stratified by gestational age, <0.1% in both groups delivered before 28 weeks of gestation, 0.6% of vaccine and 0.3% of placebo recipients delivered at 28 to <34 weeks of gestation, and 5.0% of vaccine and 4.4% of placebo recipients delivered at 34 to <37 weeks of gestation. The median gestational age at vaccination was 31.3 weeks, and 60% of preterm infants were born >30 days

following vaccination. Among the preterm births, infant deaths occurred in 5 (0.1%) of the vaccinated group, as opposed to 12 (0.3%) in the placebo group.

The overall incidence of preterm birth in the study was low in both groups and below the background preterm birth rates for most of the participating countries. Further, the findings were driven by imbalances in preterm births in low- and middle-income countries. In an analysis of US births only, the preterm birth rate was 5.1% (126/2494) in the vaccine group, as opposed to 5.1% (126/2484) in the control group. In addition, an analysis of US participants enrolled during the approved dosing interval (32–36 weeks of gestation) demonstrated that the imbalance was reversed, with preterm births occurring in 4.0% (721/1628) in the vaccine group, as opposed to 4.4% (732/1604) in the control group.[26] Nonetheless, the study was underpowered to detect a 20% difference in prematurity, and the study exclusion criteria selected for populations at low risk for preterm birth.

The concern regarding an increased risk of preterm birth following maternal RSV vaccination is heightened in light of a previous RSV trial investigating a similar maternal RSV vaccine (stabilized prefusion F protein vaccine without an adjuvant). In February 2022, GSK halted enrollment and vaccination across 3 phase-3 trials of a maternal RSV vaccine candidate after interim analysis demonstrated that preterm birth before 37 weeks of gestation occurred in 6.81% of the vaccine arm, as opposed to 4.95% of the placebo arm (RR, 1.38; 95% CI, 1.05–1.38).[27] In addition, neonatal deaths, which occurred in 0.37% of vaccine recipients, as opposed to 0.13% of placebo recipients (RR, 2.16; 95% CI, 0.62–7.55), were attributed to this imbalance. Most preterm births occurred in low- and middle-income countries. This vaccine is not licensed for use in pregnancy.

A clinical trial of a recombinant RSV F protein nanoparticle vaccine, not stabilized in prefusion form, did not show an increased risk of preterm birth following vaccination. The maternal vaccine did not reach prespecified efficacy end points against RSV-associated medically significant LRTI, precluding licensure and authorization.[28]

Available data are insufficient to establish or exclude a causal relationship between vaccination and preterm birth. The FDA is requiring the company to conduct postmarketing studies to assess the risk of preterm birth. Furthermore, the FDA approval dosing window is not the same as the trial dosing to mitigate concerns regarding preterm birth. In addition, the Centers for Disease Control and Prevention (CDC) Vaccine Adverse Event Reporting System (VAERS) program, Vaccine Safety Datalink (VSD) program, and V-safe will provide national vaccine surveillance for safety. Patients will need to be counseled regarding this uncertainty, and prenatal care providers will need to remain aware of evolving data from ongoing postmarketing surveillance.

Coadministration with the tetanus-diphtheria-acellular pertussis vaccine

A phase 2b, placebo-controlled, randomized, observer-blind study[29] was conducted in nonpregnant women aged 18 through 49 years to evaluate the safety, tolerability, and immunogenicity of the RSV preF vaccine when administered concomitantly with the Tdap vaccine. Antibody responses to antigens contained in both vaccines were assessed after one month. Lower concentrations of antibodies to acellular pertussis antigens were observed with concomitant administration compared with administration of Tdap alone; however, concentrations did not reach noninferiority thresholds. The clinical relevance of this finding is unknown. There was no effect on RSV antibody concentrations.

The implications of coadministration of Tdap with RSV vaccine for infant protection are not known. The CDC currently recommends Tdap immunization during pregnancy from 27 through 36 weeks of gestation, regardless of previous immunization status.[30] Whether concomitant administration of Tdap and RSV preF vaccines interferes with infant antibody concentrations, and therefore infant disease outcomes, has not been examined.

Studies have demonstrated that umbilical cord antibody concentrations are higher in newborns of women immunized at 27 to 30+6 weeks of gestation compared with newborns of women immunized at 31 to 36 and >36 weeks of gestation.[31,32] Additional factors influencing transplacental antibody transfer are placental integrity, total immunoglobulin G concentration in maternal blood, time of immunization, and time elapsed between immunization and delivery.[33] However, there is no generally accepted level of pertussis-specific antibodies that protects against infection. In addition, placental antibody transfer efficiency may compensate for reduced maternal antibody concentrations.

In the absence of data, patients should be aware that one study in nonpregnant adults demonstrated reduced immunity against pertussis when Tdap vaccine was given concomitantly with the RSV vaccine. However, antibody levels still met criteria for vaccine efficacy. The implications for infant protection are not known. Prenatal care providers should continue to recommend Tdap vaccination and may consider providing this earlier in pregnancy (e.g., 27 to 30+6 weeks of gestation) given the existing data supporting neonatal and infant benefit from earlier administration. However, current recommendations indicate that patients can receive both vaccines simultaneously and can be informed that coadministration is safe and well-tolerated.

Coadministration with seasonal influenza and COVID-19 vaccines

The data regarding safety and immunogenicity of coadministration with other vaccines are limited. Coadministration of RSV with seasonal quadrivalent inactivated influenza

vaccine (SIIV) met noninferiority criteria for immunogenicity when studied in one phase 1/2 randomized study of 534 nonpregnant adults aged 18 to 49 years. However, influenza antibody titers were lower when RSVpreF was administered with SIIV compared with when SIIV was administered alone. The clinical significance of this is not known. There was no impact of coadministration on RSV immunogenicity.[34]

Incidence and severity of local reactions were similar when RSVpreF was administered with and without SIIV. Systemic reactions (fatigue, myalgia, fever) were higher when RSVpreF was administered with SIIV compared with when SIIV was administered alone (24.4% vs 7.3%), although none were reported as severe vaccine-related adverse events.

It is currently recommended that all persons aged ≥6 months who do not have a contraindication receive a licensed and age-appropriate seasonal influenza vaccine.[35] Influenza vaccine should be given annually during the influenza season, ideally by the end of October. The Advisory Committee on Immunization Practices also recommends that persons aged ≥6 months who do not have any contraindications receive an updated 2023–2024 monovalent, XBB-containing COVID-19 vaccine.[36] Pregnant people are included in these recommendations.

Prenatal care providers should continue to recommend that pregnant patients remain up to date with influenza and COVID-19 vaccines, given the known benefit against disease-related maternal critical illness, hospitalization, mortality, and adverse perinatal outcomes. Currently, seasonal influenza, COVID-19, and Tdap vaccines may be coadministered safely in different limbs.

Pregnant patients should be counseled that the data regarding immunogenicity and reactogenicity of coadministration of RSV vaccines with seasonal influenza are limited but thus far support coadministration. There are no data evaluating immunogenicity and reactogenicity of RSV coadministration with COVID-19 vaccines. Coadministration of RSV vaccine with other recommended vaccines during pregnancy can be offered per CDC guidance; however, it is also acceptable for patients to delay RSV vaccine following receipt of other vaccines.[37]

The effects of vaccination on lactation and of breastfeeding on infant protection

It is not known whether the RSV preF vaccine is excreted in human milk. Data are not available to assess the effects of vaccination on the breastfed infant or on milk production and excretion; antibody concentrations in breast milk; or the impact of antibody transfer in breast milk on infant outcomes. However, it is known that RSV antibodies are transferred through breast milk following maternal infection and that they do confer some protection.[38] On the basis of experience from other vaccines, it is reasonable to assume that breastfeeding should augment immunity following vaccination. Breastfeeding should continue to be encouraged in vaccine recipients.

Is there a potential benefit of respiratory syncytial virus vaccination in protecting pregnant persons against respiratory syncytial virus illness?

Pregnant persons are susceptible to RSV infection, like all adults. RSV is likely the etiology in up to 10% to 13% of women presenting with respiratory infectious symptoms.[39] Severe cases of RSV-associated respiratory infection have been reported.[40,41] Although pregnancy poses increased risk for increased susceptibility and worsened outcomes following respiratory infections, the data are insufficient to estimate RSV-associated risk, and the benefits of RSV vaccination during pregnancy for pregnant people are not known.

What are the risk–benefit, cost, and equity considerations for vaccination compared with nirsevimab?

Although there are no data directly comparing the efficacy of vaccination and nirsevimab, there are advantages and disadvantages associated with each that will factor into patient decision-making (Box 2). The benefits of vaccination over nirsevimab include infant protection at birth, especially given the unpredictable RSV seasonal patterns in some parts of the United States. However, infants may not receive the full benefit of vaccination, especially those born within 2 weeks of vaccination. Another benefit is that vaccination induces a polyclonal antibody response which could confer added protection against viral mutation compared with a monoclonal antibody response.[42]

In comparison, nirsevimab provides passive immunity directly to the infant, rather than through the placenta, and has an extended half-life. It may avert uncertainty regarding the risk of preterm birth. Finally, deferring RSV vaccine administration may allow for prioritization of vaccines with known maternal benefit (e.g., seasonal influenza, COVID-19) and those where infant treatment and preventive options are limited (e.g., pertussis, tetanus).

Both products have been included in the Vaccines For Children (VFC) program, which is a federally funded program that provides vaccines at no cost to children aged <19 years, who might otherwise not receive the vaccine because of inability to pay. The high cost of nirsevimab and the limited number of hospitals and outpatient pediatric offices that participate in the VFC program will create barriers to nirsevimab access. However, there is an existing infrastructure for vaccination in pregnancy, and the vaccine is already being distributed for adults aged >60 years. These barriers may preclude equitable availability of nirsevimab, particularly in racial and ethnic minorities who bear the largest burden of severe RSV illness. Issues around administration, coding, and payment remain undetermined. Where feasible, maternal–fetal medicine subspecialists should work with their local health care facilities and health departments to plan an approach to RSV prevention in infants that is both cost-effective and equitable.[43]

BOX 2
Comparison of recently approved immunization products for the prevention of respiratory syncytial virus disease in infants

Characteristics	RSV preF vaccine	Nirsevimab
Brand name (manufacturer)	Abrysvo (Pfizer)	Beyfortus (Sanofi and AstraZeneca)
Indications	Active immunization of pregnant individuals for the prevention of lower respiratory tract disease in infants from birth through 6 mo of age	Passive immunization in neonates and infants born during or entering their first RSV season and in children up to 24 mo of age who remain vulnerable to severe RSV through their second RSV season
Mechanism	Bivalent recombinant protein subunit vaccine consisting of equal amounts of RSV A and B stabilized prefusion F antigen	Monoclonal antibody
Efficacy	76.5% (95% CI, 41.3–92.1) at 180 d in protecting infants from medically attended RSV-related severe lower respiratory tract infection	79.5% (95% CI, 65.9–87.7) at 150 d in protecting infants from medically attended RSV-related severe lower respiratory tract infection
Eligibility	Pregnant persons without contraindication or hypersensitivity to vaccine components	Infants born to nonimmunized pregnant persons without contraindication or hypersensitivity to vaccine components
Timing of administration	Administer seasonally between 32 0/7 and 36 6/7 weeks of gestation. May be coadministered with other vaccines.	Infants aged <8 mo born during or entering their first RSV season. Infants and children aged 8–19 mo entering their second RSV season.
Adverse effects	Injection site pain (40.6%), headache (31.0%), muscle pain (26.5%), nausea (20.0%), and fever (3%)	1.25% (rash [0.3%] and injection site pain [0.9%])

CI, confidence interval; *preF*, prefusion form of the RSV glycoprotein F; *RSV*, respiratory syncytial virus.

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Future research

Continued research regarding the safety and efficacy of maternal RSV preF vaccination and infant preexposure prophylaxis with nirsevimab is warranted, specifically with regard to concern for preterm birth, effects of vaccine coadministration on infant outcomes, and implications for lactation. In addition, evaluation of implementation programs with specific considerations related to cost and equity is needed. We will continue to follow advances in this area to assure optimal care for all people who experience pregnancy and to provide up-to-date guidance for maternal–fetal medicine subspecialists.

Summary

1. The Society for Maternal-Fetal Medicine supports CDC recommendations that all infants be protected against RSV-associated LRTI with either active immunization of the birthing parent using the Pfizer RSVpreF vaccine or passive immunization direct to infants using nirsevimab. The GSK RSV vaccine is not licensed for use in pregnancy.
2. The RSV preF vaccine can be given to pregnant people between 32 0/7 and 36 6/7 weeks of gestation using seasonal administration (September though January in most of the continental United States).
3. Nirsevimab should be given to infants aged <8 months who are born during or entering their first RSV season, who was born two weeks following birthing parent vaccination, or in instances where the birthing parent was not vaccinated or whose vaccination status is not known.
4. Pregnant persons should be counseled that the benefits of vaccination include high efficacy, immediate infant protection, potential resistance to viral mutations, and potential ongoing immunity through breastfeeding, yet there is uncertainty regarding the risk of preterm birth.
5. Pregnant persons should be counseled that the benefits of nirsevimab include passive immunization directly to infant and longer duration of antibodies; however, it does require an infant injection and seasonal availability is uncertain.
6. Parental choice for infant protection against RSV should be documented in the prenatal care record, when possible, to facilitate communication to pediatric providers.
7. Providers should counsel pregnant persons and strongly recommend vaccination in pregnancy; seasonal influenza, COVID-19, and pertussis immunization should be prioritized.

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