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

Society for Maternal- Fetal Medicine (SMFM); Naima T. Joseph, MD, MPH; Jeffrey A. Kuller, MD; Judette M. Louis, MD, MPH; and Brenna L. Hughes, MD, MSc

Corresponding Author:

The Society for Maternal-Fetal Medicine

PO Box 420016

Washington, DC 20042

Phone: 202-863-2476

Fax: 202-554-1132

Condensation: This guidance summarizes current knowledge regarding respiratory syncytial virus disease in infants, the available strategies for primary prevention of infant respiratory syncytial virus, and recommendations for guiding pregnant people in choosing vaccination during pregnancy or treatment in neonates.

Abstract: Respiratory syncytial virus is a leading cause of lower respiratory tract illness globally in children under 5 years. Each year, approximately 58,000 hospitalizations in the United States are attributed to respiratory syncytial virus. Infants aged 6 months and younger 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, two 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 up to 8 months entering their first respiratory syncytial virus season. With few exceptions, administering both the vaccine to the pregnant person and 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 versus 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:

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

Introduction

Despite the global impact of respiratory syncytial virus (RSV) on infant and childhood morbidity and mortality, preventive strategies have been limited. The Food and Drug Administration recently approved two new immunization products. The RSV vaccine approved for use in pregnancy, marketed as Abrysvo and developed by Pfizer, 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 and AstraZeneca, is a monoclonal antibody that inhibits the RSV F protein and is administered to neonates and infants under 8 months of age who are either born during or entering their first RSV season.[2] It has also been licensed for use in children up to 24 months of age 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, the available strategies for primary prevention of infant RSV, and recommendations for guiding pregnant people in choosing vaccination during pregnancy versus treatment in their infant.

Burden of RSV in Infants

RSV is a leading cause of respiratory disease and hospitalization in infants and children. Global estimates from 2019 indicated that 33 million RSV-associated LRTI episodes occur annually in children aged 0 – 60 months, with 1 in 5 episodes occurring in infants aged 0-6 months (6.6 million, range 4.6 – 9.7 million), contributing to 1.4 million medically attended outpatient visits or hospitalizations in this age group. In 2019, RSV contributed to 1 in every 28 deaths among infants aged 28 days to six months.[4]

In the United States, RSV contributes to 80,000 annual hospitalizations and 100 -300 annual deaths in children under 5 years.[5,6] Morbidity and mortality are heightened in infants under 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 to achieving the most significant reduction in the burden of RSV-related disease.

RSV transmission

Human RSV is a filamentous enveloped negative sense single-stranded RNA virus of the Pneumoviridae family.[9] The two 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 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 mucous 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 (US) Virgin Islands, and US-Affiliated Pacific Islands) and Alaska may have RSV circulation patterns that are unpredictable and differ from most of the continental US.

RSV 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 -2 weeks. However, those with weakened immunity may remain contagious for as long as 4 weeks.[11] Treatment is supportive.

Rationale for RSV 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 up to 6 months of age.[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 usage for respiratory tract infections, and childhood wheezing.[16] However, data suggest protective thresholds to protect infants from hospitalization following natural immunity are insufficient and 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 under six months (68% hospitalization and 6.7% mortality) after subsequent infection,[18] thus driving the need for passive immunization strategies.

Efficacy and Safety of RSV preF vaccine and infant pre-exposure prophylaxis with nirsevimab against RSV disease in infants

Immunization of birthing persons against RSV

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 ≤49 years of age, between ≥24 weeks and ≤36 weeks of gestation, with

uncomplicated, singleton pregnancies. Pregnant individuals with high-risk pregnancies were excluded from the study. Exclusion criteria included BMI>40 kg/m^2 prior to 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 medically attended RSV LRTI or medically attended severe LRTI within 180 days after birth. Medically attended RSV LRTI was defined as medically attended visit (e.g., physician's office, urgent care visit, emergency room, or hospitalization) and 1 or more of the following: tachypnea, pulse oximetry reading (SpO_2) < 95%, chest wall excursions. Medically attended severe RSV LRTI was defined as medically attended visit and 1 or more of the following: tachypnea, SpO_2< 93%, need for high flow nasal cannula or other assisted ventilation, ICU admission > 4 hours, and altered mental status.

The final analytic cohort included 3,568 infants born in the vaccine group and 3,558 infants born in the placebo group. Regarding the primary efficacy objective, vaccine efficacy was 69.4% (97.58% CI 44.3 – 84.1, 19 (0.5%) in vaccine and 62 (1.8%) in placebo group) against severe LRTI and 56.8% (97.58% CI 10.1 – 80.7, 19 (0.5%) in vaccine and 44 (1.3%) in placebo) against hospitalization at 180 days. 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 against severe LRTI was 81.8% (99.5% CI 40.6 – 90.3, 6(0.2%) in vaccine and 33 (0.9%) in placebo) and 67.7% (99.5% CI 15.9 – 89.5, 10 (0.3%) in vaccine and

31 (0.9%) in placebo) against RSV related hospitalizations. Approved dosing interval efficacy against severe LRTI at 90 days was 91.1% (95% CI 38.8 – 99.8).

The most commonly solicited 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%). No cases of inflammatory neuropathy were observed, although two events were noted among the 26,000 vaccine recipients in the adult (age >60 years) trial.

Imbalances were observed in absolute numbers of preterm birth (5.7% in vaccine group compared to 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 two times the antigen content of a single human dose of the RSV preF vaccine.[1]

Pre-exposure prophylaxis with monoclonal antibody in infants

Palivizumab (Synagis) 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 five doses, initiated prior to the start of RSV season. High-risk infants include preterm infants born before 29 weeks of gestation who are younger than 12 months at the start of the RSV season, preterm infants with chronic lung disease, infants ≤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 was limited by burden of administration (monthly injection throughout RSV season) and cost.[21]

The efficacy of nirsevimab was supported in multiple clinical trials. The phase 2B MELODY trial included 1,453 preterm infants born between 29+0 to 34+6 weeks[22] gestational age during or entering their first RSV season, in which infants were randomized 2:1 to nirsevimab vs placebo. Among those who were treated, 25 (2.6%) experienced medically attended (MA) RSV LRTI compared with 46 (9.5%) infants in the placebo group. Nirsevimab was associated with a 70.1% (95% CI 52.3 – 81.2, p<0.001) reduction in MA RSV-associated LRTI and a 78.4% (95% CI 51.9 – 90.3, p>0.001) 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 compared with 25 (5.0%) who received placebo, corresponding to an efficacy of 74.5% (95% CI 49.6 – 87.1, p<00.001) against MA LRTI and 62.1% (95%CI -8.6 – 86.6, p=0.07) against hospitalization. Subsequently, a pooled analysis demonstrated that nirsevimab was effective in reducing medically attended RSV-associated LRTI by 79.5% (95% CI 65.9 – 87.7, 51 (6%) in placebo vs 19 (1%) in treatment group), reduced hospitalization by 77.3% (95% CI 50.3 – 89.7, 21 (3%) in placebo vs 9 (1%) in treatment), and reduced ICU admission by 86.0% (95% CI 62.5 – 94.8%, 18 (2%) placebo vs 5 (<1%) in treatment).[24] The 150-day vaccine efficacy against severe LRTI seen 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) in comparison. Adverse reactions were reported in 1.2% of subjects and included rash (0.3%) and injection site pain (0.9%).[2]

Current recommendations for infant protection using Pfizer maternal RSV preF vaccine or nirsevimab

Passive immunity delivered either through maternal vaccination or nirsevimab in the infant are recommended to prevent RSV severe infection in infants; 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 vaccine 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 vaccine (See Box 1. Key points for counseling pregnant persons regarding RSV vaccination).

Nirsevimab is recommended in the following scenarios:

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

- Pregnant patient vaccinated within 14 days of delivery.
- Infants and children aged 8 – 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 (organ transplant, 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 RSV preF 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 amongst 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 prior to pregnancy, 27.3% had received a COVID-19 booster during or prior to pregnancy, and 55.4% had received Tdap vaccination during pregnancy, with coverage lowest among non-Hispanic Black women and Hispanic or Latino women.[25]

Vaccine hesitancy amongst pregnant patients is increasing and stems from concerns related to safety for their pregnancy and unknown long-term side effects of vaccines perceived to be new, and limited access. However, prenatal care providers recommendations are among the most important factor impacting 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. Seasonal influenza, COVID-19, and pertussis immunization should be prioritized during counseling as these are important for the health of the pregnant person.

Uncertainty regarding the risk of vaccination on preterm birth

The first concern is regarding signal of preterm birth between associated with vaccination. The data demonstrate a nonsignificant difference in preterm births between both groups. Preterm events occurred in 5.7% (95% CI 4.9 – 6.5, 202 of 3,568) in the vaccine group compared to 4.7% (95% CI 4.1 –5.5, 169 of 3,558) in the placebo group, correlated to a relative risk (RR) of 1.19 (0.97 – 1.45). When stratified by gestational age, <0.1% delivered prior to 28 weeks of gestation in both groups, 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 compared to 12 (0.3%) in the placebo groups.

The overall incidence of preterm birth in the study was low in both groups and below the background preterm birth rates for the majority 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 compared to 5.1% (126/2484) in the control group. Additionally, an analysis of U.S. 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 compared 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 prior RSV trial investigating a similar maternal RSV vaccine (stabilized prefusion F protein vaccine without an adjuvant). In February 2022, GlaxoSmithKline (GSK) halted enrollment and vaccination across three phase 3 trials of a maternal RSV vaccine candidate after interim analysis demonstrated preterm birth prior to 37 weeks of gestation occurred in 6.81% of the vaccine arm compared to 4.95% of the placebo arm (RR 1.38, 95% CI 1.05 – 1.38).[27] Additionally, neonatal deaths, which occurred in 0.37% of vaccine recipients

compared to 0.13% of placebo recipients (RR 2.16, 95% CI 0.62 – 7.55), were attributed to this imbalance. The majority of preterm births occurred in low- and middle-income countries.

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 endpoints 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 post marketing studies to assess the risk of preterm birth. Also, the FDA approval dosing window is not the same as the trial dosing to mitigate concerns regarding preterm birth. Additionally, the CDC's Vaccine Adverse 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 post-marketing surveillance.

Co-administration with the tetanus-diphtheria-acellular pertussis vaccine

A Phase 2b, placebo-controlled, randomized, observer-blind study[29] was conducted in non-pregnant women, 18 through 49 years of age, to evaluate the safety, tolerability, and immunogenicity of the RSV preF vaccine when administered concomitantly with tetanus-diphtheria-acellular pertussis (Tdap); antibody responses to antigens contained in both vaccines were assessed after 1 month. Lower antibody concentrations to acellular pertussis antigens were

observed with concomitant administration, compared to when Tdap was given 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 co-administration of Tdap with RSV vaccine on infant protection is 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 when compared with newborns of women immunized at 31 to 36 weeks of gestation and >36 weeks of gestation.[31,32] Additional factors influencing transplacental antibody transfer are placental integrity, total IgG 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. Additionally, placental antibody transfer efficiency may compensate for reduced maternal antibody concentrations.

In the absence of data, patients should be aware that one study in non-pregnant 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 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 co-administration is safe and well-tolerated.

Co-administration with seasonal influenza and COVID-19 vaccines.

The data regarding safety and immunogenicity of co-administration with other vaccines are limited. Co-administration of RSV with seasonal quadrivalent inactivated influenza vaccine (SIIV) met noninferiority criteria for immunogenicity when studied in one Phase1/2 randomized study of 534 non-pregnant adults aged 18 - 49 years. However, influenza antibody titers were lower when RSVpreF was administered with SIIV compared to when SIIV was administered alone. The clinical significance of this is not known. There was no impact of co-administration on RSV immunogenicity.[34]

Incidence and severity of local reactions were similar whether RSVpreF was administered with or without SIIV. Systemic reactions (fatigue, myalgia, fever) were higher when RSVpreF was administered with SIIV compared to 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. ACIP also recommends that persons ≥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 co-administered safely in different limbs.

Pregnant patients should be counseled that the data regarding immunogenicity and reactogenicity of co-administration of RSV vaccines with seasonal influenza are limited but thus far support co-administration. There are no data evaluating immunogenicity and reactogenicity of RSV co-administration with COVID-19 vaccines. Co-administration 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 effect of vaccination on lactation and 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. Data are not available to assess 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 breastmilk following maternal infection and do confer some protection.[38] Based on 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. Vaccine and nirsevimab surveillance will be ongoing through pharmaceutical Phase IV studies, and the CDC's Vaccine Adverse Reporting System (VAERS) program, Vaccine Safety Datalink (VSD) and V-safe.

Is there a potential benefit of RSV vaccination in protecting pregnant persons against RSV illness?

Pregnant persons are susceptible to RSV infection, like all adults. RSV is likely the etiology in up to 10-13% 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 risk-benefit, cost, and equity considerations for vaccination compared to nirsevimab?

While there are no direct data directly comparing the efficacy of vaccination and nirsevimab, there are advantages and disadvantages associated with each that will factor into patient decision-making (see Box 2. Considerations for RSV preF vaccine and nirsevimab). The benefits of vaccination over nirsevimab include infant protection at birth, especially given 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 two weeks of vaccination. Another

benefit is that vaccination induces a polyclonal antibody response, theoretically could confer enhanced protection against viral mutations compared to monoclonal antibody.[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. And finally, deferring RSV vaccine 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 age <19, 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 who 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 age >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 healthcare facilities and health departments to plan an approach to RSV prevention in infants that is both cost-effective and equitable.[43]

Future Research

Continued research regarding the safety and efficacy of maternal RSV preF vaccination and infant preexposure prophylaxis with nirsevimab is warranted, specifically with regards to concern for preterm birth, effects of vaccine co-administration on infant outcomes, and implications for lactation. Additionally, 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. SMFM supports CDC recommendations that all infants are protected against respiratory syncytial virus-associated lower respiratory tract infection by either vaccinating the birthing parent vaccination with Pfizer RSV PreF vaccine or providing direct infant immunity using the monoclonal antibody nirsevimab. Importantly, while there is a second RSV vaccine from GSK approved for use in older adults, currently the only RSV vaccine approved for use in pregnancy is the Pfizer vaccine.
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 <8 months whose pregnant parent was not vaccinated, under vaccinated, or whose vaccine status is not known and are born during or entering their first RSV season.

4. Pregnant persons should be counseled that the benefits of vaccination include high efficacy, immediate infant protection, potential resistant to viral mutations, potential ongoing immunity through breastfeeding, yet there is uncertainty regarding the risk of preterm birth.
5. Pregnant persons should be counseled that the benefit of nirsevimab includes direct infant administration and long duration of antibody protection, however, requires an infant injection and that availability this season 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.

Box 1. Key points for counseling pregnant persons regarding RSV vaccination

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

Box 2. Comparison of recently approved immunization products for the prevention of RSV disease in infants		
	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 months of age	Passive immunization in neonates and infants born during or entering their first RSV season and in children up to 24 months 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 days in protecting infants from medically attended RSV-related severe lower respiratory tract infection	79.5% (95% CI 65.9 – 87.7) at 150 days 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 months born during or entering their first RSV season. Infants and children aged 8 – 19 months entering their second RSV season
Side 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%)

[*]Indications for nirsevimab:

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