FAQ: Pediatric RSV Prevention Strategies

October 2023

Key Takeaways

- There are 3 FDA-approved products for the prevention of RSV lower respiratory tract disease in pediatric patients, which include the monoclonal antibodies, palivizumab (Synagis) and nirsevimab (Beyfortus), and a maternal RSV vaccine (Abrysvo).
- Palivizumab is only approved and recommended for use in pediatric patients at increased risk of serious lower respiratory tract infection due to RSV. Nirsevimab is recommended for use in all infants < 8 months born during or entering their first RSV season; nirsevimab may also be used in children at increased risk of severe RSV disease entering their second RSV season. The maternal RSV vaccine is recommended for pregnant individuals at 32 through 36 weeks gestation to prevent RSV lower respiratory tract disease in infants.
- ACIP recommends that *either* nirsevimab or the maternal RSV vaccine be used to prevent RSV lower respiratory tract infection. The use of both products is not recommended for most infants. Available data indicate the duration of protection for nirsevimab and the maternal RSV vaccine extends through 5 months and 6 months, respectively.
- AAP issued preferential guidance in favor of nirsevimab over palivizumab when available.
- Nirsevimab and the maternal RSV vaccine have demonstrated efficacy in reducing the risk of medically attended RSV lower respiratory tract infections in infants. Few RSV-related hospitalizations and deaths occurred in trials; therefore trials were underpowered to evaluate these clinically important endpoints.
- There was an imbalance in late preterm births with the maternal RSV vaccine in the MATISSE trial. Post marketing studies will be necessary to determine if prematurity is a safety signal.

1. What products are FDA-indicated for the prevention of RSV lower respiratory tract disease in the pediatric population?

Until recently, the only available therapy for prevention of RSV in pediatric patients was the monoclonal antibody therapy, palivizumab (Synagis), which was approved in 1998. Palivizumab is specifically indicated for use in high-risk infants and pediatric patients, which includes premature birth (≤ 35 weeks), children with bronchopulmonary disease (also referred to as chronic lung disease [CLD]), and children with hemodynamically significant congenital heart disease (CHD). Palivizumab is administered as a monthly intramuscular (IM) injection throughout the RSV season.[1] On July 17, 2023, AstraZeneca and Sanofi's nirsevimab (Beyfortus) was approved. Nirsevimab is a new, long-acting monoclonal antibody for the prevention of RSV lower respiratory tract disease (LRTD), also referred to as lower respiratory tract infection (LRTI), in infants and children.[2] Nirsevimab targets a unique antigenic site on the prefusion RSV F protein and is a more potent inhibitor of RSV than palivizumab *in vitro*. Nirsevimab also has a substantially longer half-life, allowing for a single IM dose for the entire RSV season.[3] In addition to use in high-risk patients, nirsevimab is also approved for use in healthy, term infants for RSV LRTD prevention, making it the first FDA-approved drug for this indication.[2] On August 21, 2023, the US Food and Drug Administration (FDA) approved Pfizer's RSV vaccine, Abrysvo, for use in pregnancy at 32 through 36 weeks gestation, to prevent LRTD and severe LRTD caused by RSV in infants from birth through 6 months of age.[4] Abrysvo was originally approved earlier this year in May for use in adults 60 years of age and older.[5] This is the first vaccine to be approved for maternal use to prevent RSV-associated LRTD in infants.[4] The other available RSV vaccine from GlaxoSmithKline, Arexvy, remains approved for use in adults 60 years of age and older only.[6]

Table 1. Prevention strategies for RSV LRTD in pediatric patients[1,2,5]

Generic (brand)	Description	Manufacturer / supplier	FDA-approved populations for prevention of LRTD caused by RSV in infants and children
Palivizumab (Synagis)	Humanized monoclonal antibody	Swedish Orphan Biovitrum	• Infants with history of premature birth (≤ 35 weeks GA) and who are ≤ 6 months of age at the beginning of RSV season • Children with BPD that required medical treatment within the previous 6 months and who are ≤ 24 months of age at the beginning of RSV season. • Children with hemodynamically significant CHD and who are ≤ 24 months of age at the beginning of RSV season
Nirsevimab (Beyfortus)	Humanized monoclonal antibody	AstraZeneca / Sanofi	• All infants and neonates born during or entering their first RSV season • Children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season
Respiratory syncytial virus vaccine (Abrysvo)	Bivalent vaccine containing RSVpreF subgroup A and B antigens	Pfizer	• Pregnant individuals 32 through 36 weeks gestation

Abbreviations: BPD = bronchopulmonary disease; CHD = congenital heart disease; GA = gestational age; RSV = respiratory syncytial virus; RSVpreF = RSV glycoprotein F stabilized in pre-fusion conformation

2. Who is recommended to receive nirsevimab?

- **All infants aged < 8 months who are born during or are entering their first RSV season**
- **Children 8 to 19 months of age who are at increased risk of severe RSV disease and entering their second RSV season**

On August 3, 2023, the Advisory Committee on Immunization Practices (ACIP) met to vote on recommendations for the use of nirsevimab. The complete recommendations were published in the *Morbidity and Mortality Weekly Report (MMWR)* on August 25, 2023. The Committee recommended nirsevimab for use in all infants aged < 8 months who are born during or are entering their first RSV season and in children 8 to 19 months of age who are at increased risk of severe RSV disease and entering their second RSV season. Patients considered at increased risk for severe disease by ACIP include children with CLD with a need for continued medical support, children who are profoundly immunocompromised, children with cystic fibrosis who have manifestations of severe disease or a weight-for-length less than the tenth percentile, and children who are American Indian and Alaska Natives.[7,8] The FDA-labeled indications for nirsevimab differ slightly from guideline recommendations. The first labeled indication is for infants and neonates born during or entering their first RSV season. The main difference here is the lack of specificity in age, while ACIP defines < 8 months as the cut-off for this population. The other FDA-approved indication for nirsevimab is for use in children up to 24 months of age who remain vulnerable to severe RSV LRTD through their second RSV season, while ACIP recommends use in higher risk populations between the ages of 8 and 19 months of age who are entering their second RSV season.[2,7,8] However, given the duration of protection provided by nirsevimab, children who are given nirsevimab at 19 months of age would be expected to be protected through 24 months of age. Additionally, ACIP voted to include nirsevimab in the Vaccines for Children (VFC) program, which will ensure access to children without health insurance. ACIP also recommended nirsevimab be added to the childhood immunization schedule.[7,8] Palivizumab is not on the ACIP childhood immunization schedule.

On August 15, 2023, the American Academy of Pediatrics (AAP) published a guidance statement on the use of nirsevimab. Recommendations addressed include eligible patient populations, timing of administration, choice of nirsevimab versus palivizumab, and co-administration of childhood vaccines. The recommended patient populations provided by AAP coincide with those recommended by ACIP (ie, infants < 8 months of age at the start of RSV season

and infants 8 to 19 months of age before the start of RSV season who are at increased risk of severe RSV disease). However, there are some points to note within the specific language behind the AAP recommendations. AAP clarifies that healthy infants born at the end of their first RSV season who did not receive nirsevimab and are < 8 months of age entering their second RSV season may receive 1 dose of nirsevimab. Additionally, there are some differences in the populations specifically identified as being high risk compared with the high-risk populations defined in the AAP 2014 guidelines for palivizumab. Risk factors identified in the AAP 2023 guidance statement for the use of nirsevimab in patients 8 to 19 months of age match those identified by ACIP and include children with CLD of prematurity who require medical support, children who are severely immunocompromised, children with cystic fibrosis who have manifestations of severe lung disease, and American Indian and Alaska Native children. Notable differences from risk factors identified in palivizumab guidance from AAP 2014 include a lack of mention of children with CHD (risk factor for children < 12 months of age in AAP 2014), lack of mention of children with anatomic pulmonary abnormalities or neuromuscular disorder that impairs their ability to clear airway secretions (risk factor for children < 12 months of age in AAP 2014), inclusion of cystic fibrosis (previously, AAP 2014 guidelines noted there was insufficient evidence in this population), and a specific recommendation for use in Alaska Native and American Indian children (previous language in AAP 2014 guidelines was in regard to consideration for use in this population versus a recommendation).[9-11] In the case of children with CHD or anatomic pulmonary abnormalities or neuromuscular disorders, these children would presumably be covered during the first year of life based on the recommendations to provide nirsevimab to all infants < 8 months of age, which may be why these are not specifically mentioned in the latest AAP guidance for nirsevimab.

3. Who is recommended to receive the maternal RSV vaccine?

- **Pregnant people during 32 through 36 weeks gestation (during September through January for the continental US)**

On September 22, 2023, ACIP met to vote on the use of the maternal RSV vaccine.[12] These recommendations are available on the Centers for Disease Control and Prevention website, but have not yet been published in *MMWR* as of October 2, 2023. ACIP recommended that the maternal vaccine be offered to pregnant people 32 through 36 weeks gestation, with seasonal administration, which encompasses September through January for most of the continental US. Jurisdictions with seasonality that differs from the continental US (eg. Alaska, tropical climates) should follow state, local, or territorial guidance for the timing of administration. The maternal RSV vaccine may be administered simultaneously with other indicated vaccinations.

4. Should both nirsevimab and the maternal RSV vaccine be used together?

- ***Either* nirsevimab or the maternal RSV vaccine are recommended to prevent RSV LRTD. The use of both products is not recommended for most infants.**

ACIP recommends that either the maternal RSV vaccination or nirsevimab be used to prevent RSV LRTD, but the administration of both products is not needed for most infants. Healthcare providers should provide information on both products to patients and consider patient-specific factors and preferences. In rare situations, nirsevimab may be clinically warranted for infants born to vaccinated mothers. This includes conditions in which pregnant individuals are expected to mount an inadequate immune response to the vaccine or have decreased placental antibody transfer, infants who have undergone cardiopulmonary bypass leading to the loss of maternal antibodies, and infants with sufficiently increased risk for severe RSV disease. It is expected that at least 14 days following maternal RSV vaccination is needed for development and transplacental transfer of maternal antibodies to protect the infant. Therefore, nirsevimab is recommended for infants born within 14 days of vaccination. Additionally, given the recommendation for administration of the maternal RSV vaccine at 32 through 36 weeks gestation, the earliest an infant can be born and have maternal vaccine-induced protection is at 34 weeks gestation. Due to the seasonality based recommended for the maternal RSV vaccine (ie, administration is only recommended during September through January in the continental US), infants born outside of RSV season (ie, born during April through September) will not have been born to vaccinated mothers and are recommended to receive nirsevimab.

5. Is palivizumab still recommended?

In a 2023 guidance statement, AAP seemingly provides a preferential recommendation for the use of nirsevimab over palivizumab. Per AAP, if nirsevimab is not available or not feasible to administer, high-risk infants who are recommended to receive palivizumab in the first or second year of life should receive palivizumab, as previously

recommended, until nirsevimab becomes available. If palivizumab is administered initially, but < 5 doses have been administered, the infant should receive 1 dose of nirsevimab, and no further palivizumab should be given. Additionally, if a child previously received palivizumab and is eligible for RSV prophylaxis in season 2, AAP recommends that the child receive nirsevimab instead of palivizumab.[11] The latest AAP guidelines on palivizumab were published in 2014 and recently reaffirmed in 2023. AAP 2014 guidelines outline specific, high-risk populations in whom palivizumab is recommended. These groups include premature infants (< 29 weeks GA), children with CLD, children with CHD, children with anatomic pulmonary abnormalities or neuromuscular disorder that impairs their ability to clear airway secretions, and children who are profoundly immunocompromised. Most of these recommendations are limited to patients within these risk groups who are < 12 months of age at the onset of RSV season. Patients with CLD who continue to require medical support and patients who are immunocompromised are also recommended to receive palivizumab up to 24 months of age. AAP also notes that special consideration may be prudent when assessing eligibility for prophylaxis in infants who are Alaska Natives or American Indian.[9,10]

6. What efficacy data support the use of nirsevimab?

FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) met on June 8, 2023, and voted unanimously (21-0) in favor of the efficacy of nirsevimab.[13] Data from 3 pivotal trials were reviewed by the Committee and included a phase 2b study in preterm infants born at ≥ 29 to < 35 weeks gestational age (GA); the phase 3 MELODY trial in predominantly healthy, late preterm and normal term infants born at ≥ 35 weeks GA; and the phase 2/3 MEDLEY trial, which was a head-to-head comparison with palivizumab in premature infants and infants with CLD or CHD.[14] The efficacy results of these studies are discussed below and summarized in Table 2. Available data indicate the duration of protection with nirsevimab extends through 5 months.[2]

Phase 2b study (Trial 03; NCT02878330):[15] This was randomized, double-blind, multicenter, placebo-controlled trial in 1,453 preterm infants born at ≥ 29 weeks to < 35 weeks GA who were ≤ 1 year of age entering their first full RSV season. Infants were randomized 2:1 to receive a single IM injection of nirsevimab (n = 969) or placebo (n = 484) prior to the start of an RSV season. Participants were excluded from the trial if they met AAP guideline criteria for receiving prophylaxis with palivizumab. As discussed above, the cut-off for RSV prophylaxis in preterm infants for palivizumab prophylaxis defined by AAP is < 29 weeks GA.[5] Participants who were immunosuppressed, had CHD or BPD, or other significant medical conditions were also excluded. Additionally, prior receipt of palivizumab or an investigational maternal RSV vaccine were also exclusion criteria. The primary end point was medically attended (ie, inpatient or outpatient care – this includes physician visits, urgent care, emergency room visits, and hospitalizations) RSV-associated LRTI (MA RSV LRTI) through 150 days after administration of the dose. MA RSV LRTI is considered a clinically meaningful endpoint by FDA.[14] The key secondary efficacy end point was hospitalization for RSV-associated LRTI through 150 days after administration of the dose. The definition for LRTI was met if an RSV test performed at the centralized study laboratory was positive, a physical examination indicated involvement of the lower respiratory tract (ie, presence of rhonchi, rales, crackles, or wheezing), and there was ≥ 1 indicator of clinical severity (ie, increased respiratory rate, hypoxemia in room air, or clinical signs of respiratory distress). Efficacy analyses were performed in the intention-to-treat (ITT) population, and the study had > 99% power to detect a 70% relative risk reduction for the primary endpoint at a 2-sided significance level of 0.05, assuming an 8% event rate in the placebo group. Hierarchical testing was done to control for type 1 error related to multiplicity. MA RSV LRTI occurred in 2.6% (n = 25) of infants in the nirsevimab group and 9.5% (n = 46) of infants in the placebo group (relative risk reduction [RRR]: 70.1%; 95% confidence interval [CI], 52.3-81.2%; $P < .001$). This corresponds to an absolute risk reduction (ARR) of 6.9% and a number-needed-to-treat (NNT) of approximately 15. Hospitalization for RSV-associated LRTI occurred in 0.8% (n = 8) of infants in the nirsevimab group and 4.1% (n = 20) of infants in the placebo group (RRR: 78.4%; 95% CI, 51.9-90.3%; $P < .001$). The estimated ARR and NNT for hospitalization are 3.3% and 31, respectively. Efficacy for both MA RSV LRTI (HR: 0.26, 95% CI, 0.16-0.43) and hospitalization (HR: 0.19; 95% CI, 0.08-0.44) were maintained over the entire 150-day efficacy period. No RSV-associated deaths occurred in either study group.

Phase 3 MELODY (Trial 04; NCT03979313):[16] This was randomized, double-blind, multicenter, international, placebo-controlled trial in 1,490 predominantly healthy, late preterm and normal term infants born at ≥ 35 weeks GA who were ≤ 1 year of age entering their first full RSV season. The majority of infants (~86%) were born at ≥ 37 weeks GA. Infants were randomized 2:1 to receive a single IM injection of nirsevimab (n = 994) or placebo (n = 496) prior to the start of an RSV season. Most infants (~58%) were administered study drug at ≤ 3 months of age. This is notable given that the risk of severe RSV infection is highest in the first few months of life. Participants were excluded from the

trial if they met AAP guideline criteria for receiving prophylaxis with palivizumab (eg, immunosuppressed, CHD, BPD, or other significant medical condition). Additionally, prior receipt of palivizumab or an investigational RSV vaccine were also exclusion criteria. The primary end point was MA RSV LRTI through 150 days after administration of the dose. The key secondary efficacy end point was hospitalization for RSV-associated LRTI through 150 days after administration of the dose. Endpoint definitions in this study were consistent with those used in the phase 2b study (Trial 03). Efficacy analyses were performed in the ITT population, and the study had > 99% power to detect a 70% relative risk reduction for the primary endpoint at a 2-sided significant level of 0.05, assuming an 8% event rate in the placebo group. Hierarchical testing was done to control for type 1 error related to multiplicity. MA RSV LRTI occurred in 1.2% (n = 12) of infants in the nirsevimab group and 5% (n = 25) of infants in the placebo group (RRR: 74.5%; 95% CI, 49.6-87.1%; *P* < .001). This corresponds to an ARR of 3.8% and a NNT of approximately 27. Efficacy for MA LRTI (HR: 0.23, 95% CI, 0.12-0.47) was maintained over the entire 150-day efficacy period. In a subgroup analysis by GA, the point estimate for prevention of RSV LRTI appeared to be higher for infants born between ≥ 35 weeks to < 37 weeks compared with ≥ 37 weeks; however, formal hypothesis testing for this analysis was not conducted. Additionally, descriptive data reported for clinical signs of RSV LRTI do not seem to demonstrate a reduction in severity of illness between nirsevimab and placebo in cases of documented RSV LRTI. For example, a larger proportion of patients with RSV LRTI who received nirsevimab (5/12; 42%) experienced hypoxemia compared with placebo (7/25; 28%). However, the number of events is low and no formal testing was conducted for these data; therefore, no conclusions can be made with regard to attenuation of illness in those infants who developed RSV LRTI. The secondary efficacy endpoint of hospitalization for RSV-associated LRTI was not significantly different between groups. Hospitalization occurred in 0.6% (n = 6) of infants in the nirsevimab group and 1.6% (n = 8) of infants in the placebo group (RRR: 62.1%; 95% CI, -8.6-86.8%; *P* = NS). While hospitalization events were low, the mean (SD) number of hospitalized days was numerically higher with nirsevimab (7.2 [4.6]) compared with placebo (4 [2.2]) in infants hospitalized due to RSV LRTI. These data are descriptive in nature and no formal conclusions may be drawn. No RSV-associated deaths occurred in either study group.

Phase 2/3 MEDLEY (Trial 05; NCT03959488):[2,14,17,18] This was a randomized, double-blind, multicenter, active-controlled trial in 925 infants at increased risk for severe RSV disease. This study is currently not published. Information discussed here comes from product labeling, ClincalTrials.gov, a letter to the editor, including a supplementary appendix, discussing high level results of Trial 05, and manufacturer data presented at the June 2023 VRBPAC meeting. Trial 05 was separated into 2 cohorts: infants with CHD or CLD (n = 310) and preterm infants ≤ 35 weeks GA (n = 615). Infants were randomized 2:1 to receive nirsevimab or palivizumab prior to RSV season 1. Infants in the CHD-CLD cohort received additional RSV prophylaxis for a second RSV season. Infants who were initially randomized to nirsevimab continued nirsevimab for RSV season 2. Infants who were initially randomized to palivizumab in season 1 received either nirsevimab or continued with palivizumab in RSV season 2. The primary endpoint of this trial was focused on safety. Efficacy analysis was descriptive and included an evaluation of MA RSV LRTI for RSV season 1 and RSV season 2. In RSV season 1, MA RSV LRTI through day 150 occurred in 0.6% (n = 4) of infants who received nirsevimab and 1% (n = 3) of infants who received palivizumab across the total study population. Results for the individual cohort groups were not reported. No infants in either nirsevimab or palivizumab groups for the total study population experienced a MA RSV LRTI in RSV season 2. RSV-associated hospitalizations are listed as another secondary efficacy outcome on ClincalTrials.gov; however, data for this outcome are not currently available. Data from Trial 03 and Trial 04 (MELODY) were used to extrapolate nirsevimab efficacy in Trial 05. Based on an exposure-response analysis in Trial 03 and Trial 04, a target AUC baseline clearance of 12.8 mg*day/mL was identified. In Trial 05, 93.6% of infants in the preterm cohort who received nirsevimab met this threshold. In the CHD-CLD cohort, 94.1% of infants with CLD and 80.3% of infants with CHD met this threshold. No RSV-associated deaths occurred in either study group.

Table 2. Summary of efficacy endpoints for pivotal nirsevimab trials[2, 14-18]

	Phase 2b (Trial 03)	Phase 3 MELODY (Trial 04)	Phase 2/3 MEDLEY (Trial 05)
N	1,453	1,490	925
Population	Preterm infants born at ≥ 29 weeks to < 35 weeks GA	Predominantly healthy, late preterm and normal term infants born at ≥ 35 weeks GA	Premature infants ≤ 35 weeks GA and infants with CHD or CLD
Comparator	Placebo	Placebo	Palivizumab
Primary endpoint	**MA RSV LRTI**	**MA RSV LRTI**	**Safety**
RRR	70.1%; 95% CI, 52.3-81.2%; *P* < .001	74.5%; 95% CI, 49.6-87.1%; *P* < .001	--
ARR (estimated)	6.9%	3.8%	--
NNT (estimated)	15	27	--
Secondary endpoint	**RSV-associated hospitalization through day 150**	**RSV-associated hospitalization through day 150**	**MA RSV LRTI (descriptive)**
RRR	78.4%; 95% CI, 51.9-90.3%; *P* < .001	62.1%; 95% CI, -8.6-86.8%; *P* = NS	RSV season 1: MA RSV LRTI occurred in 0.6% (n = 4) of infants who received nirsevimab and 1% (n = 3) palivizumab RSV season 2: No cases of MA RSV LRTI occurred in patients who received nirsevimab or palivizumab
ARR (estimated)	3.3%	NA[a]	NA[a]
NNT (estimated)	31	NA[a]	NA[a]

Abbreviations: ARR = absolute risk reduction; CHD = congenital heart disease; CI = confidence interval; CLD = chronic lung disease; GA = gestational age; MA RSV LRTI = medically attended RSV lower respiratory tract infection; NA = not applicable; NS = not statistically significant; NNT = number-needed-to-treat; RRR = relative risk reduction; RSV = respiratory syncytial virus

[a] ARR and NNT not calculated for results that are not statistically significant or descriptive.

7. What efficacy data support the use of the maternal RSV vaccine?

On May 18, 2023, the FDA's VRBPAC met to consider the efficacy and safety of immunization with Abrysvo during the second or third trimester of pregnancy, to prevent RSV LRTD and severe RSV LRTD in infants from birth through 6 months of age. All 14 panelists voted that the totality of data, including data from the phase 3 trial MATISSE, supported the vaccine's effectiveness.[19] The MATISSE trial[20] was a randomized, double-blind, placebo-controlled trial, conducted in 18 countries over 4 RSV seasons during the COVID-19 pandemic, that enrolled over 7,300 maternal participants. The results for the primary efficacy endpoints in the MATISSE trial are summarized in Table 3. The 2 primary efficacy endpoints were severe MA RSV LRTI and MA RSV LRTI in infants within 90, 120, 150, and 180 days after birth. A lower boundary of the confidence interval for vaccine efficacy (99.5% CI at 90 days; 97.58% CI at later intervals) greater than 20% was considered to meet the success criterion for vaccine efficacy with respect to the primary endpoints. The definition for MA RSV LRTI was similar to what was used in the nirsevimab trials. Severe MA RSV LRTI included MA RSV LRTI in addition to ≥ 1 of the following: elevated respiratory rate, decreased oxygen saturation, requirement for high-flow nasal cannula or mechanical ventilation, intensive care unit admission for > 4 hours, or a failure to respond or unconsciousness. The trial was stopped early after a second interim analysis when the success criterion was met for 1 of the 2 primary endpoints. Severe MA RSV LRTI at 90 days occurred in 0.2% (n = 6) of infants in the vaccine group compared with 0.9% (n = 33) of infants in the placebo group (RRR: 81.8%; 99.5% CI, 40.6-96.3%). This corresponds to an estimated ARR of 0.7% and an approximate NNT of 143. The difference in severe MA RSV LRTI remained significant through 180 days following birth. The lower boundary of the CI for the

other primary endpoint, MA RSV LRTI at 90 days, did not exceed the success criterion threshold. However, starting at 120 days after birth, and continuing through 180 days, the success criterion was met for this endpoint. Hospitalization rate was evaluated separately but was low overall in both vaccine and placebo groups, which creates uncertainty in the effect size. The vaccine point estimate for hospitalization was > 50% for up to 180 days after birth; however, the lower boundary of the confidence intervals was below 20% at all time points and the range of the true effect sizes against hospitalization was large at each assessed time interval with the lower limit of efficacy as low at 5.2% at 150 days after birth. The vaccine had a null effect against all-cause MA LRTI within 90 to 360 days after birth. Its effect may have been attenuated by COVID-19 pandemic-related changes in RSV occurrence and seasonality. During the trial, RSV accounted for just 22% of the all-cause MA LRTIs. One death considered to be associated with RSV infection occurred in the placebo group 120 days after birth.

Table 3. Summary of primary efficacy endpoints for maternal RSV vaccine[20]

	MATISSE trial results			
N	6,975			
Population	Infants born to mothers administered RSV vaccine or placebo at 24 through 36 weeks gestation			
MA severe RSV LRTI	**90 days after birth**	**120 days after birth**	**150 days after birth**	**180 days after birth**
RRR	81.8%; 99.5% CI, 40.6-96.3%	73.9%; 97.58% CI, 45.6-88.8%	70.9%; 97.58% CI, 44.4-85.9%	69.4%; 97.58% CI, 44.3-84.1%
ARR (estimated)	0.7%	1%	1.1%	1.3%
NNT (estimated)	143	100	91	77
MA RSV LRTI	**90 days after birth**	**120 days after birth**	**150 days after birth**	**180 days after birth**
RRR	57.1%; 99.5% CI, 14.7-79.8%	56.8; 97.58% CI, 31.2-73.5%	52.5%; 97.58% CI, 28.7-68.9%	51.3%; 97.58% CI, 29.4-66.8%
ARR (estimated)	NA[a]	1.3%	1.5%	1.8%
NNT (estimated)	NA[a]	77	67	56

Abbreviations: ARR = absolute risk reduction; CI = confidence interval; MA RSV LRTI = medically attended RSV lower respiratory tract infection; NA = not applicable; NNT = number-needed-to-treat; RRR = relative risk reduction; RSV = respiratory syncytial virus

[a] ARR and NNT not calculated for results that did not meet the success criterion of exceeding the lower boundary of the CI by ≥ 20%

8. Are there safety concerns with nirsevimab?

Overall, nirsevimab appears to be safe and well tolerated across clinical studies. No cases of anaphylaxis have occurred in the clinical studies presented above.[14] The rates of adverse events and event rates, including serious adverse events, between nirsevimab and placebo were similar in the phase 2b study (Trial 03) and MELODY (Trial 04). No serious adverse event in either study was considered related to study drug.[15,16] Safety was the primary endpoint in the MELEDY study (Trial 05), which compared nirsevimab with palivizumab. The incidence of adverse reactions, including serious adverse reactions was similar across treatment groups and cohorts. Treatment-related adverse events were reported in 1.5% (n = 6) infants who received nirsevimab and 1.9% (n = 1) infants who received palivizumab. No cases of serious adverse reactions were attributed to study drug.[17] The most common adverse reactions reported in product labeling for nirsevimab are rash (0.9%) and injection-site reactions (0.3%).[2] FDA's VRBPAC voted 19-2 in support of nirsevimab's safety.[13] The Committee raised hypersensitivity reactions and an imbalance of deaths in trials with nirsevimab as key safety considerations. While no cases of anaphylaxis occurred in trials with nirsevimab, these reactions have been reported with palivizumab and other monoclonal antibodies. Therefore, postmarketing reports will be needed to further evaluate this potential with nirsevimab. Across clinical studies reviewed by the Committee, there were 12 deaths (0.32%) in infants who received nirsevimab compared with 4 deaths (0.22%) in infants who received control (placebo or palivizumab). While the absolute number of deaths with nirsevimab was higher than control arms, the percentage of deaths was low and similar between groups. Additionally, none of the deaths were attributed to study drug in either group.[14]

9. Are there safety concerns with the maternal RSV vaccine?

The most commonly reported solicited local and systemic adverse reactions in pregnant individuals were pain at the injection site (40.6%), headache (31.0%), muscle pain (26.5%), and nausea (20%).[5] FDA's VRBPAC voted 10-4 in favor of the maternal RSV vaccine regarding the question of whether Pfizer's data were adequate to demonstrate safety. VRBPAC members expressed concern over a numeric imbalance in the occurrence of late preterm births (≤ 37 weeks of gestation) in the vaccine arm (5.7% vs. 4.7% for placebo). This imbalance was also observed in the Abrysvo phase 2 trial and in the suspended clinical trial program of GlaxoSmithKline's RSV vaccine candidate. Abrysvo was associated with an increased occurrence of low birth weight (5.1% vs. 4.4% for placebo), but not for infant mortality. The MATISSE trial enrolled low-risk participants; therefore, the 5.2% rate of prematurity in the trial was lower than the US background rate of approximately 10% and not enough participants were studied to determine if prematurity was a safety signal or a statistical anomaly.[19] With enrollment stopped at the second interim analysis, postmarketing studies will be necessary to determine if prematurity is a safety signal. Due to this potential concern, FDA-approved Abrysvo for use in pregnant individuals 32 through 36 weeks gestation, which is narrower than the population studied in the MATISSE trial (ie, 24 through 36 weeks gestation).

10. Will the nirsevimab and the maternal RSV vaccine be covered by insurance?

Both nirsevimab and the maternal RSV vaccine will be added to the ACIP immunization schedules. ACIP-recommended products considered preventive care are required to be covered by private insurance plans based on the Affordable Care Act. Nirsevimab will also be included in the VFC, providing access to uninsured patients at no cost. The maternal RSV vaccine will also be available via the VFC for pregnant individuals < 19 years of age who are uninsured.[21,22]

11. How much do these products cost?

The costs of the different RSV immunization strategies are summarized in Table 4.

Table 4. Wholesale acquisition cost RSV immunization strategies[23]

Generic (brand)	Recommended dose	Wholesale acquisition cost	Typical number of recommended doses per RSV season
Palivizumab (Synagis)	15 mg/kg body weight	• **50 mg vial:** $1,821 • **100 mg vial**: $3,438	5
Nirsevimab (Beyfortus)	**Neonates and infants – first RSV season:** • < 5 kg: 50 mg • ≥ 5 kg: 100 mg **Children at risk for severe RSV disease – second RSV season:** • 200 mg (2 x 100 mg)	• **50 mg pre-filled syringe**: $495 • **100 mg pre-filled syringe:** $495 (200 mg dose will be $990 – 2 x 100 mg syringes)	1
Respiratory syncytial virus vaccine (Abrysvo)	0.5 mL	**Single dose vial:** $295	1

Abbreviations: RSV = respiratory syncytial virus

12. Are there any operational or logistical considerations with these products?

The following are potential operational and logistical issues that warrant consideration:

- Maternal RSV vaccination status is essential to determine if nirsevimab is indicated. Immunization information systems vary by state for adult immunization capture and may not be able to link to infant immunization records, which may present challenges in verifying maternal vaccination status.[22]

- The available data for the maternal RSV vaccination are predominantly focused on protection of the infant during the first RSV season. There are currently a lack of data regarding efficacy of the vaccine for subsequent pregnancies. Additional data and guidance are needed.
- Documentation of nirsevimab administration within immunization records in electronic health records may present a challenge, given that nirsevimab is not a vaccine.[21]
- Billing issues with nirsevimab administration may occur given that it is classified as a drug or therapeutic per its CPT code, but will be administered as an immunization.[21]
- Differences in scope of practice regulations related to who is allowed to administer nirsevimab should also be considered since it is not a traditional vaccine. Most states allow medical assistants to also deliver injectable drugs; however, this will be important to verify before implementing this into practice. Organizations may also have different policies in place around medication administration that may need to be considered.[21]
- Ambulatory practices will need to carry both VFC and private stock of eligible products, similar to other VFC vaccines, which may be challenging from an inventory management standpoint.[21]
- Health systems will need to determine how they will decide between inpatient and outpatient administration of nirsevimab. It is likely that administration in both settings will need to be available depending on timing, patient characteristics, and other factors. Per AAP 2023 guidance, nirsevimab should be administered within the first week of life to infants born shortly before or during the RSV season. AAP states that this may occur during the birth hospitalization or in the outpatient setting.[11] If deferred to the outpatient setting, coordination of care and confidence in patient follow-up will be essential. Children who require nirsevimab for their second RSV season will likely receive this in the outpatient setting.
- Reporting of suspected adverse effects with nirsevimab will also be more complicated compared with other immunizations. Suspected adverse effects should be reported through MedWatch when nirsevimab is administered alone. However, if nirsevimab is given concomitantly with any vaccine, suspected adverse effects should be reported through the Vaccine Adverse Event Reporting System (VAERS); an additional report to MedWatch is not needed.[21]

13. Does Vizient have any additional resources for RSV prevention strategies?

Vizient has the following additional resources available:

- Monoclonal antibodies for prevention of RSV LRTD in pediatric patients side-by-side comparison
- RSV vaccines in adults side-by-side comparison

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