National Perinatal Association 2024 Respiratory Syncytial Virus (RSV) Prevention Clinical Practice Guideline: Clinical Presentation, Prevention Strategies, and Social Impacts in Children: An Evidence-Based Interdisciplinary Collaboration

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The National Perinatal Association (NPA) is an interdisciplinary organization that strives to be a leading voice for perinatal care in the United States. Our diverse membership is comprised of healthcare providers, parents & caregivers, educators, and service providers, all driven by their desire to give voice to and support babies and families at risk across the country.

Members of the NPA write a regular peer-reviewed column in Neonatology Today.

National Perinatal Association

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Introduction:

Respiratory syncytial virus (RSV) causes a spectrum of respiratory illnesses in infants and young children. It is the leading cause of lower respiratory tract infections (LRTI) in newborns in the first five years of life and is especially concerning in the first year of life. (1-4) RSV can lead to hospitalizations, with the most common admitting diagnosis of bronchiolitis, pneumonia, and septicemia. (3, 5) There is an increased risk of severe lower respiratory tract RSV in infants born prematurely, with hemodynamically significant congenital heart disease, bronchopulmonary dysplasia, neuromuscular disease, congenital and inherited airway anomalies, immunosuppression, and male sex. (2, 6) However, most hospitalizations happen to otherwise healthy infants. (3) Upon admission, the median age was three months, and the median length of stay was three days (5). RSV is associated with adverse long-term outcomes, such as asthma, excess morbidity, and reduced quality of life (2, 5). RSV is a global illness considered a global health priority; in 2019, a meta-analysis estimated that RSV was associated with 33 million acute lower respiratory tract infections and 3-6 million hospitalizations for acute lower respiratory tract infection annually. (1, 3)

"Respiratory syncytial virus (RSV) causes a spectrum of respiratory illnesses in infants and young children. It is the leading cause of lower respiratory tract infections (LRTI) in newborns in the first five years of life and is especially concerning in the first year of life. (1-4) RSV can lead to hospitalizations, with the most common admitting diagnosis of bronchiolitis, pneumonia, and septicemia. (3, 5)"

RSV has traditionally been a seasonal disease observed primarily in winter; however, multiple countries reported out-of-season RSV resurgences. (1, 2) During the winter of 2020-2021, at the height of the COVID-19 pandemic, non-pharmaceutical interventions, such as hand hygiene and social distancing, slowed the spread of RSV. (1) These non-pharmaceutical interventions decreased population immunity due to a prolonged period of minimal RSV exposure (1). RSV is now appearing year-round, with spikes in spring, summer, and fall. (1)

"Current prevention strategies include hygiene, breastfeeding, maternal immunizations, and immunization with either Nirsevimab-alip (BEYFORTUS) or palivizumab (SYNAGIS), monoclonal antibodies (mAb). (2, 3) Before 2023, palivizumab (SYNAGIS) was the only mAb available and had been indicated for only for preterm infants and infants with co-morbidities, which left most of the infant population unprotected. (4)"

Prevention remains the most effective strategy to decrease RSV-related morbidity and mortality. Current prevention strategies include hygiene, breastfeeding, maternal immunizations, and immunization with either Nirsevimab-alip (BEYFORTUS) or palivizumab (SYNAGIS), monoclonal antibodies (mAb). (2, 3) Before 2023, palivizumab (SYNAGIS) was the only mAb available and had been indicated for only for preterm infants and infants with co-morbidities, which left most of the infant population unprotected. (4)

However, new RSV prevention strategies have been developed (2, 7-9). Thirty-one RSV prevention treatments are in clinical development, with seven preventative therapies in phase 3 clinical trials, focusing on the methods of recombinant vector, subunit, particle-based, live attenuated, chimeric, and nucleic acid vaccines,

and monoclonal antibodies. (7) Vaccine development has encountered numerous challenges, primarily the immaturity of the infant's immune system (3). With these challenges, there are new treatment strategies that are now FDA-approved, including maternal RSVpreF (ABRYSVO) and infant immunization with a long-acting nirsevimab-alip (BEYFORTUS). (3)

Nirsevimab-alip (BEYFORTUS) is a long-acting intramuscular recombinant neutralizing human IgG mAb against the RSV F protein (8, 9). The extended half-life allows a single dose of Nirsevimab to cover the entire RSV season and can be given to preterm, high-risk, and term infants (8, 9). A single dose of Nirsevimab protected hospitalizations throughout the RSV season in 74.5-78.6% (10). nirsevimab-alip (BEYFORTUS) protects against RSV subtypes A and B, lower respiratory tract infection, and hospitalization due to lower respiratory tract infection (10). nirsevimab-alip (BEYFORTUS) adverse events were on par with placebo at 1.3% and 1.5%, respectively (10). Even with the recent approval of nirsevimab-alip (BEYFORTUS), there remains a need for an RSV vaccine and additional treatment options.

RSVpreF (ABRYSVO) is a vaccine for pregnant individuals between 32 and 36 weeks of pregnancy to prevent respiratory syncytial virus (RSV) related lower respiratory tract disease (LRTD) in infants up to six months old. If timed correctly, it may provide similar protection to infants as nirsevimab-alip (BEYFORTUS). (11, 12)

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Even with new preventative treatment options, there are still significant disparities in medical treatment depending on race, ethnicity, and socioeconomic status. Twice as many children from racial/ethnic diverse minorities are admitted to the hospital with RSV infections when compared to all other admissions during the same year (5). Infants less than a year from a low socioeconomic status accounted for the most significant proportion of RSV-related respiratory hospitalizations (13, 14). RSV causes a considerable burden in young children, varying socioeconomic groups (14). The financial burden caused by RSV affects both the individual and the hospital system. Under current standards of care, RSV causes hospitalizations to cost $1.2 billion annually (2021 USD) (15). Implementing universal immunization with nirsevimab-alip (BEYFORTUS) may reduce costs by up to $612 million (15). It is crucial to understand the burden of hospitalizations and disparities between population groups, and there is a need for systemic analysis of the impacts of RSV on minority groups as well as those affected by disparity. Interestingly, the impact of the Vaccines for Children Program may create instances where those considered most at risk for disparity are more likely to receive prophylaxis. (16, 17)

The health impacts of RSV go beyond the acute episode phase and represent a burden for healthcare costs and resources. (2, 4, 6) Interventions should reduce RSV infection's effects through health education, information, monitoring of population immunity, and prevention in high-risk populations. (1, 6) One of the key concerns is that healthcare decision-makers and systems must be capable of taking advantage of upcoming technological advancements in prophylaxis and resources to make sure that at risk individuals have access to these enhancements (4). This can be approached through a multi-stakeholder implementation to cover data gaps and ensure knowledge is available to parents and doctors about prevention options. (4)

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Protecting all infants against RSV is critical by implementing an immunization strategy with Nirsevimab to reduce infants' health and economic burden. (4, 15) Most infants, including high-risk palivizumab (SYNAGIS)-eligible infants, will benefit from nirsevimab-alip (BEYFORTUS) immunization if maternal RSVpreF is not given or timed correctly. (15, 18) Newer immunizations and vaccines may further leverage additional advantages and protections that are even more durable resulting in single dose protection. The need for monthly prophylaxis may be problematic for compliance in some situations.

RSVpreF (ABRYSVO) (maternal vaccination):

RSVpreF (ABRYSVO) is a vaccine with an antigen component containing recombinant RSV preF A and RSV preF B. The RSV preF A and RSV preF B recombinant proteins are lyophilized. After reconstitution, each RSVpreF (ABRYSVO) dose is approximately 0.5 mL. The vaccine is formulated to contain 120 mcg of RSV stabilized prefusion F proteins (60 mcg RSV preF A and 60 mcg RSV preF B) per 0.5 mL. (11)

RSVpreF (ABRYSVO) is a vaccine for pregnant individuals between 32 and 36 weeks. It can prevent respiratory syncytial virus (RSV) related lower respiratory tract disease (LRTD) in infants up to six months old. Individuals aged 60 may also be given this vaccine to prevent RSV-related LRTD. Despite other risk factors, This vaccine is not FDA-approved for anyone other than pregnant individuals and those 60 years or older. Notably, it has not been studied in patients under age ten, and there may

not be adequate data to ascertain safety in very young pregnant individuals. (11)

"Two clinical studies found more preterm births in those pregnant individuals receiving RSVpreF (ABRYSVO) compared to placebo. However, there was not enough statistical strength to this finding to categorically link ABRYSVO to preterm birth. RSVpreF (ABRYSVO) should only be given to pregnant individuals between 32 and 36 weeks gestation to minimize the risk of preterm birth at still earlier gestations."

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In the first study, 5.7% of the ABRYSVO group (202 out of 3,568) had preterm births versus 4.7% in the placebo group (169 out of 3,558). In the second, 5.3% of RSVpreF (ABRYSVO) recipients (6 out of 114) had preterm births, while 2.6% of placebo recipients (3 out of 116) did. Some prematurely born infants required hospital care within 30 days after birth, with 83 in the RSVpreF (ABRYSVO) group and 80 in the placebo group. Based on the available data, it is uncertain if RSVpreF (ABRYSVO) directly causes preterm birth.

A similar trend with an increase in the rate of prematurity was seen among infants born to participants vaccinated between 32 and 36 weeks of gestation, with 4.2% in the RSVpreF (ABRYSVO) group (68 out of 1,631) and 3.7% in the placebo group (59 out of 1,610). RSVpreF (ABRYSVO) has not been studied in pregnant individuals under 24 weeks gestational age or those at increased risk for preterm birth. (11)

Within the first month of life, 37.1% of infants whose mothers received RSVpreF (ABRYSVO) experienced adverse events, compared to 34.5% of those whose mothers received a placebo. Higher delivery rates were at a low birth weight (5.1% in the RSVpreF (ABRYSVO) group versus 4.4% in the placebo group). Congenital abnormalities occurred in 5.0% of the RSVpreF (ABRYSVO) group and 6.2% in the placebo group. Neonatal jaundice was observed in 7.2% of the RSVpreF (ABRYSVO) group and 6.7% of the placebo group. (11)

Severe adverse reactions were observed in pregnant individuals at a higher rate in the RSVpreF (ABRYSVO) group compared to the placebo group, including preeclampsia (1.8% versus 1.4%) and gestational hypertension (1.1% versus 1.0%). Both may contribute to a higher rate of preterm birth. (11)

Concerning safety data, there were ten fetal deaths (0.3%) in the RSVpreF (ABRYSVO) group and eight (0.2%) in the placebo group. Regarding mortality during the neonatal period for babies born to pregnant individuals, there were two deaths in the RSVpreF (ABRYSVO) group and five in the placebo group. There were five deaths in the RSVpreF (ABRYSVO) group and 12 in the placebo group, looking at overall mortality, including deaths beyond the neonatal period.

"The presence of RSVpreF (ABRYSVO) in human milk has not been studied adequately, and there is no data on how it may affect breastfed infants or milk production. Should a pregnant individual need RSVpreF (ABRYSVO), weighing the benefits of breastfeeding for the infant's development (i.e., the result of a previous pregnancy) and health against any potential risks from the vaccine or the pregnant individual's condition is crucial."

Among the infants born to individuals in the RSVpreF (ABRYSVO) group and the placebo group, 202 (5.7%) and 169 (4.7%), respectively, were delivered prematurely. 180 (5.0%) and 220 (6.2%) had congenital malformations or anomalies, respectively. 10 (0.3%) fetal deaths occurred in the RSVpreF (ABRYSVO) group and 8 (0.2%) in the placebo group. (11)

The presence of RSVpreF (ABRYSVO) in human milk has not been studied adequately, and there is no data on how it may affect breastfed infants or milk production. Should a pregnant individual need RSVpreF (ABRYSVO), weighing the benefits of breastfeeding for the infant's development (i.e., the result of a previous pregnancy) and health against any potential risks from the vaccine or the pregnant individual's condition is crucial. No data suggests a significant increased risk to the infant following breastfeeding.

A trial assessed the effectiveness of RSVpreF (ABRYSVO) in preventing RSV-related lower respiratory tract disease (LRTD) in

babies born to individuals who were vaccinated during pregnancy. The study measured how well RSVpreF (ABRYSVO) prevented severe RSV-associated LRTD in infants after birth. Participants were randomly assigned to receive RSVpreF (ABRYSVO) or a placebo, and this study included sites worldwide. Vaccine efficacy (VE) gauged the risk reduction of severe LRTD caused by RSV and LRTD caused by RSV in infants born to vaccinated individuals compared to those born to individuals who received a placebo. Maternal participants were also randomly divided into those who received RSVpreF (ABRYSVO) and those who received a placebo. RSV-associated LRTD in infants was diagnosed through a medical visit with confirmed RSV illness using specific respiratory symptoms. Severe RSV-associated LRTD identified those with more severe symptoms. Hospitalizations due to RSV were also tabulated. (19)

A medically attended visit with an RT-PCR (reverse transcription-polymerase chain reaction) confirmed RSV with one or more of the following tachypnea: respiratory rate ≥60 breaths/minute, ≥50 breaths/minute, ≥ 60 days to 1 year of age, or ≥ 40 breaths/minute ≥12 months to one year of age; SpO2 measured in room air <95%; retractions ("chest wall indrawing") or was defined as a RSV-associated LRTD.

RSV-associated severe LRTD was defined by having tachypnea respiratory rate ≥70 breaths per minute <60 days of age, ≥ 60 breaths per minute ≥ 60 days to one year, or ≥50 bpm ≥ one to two years; SpO2 measured in room air <93%; high-flow nasal cannula (greater than 2 LPM in the younger infants) or mechanical ventilation (invasive or noninvasive), ICU admission for >4 hours or loss of consciousness. Hospitalizations due to RSV were monitored as a secondary endpoint.

"The results showed a statistically significant reduction in severe lower respiratory tract disease in infants under six months of age but did not demonstrate a reduction for non-severe respiratory tract disease; however, clinically efficacy was present after 90 days through 180 days after birth. Moreover, these infants were not hospitalized and may have seen a reduction in disease severity based on maternal vaccination."

The results showed a statistically significant reduction in severe lower respiratory tract disease in infants under six months of age but did not demonstrate a reduction for non-severe respiratory tract disease; however, clinically efficacy was present after 90 days through 180 days after birth. Moreover, these infants were not hospitalized and may have seen a reduction in disease severity based on maternal vaccination. This decreased efficiency in the non-severe respiratory tract disease cohort to 90 days may indicate the need for additional prophylaxis with palivizumab (SYNAGIS) or nirsevimab-alip (BEYFORTUS) during this interval for high-risk individuals. However, no data exists as to the effectiveness or safety of this strategy.

Nirsevimab-alip (BEYFORTUS):

Nirsevimab-alip (BEYFORTUS) is a respiratory syncytial virus F protein-directed fusion inhibitor based on a recombinant human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody. The molecular weight is approximately 146.3 kDa. There is a correlation between a serum nirsevimab-alip (BEYFORTUS) AUC of at least 12.8 mg day/mL and decreased medically attended RSV lower respiratory tract infection (MA RSV LRTI). No formal drug interaction studies with other medications, including RSVpreF or Palivizumab (SYNAGIS), have been studied with nirsevimab-alip (BEYFORTUS). (19)

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The PK of nirsevimab-alip (BEYFORTUS) is dose-proportional and ranges from 25 mg (0.5 times the lowest approved recommended dosage) to 200 mg in the index population. The nirsevimab-alip (BEYFORTUS) serum exposures were similar in those born during or entering the first RSV season and in those born at ≤ 35 weeks (including ≤ 29 weeks GA) in the first RSV season and up to two years in those patients with CLD or CHD in the first and second RSV season. (19)

Nirsevimab-alip (BEYFORTUS) provides passive immunity by targeting the RSV F protein. The triple amino acid substitution (YTE) in the Fc region extends serum half-life. Nirsevimab-alip (BEYFORTUS) binds to antigenic site Ø with dissociation KD = 0.12 nM and KD = 1.22 nM for RSV subtypes A and B, respectively. The F protein, which causes fusion of the viral and cellular membranes and facilitates viral entry, is effectively prevented from causing virulence. Nirsevimab-alip (BEYFORTUS) neutralized clinical RSV isolates collected worldwide between 2003 and 2017 with median EC50 values for RSV A of 21 pM (3.2 ng/mL); and for RSV B, of 19 pM (2.9 ng/mL). (19)

No resistance-associated substitutions occurred at ≥ 25% frequency. Of those who received a single dose of 50 mg Nirsevimab-alip (BEYFORTUS), 5% (2 of 40) of subjects with RSV infections had a variant containing nirsevimab-alip (BEYFORTUS) resistance-associated substitutions. The two subjects each received less than the recommended nirsevimab-alip (BEYFORTUS) dose but had different substitutions. (19)

Some data show that variants resistant to nirsevimab-alip (BEYFORTUS) could have cross-resistance to palivizumab (SYNAGIS). Palivizumab (SYNAGAIS) retained full neutralization potency against resistance-associated substitutions identified in nirsevimab-alip (BEYFORTUS). Nirsevimab-alip (BEYFORTUS) retained activity against recombinant RSV harboring palivizumab (SYNAGIS) resistance-associated substitutions. (19)

" The efficacy of nirsevimab-alip (BEYFORTUS) against MA RSV LRTI with hospitalization in infants of GA > 29 weeks to < 35 weeks, receiving a single dose of 50 mg nirsevimab-alip (BEYFORTUS), based on the relative risk reduction was 78.4% (p=0.0002), through 150 days post-dose. (19)"

A double-blind, placebo-controlled multicenter trial to prevent Medically Attended Respiratory Syncytial Virus Lower Respiratory Tract Infection (MA RSV LRTI) was performed in preterm infants born at gestational age (GA) ≥ 29 weeks and < 35 weeks. All subjects in the nirsevimab-alip (BEYFORTUS) arm received 50 mg IM of nirsevimab-alip (BEYFORTUS) regardless of body weight. The nirsevimab-alip (BEYFORTUS) dose for those during the first RSV season is a single (not monthly) IM 50 mg (< 5 kg) or 100 mg dose (≥ 5 kg, respectively. 20% were GA ≥ 29 weeks and < 32 weeks; 80% were GA ≥ 32 and < 35 weeks. The efficacy of nirsevimab-alip (BEYFORTUS) against MA RSV LRTI with hospitalization in infants of GA ≥ 29 weeks to < 35 weeks, receiving a single dose of 50 mg nirsevimab-alip (BEYFORTUS), based on the relative risk reduction was 78.4% (p=0.0002), through 150 days post-dose. (19)

Nirsevimab-alip (BEYFORTUS) was evaluated in a randomized, double-anonymized, placebo-controlled multicenter trial to prevent MA RSV LRTI in term and late preterm infants GA > 35 weeks into their first RSV season. At randomization, 14% were GA ≥ 35 weeks and < 37 weeks; 86% were GA ≥ 37 weeks. (19)

" Nirsevimab-alip (BEYFORTUS) demonstrated decreased MA RSV LRTI with hospitalization in infants born at > 35 weeks, receiving a single IM 50 mg or 100 mg dose for those < 5 kg and > 5 kg, respectively. The relative risk reduction was 60.2% (p=0.09) up to 150 days post-dose."

Nirsevimab-alip (BEYFORTUS) demonstrated decreased MA RSV LRTI with hospitalization in infants born at ≥ 35 weeks, receiving a single IM 50 mg or 100 mg dose for those < 5 kg and ≥ 5 kg, respectively. The relative risk reduction was 60.2% (p=0.09) up to 150 days post-dose. This group, based on increased gestational age at birth, may have a statistically decreased risk of severe disease. (19)

" There were no MA RSV LRTI through Day 150 post-dose cases in subjects who received either nirsevimab-alip (BEYFORTUS) or palivizumab (SYNAGIS). (19)"

Another study enrolled certain infants at a higher risk for severe RSV disease during the first RSV season: preterm infants (< 35 weeks) and infants with CLD related to prematurity or hemodynamically significant CHD. Other high-risk groups with other anatomical malformations or immunological issues that could place them at higher risk for infection were not studied. Infants were randomized to preterm (n=615) and CLD/CHD (n=310) cohorts to receive nirsevimab-alip (BEYFORTUS) or palivizumab (SYNAGIS). Infants received a single IM dose of nirsevimab-alip (BEYFORTUS) (50 mg if < 5 kg body weight or 100 mg if > 5 kg body weight at the time of dosing), followed by four once-monthly IM doses of placebo or five once-monthly IM doses of 15 mg/kg palivizumab (SYNAGIS), respectively. At randomization, 77 infants (13%) were < 29 weeks GA and 499 (81%) were GA ≥ 29 to < 35 weeks. In the CLD/CHD cohort, 70% had CLD of prematurity; 34% had hemodynamically significant CHD; 123 (40%) were < 29 weeks GA, 28% were ≥ 29 weeks to < 35 weeks GA; and 32% ≥ 35 weeks GA. In the first RSV season, the incidence of MA RSV LRTI through 150 days post-dose was 0.6% (4/616) in the nirsevimab-alip (BEYFORTUS) group and 1.0% (3/309) in the palivizumab (SYNAGIS) group. (19)

"For infants born outside the RSV season, nirsevimab-alip (BEYFORTUS) should be administered once before the RSV season starts, subject to whether the patient's mother received RSVpreF (ABRYSVO) or palivizumab (SYNAGIS), considering the duration of protection provided by nirsevimab-alip (BEYFORTUS)"

Those with CLD of prematurity or hemodynamically significant CHD up to two years of age continued in the trial for a second season. Subjects who received nirsevimab-alip (BEYFORTUS) during the first season received 200 mg of nirsevimab-alip (BEYFORTUS) entering the second season, followed by a monthly placebo. Subjects who received palivizumab (SYNAGIS) during their first RSV season were randomized to receive either nirsevimab-alip (BEYFORTUS) or palivizumab (SYNAGIS) during

the second season. There were no MA RSV LRTI through Day 150 post-dose cases in subjects who received either nirsevimab-alip (BEYFORTUS) or palivizumab (SYNAGIS). (19)

Nirsevimab-alip (BEYFORTUS) is indicated for preventing MA RSV LRTI in the first season. Children up to two years of age may remain susceptible to severe disease through two years of age. Nirsevimab-alip (BEYFORTUS) may be administered shortly after birth. For infants born outside the RSV season, nirsevimab-alip (BEYFORTUS) should be administered once before the RSV season starts, subject to whether the patient's mother received RSVpreF (ABRYSVO) or palivizumab (SYNAGIS), considering the duration of protection provided by nirsevimab-alip (BEYFORTUS). Patients should receive dosage based on weight, with those less than 5 kg receiving 50 mg by IM injection and those above 5 kg 100 mg by IM injection.

During the first RSV season, if surgery is performedwithin 90 days after nirsevimab-alip (BEYFORTUS), an additional dose based on body weight should be given. If more than 90 days have elapsed since nirsevimab-alip (BEYFORTUS), the additional dose should be 50 mg. For children up to two years of age with increased risk in the second season, the recommended nirsevimab-alip (BEYFORTUS) dosage is a 200 mg dose given in two IM injections (2 x 100 mg). If more than 90 days have elapsed since receiving nirsevimab-alip (BEYFORTUS), the additional dose should be 100 mg, regardless of weight. (19)

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In either case, for children undergoing cardiac surgery with cardiopulmonary bypass or ECMO, an additional dose of nirsevimab-alip (BEYFORTUS) is recommended as soon as the child is stable off bypass following surgery to ensure that nirsevimab-alip (BEYFORTUS) is not filtered from the serum or diluted by the circuit. (19)

Nirsevimab-alip (BEYFORTUS) may be given with other vaccines. There is no information regarding the co-administration of nirsevimab-alip (BEYFORTUS) with other immunoglobulin products. There is no data regarding substituting nirsevimab-alip (BEYFORTUS) for palivizumab (SYNAGIS) once prophylaxis treatment is initiated with palivizumab (SYNAGIS) or whether palivizumab (SYNAGIS) may be given following administration of nirsevimab-alip (BEYFORTUS) or RSVpreF (ABRYSVO) received by the patient's mother. No data suggests that nirsevimab-alip (BEYFORTUS) may not given during the second season to children up to 2 years of age who are at significant risk of severe RSV disease and who received palivizumab (SYNAGIS) in their first RSV season or whose mothers received RSVpreF (ABRYSVO). Palivizumab (SYNAGIS) may also be administered with the appropriate indication during the first or second year of eligibility. In certain circumstances, policy limitations may curtail the use of nirsevimab-alip (BEYFORTUS). In these circumstances, it is essential to remember that palivizumab (SYNAGIS) may be used. (12, 19)

"No data suggests that nirsevimab-alip (BEYFORTUS) may not given during the second season to children up to 2 years of age who are at significant risk of severe RSV disease and who received palivizumab (SYNAGIS) in their first RSV season or whose mothers received RSVpreF (ABRYSVO). Palivizumab (SYNAGIS) may also be administered with the appropriate indication during the first or second year of eligibility."

Nirsevimab-alip (BEYFORTUS) is contraindicated in infants and children with a history of severe hypersensitivity, including anaphylaxis, to nirsevimab-alip (BEYFORTUS) or related compounds. Severe hypersensitivity reactions and anaphylaxis have occurred by administering other monoclonal antibodies. With IM injections, the risk of thrombocytopenia, coagulation disorder, or individuals on anticoagulation therapy should be taken into consideration.

A randomized, double-blind, controlled multicenter trial in infants at high risk for severe disease evaluated the safety of nirsevimab-alip (BEYFORTUS). Palivizumab (SYNAGIS) was given to the control group. Subjects received nirsevimab-alip (BEYFORTUS) or palivizumab (SYNAGIS) (SYNAGIS). Six hundred fourteen infants received nirsevimab-alip (BEYFORTUS). 214 and 103, respectively, had CLD associated with prematurity or hemodynamically significant CHD. 12 infants had both CLD and CHD. Subjects with CLD or hemodynamically significant CHD could continue receiving nirsevimab-alip (BEYFORTUS) or palivizumab (SYNAGIS) before the second RSV season. All subjects who received nirsevimab-alip (BEYFORTUS) also received nirsevimab-alip (BEYFORTUS) in the second RSV season (N=180). Those who received palivizumab (SYNAGIS) in the first season were randomized to receive nirsevimab-alip (BEYFORTUS) or palivizumab (SYNAGIS) in the second RSV season. The safety profile of nirsevimab-alip (BEYFORTUS) during their second RSV season was comparable with the safety profile during the first RSV season. (12, 19)

The safety and effectiveness of nirsevimab-alip (BEYFORTUS)

have been established for preventing RSV lower respiratory tract disease up to two years of age for those who remain vulnerable to severe RSV disease. The indications for risk should be similar to those reported for palivizumab (SYNAGIS). The use of nirsevimab-alip (BEYFORTUS) is supported by evidence from controlled studies in neonates and infants from birth up to one year, with additional pharmacokinetic and safety data in children up to two years of age. (12, 19)

"There has been some concern about the possibility of associated preterm birth if RSVpreF (ABRYSVO) was given sooner than 32 weeks gestation. It takes approximately two weeks for maternal antibodies to cross the placenta, and passage of these antibodies is more certain during the later part of the third trimester. (11, 20) Passage of the immune active antibody is optimal in late gestation."

There has been some concern about the possibility of associated preterm birth if RSVpreF (ABRYSVO) was given sooner than 32 weeks gestation. It takes approximately two weeks for maternal antibodies to cross the placenta, and passage of these antibodies is more certain during the later part of the third trimester. (11, 20) Passage of the immune active antibody is optimal in late gestation. According to the FDA indication, babies at term will have at least six months of protection from more severe illness. This means that a term baby born in October at term will have protection through the typical duration of the RSV season, but this protection may wain if the season is prolonged. '

"Babies born in November through March at late preterm or term gestation will be protected during the season. The additional protection may not provide benefits if the RSV season ends in April. This analysis may not be valid if COVID continues to produce alterations in the RSV season. (21)"

Babies born in November through March at late preterm or term gestation will be protected during the season. The additional protection may not provide benefits if the RSV season ends in April. This analysis may not be valid if COVID continues to produce alterations in the RSV season. (21) For babies born at term in April, nirsevimab-alip (BEYFORTUS) will only protect through October; these babies may require additional prophylaxis as the protective effect may decrease before the RSV season starts. In deciding whether to use nirsevimab-alip (BEYFORTUS) or palivizumab (SYNAGIS), the mother's history of receiving RSVpreF (ABRYSVO) is essential. (11, 12, 19, 20, 22)

Financial, availability, and contracting may drive the use of one versus another prophylaxis strategy. The current indication of RSVpreF (ABRYSVO) extends prophylaxis to all babies born at least two weeks after immunization except those born to mothers at risk of a reaction from the immunization administration. (22) Palivizumab (SYNAGIS) remains indicated for preterm infants born up to 35 6/7 weeks and those with significant risk factors. Palivizumab (SYNAGIS) may be used instead of nirsevimab-alip (BEYFORTUS), subject to availability in these patients. (23) Although palivizumab (SYNAGIS) has been used in term gestation neonates with additional risk factors (e.g., congenital heart disease), palivizumab (SYNAGIS) has an FDA indication for those neonates. This guidance does not endorse the dosing of term neonates with palivizumab (SYNAGIS) as this purpose is not compliant with the FDA indication. A cost-effective strategy should include analyzing whether maternal RSVpreF (ABRYSVO) will provide significant protection during the RSV season, the potential need for palivizumab (SYNAGIS) or nirsevimab-alip (BEYFORTUS), and whether a second season is indicated. (17, 22) Again, this guidance provides a roadmap for navigating the FDA indication. Abridging the indication by shortening the eligibility interval in the first or second seasons is not recommended and not to full FDA indication.

"A cost-effective strategy should include analyzing whether maternal RSVpreF (ABRYSVO) will provide significant protection during the RSV season, the potential need for palivizumab (SYNAGIS) or nirsevimab-alip (BEYFORTUS), and whether a second season is indicated. (17, 22) Again, this guidance provides a roadmap for navigating the FDA indication. Abridging the indication by shortening the eligibility interval in the first or second seasons is not recommended and not to full FDA indication."

Palivizumab (SYNAGIS)

Palivizumab (SYNAGIS) is a respiratory syncytial virus (RSV) F protein inhibitor monoclonal antibody that prevents severe LRTD caused by RSV in pediatric patients who were born prematurely (≤35 weeks gestational age) and who are ≤ six months of age at the beginning of RSV season, with bronchopulmonary dysplasia (BPD) that required medical treatment within the previous six months and who are ≤ two years at the beginning of RSV season,

with hemodynamically significant congenital heart disease (CHD)

and who are two years of age or younger at the beginning of RSV season. Synagis's safety and efficacy are unknown for treating RSV disease. (12)

Palivizumab (SYNAGIS) is dosed at 15 mg per kg of body weight intramuscularly before the RSV season. The remaining doses are administered monthly throughout the RSV season.

After cardio-pulmonary bypass, patients should receive an additional dose of palivizumab (SYNAGIS) promptly following the cardio-pulmonary bypass. After that, monthly doses should be administered. (12)

Anaphylaxis or severe acute hypersensitivity reactions have been reported. If such reactions occur, discontinue palivizumab (SYNAGIS) and administer appropriate medications. Palivizumab (SYNAGIS) should be given with caution to children with thrombocytopenia or any coagulation disorder. Palivizumab (SYNAGIS) may interfere with immunological-based RSV diagnostic tests, such as some antigen detection-based assays. Fever and rash occur in greater than or equal to 10% and at least 1% more frequently than placebo. (12)

Safety and effectiveness in children older than two years old have not been established.

"Palivizumab (SYNAGIS) is indicated to prevent RSV-related severe lower respiratory tract disease in those with a history of premature birth (< 35 weeks gestational age), six months of age or younger at the start of the season, with bronchopulmonary dysplasia (BPD) that required medical treatment within the previous six months and who are two years or younger at the beginning of RSV season, with hemodynamically significant congenital heart disease (CHD) and who are two years or younger at the beginning of RSV season. (12)"

Palivizumab (SYNAGIS) is indicated to prevent RSV-related severe lower respiratory tract disease in those with a history of premature birth (≤ 35 weeks gestational age), six months of age or younger at the start of the season, with bronchopulmonary dysplasia (BPD) that required medical treatment within the previous six months and who are two years or younger at the beginning of RSV season, with hemodynamically significant congenital heart disease (CHD) and who are two years or younger at the beginning of RSV season. (12)

The first palivizumab (SYNAGIS) dose should be administered before the RSV season. The subsequent doses should be administered monthly. Those who are symptomatic with RSV infection should continue to receive monthly doses. In the northern hemisphere, the RSV season typically commences in November and lasts through April. However, it may begin earlier or persist later due to geographical considerations or modulation of the pattern secondary to COVID-19 or influenza seasonality and control measures. (12)

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Other acute severe hypersensitivity reactions have been reported on exposure to palivizumab (SYNAGIS), including urticaria, pruritus, angioedema, dyspnea, respiratory failure, cyanosis, hypotonia, hypotension, and unresponsiveness. (12)The relationship between these reactions and developing antibodies to palivizumab (SYNAGIS) is unknown. If a significant hypersensitivity reaction occurs with palivizumab (SYNAGIS), its use should be permanently discontinued. If a mild hypersensitivity reaction occurs, a risk-benefit analysis should guide further palivizumab administration (SYNAGIS). (12)

Palivizumab (SYNAGIS) may interfere with immunological-based diagnostic tests, including RSV antigen detection-based assays. In addition, palivizumab (SYNAGIS) inhibits virus replication in cell culture and may also interfere with viral culture assays. Palivizumab (SYNAGIS) does not interfere with reverse transcriptase-polymerase chain reaction-based assays. These diagnostic test results and clinical findings can guide medical decision-making. The safety and efficacy of palivizumab (SYNAGIS) have not been established for treating RSV disease. (12)

Palivizumab (SYNAGIS) has been studied in randomized control clinical trials. One study involved children two years or younger with BPD or infants with premature birth (≤ 35 weeks) who were less than or equal to 6 months of age at study entry. Another study evaluated consecutive seasons among children two years or under with hemodynamically significant congenital heart disease. In the combined studies, fever and rash were more frequent among palivizumab (SYNAGIS) than those who received placebo, 27% versus 25% and 12% versus 10%, respectively. (12)

The incidence of anti-palivizumab antibodies was not significant. In children receiving palivizumab (SYNAGIS) for a second

season, a transient, low titer reactivity was identified in a single individual. This reactivity was not associated with adverse events or alteration in serum concentrations. (12)

These findings represent the percentage of test results indicating antibodies to palivizumab (SYNAGIS) in an enzyme-linked immunosorbent assay (ELISA), and the assay's sensitivity and specificity heavily influence their accuracy. The ELISA has notable limitations in detecting anti-palivizumab antibodies when palivizumab is present. Immunogenicity samples tested using the ELISA assay likely contained palivizumab at levels that could hinder the detection of anti-palivizumab antibodies. To address this, an electrochemical luminescence (ECL)-based immunogenicity assay, which exhibits greater tolerance for the presence of palivizumab compared to the ELISA, assessed anti-palivizumab antibodies from two additional clinical trials. The rates of positive results for anti-palivizumab antibodies in these trials were 1.1% and 1.5%. (12)

Adverse reactions have been identified during the post-approval use of palivizumab (SYNAGIS). These reactions are from a population with unknown dimensions and compliance. One cannot estimate frequency or establish a causal relationship to palivizumab (SYNAGIS). Severe thrombocytopenia has been associated with receiving palivizumab (SYNAGIS) as well as injection site reactions. Post-marketing reports suggest that, within a single RSV season, adverse events after six doses of Synagis are no different than if the patient received only five doses.

No formal drug-drug interaction studies were conducted. The safety and effectiveness of palivizumab (SYNAGIS) in children older than two years or persons of reproductive age have not been established. Overdoses up to 85 mg/kg have been reported. In some cases, adverse reactions were reported.

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Palivizumab (SYNAGIS), a humanized monoclonal antibody (IgG1κ) produced through recombinant DNA technology, targets an epitope of the F protein of RSV (the "A" antigenic site). Its human heavy chain sequence (95% human and 5% murine antibody sequences) originates from constant domains of human IgG1 and variable regions of the VH genes Cor and Cess. The human light chain sequence is sourced from constant domains of Cκ and the variable framework regions of the VL gene K104 and Jκ -4. Murine sequences are sourced from a murine monoclonal antibody, Mab 1129, with a process involving grafting the murine complementarity-determining regions into the human antibody frameworks. Palivizumab consists of two heavy chains and two light chains, possessing a molecular weight of approximately 148,000 Daltons. Palivizumab (SYNAGIS) is a recombinant humanized monoclonal antibody with anti-RSV F protein activity. (12)

In children under two years of age without congenital heart disease (CHD), the average half-life of palivizumab (SYNAGIS) was 20 days. Monthly intramuscular doses of 15 m /kg resulted in mean ± SD 30-day trough serum drug concentrations of 37 ± 21 mcg/mL after the initial injection, 57 ± 41 mcg/mL after the second injection, 68 ± 51 mcg/mL after the third injection, and 72 ± 50 mcg /mL after the fourth injection. Trough concentrations were comparable between children with CHD and those without cardiac conditions. For children receiving Synagis for a second season, the mean ± SD serum concentrations after the first and fourth injections were 61 ± 17 mcg/mL and 86 ± 31 mcg/mL, respectively. (12)

"In children, < two years with hemodynamically significant CHD who received palivizumab (SYNAGIS) and underwent cardio-pulmonary bypass for open-heart surgery, the mean serum palivizumab (SYNAGIS) concentration declined by 58%. (12)"

In children, ≤ two years with hemodynamically significant CHD who received palivizumab (SYNAGIS) and underwent cardio-pulmonary bypass for open-heart surgery, the mean serum palivizumab (SYNAGIS) concentration declined by 58%. (12)

Palivizumab (SYNAGIS) serum trough concentrations were independent of gender, age, body weight, or race in those with CHD (≤ two years) receiving monthly IM palivizumab (SYNAGIS). (12)

A pharmacokinetic analysis described palivizumab (SYNAGIS) pharmacokinetics. Palivizumab pharmacokinetics are best described as a two-compartment linear model with an elimination half-life of 24.5 days. Clearance of palivizumab (SYNAGIS) in a typical pediatric patient (body weight 4.5 kg) ≤ two years without CHD was estimated to be 11 mL/day with a bioavailability of 70% following IM administration. (12)

Palivizumab (SYNAGIS) is a recombinant humanized monoclonal antibody that provides passive immunity against RSV by binding the envelope fusion protein (RSV F) on the virus surface. This configuration blocks a critical step in the membrane fusion process. Palivizumab (SYNAGIS) also prevents cell-to-cell fusion of RSV-infected cells. This process prevents the formation of the syncytial membrane that makes up the name of the virus. (12)

Palivizumab (SYNAGIS) activity was assessed in a microneutralization assay. Following an incubation period of 4-5 days, the RSV antigen was quantified using an ELISA assay. The neutralization titer, represented as the 50% effective concentration (EC50), denotes the antibody concentration needed to decrease the detection of RSV antigen by 50% in comparison to untreated virus-infected cells. Palivizumab (SY

nAGIS) exhibited median EC50 values of 0.65 mcg/mL and 0.28

mcg /mL against clinical RSV A and RSV B isolates. These isolates encoded the most common RSV F sequence polymorphisms among clinical isolates worldwide. (12)

Palivizumab serum concentrations greater than or equal to 40 mcg/mL have reduced pulmonary RSV replication *in vitro* by 100-fold. Palivizumab (SYNAGIS) binds a highly conserved region on RSV F, antigenic site II or site A, encompassing amino acids 262 to 275. Resistance to palivizumab (SYNAGIS) has been observed with specimens with mutations in this region. (12)

Virus escape from palivizumab demonstrated a correlation between antibody binding and virus neutralization. RSV variants with substitutions in antigenic site A did not bind to palivizumab (SYNAGIS). No association between the antigenic A site sequence changes and disease severity was demonstrated. (12)

Clinical isolates collected from immunoprophylaxis-naïve subjects revealed palivizumab (SYNAGIS) resistance-associated substitutions in only two specimens. There is a resistance-associated mutation frequency of 0.79%. Palivizumab (SYNAGIS) susceptibility of common F protein sequence polymorphisms proximal to antigenic site A has been studied. No known polymorphic or non-polymorphic sequence variations external to antigenic site A on protein F confer RSV resistance to neutralization by palivizumab (SYNAGIS). (12)

Palivizumab (SYNAGIS) has been shown to interfere with immunologically-based RSV assays, such as rapid chromatographic/enzyme immunoassays (CIA/EIA), immunofluorescence assays (IFA), and direct immunofluorescence assays (DFA). It is essential to exercise caution when interpreting negative results from immunological assays, especially if clinical observations align with RSV infection. A reverse transcriptase-polymerase chain reaction (RT-PCR) assay, unaffected by palivizumab (SYNAGIS), can be utilized to enhance laboratory confirmation. (12)

"The safety and efficacy of palivizumab (SYNAGIS) prophylaxis were studied in randomized, double-masked, placebo-controlled trials in children at high risk of RSV-related hospitalization. The IMPACT RSV was conducted during a single RSV season and studied children less than or equal to two years with BPD or infants with premature birth (< 35 6/7 weeks) who were less than or equal to 6 months of age at study entry."

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In IMPACT-RSV, RSV hospitalization reduction was observed in children with BPD 12.8% versus 7.9% and in premature infants without BPD 8.1% versus 1.8%. In the CHD trial, reductions were observed in acyanotic children at 11.8% versus 5.0% and cyanotic children at 7.9% versus 5.6%. (12, 24)

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The studies do not suggest RSV infection was less severe among those hospitalized with RSV infection who received palivizumab (SYNAGIS) for RSV prophylaxis compared with placebo. (12)

"For infants and young children who were supposed to receive nirsevimab-alip but received Pfizer (ABRYSVO) or GSK (AREXVY) RSV vaccine in error, it is recommended to administer a dose of nirsevimab-alip (BEYFORTUS) or initiate palivizumab (SYNAGIS). (11, 12, 19, 25) Pregnant individuals who received the GSK RSV vaccine (Arexvy) in error should not be given the Pfizer RSV vaccine (ABRYSVO). Instead, if the infant is younger than one year, they should receive nirsevimab-alip during the RSV season."

RSV Prophylaxis In Non-Indicated Patients or Indications for Redosing:

Healthcare providers who have inadvertently administered incorrect RSV vaccine products are advised to take specific actions. For infants and young children who were supposed to receive nirsevimab-alip but received Pfizer (ABRYSVO) or GSK (AREXVY) RSV vaccine in error, it is recommended to administer a dose of nirsevimab-alip (BEYFORTUS) or initiate palivizumab

(SYNAGIS). (11, 12, 19, 25) Pregnant individuals who received the GSK RSV vaccine (Arexvy) in error should not be given the Pfizer RSV vaccine (ABRYSVO). Instead, if the infant is younger than one year, they should receive nirsevimab-alip during the RSV season.

To prevent vaccine administration errors, healthcare providers and facilities should ensure that the correct RSV prevention product is used in the correct population. This involves implementing error prevention alerts in electronic health record systems, providing proper education and training, paying attention to labeling, and following storage and administration best practices. Healthcare providers are strongly encouraged to report vaccine administration errors to VAERS; questions can be submitted to NIPINFO@cdc.gov for inquiries. Additionally, healthcare providers with complex vaccine safety questions may request consultation through the Clinical Immunization Safety Assessment (CISA) Project. (25)

I. Background:

Respiratory Syncytial Virus (RSV) is a virus that typically causes mild, cold-like symptoms in adults, children, and most term infants. In premature and "at-risk" infants, as well as those over age 60, RSV can cause severe disease and is a grave health concern. RSV is a leading cause of worldwide morbidity and mortality in children less than five years of age and causes approximately 3.4 million hospitalizations and more than 66,000 deaths per year in this group. (26) Although 99% of these deaths occur in developing countries, of all infectious diseases affecting children worldwide, only malaria is more deadly. (27)

"Many different strategies have been studied to reduce the risk of RSV. Although efforts to reduce droplet transmission, good handwashing, and avoidance of known infected patients are practical, palivizumab (SYNAGIS) and nirsevimab-alip (BEYFORTUS) are currently the only FDA-approved biologics for RSV prophylaxis following delivery. (12, 19)"

Many different strategies have been studied to reduce the risk of RSV. Although efforts to reduce droplet transmission, good handwashing, and avoidance of known infected patients are practical, palivizumab (SYNAGIS) and nirsevimab-alip (BEYFORTUS) are currently the only FDA-approved biologics for RSV prophylaxis following delivery. (12, 19)There is a high level of evidence that RSV prophylaxis is effective. The best data available at this time supports continuing to ensure access to RSV prophylaxis for neonatal and pediatric patients at the most significant risk. (28-31) Over the past several years, the proportion of infants eligible for RSV prophylaxis who have received it has decreased as providers and insurers have increasingly followed guidelines and policies that do not comply with Food and Drug Administration (FDA) indications, resulting in needless morbidity and increased hospitalization. (32, 33) Many babies at risk for RSV are now deemed ineligible for complete prophylaxis by such guidelines and policies. (24, 34, 35) Although the guidance for nirsevimab-alip (BEYFORTUS) is more relaxed than previously for palivizumab (SYNAGIS), parent groups concerned about this trend have published recommendations for obtaining FDA-approved coverage for RSV prophylaxis using appeals, letter-writing campaigns, and political activism. Several examples are documented on the "preemiebabies101" website http://www.preemiebabies101.com/2014/08/12-tips-getting-synagis-injections-approved/ as well as the "Hand to Hold" website http://handtohold.org/resources/helpful-articles/rsv-101-what-every-nicu-parent-needs-to-know/. The continued need to appeal what should be covered by FDA indication, delays in the appeals process, and complete denials have all contributed to delays in the administration of immunization to babies at risk, resulting in irregular, sub-optimal dosing regimens and a reduction of palivizumab (SYNAGIS) levels necessary to prevent illness. This leads to leads to increased hospital admission as well as increased morbidity. (33, 36)

"Provider confusion is a serious concern. Although there is no substitute for clinical judgment, recommendations on dosing and timing should be issued consistent with the broadest FDA indication for dosing to accommodate provider discretion. (32) Guidelines do not apply to every condition and case. Variation from the guideline is still acceptable; however these guidelines should never deny access."

Provider confusion is a serious concern. Although there is no substitute for clinical judgment, recommendations on dosing and timing should be issued consistent with the broadest FDA indication for dosing to accommodate provider discretion. (32) Guidelines do not apply to every condition and case. Variation from the guideline is still acceptable; however these guidelines should never deny access. A policy that mandates attenuated palivizumab (SYNAGIS) or nirsevimab-alip (BEYFORTUS) administration is unreasonable when that policy countermands the FDA indication. (12, 19)The indication provides the most clarity in preventing the use of a pharmaceutical product outside of its carefully studied parameters. Following the FDA indication is essential from a medico-legal perspective, as insurers should use the FDA indication to guide remuneration without *a proviso* for denials due to consensus guidance that deviates from the FDA indication. Significant deviation from the established FDA indication and insurance reimbursement based on policy statements created from consensus guidance contributes to much confusion for providers and parents. It may also lead to provider disenfranchisement and a lack of universal acceptance of a standard of practice (http://www.infanthealth.org/rsv). This situation is unfortunate. Despite precise Medicaid regulation, State Medicaid formularies have not met all of the requirements of section 1927(d)(4)(C) of the Social Security Act since they exclude

treatment with an approved therapy despite clear FDA indication. Palivizumab (SYNAGIS) and nirsevimab-alip (BEYFORTUS) meet all the criteria (significant and clinically meaningful therapeutic advantage, safety profile, and effectiveness in clinical outcomes) necessary for coverage by Medicaid programs via the "medically acceptable indication" criteria. The ramifications of a policy for reduced dosing are concerning, as it restricts access and causes state Medicaid programs to violate their legislative mandate. Under the legal doctrine of "loss of chance," practitioners assume legal liability for not offering and advocating for the use of the only approved pharmaceutical for a specific approved indication. (37)

"Of particular public concern has been a de-emphasis on the best available evidence and a focus on adjudicated studies to generate selective expert opinion. Regimens with fewer doses than FDA indication or decreased months of eligibility were not tested in a randomized clinical trial (RCT). The use of an abbreviated dosing or calendar schedule for immunoprophylaxis of RSV to ration therapy and reduce costs is contrary to published evidence and the FDA-approved product indications for palivizumab (SYNAGIS) and nirsevimab-alip (BEYFORTUS). (38)"

Of particular public concern has been a de-emphasis on the best available evidence and a focus on adjudicated studies to generate selective expert opinion. Regimens with fewer doses than FDA indication or decreased months of eligibility were not tested in a randomized clinical trial (RCT). The use of an abbreviated dosing or calendar schedule for immunoprophylaxis of RSV to ration therapy and reduce costs is contrary to published evidence and the FDA-approved product indications for palivizumab (SYNAGIS) and nirsevimab-alip (BEYFORTUS). (38) Not dosing according to indication (underdosing) is considered an "off-label" use of medication. (39) Although cost-effectiveness is increasingly essential, decisions regarding appropriate RSV prophylaxis must be based on the evidence. (40-43) Denial of full coverage based on gestational age, without consideration of other risk factors, discriminates against certain populations of infants and may put specific populations at even greater risk due to health disparities. (44, 45) Making RSV a reportable disease may be necessary to document the extent of RSV prevalence and costs. (44) To date, despite widespread efforts to protect infants according to the FDA indications, further restrictions on the use of palivizumab (SYNAGIS) and nirsevimab-alip (BEYFORTUS) have made prophylaxis potentially unavailable for as many as 75% of the infants in whom it is indicated by FDA guidance. (32, 46)

Even in high-risk infants from 32-35 wGA (weeks' gestational age), RSV can result in severe morbidities. Ambrose et al. evaluated 1642 subjects across many outpatient clinics in 38 states and the District of Columbia in one study. In two RSV seasons (2009-2011), ED visits, outpatient respiratory infection, and other clinical factors that place babies at risk for RSV disease were evaluated. Of the preterm infants 32-35 wGA who were <6 months on November 1, 4.9% were hospitalized with RSV-related illnesses each season. Pre-school-aged siblings and daycare attendance increased the risk of RSV disease. Among the subset of 32-34 wGA infants eligible under risk-related criteria, the RSV-related hospitalization rate was 9.1%. (36, 47) A study by Blanken et al. supports the original evidence presented in the IMpact RSV trial. Palivizumab (SYNAGIS) decreased RSV-related hospitalization in 33-35 wGA infants by 82%, whereas the original IMpact study described a 78% decrease. (24, 48) A Cochrane review using data from many randomized controlled trials found high-quality evidence to support the association of palivizumab (SYNAGIS) and reduction in RSV-related hospitalization (RR 0.49, 95% CI 0.37-0.64) as well as high-quality evidence to support an association of palivizumab (SYNAGIS) and reduction in RSV ICU admissions (RR 0.5, 95% CI 0.3-0.81). (24, 49-51) Data regarding nirsevimab-alip (BEYFORTUS) and changes to the FDA indication by various current guidelines have not been covered adequately.

Confoundation by indication limits the effectiveness of well-designed randomized control studies designed to study the efficacy of palivizumab (SYNAGIS) and nirsevimab-alip (BEYFORTUS). Farber et al. described a 38% lower hospitalization rate for RSV in infants born at 29 to 32 wGA, with ≥1 insurance claim for palivizumab (SYNAGIS). (52) This group received ≤ 50% of the indicated doses. Studies that are retrospective, nonrandomized, and with confounding of the indication should not supersede the data from carefully designed randomized trials. (53)

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Winterstein et al. evaluated 247,566 patients in Florida and Texas to determine the age at which at-risk infants born from 32-34 wGA experienced a risk of developing RSV equivalent to that of term

babies. At one month of age, these babies had a risk of being hospitalized comparable to that of term babies. The RSV-related hospitalization rate of these preterm infants was 3.1% in Florida and 4.5% in Texas. Incomplete coding and testing for RSV was a consistent issue. Increased prematurity was associated with a higher risk for hospitalization, and the disparity issues could not be separately identified in the populations studied. (54) In another at-risk population in Florida, Winterstein et al. demonstrated that palivizumab (SYNAGIS) prophylaxis was associated with reduced severe RSV infection. (55) Analysis of the Kids' Inpatient Database of hospitalizations between 2000-2009 (n=325,494) showed that while, overall, bronchiolitis-related hospitalizations were decreased by 17% among all children less than two years of age, bronchiolitis hospitalizations increased by 29% in the sub-group in which there was an FDA indication for palivizumab (SYNAGIS) prophylaxis. (35, 56) As nirsevimab-alip (BEYFORTUS) does not yet have significant clinical data with changes to the FDA indication in clinical practice, whether this proposed guidance and protocols will impact prophylaxis remains to be seen.

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In a study by Hall et al., RSV-related hospitalizations among preterm and term infants were evaluated in three United States counties. RSV acute respiratory illnesses were tallied, and relative risk was identified by age from birth certificate data. This study has been used to justify reduced immunoprophylaxis of prophylaxis with palivizumab (SYNAGIS), yet the study included insufficient premature infants to justify generalizing the results to this population. Premature infants represented only 10% of the 2,140 subjects studied. RSV rates in this study were not found to be significantly different between preterm and term infants, an expected result since 70% of the palivizumab (SYNAGIS) - eligible patients in the study populations had received palivizumab (SYNAGIS) (supporting the efficacy of palivizumab (SYNAGIS) in decreasing the rate of RSV infection in preterm infants to be closer to that of term infants). Black infants greater than or equal to 6 months of age were hospitalized more often, documenting ethnic disparities in RSV-related health risks. (45) Previous studies, such as that by Boyce et al., had identified a two-fold higher hospitalization rate for preterm infants. (57) This higher hospitalization rate might drop if adequate compliance with RSV prophylaxis could be assured. (58)

Since 2014, more restrictive control over the prescription of palivizumab (SYNAGIS) has resulted in increased morbidity. Zuccotti et al. demonstrated worse outcomes in the 29-32 wGA group who did not receive prophylaxis and increased hospitalization costs. (59) In another study, Capizzi et al. found a high proportion of admission for the <36 wGA infants, the great majority born at 33 to <36 wGA and a chronological age of <6 months. Of those admitted, many preterms were treated with high-flow nasal cannula ventilation, delivering continuous positive airway pressure. These results suggest the need to re-evaluate the role of prophylaxis in infants up to 36 wGA.(60) In a multicenter test case negative control study, palivizumab (SYNAGIS) efficiency for preventing Intensive Care Unit (ICU) admission of infants 29-35 wGA and ≤6 months of chronologic age (without chronic lung disease of prematurity or congenital heart disease) was 74% (95% CI 56%-85%).(61)

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SENTINEL1 evaluated 29-35 wGA < 12 months old infants hospitalized for confirmed RSV disease who had not received prophylaxis. 42% were admitted to the ICU, and 20% required intubation and mechanical ventilation. In the younger group, 29-32 wGA and < 3 months of age, 68% required ICU admission, and 44% required intubation and mechanical ventilation. These results corroborate the original RSV IMpact study and provide additional information regarding the hospitalization course's acuity level. (33)

Following a change in palivizumab (SYNAGIS) dosing patterns for the 2014-2015 season, the TRUVEN database study demonstrated that with a decline in RSV prophylaxis, hospitalization increased among infants born at 29-34 wGA and aged <3 Months. Compared with the 2013–2014 season, RSV hospitalization increased by 2.7-fold (p = 0.02) in the at-risk group. RSV hospitalizations for infants 29-34 wGA were up to seven times higher than for normal-term infants. (62)

"Increased risk for hospitalization is not the only factor to consider. Several studies document RSV's association with wheezing and the risk of subsequent development of reactive airway disease. (63-65) Blanken et al., demonstrated a significant reduction in wheeze in an at-risk group of infants born at 33-35 wGA that received palivizumab (SYNAGIS) prophylaxis."

Increased risk for hospitalization is not the only factor to consider. Several studies document RSV's association with wheezing and the risk of subsequent development of reactive airway disease. (63-65) Blanken et al., demonstrated a significant reduction in wheeze in an at-risk group of infants born at 33-35 wGA

that received palivizumab (SYNAGIS) prophylaxis. Recurrent wheeze was ten percentage points lower in patients treated with palivizumab (SYNAGIS) (11% vs. 21%, p=0.01). (48) Yoshihara et al. demonstrated reduced wheeze in patients who received palivizumab (SYNAGIS) prophylaxis regardless of whether an at-risk patient was documented to have contracted RSV.(66) Subclinical RSV disease that is not identified in the course of a provider interaction may be clinically significant and result in increased long term morbidity. (41)

"Yoshihara et al. demonstrated reduced wheeze in patients who received palivizumab (SYNAGIS) prophylaxis regardless of whether an at-risk patient was documented to have contracted RSV.(66) Subclinical RSV disease that is not identified in the course of a provider interaction may be clinically significant and result in increased long term morbidity. (41)"

In an observational case-control prospective multicenter trial of palivizumab (SYNAGIS) prophylaxis, Mochizuki et al. were able to establish a two-fold increase in the development of recurrent wheezing (15.3% versus 31.6% in the treated and untreated groups (p=0.003). Although the study did not show a difference in atopic asthma, the risk for subsequent development of asthma and morbidity associated with recurrent wheezing cannot be discounted. (67) Feldman et al. discussed how RSV infection may not be necessary but is sufficient to increase the likelihood of pediatric asthma. Immune mediation and cytokine production common to both conditions may be set into the process if RSV infection occurs at a certain point. (68) REGAL (RSV Evidence-a Geographical Archive of the Literature) reviewed 20 years of RSV-related research. Of the 74 prospective epidemiologic studies qualified by the review, the meta-analysis consistently demonstrated that RSV infection early in life is a significant risk factor for respiratory morbidity characterized by early wheezing and recurrent wheezing, as well as asthma within the first decade of life and possibly later. (69) An expert panel sponsored by the Bill and Melinda Gates Foundation concluded that the association between early onset RSV and subsequent wheezing and asthma has been well-defined. The effect of prevention of RSV in infancy on the reduction of recurrent wheezing and asthma across multiple gestational ages may ultimately demonstrate a causal link. (70)

Children at high risk for RSV include those with other co-morbidities besides prematurity, including chronic lung disease and congenital heart disease. Using a structured case analysis of the Medline database, Welliver et al. described a series of patients with severe underlying comorbidities, as well as those with nosocomial RSV who appear to be at increased risk for death after RSV hospitalization. (71) Actual RSV worldwide fatality data may help determine whether including co-morbidities in evaluating acceptable risk is appropriate. (26, 41, 72)

"Using a structured case analysis of the Medline database, Welliver et al. described a series of patients with severe underlying comorbidities, as well as those with nosocomial RSV who appear to be at increased risk for death after RSV hospitalization. (71) "

II. Financial Considerations:

Cost stewardship is essential. Patients should receive the best possible care at the lowest possible cost. (38) However, any reduction in qualification for RSV prophylaxis must be associated with a model that demonstrates the unequivocal financial benefit without increased attendant morbidity and mortality. Maternal vaccination not withstanding; estimates of cost savings must incorporate realistic estimates of palivizumab (SYNAGIS) or nirsevimab-alip (BEYFORTUS) cost and all hospitalization and follow-up care costs. Included in this consideration must be a risk-stratified cost analysis of a patient likely to be hospitalized for RSV-related disease as well as an estimate of actual prophylaxis cost related to the month of birth, extrapolated or actual dosing weight at the time of prophylaxis and level of discount applied to the list price of palivizumab (SYNAGIS) or nirsevimab-alip (BEYFORTUS). McLauren et al. analyzed modeled costs of 55 to 85% less than list pricing using a blended drug discount of 33% coupled with seasonal and patient weight considerations. (41, 73, 74) For this model, contemporary hospitalization claim data were used to quantify payer-related costs, and cost neutrality was demonstrated in patient groups up to 34 wGA.(41, 75) Medicaid-related cost discounts were most significant, and prophylaxis of patients in this cohort produced cost savings.

"Changes to nirsevimab-alip (BEYFORTUS) eligibility proposed by various guidance and policies require a more complete analysis. Long-term epidemiologic data from 16 seasons of national palivizumab (SYNAGIS) prophylaxis in Austria, reported by Resch et al., demonstrated an unequivocal seasonal benefit and long-term societal cost savings. (76)"

However, commercial or government insurance programs did not consider physician fees, follow-up costs, parent time off work, and patient factors, including the "cost" of discomfort. Extending this model to include these considerations and dosing according to the full FDA indication may provide additional cost reduction and further tip the balance toward financial justification for prophylaxis. Changes to nirsevimab-alip (BEYFORTUS) eligibility proposed by

various guidance and policies require a more complete analysis. Long-term epidemiologic data from 16 seasons of national palivizumab (SYNAGIS) prophylaxis in Austria, reported by Resch et al., demonstrated an unequivocal seasonal benefit and long-term societal cost savings. (76)

"RSV is the leading cause of hospitalization for all children less than 12 months of age in the United States. (57, 77, 78) The majority of these hospitalizations occur in otherwise healthy infants. Sixty percent of the top five hospital discharge diagnoses are attributable to bronchiolitis."

III. Introduction:

RSV is the leading cause of hospitalization for all children less than 12 months of age in the United States. (57, 77, 78) The majority of these hospitalizations occur in otherwise healthy infants. Sixty percent of the top five hospital discharge diagnoses are attributable to bronchiolitis. Certain groups of infants and children have higher rates of re-hospitalization, including those with Chronic Lung Disease (CLD)/Bronchopulmonary Dysplasia (BPD), Congenital Heart Disease (CHD), and a history of preterm birth. (79-86) Treatment options for RSV are limited, but opportunities for prophylaxis have increased over the previous. Supportive care is the only medical therapy available. In addition to strategies to minimize exposure to RSV, prophylaxis with RSV monoclonal antibodies effectively decreases hospitalization. The best approach to RSV in at-risk groups is prevention. (24, 51, 81, 87-89) In patients with CLD/BPD and premature infants born at less than 36 wGA, prophylaxis decreased hospitalization by 55%; in the subgroup of patients born between 32-35 wGA, hospitalization rates decreased by 80%. (24) Risk reduction in the larger cohort, including term newborns from administration of nirsevimab-alip (BEYFORTUS), is anticipated, subject to supply considerations. Although palivizumab (SYNAGIS) may be safe for term infants with no underlying co-morbidities, immunization of otherwise healthy term infants is considered outside the accepted FDA indication for palivizumab (SYNAGIS).

IV. Respiratory Syncytial Virus Prophylaxis

A. Prophylaxis to prevent RSV is available as an intramuscular monoclonal antibody preparation (palivizumab (SYNAGIS) or nirsevimab-alip (BEYFORTUS)). (90, 91)

B. Maternal vaccination may preclude the need for further immunization during the first season, depending on the timing and gestational of the patient.

C. RSV infection is responsible for significant hospitalizations, morbidity, and mortality in infants less than 24 months of age who have chronic lung disease, congenital heart disease, compromised respiratory or immune systems, or impaired nutritional status and growth. (51, 87, 92)

D. Candidates for RSV Prophylaxis: Areas where robust data exist.

"Risk reduction in the larger cohort, including term newborns from administration of nirsevimab-alip (BEYFORTUS), is anticipated, subject to supply considerations. Although palivizumab (SYNAGIS) may be safe for term infants with no underlying co-morbidities, immunization of otherwise healthy term infants is considered outside the accepted FDA indication for palivizumab (SYNAGIS)."

1. All infants whose mothers did not receive vaccination and who do not otherwise have a contraindication for the administration of palivizumab (SYNAGIS) or nirsevimab-alip (BEYFORTUS)
2. Infants with bronchopulmonary dysplasia (BPD) or chronic lung disease (CLD) will benefit from RSV prophylaxis using either palivizumab(SYNAGIS) or nirsevimab-alip (BEYFORTUS).
    a. BPD may be defined by oxygen requirement at 36 weeks corrected gestational age or at 28 days, regardless of the birth gestational age.
    b. CLD includes these infants and others who have subsequently developed an oxygen requirement or other pulmonary condition requiring treatment or close medical observation.
    c. Infants with CLD/BPD who are less than 24 months of age at the start of the RSV season and who have required intervention or maintenance therapy for their BPD/CLD within six months of the start of the RSV season will benefit from RSV prophylaxis. The administration of palivizumab (SYNAGIS) in a previous month may be sufficient to qualify for administration in a subsequent qualified month.
    d. Other interventions for CLD/BPD may include the use of corticosteroid preparations, methylxanthines (e.g., aminophylline or caffeine), supplemental oxygen, bronchodilators, home apnea monitoring, home pulse oximetry, or diuretics. (84, 93, 94)
3. Infants born at 32 wGA or less without CLD/BPD will also benefit from prophylaxis. (95) Maternal vaccination generally occurs after this gestation and should not be a factor in guiding prophylaxis.
    a. Infants born at less than 28 0/7 wGA will

benefit from prophylaxis if they are less than 12 months of age at the start of the RSV season. Infants born during RSV season who are less than 12 months of age at the start of the subsequent RSV season are still candidates for prophylaxis. Although all of these babies qualify for nirsevimab-alip (BEYFORTUS), management in the neonatal intensive care unit and continuous positive airway pressure in this cohort to promote lung growth will qualify these infants for palivizumab (SYNAGIS).

b. Infants born at 28 0/7-32 0/7 wGA will benefit most from prophylaxis if they are less than six months of age at the start of RSV season if only palivizumab (SYNAGIS) is available; however, their course in the neonatal intensive care unit should be evaluated carefully. These patients are eligible for nirsevimab-alip (BEYFORTUS) for up to 12 months.

"Infants born at a late preterm gestation (34 0/7-36 6/7 wGA) may merit special consideration. (96-98) However, prophylaxis with palivizumab (SYNAGIS) for infants born at 32 1/7-35 6/7 wGA should be reserved for those infants with additional risk factors that increase the risk of RSV exposure or morbidity from RSV disease. These infants are eligible for nirsevimab-alip (BEYFORTUS) for up to 12 months."

4. Infants born at a late preterm gestation (34 0/7-36 6/7 wGA) may merit special consideration. (96-98) However, prophylaxis with palivizumab (SYNAGIS) for infants born at 32 1/7-35 6/7 wGA should be reserved for those infants with additional risk factors that increase the risk of RSV exposure or morbidity from RSV disease. These infants are eligible for nirsevimab-alip (BEYFORTUS) for up to 12 months.

    a. An RSV relative risk scale has been proposed and may be helpful to the practitioner in identifying at-risk patients who may benefit from RSV prophylaxis. (99) A neonatologist, pediatrician, or other primary care provider is often best positioned to assess and interpret relative risk factors. Universal prophylaxis with nirsevimab-alip (BEYFORTUS) is consistent with the FDA indication. Where supply is limited, consideration should be given to whether the patient is eligible for palivizumab (SYNAGIS).

    b. The most consistently identified factors that are associated with increased risk of RSV disease are childcare attendance, school-aged siblings, twin or greater multiple gestation, young chronological age at the start of RSV season, and parental smoking; however, exposure to environmental air pollutants, congenital abnormalities of the airways, or severe neuromuscular disease may also justify concern. (65, 93, 100-103) Correlations exist between air quality and respiratory function. (64, 102-112) Thus, environmental air quality assessment is vital for these patients with special consideration given the unique circumstances of unwarranted air pollution, such as residence near a bus station or industrial plant or use of a wood-burning or coal-burning stove as a primary heat source. Efforts to reduce risk by isolation of the at-risk child, smoking cessation strategies for the parents/caregivers, or relocation to an area with cleaner air may not be practical or workable.

    c. Certain risk factors may have a more significant impact based on the level of exposure (i.e., one school-aged sibling versus three school-aged siblings in three different schools); however, no identifiable risk factor is unique in its predictive value, and frequently many risk factors may exist simultaneously. (64, 86) The greater the risk factors, the higher the likelihood of RSV hospitalization. (113) A history of maternal smoking during pregnancy may be ameliorated as a risk factor by a history of breastfeeding for greater than two months. (106, 114-117) The risk assessment must account for these circumstances.

"The provider must know the risk created and enhanced by diversity, equity, and inclusion (DEI) based disparity. Minority African American and Hispanic populations in blighted inner-city neighborhoods are at a higher cumulative risk. (44) "

    d. The provider must know the risk created and enhanced by diversity, equity, and inclusion (DEI) based disparity. Minority African American and Hispanic populations in blighted inner-city neighborhoods are at a higher cumulative risk. (44)

    e. After assessment of an individual patient, if a provider determines that the patient is at high risk for RSV disease complicated

by hospitalization, prophylaxis should be provided. (118) Planning for prophylaxis must begin before discharge if the at-risk patient has been hospitalized for any conditions that have a known association with increased risk. In one study, more than 50% of eligible patients received no prophylaxis before or after discharge. (119) Lack of parental education, language difficulties, transportation challenges, vaccines for children access and potential problems with insurance coverage must be resolved before the patient's discharge home. (120-122)

f. The cost of prophylaxis should be weighed against the risk of severe RSV disease requiring hospitalization and associated costs to the family, as well as the potential for long-term sequelae. Direct costs are not the only expenses involved in the long-term care of a child who has had RSV. Costs associated with loss of family income with a parent taking time off for initial hospitalization and later to care for a child with chronic disability, frequent follow-up appointments, and indirect costs involved in providing support for developmental disability, as well as loss of academic potential, must also be considered. (123-126)

"Infants with congenital heart disease have been shown to benefit from palivizumab (SYNAGIS) and nirsevimab-alip (BEYFORTUS). (51, 127-129) The degree and severity of the heart disease may factor into the decision to provide RSV prophylaxis. Cyanotic heart disease places a patient at considerable risk since oxygen delivery is already compromised."

5. Infants with congenital heart disease have been shown to benefit from palivizumab (SYNAGIS) and nirsevimab-alip (BEYFORTUS). (51, 127-129) The degree and severity of the heart disease may factor into the decision to provide RSV prophylaxis. Cyanotic heart disease places a patient at considerable risk since oxygen delivery is already compromised. Although acyanotic heart disease has been shown to increase the relative risk for RSV-related hospital admission to even higher than that of cyanotic disease, admission rates of palivizumab (SYNAGIS)-immunized infants are similar in both categories. (51) Infants with complex congenital heart disease are at risk. They should be considered for RSV prophylaxis, including babies with hypoplastic left or right heart syndrome, truncus arteriosus, tetralogy of Fallot, pulmonary atresia, transposition of the great arteries, interrupted aortic arch, ventricular septal defect or patent ductus arteriosus with demonstrated heart failure, cardiomyopathies, arrhythmias capable of causing hemodynamic compromise, and infants who are candidates for potential heart transplant. Children who are post-cardiac transplantation are in a particularly high-risk group and should be given RSV prophylaxis. (127, 129, 130) No data suggests that patients cannot receive prophylaxis in the second RSV season with palivizumab (SYNAGIS) if nirsevimab-alip (BEYFORTUS) is unavailable. To exclude an infant from receiving palivizumab (SYNAGIS) in the absence of nirsevimab-alip (BEYFORTUS), the infant must have a documented waiver provided by a board-certified pediatric cardiologist, which documents that their cardiac defect is hemodynamically insignificant and poses no additional risk for RSV. During RSV season, children who have received Extracorporeal Membrane Oxygenation (ECMO) or any other form of cardiac bypass should receive monthly prophylaxis. If the baby is receiving palivizumab (SYNAGIS) or nirsevimab-alip (BEYFORTUS) during the active RSV season, an extra dose of prophylaxis or a series of prophylaxis should be considered as soon as the baby comes off bypass support. (131)

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E. Candidates for RSV Prophylaxis: Areas where decisions regarding the appropriateness of RSV prophylaxis must be individualized during the second season.

1. Infants with severe neuromuscular disease affecting respiratory function (e.g., myotonic or muscular dystrophy) may be candidates for palivizumab (SYNAGIS) or nirsevimab-alip (BEYFORTUS) prophylaxis, including those with neuromuscular maturational disease common in premature infants. (132) CNS injury prior to,

during, or after delivery including, but not limited to, intraventricular hemorrhage (IVH), hypoxic-ischemic encephalopathy (HIE), spinal cord injury, disease of the peripheral nervous system, disease of the neuromuscular junction, and periventricular leukomalacia (PVL) are all possible indications for RSV prophylaxis. (92, 94, 132) IVH, HIE, and PVL may cause cerebral palsy (CP) later. CP alone may qualify an infant for RSV prophylaxis if there is any association with impaired respiratory function. (133, 134)

2. Patients with congenital abnormalities of the airways that compromise respiratory function should receive prophylaxis. (80, 135-138) Other respiratory viruses may also be implicated in morbidity, including persisting wheeze, symptomatology and family history that suggests the possibility of later asthma or disorders of abnormal lung growth. (66) Congenital diaphragmatic hernia is included in this category. Although large-scale randomized control trials have not been performed, patients with surfactant protein deficiencies may also benefit from prophylaxis, as may infants with childhood interstitial lung diseases such as neuroendocrine hyperplasia of infancy (NEHI) or pulmonary interstitial glycogenosis (PIG).

3. Although large-scale randomized control trials in patients with individual at-risk respiratory disorders have not been performed, patients with cystic fibrosis and other diseases such as α1-antitrypsin deficiency where there is a genetic basis for changes in the lung milieu may also benefit from prophylaxis. (139) Respiratory symptomatology is not generally associated with α1-antitrypsin deficiency during infancy; based on pulmonary involvement, palivizumab (SYNAGIS) may only be considered if the respiratory compromise is associated with another qualifier (e.g., prematurity). (140) Primary Ciliary Dyskinesia may also be an indication of prophylaxis. (141) Identification of cystic fibrosis on a newborn screen may merit special consideration. (136, 139, 142-144) Cystic fibrosis occurring with transient infantile wheezing has been associated with worse lung function in later life, and RSV is the most common cause of transient infantile wheezing. (145) Infants who would otherwise qualify for palivizumab (SYNAGIS) or nirsevimab-alip (BEYFORTUS) based on the indication should be screened for cystic fibrosis if the clinical course and history indicate.

4. Immune deficiencies are rare disorders and require collaborative management by pediatricians, infectious disease specialists, and immunologists. (146, 147) HIV, SCID, primary or secondary bone marrow depletion, and any defect of humoral or cellular immunity, including that occurring with transplantation, place a patient at risk of severe infection. Palivizumab (SYNAGIS) prophylaxis has been associated with improved survival after bone marrow transplantation. (148) Data do not exist for nirsevimab-alip (BEYFORTUS). Although no conclusive evidence exists for any particular disease category, RSV prophylaxis is indicated because of the understood high risk of any infectious process unless a waiver can be obtained from a board-certified pediatric immunologist or infectious disease specialist.

5. Certain genetic diseases may place a patient at more cumulative risk for RSV. For the present time, patients should receive prophylaxis to the extent that other qualifiers are met. However, including infants with Trisomy 21 in the recommendations for immunoprophylaxis of RSV disease should be considered. (149)

6. Exceptional risk circumstances may occur in homes where another individual is at high risk for RSV infection (e.g., an elderly immunocompromised relative) who may not be able to receive RSV prophylaxis or vaccination (i.e., less than age 60). Although palivizumab (SYNAGIS) and nirsevimab-alip (BEYFORTUS) do not prevent RSV infection, decreased cough and aerosolization of RSV may provide some protection. Providers should determine if providing prophylaxis to other household members is reasonable. (26, 150, 151)

"Although palivizumab (SYNAGIS) and nirsevimab-alip (BEYFORTUS) do not prevent RSV infection, decreased cough and aerosolization of RSV may provide some protection. Providers should determine if providing prophylaxis to other household members is reasonable. (26, 150, 151)"

F. Administration (See Table 1.)

1. The National Perinatal Association Guidelines for RSV Prophylaxis are interdisciplinary peer-reviewed and evidence-based guidelines but do not represent the sole management criteria for medical care of at-risk infants. Depending on individual case presentations, in selected populations and unique circumstances, these recommendations may not apply. There is no substitute for the clinical judgment of a neonatologist, pediatrician, nurse practitioner, or other licensed provider of pediatric services.

2. RSV prophylaxis should be initiated prior to the onset of the RSV season and terminated at the end of the RSV season. (30, 152, 153) Although regional variations exist in the United States, RSV outbreaks begin as early as October and decrease between March and May. During the COVID-19 pandemic, disruptions in RSV seasonality occurred regularly. (21) Providers

should review local historical RSV surveillance data to assist in decision-making. Some locales in the Southern United States (e.g., Florida), Hawaii, and Alaska have a high enough incidence of RSV to justify initiation in the late summer months and continuation of monthly prophylaxis into the late spring. (154-158) Transport distance of ill infants and resource allocation, as well as socioeconomic factors (e.g., lack of running water), may be considered in the justification of enhanced RSV prophylaxis coverage where the costs to provide hospitalization for patients at great distances greatly exceed that of most urban locales (e.g., Alaska and Canadian Arctic). (159) The burden of severe RSV disease on healthcare resources is more significant than other respiratory viruses. (160) Although various cost containment models have been proposed to provide relative risk adjustment based on post-conceptual age at a specific month during RSV season, there is a risk that adequate levels of palivizumab (SYNAGIS) or nirsevimab-alip (BEYFORTUS) will not be achieved or maintained during months when RSV is widespread using this type of model. (24, 36, 153, 161) Use of an abbreviated schedule of RSV prophylaxis is contrary to published evidence and FDA-approved product indication for palivizumab (SYNAGIS) and nirsevimab-alip (BEYFORTUS) and is strongly discouraged. (162) Recent issues with COVID-19 and shifting of RSV seasonality may change the demographic, resulting in a prolonged duration of risk, risk during the summer months, or a season with no identified RSV-related risk. In these situations, a modified schedule may be considered. Although second-season data is available for nirsevimab-alip (BEYFORTUS) after initial palivizumab (SYNAGIS), data does not exist for palivizumab (SYNAGIS) following nirsevimab-alip (BEYFORTUS). A risk-based model should be considered when there is a shortage of supply.

"Although second-season data is available for nirsevimab-alip (BEYFORTUS) after initial palivizumab (SYNAGIS), data does not exist for palivizumab (SYNAGIS) following nirsevimab-alip (BEYFORTUS). A risk-based model should be considered when there is a shortage of supply."

3. Once an infant begins RSV prophylaxis for the RSV season, if the infant does not receive an initial dose of nirsevimab-alip (BEYFORTUS), the infant must receive palivizumab (SYNAGIS) monthly through the end of the season unless a subsequent dose of nirsevimab-alip (BEYFORTUS) is given. (49)
4. During the first season, nirsevimab-alip (BEYFORTUS) 50 mg IM as a single injection or Palivizumab (SYNAGIS) 15 mg/kg IM monthly should be given during the RSV season to increase the likelihood of achieving and maintaining appropriate levels for prophylaxis. (90) A dose should be given 24-48 hours before discharge from the hospital if the patient meets the criteria or at the earliest possible interval well child appointment before the start of the season. (90) If a second season is indicated, nirsevimab-alip (BEYFORTUS) dosing is increased to 200 mg IM as a one-time injection.

"Although prophylaxis during active infection will not impact the course of the symptomatology, RSV disease is not a contraindication to continuing palivizumab (SYNAGIS) or nirsevimab-alip (BEYFORTUS) prophylaxis. Infection does not confer lasting immunity. "

5. Although prophylaxis during active infection will not impact the course of the symptomatology, RSV disease is not a contraindication to continuing palivizumab (SYNAGIS) or nirsevimab-alip (BEYFORTUS) prophylaxis. Infection does not confer lasting immunity. There is more than one genotype of RSV. Although less common, patients can be re-infected with RSV multiple times during the same RSV season. Thus, one-time dosing with nirsevimab-alip (BEYFORTUS) or monthly dosing with palivizumab (SYNAGIS) should be continued even if the patient has been infected with RSV.(90)
6. Fever or other illnesses, including viral syndromes such as COVID-19, are not contraindications to administering palivizumab (SYNAGIS), nirsevimab-alip (BEYFORTUS), or another monoclonal antibody.
7. There are no restrictions on concurrent RSV prophylaxis with any immunization. (163) Immunization with Measles-Mumps-Rubella (MMR) and Varicella vaccines need not be deferred in infants receiving RSV prophylaxis. RSV prophylaxis does not interfere with the Hepatitis B vaccine, Diphtheria, Tetanus, Pertussis (DTaP) primary immunization schedule, H. Influenza type B (Hib), seasonal influenza vaccination, Pneumococcal Conjugate Vaccine (PCV), or Inactivated Poliovirus Vaccine (IPV).
8. The safety and efficacy of palivizumab (SYNAGIS) or nirsevimab-alip (BEYFORTUS) have not been demonstrated for treating established RSV

disease. RSV prophylaxis does not alter an active RSV infection's disease severity or course.

9. Contraindications and Adverse Reactions

   a. Palivizumab (SYNAGIS) or nirsevimab-alip (BEYFORTUS) should not be used in pediatric patients with a history of a severe prior reaction to RSV prophylaxis. (90) It is unknown whether a history of a severe prior reaction to one will crossover to the other.

   b. Fever, irritability, and injection site reactions are the most commonly reported adverse events. (164)

V. Nosocomial Infection

   A. RSV may be horizontally transmitted in the hospital setting and causes severe disease in high-risk infants and young children.

   B. The best way to prevent RSV disease is strict adherence to infection control practices and in-hospital screening studies to identify and isolate RSV-infected infants. (77) Proper hand washing is of paramount importance.

"Cohorting of children with suspected RSV disease is not recommended. Not only are there other contagious viral and bacterial diseases that mimic RSV, but infection with RSV does not preclude co-infection with bacteria, other viruses, or another subgroup of RSV. The advice of infectious disease and hospital-based infection control experts should be obtained to manage suspected nosocomial outbreaks of RSV occurring within a pediatric ward, pediatric critical care unit, or neonatal intensive care unit. (77, 165)"

   C. Cohorting of children with suspected RSV disease is not recommended. Not only are there other contagious viral and bacterial diseases that mimic RSV, but infection with RSV does not preclude co-infection with bacteria, other viruses, or another subgroup of RSV. The advice of infectious disease and hospital-based infection control experts should be obtained to manage suspected nosocomial outbreaks of RSV occurring within a pediatric ward, pediatric critical care unit, or neonatal intensive care unit. (77, 165)

VI. Using palivizumab (SYNAGIS) or nirsevimab-alip (BEYFORTUS) outside of the FDA indications constitutes off-label use (12, 19)

   A. Off-label use of any medication places the provider at medico-legal risk. The FDA's Center for Drug Evaluation and Research (CDER) has initiated the Bad Ad outreach program to encourage healthcare providers to recognize and report suspected untruthful or misleading drug promotion. "Assuring prescription drug information is truthful, balanced, and accurately communicated" is the intent. Led by the Division of Drug Marketing Advertising and Communications (DDMAC), this effort informs providers about what constitutes misleading promotion and provides a process for reporting suspected violations to the FDA. Violators may include state or professional organizations, those who may profit by modifying FDA-approved dosing or indications for a medication, manufacturers, or individuals who make unrealistic claims about the enhanced action of a medication. There is no safe harbor for government-sponsored organizations that make recommendations outside the FDA indication (e.g., Advisory Committee on Immunization Practices).

   B. Reports can be initiated by contacting the United States Food and Drug Administration's Division of Drug Marketing, Advertising, and Communications at 855-RX-BADAD or (855-792-2323), E-Mail: BadAd@fda.gov, by mail: FDA/CDER/DDMAC, 5901-B Ammendale Rd., Beltsville, MD 20705-1266, or Fax: 301-847-8444.(166) In the past, however, the FDA has not had the resources to act quickly on reports of wayward drug misinformation. The False Claims Act provides another alternative to the Bad Ad outreach program. This fraud-fighting law not only provides substantial rewards for whistleblowers but also includes an action-enforcing mechanism that statutorily requires the government to investigate allegations of fraud. If providers want to ensure that the government will consider their concerns, a False Claims Act *qui tam* action may be filed.

"Reports can be initiated by contacting the United States Food and Drug Administration's Division of Drug Marketing, Advertising, and Communications at 855-RX-BADAD or (855-792-2323), E-Mail: BadAd@fda.gov, by mail: FDA/CDER/DDMAC, 5901-B Ammendale Rd., Beltsville, MD 20705-1266, or Fax: 301-847-8444.(166) In the past, however, the FDA has not had the resources to act quickly on reports of wayward drug misinformation."

Table 1. Proposed Strategy for RSV Prophylaxis

Prophylaxis Indication	Chronological Age	Dosing
Areas Where Strong Data Exist		
Born at < 28 0/7 weeks' gestational age (wGA)	Less than 12 months at the start of the RSV season	Nirsevimab (BEYFORTUS) once or palivizumab (SYNAGIS) monthly during the RSV season
Born at 28 0/7-32 0/7 wGA	1. Less than 12 months at the start of the RSV season 2.Less than six months at the start of the RSV season	1. Nirsevimab (BEYFORTUS) once or 2. palivizumab (SYNAGIS) monthly during the RSV season
Born at 32 1/7-35 6/7 wGA	1. Less than 12 months at the start of the RSV season 2. Less than six months at the start of RSV season with significant provider-identified risk factors	1. Nirsevimab (BEYFORTUS) once or 2. palivizumab (SYNAGIS) monthly during the RSV season
Born at 36 wGA or greater, no other risk factors	Less than 12 months at the start of the RSV season	Maternal RSVpreF (ABRYSVO) (first season) or nirsevimab (BEYFORTUS) once
Chronic lung disease requiring medical management	Less than 24 months at the start of the RSV season	Maternal RSVpreF (ABRYSVO) (first season) or nirsevimab once or palivizumab (SYNAGIS) monthly during the RSV season
Hemodynamically significant congenital heart disease	Less than 24 months at the start of RSV season unless a cardiology waiver is obtained	RSVpreF (ABRYSVO) (first season) or nirsevimab once or palivizumab (SYNAGIS) Monthly during the RSV season
Areas Where Individualized Guidance is Indicated		
Neuromuscular disease affecting respiratory function	Less than 24 months at the start of the RSV season	RSVpreF (ABRYSVO) (first season) or nirsevimab once or palivizumab (SYNAGIS) Monthly during the RSV season
Congenital abnormalities of the airways (e.g., Congenital Diaphragmatic Hernia)	Less than 24 months at the start of the RSV season	RSVpreF (ABRYSVO) (first season) or nirsevimab once or palivizumab (SYNAGIS) Monthly during the RSV season
Immune disorders (e.g., HIV, SCID, DiGeorge, IgA deficiency, Hypergammaglobulinemia)	Less than 24 months at the start of RSV season unless infectious disease or immunology waiver is obtained	RSVpreF (ABRYSVO) (first season) or nirsevimab once or palivizumab (SYNAGIS) monthly during the RSV season
Cystic Fibrosis, Primary Ciliary Dyskinesia, or other rare lung disease resulting in chronic respiratory insufficiency	Less than 24 months at the start of RSV season; consultation with pediatric pulmonology suggested	RSVpreF (ABRYSVO) (first season) or nirsevimab once or palivizumab (SYNAGIS) monthly during the RSV season

The MEDLINE database, the Cochrane Library, and the National Perinatal Association's internal resources and documents were used to search the literature to identify relevant articles published on Respiratory Syncytial Virus (RSV). The search was restricted to articles published in the English language. Priority was given to the outcomes of the original research. Review articles and commentaries were also consulted when their inclusion added substantively to the guidance. Abstracts of research presented at scientific conferences were eligible for inclusion in this document if the abstract was peer-reviewed prior to its publication. Guidelines published by other organizations were evaluated for merit and included where their inclusion was both elucidative and topical. Further, sources from the bibliographies of these guidelines were evaluated and included where appropriate. While necessary for interpreting the studies, expert opinion was not judged to be valid independently without substantiating high-level evidence.

Studies were evaluated for quality using the metric provided by the United States Preventive Services Task Force (167, 168)

I. Evidence obtained from at least one properly designed randomized controlled trial.

II-1. Evidence obtained from well-designed controlled trials without randomization.

II-2. Evidence is obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

II-3. Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.

III. Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A - Recommendations based on good and consistent scientific evidence.

Level B – Recommendations based on limited or inconsistent scientific evidence.

Level C – Recommendations based largely on consensus and expert opinion

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