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SYNAGIS FOR RESPIRATORY SYNCYNTIAL VIRUS (RSV) PROPHYLAXIS

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Contents

Introduction

Respiratory syncytial virus (RSV) is a common pathogen infecting all age groups and usually causes a self-limiting upper respiratory illness. In the more vulnerable, such as preterm or young infants with certain chronic conditions, RSV can lead to severe lower respiratory tract infections (LRTI) such as bronchiolitis and pneumonia.[1] Between 2 to 3 percent of infants in the first year of life develop an RSV infection severe enough to require hospitalization until symptoms improve.[2] Palivizumab is the first and only immunoprophylaxis available, licensed by the Food and Drug Administration (FDA) in 1998, to help prevent serious RSV-mediated LRTI in high-risk pediatric patients 2 years of age or younger.

Recommendations regarding RSV prophylaxis from the American Academy of Pediatrics (AAP) have evolved with data that has become available since the product's approval. The most recent AAP guideline was published in 2014, when the AAP's Committee on Infectious Diseases and Bronchiolitis provided more precise definitions of the 'high risk' pediatric patient to better define who should be treated.[3] In general, the AAP guideline does not recommend use for any individual beyond 24 months. Some prophylaxis criteria developed by the committee are more restrictive compared to the product's labeling, while some recommendations are less restrictive.[3,4] These differences are described further in the guideline section of this review. Relevant systematic reviews were also taken into consideration to explore evidence addressing the use of palivizumab in children over 2 years old. Finally, Medicaid utilization data is provided in addition to points for consideration to facilitate the development of prior authorization criteria for palivizumab.

Methodology

Websites for the FDA, Medline (PubMed), Centers for Disease Control and Prevention, American Academy of Pediatrics, Guidelines.gov, and the National Institute for Health Care Excellence were searched for background information on RSV, bronchiolitis, and palivizumab use. The Cochrane Library was searched for systematic reviews, with particular focus given to randomized-controlled evidence regarding the efficacy of palivizumab published after the 2014 AAP palivizumab-prophylaxis guideline. The drug information resources, Lexicomp and Micromedex, were also used.

Utilization data was queried for the fee-for-service (FFS) Medicaid population, looking at claims related to the product's National Drug Code (NDC) and related to the Current Procedural Terminology (CPT) code 90378 (Respiratory syncytial virus, immune globulin, for intramuscular use, 50 mg).

Palivizumab for Respiratory Syncytial Virus (RSV)

I. RSV Overview

Respiratory syncytial virus (RSV) is a frequent infection affecting all age groups.[5] Most people become infected by 2 years old and develop only upper-respiratory symptoms which may include rhinorrhea, pharyngitis, cough, headache, fatigue, and fever.[1,5] In the more vulnerable, mainly young infants and older adults with chronic conditions, RSV can cause more severe lower-respiratory tract infections such as bronchiolitis and pneumonia.[5] RSV can also exacerbate serious conditions such as asthma, chronic obstructive pulmonary disease, and congestive heart failure.

Between 2 to 3 percent of infants in the first year of life develop a lower-respiratory tract infection severe enough to require hospitalization.[2] Among the pediatric age group below five years old, there are approximately 58,000 hospitalizations each year in the United States (US) due to RSV infection.[2,5] About 58 to 64% of pediatric hospitalizations occur in patients who are 5 months or younger. Table 1 lists risk factors associated with severe RSV disease.[2]

Table 1. Risk Factors for Severe Respiratory Syncytial Virus Disease[5]

Risk factors for the young	Risk factors for adults
▪ infant prematurity ▪ children younger than 2 years old with chronic lung or heart disease ▪ children with suppressed immune systems ▪ children who have neuromuscular disorders, including those who have difficulty swallowing or clearing mucus secretion	▪ older adults, especially those ≥65 years of age ▪ adults with chronic lung or heart disease ▪ adults with weakened immune systems

In young children that progress to an LRTI, rhinorrhea and decreased appetite are usually the first symptoms to present. A cough emerges 1 to 3 days later, followed by sneezing, fever, and wheezing.[5] Infants in the first few weeks of life may present with little respiratory signs, but mainly with irritability, decreased activity, poor feeding, and apnea.[1,5] About 1 to 2 percent of infected children under 6 months old require hospitalization where oxygen, intubation, and/or mechanical ventilation may be employed until symptoms improve.[5]

RSV causes 50 to 80% of all bronchiolitis cases and between 10 and 30% of these cases involve coinfection with another virus (e.g. enterovirus/rhinovirus, influenza, human metapneumovirus, and parainfluenza virus).[6] Bronchiolitis is characterized by tachypnea, increased respiratory effort, rales, and wheezing from debris accumulation in the small airways.[1,6] Risk factors for severe bronchiolitis include a history of preterm birth, age less than 12 weeks old, immunocompromised status, congenital cardiac disease, chronic lung disease of prematurity, congenital/genetic abnormalities (e.g. cystic fibrosis, Down syndrome, cerebral palsy), and exposure to cigarette smoke in utero or postnatal.[7] Bronchiolitis symptoms usually last between 2 to 3 weeks;[6] however, up to 50% of hospitalized patients will experience recurrent wheezing episodes for several years.[8,9]

RSV is highly transmittable via particle aerosol or direct contact. The incubation period ranges from 2 to 8 days.[1] Hosts with RSV can shed the virus for as long as 3 weeks.[6] Laboratory tests are utilized

to confirm RSV infection since symptoms are nonspecific and can overlap with other viral or bacterial infections.[5] Common tests include antigen testing and real-time reverse transcriptase-polymerase chain reaction (rRT-PCR), which is more sensitive and more frequently performed compared to antigen testing.[5,10] Both methods, however, are effective for diagnosing RSV infection in infants and young children.[5]

RSV persists on a seasonal basis, generally during fall, winter, and spring in the western region of the US. Timing and severity varies from year to year and between localities.[5,11] Participating laboratories report RSV-testing results to the National Respiratory and Enteric Virus Surveillance System (NREVSS). The ongoing RSV-circulation prevalence can be viewed per state, divisional, regional, and national summaries provided on the Centers for Disease Control and Prevention (CDC) website, although there is considerable lag time for the most recent data points.[10] State-level information for Utah can be found at the CDC website which provides a 3-week moving average of positive RSV tests for the current RSV season.[10] Appendix A provides surveillance data compiled by the US Department of Health and Human Services that can be found on the CDC website: Table 1 provides the 3-week moving average data for the current season in Utah,[10] and Table 2 provides previous RSV-season trends for Region 8 which includes Utah.[12,13] Nonetheless, internal hospital surveillance systems may best reflect the RSV-prevalence for the current season since there is lag time in the CDC state-level data and past regional trends may not necessarily reflect what occurs currently at the local level.

Experimental studies are currently underway for a vaccine, monoclonal antibodies, and antiviral therapies for the prevention and treatment of RSV.[5] The only FDA-approved prophylaxis for RSV is palivizumab—approved only for use in high-risk infants and young children. Other measures that decrease the risk of RSV infection include diligent hand washing hygiene, continued breast feeding for at least six months, and elimination of tobacco smoke exposure to vulnerable children.[6]

Guidelines for the treatment of pediatric bronchiolitis do not list palivizumab as an option for active RSV bronchiolitis infection.[14,15] The use of palivizumab is recommended by practice guidelines only for prophylaxis of RSV.[3,15] Prophylaxis guidelines are expounded beginning on page 7. Treatment of patients hospitalized with RSV-induced bronchiolitis primarily relies on supportive care which may include hydration, feeding support, supplemental oxygen, suction of the upper airway, and mechanical ventilation for very severe cases.[14,15] Ribavirin, in an aerosol formulation, is the only agent approved to treat hospitalized infants and young children with severe RSV LRTI.[16] Ribavirin, however, is used sparingly and reserved for life-threatening cases because of its limited efficacy and toxicity profile (e.g. possible bone marrow suppression, carcinogenicity, and teratogenicity).[1,8] The 2015 AAP Red Book notes that the efficacy of ribavirin has been inconsistent in clinical trials, yet is associated with a small, statistically-significant increase in oxygen saturation during acute RSV infection.[1] Nonetheless, a consistent decrease in the need for mechanical ventilation, length of stay in the intensive care unit, or total days of hospitalization has not been demonstrated, and there are potential toxic effects to exposed health care personnel.[1]

II. Palivizumab (Synagis)

Palivizumab is an antibody that provides passive immunity by inhibiting viral fusion to host respiratory epithelial cells.[1,4] This immunoprophylaxis is able to hamper viral infection of both A and B RSV subtypes.[17] Although the FDA patent protection has expired for the branded product, a biosimilar for palivizumab has not yet entered the US market.

Palivizumab is indicated only for high-risk pediatric patients who are 2 years of age or younger meeting certain criteria. It is administered intramuscularly, on a monthly basis, per weight-based dosing. Its FDA approval was based on two placebo-controlled randomized trials that provided 5 total monthly injections for the RSV season: one trial (IMpact-RSV) was in children ≤ 24 months of age with a history of prematurity (born at or before 35 week's gestation) and the second trial was in children ≤ 24 months of age with hemodynamically significant congenital heart disease.[4,18,19] The former study showed a significant 5.8% absolute reduction (55% relative reduction) in the incidence of RSV hospitalizations for palivizumab compared to placebo (4.8% versus 10.6%, p<0.001). The later trial showed a 4.4% absolute reduction (45% relative reduction) for palivizumab versus placebo (5.3% versus 9.7%, p=0.003). [4,18,19]

There are key differences between the approved labeling for palivizumab and the 2014 AAP guideline. With respect to the continuation of therapy upon an RSV infection, the product labeling recommends continued monthly administration of palivizumab until the end of the RSV season.[4] However, the AAP recommends discontinuing prophylaxis for the remainder of the season upon experiencing an RSV-related hospitalization because the risk of a second RSV-related hospitalization in the same season is very low.[3]

Table 2 summarizes the labeled indications, dosing, and warning/precaution information for palivizumab.

Table 2. Synagis (palivizumab) Indications, Dosing, and Warnings [4]

Formulations and Indications
Synagis— palivizumab: Available in 50 mg/0.5 mL and 100 mg/ 1 mL single dose vials, preservative-free o Store under refrigeration at 36-46°F upon receipt and until use; do not freeze
For the prevention of serious lower respiratory tract disease caused by RSV in pediatric patients having the following: 1) History of premature birth (≤35 weeks gestational age) and who are 6 months of age or younger at the beginning of RSV season 2) Bronchopulmonary dysplasia that required medical treatment within the previous 6 months and who are 24 months of age or younger at the beginning of RSV season 3) Hemodynamically significant congenital heart disease and who are ≤24 months of age at the beginning of RSV season *Limitations of use*— safety and efficacy have not been established for treatment of RSV

Table 2. Synagis (palivizumab) Indications, Dosing, and Warnings [4]

Dosage and Administration
Dosed as 15 mg/kg of body weight given monthly by intramuscular injection *Initial dose*— administer prior to commencement of the RSV season; the remaining doses should be administered monthly throughout the RSV season. o Children who develop an RSV infection should continue receiving monthly doses to the RSV season end. o In the northern hemisphere, the RSV season typically commences in November and lasts through April, but it may be a different time frame in certain communities *Dose adjustments*— Children undergoing cardio-pulmonary bypass should receive an additional dose as soon as possible after the cardio-pulmonary bypass procedure (even if sooner than a month from the previous dose), since serum levels are reduced during this procedure *Limitations*—efficacy of palivizumab at doses below or less frequently than the recommended dose, has not been established *Administration labeling* includes the following: the vial should not be diluted, shaken, or vigorously agitated; do not use if vial contents contain particulate matter or discoloration; employ aseptic technique, preferably into the anterolateral aspect of the thigh; and volumes over 1 mL should be given as a divided dose. *Elimination half-life* in the pediatric population is approximately 24.5 days; however, there is substantial variability between individuals.[4,20]
Warnings, Precautions, and Adverse Reactions
Contraindications— hypersensitivity to palivizumab **Hypersensitivity Reactions**— Anaphylaxis/shock, including fatal cases upon initial exposure or re-exposure to palivizumab have occurred. Permanently discontinue use upon a significant hypersensitivity reaction occurs. The relationship between these reactions and the development of antibodies to palivizumab is unknown. The clinical trial incidence of anti-palivizumab antibody is reported as high as 1.5% in the product label. **Coagulation abnormalities—** As with any intramuscular injection, use caution for children with thrombocytopenia or any coagulation disorder. **RSV Diagnostic Test Interference—** May interfere with immunological-based RSV diagnostic tests (e.g. antigen detection-based assays, viral culture assays), however does not interfere with reverse transcriptase-polymerase chain reaction assays. Assay interference could lead to false-negative RSV diagnostic test results. **Proper Administration—** Administration should occur immediately after dose withdrawal from the vial. **Adverse Reactions**— The most serious adverse reactions are anaphylaxis and other acute hypersensitivity reactions**.** In clinical trials, as discussed in the package insert, fever and rash were each reported more frequently among palivizumab than placebo recipients, 27% versus 25%, and 12% versus 10%, respectively **Post Marketing Blood Dyscrasia—** severe thrombocytopenia (platelet count less than 50,000 per µL) is noted

Abbreviation: RSV, respiratory syncytial virus

III. Guidelines for RSV Prophylaxis

As additional information has become available since the approval of palivizumab, the AAP has updated recommendations for the use of palivizumab prophylaxis. In the most recent 2014 update, the committee set out to establish more precise definitions of the 'high risk' patient to clarify where evidence most clearly supported prophylaxis.[2] The updated guideline was composed in consultation with the American College of Chest Physicians, American College of Emergency Physicians, American Thoracic Society, Emergency Nurses Association, National Association of Neonatal Nurses, National Association of Neonatal Nurse Practitioners, and Society of Hospital Medicine.[3] The committee's technical report pointed out that prospective population-based studies of laboratory-confirmed RSV-hospitalized cases showed mortality rates that were lower than previously estimated and that cost-benefit reports showed high cost versus limited benefit of palivizumab prophylaxis.[2]

The committee summarized that "[p]alivizumab prophylaxis has limited effect on RSV hospitalizations on a population basis, no measurable effect on mortality, and a minimal effect on subsequent wheezing."[3] There are several populations for which the AAP recommendations are more restrictive compared to the product labeling, as the committee considered data beyond the pivotal clinical trials leading to drug's approval. There are also areas in which the AAP recommendations are broader (i.e. less restrictive) compared to the product labeling. Table 3 provides the recommended populations for palivizumab prophylaxis based on the AAP 2014 guideline, in addition to contrasting labeled indications. Table 4 provides a condensed version of this information, structured by indication category and additional qualifying criteria.

Table 3. AAP Recommendations for Palivizumab Prophylaxis vs. Palivizumab Labeling

American Academy of Pediatrics (AAP) 2014 Palivizumab Prophylaxis Guideline [2,3]	Palivizumab Labeled Indications [4]
I. PRETERM INFANTS WITHOUT CHRONIC LUNG DISEASE (CLD) OF PREMATURITY OR CONGENITAL HEART DISEASE (CHD) ▪ May consider PAL for infants born before 29 weeks, 0 days' gestation who are younger than 12 months at the start of the RSV season. ▪ May consider PAL for infants born later than 29 weeks, 0 days' gestation who are younger than 12 months at the start of the RSV season based on additional risk factors: congenital heart disease, chronic lung disease, or another condition as described below. ▪ A second season of palivizumab is not recommended on the basis of prematurity alone. (See section 'X. Use of Palivizumab in the Second Year of Life') **Rationale**-- Data available for infants born at 29weeks, 0 days' gestation or later does not identify a clear gestational age cutoff for which the benefits of prophylaxis are clear. Thus a universal recommendation is reserved for where the benefits are most clear. Exceptions can be made for infants born later than 29 weeks, 0 days' gestation with additional risk factors such as congenital heart disease, chronic lung disease, etc. as reviewed below.	I. Approved for infants with a history of premature birth (≤35 weeks gestational age) and who are 6 months of age or younger at the beginning of RSV season • The labeled age at the start of RSV season is more restrictive • AAP is more restrictive on the gestational birth age for eligibility • *Off-label* use for infants qualifying based on gestation age, without CLD or CHD, but who are over 6 months of age at the beginning of the RSV season
II. PRETERM INFANTS WITH CHRONIC LUNG DISEASE (CLD) ▪ May consider PAL for the RSV season during the first year of life for preterm infants who develop CLD of prematurity defined as gestational age <32 weeks, 0 days and a requirement for >21% oxygen for at least the first 28 days after birth. ▪ During the second year of life, consideration of PAL is recommended only for infants who satisfy this definition of CLD of prematurity and continue to require medical support (chronic corticosteroids, diuretics, or supplemental oxygen) during the 6-month period before the start of the second RSV season. For infants with CLD who do not continue to require medical support in the second year of life, prophylaxis is not recommended.	**II.** Approved for infants with bronchopulmonary dysplasia (BPD) that required medical treatment within the previous 6 months and who are ≤24 months of age at the beginning of RSV season • AAP is more specific on medical treatment required in the first 28 days of life • *Off-label* use when initiating PAL at the beginning of the season for an infant that is between 2 and 3 years old
III. INFANTS WITH HEMODYNAMICALLY SIGNIFICANT CHD ▪ Children younger than 2 years who undergo cardiac transplantation during the RSV season may be considered for palivizumab prophylaxis ▪ Certain children who are 12 months or younger with hemodynamically significant CHD may benefit from PAL prophylaxis. Those most likely to benefit include infants with the following: - acyanotic heart disease who are receiving medication to control congestive heart failure and will require cardiac surgical procedures - infants with moderate to severe pulmonary hypertension Notes: Decisions regarding prophylaxis for infants with cyanotic heart defects in the first year of life may be made in consultation with a	**III.** Approved for infants with hemodynamically significant congenital heart disease who are ≤24 months of age at the beginning of RSV season • AAP recommendation is more restrictive for certain CHD patients between 12 and 24 months old

Table 3. AAP Recommendations for Palivizumab Prophylaxis vs. Palivizumab Labeling

American Academy of Pediatrics (AAP) 2014 Palivizumab Prophylaxis Guideline [2,3]	Palivizumab Labeled Indications [4]
pediatric cardiologist. For infants < 24 months who continue to require prophylaxis after cardiopulmonary bypass, a postoperative dose of PAL (15 mg/kg) should be considered. The following groups of infants with CHD are not at increased risk of RSV infection and generally should not receive immunoprophylaxis: - Infants/children with hemodynamically insignificant heart disease (eg, secundum atrial septal defect, small ventricular septal defect, pulmonic stenosis, uncomplicated aortic stenosis, mild coarctation of the aorta, and patent ductus arteriosus) - Infants with lesions adequately corrected by surgery, unless they continue to require medication for congestive heart failure - Infants with mild cardiomyopathy who are not receiving medical therapy - Children in the second year of life with CHD	
IV. CHILDREN WITH ANATOMIC PULMONARY ABNORMALITIES OR NEUROMUSCULAR DISORDER ▪ May consider prophylaxis for infants <1 year old with neuromuscular disease or congenital anomaly that impairs the ability to clear secretions from the upper airway because of ineffective cough	**IV.** Approved for infants with BPD that required medical treatment within the previous 6 months and who are ≤24 months of age at the beginning of RSV season
V. IMMUNOCOMPROMISED CHILDREN ▪ Consider PAL for children < 24 months of age who are profoundly immunocompromised during the RSV season. Authors comment that (1) palivizumab has not been associated with improved outcomes in hematopoietic stem cell transplant recipients and that no data was available to support a benefit from palivizumab use among immunocompromised patients. They also note that practices vary nationwide and further research is required to develop definitive recommendations for the use of palivizumab in such a heterogeneous group of children.	**V.** *Off-label* use if based solely on immunocompromised diagnosis; may meet labeled indications based on other conditions
VI. CHILDREN WITH DOWN SYNDROME ▪ Routine use of PAL is not recommended in this population unless the patient has a qualifying condition such as CHD, airway clearance issues, or prematurity history of GA<29 weeks.	**VI.** *Off-label* use if based solely on Down Syndrome diagnosis; may meet labeled indications based on other conditions
VII. CHILDREN WITH CYSTIC FIBROSIS ▪ May consider PAL for infants <1 year old with cystic fibrosis who have CLD *and/or* nutritional compromise ▪ Can consider PAL for the second year of life for infants with severe lung disease (previous hospitalization for pulmonary exacerbation in the first year of life or abnormalities on chest radiography or chest computed tomography that persist when stable) or weight for length less than the 10th percentile	**VII.** Approved for infants with BPD that required medical treatment within the previous 6 months and who are ≤24 months of age at the beginning of RSV season

Table 3. AAP Recommendations for Palivizumab Prophylaxis vs. Palivizumab Labeling

American Academy of Pediatrics (AAP) 2014 Palivizumab Prophylaxis Guideline [2,3]	Palivizumab Labeled Indications [4]
Rationale—most studies show that the incidence of RSV hospitalization in CF pediatric patients is uncommon. Moreover, clear evidence to support the efficacy of palivizumab prophylaxis for the broad group of CF patients was lacking per RCT and observational data.	
VIII. RECOMMENDATION FOR AMERICAN INDIAN INFANTS ▪ Special consideration may be prudent for Navajo and White Mountain Apache infants in the first year of life.	**VIII.** *Off-label* use if based solely on American Indian ethnicity; may meet labeled indications based on other conditions
IX. DISCONTINUATION OF PALIVIZUMAB WITH BREAKTHROUGH RSV HOSPITALIZATION ▪ If any infant or child experiences a breakthrough RSV hospitalization, monthly **prophylaxis should be discontinued** **Rationale**—the risk of a repeat RSV hospitalization in the same season is very low (<0.5%). In addition, repeat RSV infections in the same season are associated with less severe clinical illness compared to the initial infection. (recommendation based on observations from RCT and observational studies)	**IX.** Labeling states that prophylaxis should continue throughout the RSV season even if the patient develops RSV infection; see the more restrictive recommendation provided by the AAP
X. USE OF PALIVUMAB IN THE SECOND YEAR OF LIFE ▪ PAL prophylaxis is recommended for the second RSV exposure season *only* for preterm infants born at <32 weeks, 0 days' gestation who required at least 28 days of oxygen after birth and who continue to require supplemental oxygen, chronic systemic corticosteroid therapy, or bronchodilator therapy within 6 months of the start of the second RSV season.	**X.** Approved for infants with a history of premature birth (≤35 weeks gestational age) and who are ≤6 months of age at the beginning of RSV season AND for infants with BPD that required medical treatment within the previous 6 months and who are ≤24 months of age at the beginning of RSV season

Abbreviations: AAP, American Academy of Pediatrics; BPD, bronchopulmonary dysplasia; CF, cystic fibrosis; CHD, congenital heart disease; CLD, chronic lung disease; hsCHD, haemodynamically significant congenital heart disease; GA, gestational age; PAL, palivizumab; RCT, randomized controlled trial, RSV, respiratory syncytial virus;

Table 4. Indications per 2014 AAP Guideline and Palivizumab Labeling

Indication Category		Additional Criteria for Qualifying Patients
Infant without CLD of Prematurity or CHD	2014 AAP Guideline	
	Hx of premature birth (GA <29 weeks)	▪ Must be < 12 months old at the start of the RSV season ▪ Treatment for only the 1st RSV season is recommended
	Palivizumab labeling	
	Hx of premature birth (GA ≤35 weeks)	▪ Must be ≤ 6 months old at the start of the RSV season
Infant with CLD of Prematurity ▪ To meet the CLD of prematurity definition, the patient must have required >21% oxygen for at least the first 28 days after birth	2014 AAP Guideline Hx of premature birth (GA <32 weeks)	▪ Must be in the first year of life **OR** ▪ Can be in the second year of life (for 2nd RSV season) but must continue to require medical support (chronic corticosteroids, diuretics, or supplemental oxygen) during the 6-month period before the start of the second RSV season.
Infant with Bronchopulmonary Dysplasia	Palivizumab labeling	▪ Must be ≤ 24 months old at the beginning of the RSV season AND must have required medical treatment within the previous 6 months of the RSV season
Infant with Anatomic Pulmonary Abnormally or Neuromuscular Disorder that Impairs Ability to Clear Secretions from Upper Airway	2014 AAP Guideline	▪ Must be in the first year of life
Infant with Hemodynamically Significant CHD[a]	2014 AAP Guideline	▪ Must be ≤ 12 months old[a] ▪ Decisions for infants <1 year with cyanotic heart defects may be made in consultation with a pediatric cardiologist **OR** ▪ Patient can be < 2 years old if they have undergone cardiac transplantation during the RSV season
	Palivizumab labeling	▪ Must be ≤ 24 months at the start of the RSV season
Profoundly Immunocompromised Child	2014 AAP Guideline	▪ Patient must be < 24 months of age
Child with Cystic Fibrosis	2014 AAP Guideline	▪ Infants in the first year of life with CF, who have CLD *and/or* nutritional compromise ▪ Infants in the second year of life with severe lung disease (hospitalization for pulmonary exacerbation in first year of life or abnormalities on chest radiography or computed tomography persisting when stable) **or** weight for length below the 10th percentile

Table 4. Indications per 2014 AAP Guideline and Palivizumab Labeling

Other APP Recommendations
The AAP specifically recommends against use of palivizumab for patients who meet the following criteria: ▪ During the patient's second RSV season, based on a history of prematurity alone; this would also be an off-label use based on the FDA-indications ▪ Based on down syndrome diagnosis alone (without any other qualifying conditions as previously described) ▪ Infants with CHD who have (a) hemodynamically insignificant heart disease (e.g. secundum atrial septal defect, small ventricular septal defect, pulmonic stenosis, uncomplicated aortic stenosis, mild coarctation of the aorta, and patent ductus arteriosus), (b) lesions adequately corrected by surgery unless continued medications are required for CHF, (c) mild cardiomyopathy who are not receiving medical therapy, and (d) children in the second year of life (see exception for cardiac transplant patients)

Abbreviations: CHD, congenital heart disease; CF, cystic fibrosis; CHF, congestive heart failure; CLD, chronic lung disease of prematurity; GA, gestational age; Hx, history; RSV, respiratory syncytial virus;
[a] The AAP states that those most likely to benefit include infants with (a) acyanotic heart disease who receive medication to control CHF and will require cardiac surgical procedures and (b) infants with moderate to severe pulmonary hypertension. Decisions regarding infants <1 year with cyanotic heart defects may be made in consultation with a pediatric cardiologist

In a retrospective review of RSV cases among an alliance of 115 academic medical centers and 165 affiliated hospitals, authors assessed the effects of the 2014 AAP guideline changes for the population between 12 and 24 months old with congenital heart disease (CHD), accounting for 1,269 RSV hospitalizations.[21] Authors found no significant changes in the length of stay, ICU admission rate, or in-hospital mortality for children hospitalized with RSV and CHD between 13 and 24 months old, in the two years following the guideline changes. They concluded that the evidence supports the 2014 AAP recommendations to limit palivizumab to children up to 12 months old with CHD.[21]

Table 5 provides a summary of two international guidance publications for the use of palivizumab including (1) a 2017 publication with international expert recommendations for the pediatric subpopulation with hemodynamically significant CHD and (2) a 2016 consensus statement prepared by Italian expert clinicians.

Table 5. Additional Guidance for Palivizumab Prophylaxis

Global Expert Exchange Recommendations for the Pediatric Subpopulation with hsCHD, 2017 [22]

Palivizumab prophylaxis is recommended for children who meet the following:

With unoperated hsCHD

A. Age <2 years with unoperated hsCHD, who require medication to manage their congestive heart failure, are cyanotic (oxygen saturations <85%), who have pulmonary hypertension or symptomatic airway abnormalities

With surgically operated hsCHD

B. Age <1 year with surgically operated hsCHD with residual defects OR aged 1–2 years up to 6 months postoperatively or on a case-by-case basis

With pulmonary hypertension

C. Age < 2 years being treated (e.g. on pulmonary vasodilators, oxygen, diuretics, or anticoagulants) for idiopathic pulmonary arterial hypertension (defined as a resting mean pulmonary artery pressure >25 mmHg beyond the first few months of life) or with pulmonary hypertension associated with CHD or secondary to cardiomyopathy

With cardiomyopathies

D. Age < 1 year with cardiomyopathies requiring medical treatment, including congestive heart failure therapy and oxygen support

With heart transplant

E. Age <2 years are in their 1st year after a heart transplant or for those in this age range who are on a heart transplant waiting list

With associated risk factors

F. Aged <2 years with a genetic condition or associated condition who have hsCHD, regardless of primary diagnosis

All key international guidelines for the use of palivizumab prophylaxis in the hsCHD pediatric population are summarized in this consensus publication. After reviewing excerpts from those guidelines published after the 2014 American Academy of Pediatrics guideline (specifically the 2015 Canadian, Japanese, and Taiwanese guidelines), no recommendations for use of palivizumab in hsCHD patients > 2 years old was found.

Consensus Conference on the Appropriateness of Palivizumab Prophylaxis in Respiratory Syncytial Virus Disease, 2016[23]

Summary conclusions regarding palivizumab prophylaxis for different clinical conditions

- Palivizumab is useful for the following clinical conditions: preterm infants <29 weeks; children with bronchopulmonary disease; and children with cardiac disease.
- Palivizumab is not recommended in preterm infants with GA of 29 weeks or more, without a qualifying co-morbidity.
- Palivizumab prophylaxis is not recommended in children based solely on diagnosis of particular primary (SCID, DiGeorge Syndrome, Wiskott–Aldrich Syndrome) or acquired (HIV, related to immunosuppressants) immunodeficiency, neuromuscular disorder, bronchopulmonary disease/malformation and cystic fibrosis.

- Children with Down Syndrome— Palivizumab is unlikely to be helpful
- Children with immunodeficiency— Insufficient evidence to base recommendation for PAL use
- Children with cystic fibrosis— Insufficient evidence to base recommendation for PAL use
- Children with neuromuscular disorder— Insufficient evidence to base recommendation for PAL use

Abbreviations: AAP, American Academy of Pediatrics; BPD, bronchopulmonary dysplasia; CHD, congenital heart disease; hsCHD, haemodynamically significant congenital heart disease; GA, gestational age; PAL, palivizumab; RSV, respiratory syncytial virus;

IV. Systematic Reviews

Systematic reviews that were identified are described in Appendix C. A Cochrane review by Robinson et al, 2016, assessed the efficacy and safety of PAL versus placebo, no prophylaxis or other prophylaxis, in preventing hospitalization and mortality from RSV in pediatric patients up to 18 years old with cystic fibrosis (CF).[24] Only one randomized controlled trial (RCT) study met the inclusion criteria. The RCT by Cohen et al, 2005,[25] included 186 infants up to two years old, where five monthly doses of palivizumab (N = 92) were administered compared to placebo (N = 94). Comparing each study arm, there was no significant difference between RSV-related hospitalizations, mortality after 6 months of follow up, the need for oxygen therapy, or any adverse events. The authors concluded that there were no clinically meaningful differences in efficacy outcomes. Kua et al, 2017, also identified only the one RCT (Cohen et al) and concluded that more well-designed RCTs are need to clarify potential benefits of palivizumab prophylaxis in the CF population.[26]

V. Evidence Summary Points

Number of doses per season— The AAP guideline stated that a maximum of 5 doses, which provides more than 24 weeks of protection, is needed for a single RSV season and recommended against providing more than 5 doses in the continental US.[3] Pivotal RCTs studied 5-dose regimens for the RSV-season to arrive at positive findings.

Navajo and White Mountain Apache Infants— The AAP states, "…special consideration may be prudent for Navajo and White Mountain Apache infants in the first year of life," because there is limited information available concerning the burden of disease in these populations.[3]

Cystic fibrosis— Palivizumab prophylaxis for an infant with cystic fibrosis may be appropriate if the infant meets criteria per the FDA-approved indications or according to the 2014 AAP guideline criteria (see Table 4). There is insufficient evidence to support the broad use of palivizumab in children with cystic fibrosis as highlighted in the 2014 AAP guideline, in a 2016 Cochrane systematic review, and in a 2016 European expert consensus statement.[2,23,24]

Immunocompromised patients— The 2014 AAP guideline notes that severe RSV-mediated disease is documented in children on chemotherapy or who are immunocompromised due to other conditions. Although the efficacy of prophylaxis in this cohort is unknown, the committee advised considering prophylaxis for profoundly immunocompromised children younger than 24 months of age during the RSV season. This would be an off-label use if the patient doesn't qualify based on the product labeling.

Other off label use—Off label, non-established uses of palivizumab include case reports where palivizumab was used for the treatment of an active RSV infection, administered intravenously, to patients who were post hematopoietic stem cell transplant[27] or in combination with ribavirin in high-risk patients.[28] Palivizumab is not approved to treat a severe active RSV infection, nor do

guidelines identified support use in this manner. Furthermore, the AAP 2014 guideline points out that controlled trials have failed to demonstrate that monoclonal antibodies such as palivizumab are therapeutically beneficial (i.e. no reduced disease severity outcomes) for the treatment of RSV.[2,29]

Age — Although there are areas where the 2014 AAP recommends off-label use for certain high-risk pediatric patients, none of these are in support of using palivizumab in children during their third year of life. The AAP recommendations are limited to children in their first or second year of life based on certain criteria as outlined in Tables 3 and 4. The FDA-labeling and AAP guidelines differ with regard to eligible patients that are 24 months of age, but neither supports use for any particular subgroup of pediatric patients who are >24 months at the start of the RSV season.

Medicaid Fee-for-Service (FFS) Utilization Data

Table 6 provides utilization for the Medicaid fee-for-service population. Data was queried from 2015 to March 5th 2018, from both pharmacy claims and medical claims using the product National Drug Code (NDC) and related Current Procedural Terminology (CPT) codes.

Table 6. All Medicaid Utilization, Fee-for-Service Fills 2015 to March 5th 2018

	2015		**2016**		**2017**		**2018**		Total unique claims (patients)
	Claims	Patients	Claims	Patients	Claims	Patients	Claims	Patients	
Claims and Patients by Palivizumab Products using NDC Codes									
Synagis (palivizumab) injection **100 mg**	179	75	164	75	128	62	45	26	516 (194)
Synagis (palivizumab) injection **50 mg**	92	46	112	45	91	40	17	10	312 (120)
Claims and Patients by Palivizumab-Related CPT Procedure Code									
CPT 90378 RSV antibody IM use, 50mg	71	33	59	35	52	34	15	12	197 (98)
Total unique Claims and Patients	342	88	335	92	271	77	77	28	1025 (232)

Abbreviations: CPT, Current Procedural Terminology; IM, intramuscular; NDC, National Drug Code, RSV, respiratory syncytial virus

Figure 1 provides the age at first fill for all patients with a palivizumab NDC or 90378-CPT claim captured from 2015 to March 5th, 2018 based on the above data in Table 6. All claims that occurred for patients 3 years or older were medical-type claims (not pharmacy claims). Administration of palivizumab to a patient who is >24 months old represents off-label use. Moreover, the 2014 AAP guideline generally does not support use beyond the second year of life.

Figure 1. Patient age breakdown for all[a] FFS claims

Age (years)	**# of unique patients** ▪ Patient counts by NDC (pharmacy; medical) ▪ Patient count by CPT
<2	**220** ▪ (185; 62) ▪ 96
2 to 5	**3** ▪ (0; 2) ▪ 2
6 to 17	0
18 to 49	**6** ▪ (0;6) ▪ 0
≥ 50	**3** ▪ (0;3) ▪ 0
Total unique patients	232

Abbreviation: FFS, fee-for-service

[a] Medical and Retail Pharmacy Claims

Table 7 provides the utilization for the fee-for-service population (2015 to March 5th 2018) from medical claims only, using product NDC codes, while Table 8 provides this data for pharmacy claims.

Table 7. Medical Claims, Fee-for-Service Fills 2015 to March 5th 2018

		2015		2016		2017		2018	
Product		Claims	Patients	Claims	Patients	Claims	Patients	Claims	Patients
palivizumab	Synagis injection 100MG/ML	37	17	46	20	44	26	6	5
palivizumab	Synagis injection 50 mg	29	10	63	15	42	12	4	3
Total of unique claims and patients		66	25	109	28	86	31	10	8

Table 8. Retail Claims, Fee-for-Service Fills 2015 to March 5th 2018

		2015		2016		2017		2018	
Product		Claims	Patients	Claims	Patients	Claims	Patients	Claims	Patients
palivizumab	SYNAGIS INJ 100MG/ML	143	69	118	65	97	51	40	26
palivizumab	Synagis injection 50 mg	64	37	50	33	51	34	14	9
Total of unique claims and patients		207	73	168	71	148	58	54	27

Table 9 provides the number of identified RSV-prophylaxis treatments per patient versus the number of patients in each season. A treatment was defined as a claim for the CPT code 90378 (RSV immune globulin for intramuscular use, 50 mg).

Table 9. Patient counts by number of treatments based on CPT 90378 claims during recent RSV seasons (medical FFS claims only)

	Full RSV Season Oct. 2016 to May 2017	Current RSV Season Oct. 2017 to March 20th 2018
Number of palivizumab treatments	**Number of Patients**	**Number of Patients**
1	17	9
2	4	4
3	3	2
4	3	0
5	0	0
≥6	0	0

Table 10 provides the number of identified RSV-prophylaxis treatments per patient versus the number of patients in each season. A treatment was defined as the occurrence of an NDC code for palivizumab, without another NDC recorded within 7 days. NDC records that occur within 7 days of one another were considered a single treatment.

Table 10. Patient counts by number of treatments based on palivizumab NDC claims during recent RSV seasons (medical and pharmacy FFS claims)

	Full RSV Season Oct. 2016 to May 2017	Current RSV Season Oct. 2017 to March 22nd 2018
Number of palivizumab treatments	**Number of Patients**	**Number of Patients**
1	26	11
2	10	12
3	10	3
4	5	5
5	9	0
≥6	0	0

Potential reasons that infants may not receive the maximum-allowed 5 doses of palivizumab in any given RSV-season include the following: (1) an infant qualifies in their first year of life whose birth occurs during the RSV season (e.g. a qualifying infant born in Feb. would need <5 doses to get them to the end of the season); (2) adherence issues; and (3) a patient may have been hospitalized with RSV and discontinued prophylaxis for the remainder of the season. There may be other potential scenarios.

Discussion Topics for Developing Prescribing Authorization (PA) Criteria

- *Indication*—Palivizumab is approved for RSV prophylaxis. Product labeling specifically states that the safety and efficacy of palivizumab for the treatment of RSV has not been established.[4] There were no practice guidelines identified that support the use of palivizumab for the treatment of active severe RSV infection in high-risk patients (e.g. bronchiolitis).

- *Age limit*—AAP recommendations are limited to children in their first or second year of life (i.e. 0 to <1 year old, and 1 to <2 years old, respectively) who meet eligibility criteria (see Table 4). The FDA-labeling and AAP guidelines for the use of palivizumab differ with regard to patients that are 12 to ≤ 24 months old, but overall, neither supports use for any particular subgroup of pediatric patients who are **>**24 months at the start of the RSV season.
  - Consider restricting coverage for CPT code 90378 (RSV immune globulin for intramuscular use) based on age, and entirely for CPT code 90379 (RSV immune globulin for intravenous use) based on off-label non-established use.

- *Off-label AAP supported uses*—Note the various categories of patients (e.g. profoundly immunocompromised) and/or broader criteria for some populations are proposed by the AAP compared to product labeling. In addition, there are some areas in which the AAP recommendations are more restrictive. In keeping with the AAP recommendations, Table 10 provides potential areas of the current criteria for adjustment.

- *Education notations*—Consider placing education notes on the PA-criteria form that may include the following:
  - The 2014 AAP recommendation is to discontinue the remaining palivizumab doses for the current season upon a breakthrough RSV hospitalization.[3]
  - The 2014 AAP guideline was composed in consultation with outside groups including the following: American College of Chest Physicians, American College of Emergency Physicians, American Thoracic Society, Emergency Nurses Association, National Association of Neonatal Nurses, National Association of Neonatal Nurse Practitioners, and Society of Hospital Medicine.[3]

Utah Medicaid has current PA criteria in place for palivizumab, as the product was last reviewed by the DUR Board in September of 2014. These were originally constructed to be in congruence with earlier AAP recommendations. While considering maintaining similar criteria consistent with the updated 2014 AAP guideline, Table 11 provides a comparison of the current Utah Medicaid PA-criteria versus differences underlined in the 2014 AAP recommendations.

Table 11. Current prior authorization criteria versus the 2014 AAP recommendation criteria[3]

Current UT-Medicaid Criteria[30]	AAP Guideline Criteria Indication Category	
Premature infants (born <29 weeks, 0 days gestation) during their first year of life	**Infants of Prematurity without CLD or CHD**	Current PA-criteria reflects AAP recommendation Hx of premature birth (GA<29 weeks) ▪ Pt must be younger than 12 months old at the start of the RSV season ▪ AAP does not recommend for prophylaxis during the patient's second RSV season— only for the first season for this subpopulation.
Premature infants (born < 32 weeks, 0 days) who received >21% oxygen for at least 28 days immediately after birth, during their first RSV season	**Infants with CLD of Prematurity**	Current PA-criteria reflects AAP recommendation for patients in the first year of life Hx of premature birth (GA <32 weeks) AND a requirement for >21% oxygen for at least the first 28 days after birth. ▪ Patient must be in the first year of life
Infants < 12 months of age if they have been diagnosed with ▪ congenital abnormalities of the airway ▪ neuromuscular disease that compromise(s) handling of respiratory secretions ▪ acyanotic heart disease AND currently being treated for CHF AND will undergo a cardiac procedure ▪ moderate to severe pulmonary hypertension	**Infants with Hemodynamically Significant CHD[a]**	Note the slight difference in the age criteria of <12 months vs. ≤12 months, and also the exception in the AAP criteria for heart transplant patients <2 years of age ▪ Must be ≤ 12 months old[a] ▪ Decisions for infants <1 year with cyanotic heart defects may be made in consultation with a pediatric cardiologist **OR** ▪ children < 2 years old who undergo cardiac transplantation during the RSV season may be considered for palivizumab prophylaxis
Children < 24 months of age with chronic lung disease of prematurity and who required ≥28 days of supplemental oxygen immediately after birth and who continue to require medical intervention (supplemental oxygen, chronic corticosteroid, or diuretic therapy)	**Infants with CLD of Prematurity**	Note the differences as underlined Must satisfy the definition of CLD of prematurity: Hx of premature birth (GA <32 weeks) AND a requirement for >21% oxygen for at least the first 28 days after birth. ▪ Patient can be in the second year of life but must continue to require medical support (chronic corticosteroids, diuretics, or supplemental oxygen) during the 6-month period before the start of the second RSV season
Children younger than 24 months who will be profoundly immunocompromised during the RSV season.	**Profoundly Immuno-compromised Child <24 months old**	Current PA-criteria reflects AAP recommendation
Maximum of 5 doses in a season		Current PA-criteria reflects AAP recommendation

Abbreviations: AAP, American Association of Pediatrics; CHD, congenital heart disease; CF, cystic fibrosis; CHF, congestive heart failure; CLD, chronic lung disease of prematurity; GA, gestational age; Hx, history; Pt, patient; RSV, respiratory syncytial virus;

[a] Those most likely to benefit include infants with (a) acyanotic heart disease receiving medication for CHF and will require cardiac surgical procedures and (b) infants with moderate to severe pulmonary hypertension

Summary

Palivizumab is the first and only immunoprophylaxis available to help prevent serious RSV-mediated respiratory infections in high-risk pediatric patients. Since the approval of palivizumab, recommendations regarding RSV prophylaxis from the American Academy of Pediatrics have evolved as the experts have refined definitions of the high-risk patients most likely to benefit from prophylaxis. The 2014 AAP guideline was composed in consultation with several other expert organizations: the American College of Chest Physicians, American College of Emergency Physicians, American Thoracic Society, Emergency Nurses Association, National Association of Neonatal Nurses, National Association of Neonatal Nurse Practitioners, and Society of Hospital Medicine.[3] Some prophylaxis criteria developed by the committee are more restrictive, compared to the original product labeling, while there are some recommendations that are less restrictive (supporting off-label use per certain criteria) as outlined in Table 4.

Overall, the AAP recommendations are limited to children in their first or second year of life who meet eligibility criteria. The FDA-labeling and AAP guidelines differ with regard to eligible patients that are 24 months of age, but neither supports use for any particular subgroup of pediatric patients who are >24 months at the start of the RSV season. Another considerable difference between the product labeling and AAP recommendation is regarding the continuation of palivizumab upon an active RSV infection. The palivizumab labeling states that children who become infected with RSV should continue receiving the remaining monthly doses for the RSV season,[4] whereas the AAP recommends discontinuing palivizumab for the remainder of the RSV season upon experiencing an RSV-hospitalization.[3]

It appears that there has been some off-label non-established use of palivizumab after reviewing the age distribution for Medicaid claims. Age criteria for prophylaxis of RSV, based on the 2014 AAP guidelines and product labeling, can be re-emphasized. In keeping with the 2014 AAP guidelines, page 20 and 21 highlight discussion topics to facilitate development of prior authorization criteria.

Appendix A: RSV Surveillance

Table 1. UT percent positive RSV PCR tests,[10] by 3-week moving average[a]

Week ending date[b]	Total # of PCR tests	% positive
9/2/2017	413	0.2
9/9/2017	409	0.3
9/16/2017	430	0.2
9/23/2017	444	0.2
9/30/2017	487	0.1
10/7/2017	514	0.1
10/14/2017	533	0.1
10/21/2017	540	0.4
10/28/2017	557	0.5
11/4/2017	577	1
11/11/2017	599	1.4
11/18/2017	620	1.7
11/25/2017	652	2.1
12/2/2017	681	2.4
12/9/2017	698	3.1
12/16/2017	785	3.6
12/23/2017	981	4.5
12/30/2017	1186	5.6
1/6/2018	1322	7.3
1/13/2018	1315	9.1
1/20/2018	1309	11.2
1/27/2018	1330	13.5
2/3/2018	1369	16
2/10/2018	1340	18.1
2/17/2018	1207	18
2/24/2018	817	16.5
3/3/2018	473	15.1
3/10/2018	188	13.5
3/17/2018	177	13.2

[a] Each data point is based on the average number of RSV tests that were performed and the average percent that were positive from three adjacent weeks (i.e. the specified week, and the week preceding and following it)-- this is also known as a centered 3-week moving average.

[b] Refer to the CDC website for more recent data points: https://www.cdc.gov/surveillance/nrevss/rsv/state.html#UT

Table 2. Region 8[a] RSV season information (2012-2017)[12 31]

RSV Season[b]	Onset week[c] ending	Peak week ending	Offset week ending	Season duration (weeks)
2012 - 2013	12/29/2012	3/2/2013	4/20/2013	17
2013 - 2014	1/18/2014	2/15/2014	4/12/2014	13
2014 - 2015	11/29/2014	2/14/2015	4/25/2015	22
2015 - 2016	12/05/2015	2/20/2016	05/14/2016	24
2016 - 2017	11/12/2016	02/11/2017	05/06/2017	26

Abbreviation: RSV, respiratory syncytial virus

[a] Region 8 includes Colorado, Montana, North Dakota, South Dakota, Utah, and Wyoming

[b] Other information: The 2014 AAP guideline notes that during the 6 RSV seasons from July 2007 to January 2013, the median duration of the RSV season ranged from 13 to 23 weeks for the contiguous US.

[c] The onset week is defined as the first of 2 consecutive weeks when the weekly percentage of all specimens testing positive for RSV antigen in all reporting laboratories in the area is ≥10%. The offset is the end of the last 2 consecutive weeks when the weekly percentage positive exceeds 10%. The peak is the week when the percentage of positive RSV antigen tests is the highest. The season duration is comprised of the onset week, the offset week, and the weeks between.

Appendix B: Relevant CPT Procedural Codes

CPT Codes	Procedure
90378	**RESP SYNCYTIAL VIRUS IMMUNE GLOBULIN,INTRAM,50 MG**
90379	RESP SYNCYTIAL VIR IMMUNE GLOBULIN,INTRAVENOUS USE

Appendix C: Systematic Reviews

Table 1. Systematic Reviews

Cochrane Systematic Reviews		
Robinson et al, 2016[24] Cochrane Review Palivizumab for prophylaxis against respiratory syncytial virus infection in children with cystic fibrosis	**Objective**— assess efficacy and safety of PAL versus placebo, no prophylaxis or other prophylaxis, in preventing hospitalization and mortality from RSV in pediatric patients up to 18 years old with cystic fibrosis. **Literature searched through** May 5th 2016. **Studies included** RCTs and quasi-RCT design	Only one study met the inclusion criteria: An RCT by Cohen et al 2005 included 186 infants up to two years old, where five monthly doses of palivizumab (N = 92) were administered compared to placebo (N = 94) during one RSV season ▪ Primary endpoint results: Comparing each study arm, there was no significant difference between the hospitalizations due to RSV, or in mortality after 6 months of follow up. ▪ Secondary endpoint results: Comparing each study arm, there was no significant difference in the need for oxygen therapy, any adverse events (defined as an abnormal laboratory finding, symptom, or disease associated with PAL, whether or not considered related to the product), or related adverse events. Authors Conclusions— "While the overall incidence of adverse events was similar in both groups, it is not possible to draw firm conclusions on the safety and tolerability of respiratory syncytial virus prophylaxis with palivizumab in infants with cystic fibrosis." "Additional randomised studies are needed to establish the safety and efficacy of palivizumab in children with cystic fibrosis."
Anadabaka et al, 2013[32] Cochrane Review Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children	**Objectives**— assess the effectiveness and safety of PAL prophylaxis for reducing hospitalization due to RSV in high-risk infants and children; assess the cost-effectiveness of PAL prophylaxis in infants and children in different risk groups **Literature searched through** July 2012 **Studies included** RCTs comparing PAL prophylaxis with placebo or another type of prophylaxis; cost-effectiveness analyses and cost-utility analyses comparing palivizumab prophylaxis with no prophylaxis	3 RCTs compared PAL with a placebo (N= 2831) ▪ All RCTs were sponsored by the drug sponsor ▪ Quality of RCTs was good ▪ Palivizumab prophylaxis was associated with a significant reduction in RSV hospitalizations (RR 0.49, 95% CI 0.37 to 0.64) and a non-significant reduction in all-cause mortality (RR 0.69, 95% CI 0.42 to 1.15) when compared to placebo. ▪ The proportion of children with any AE or any AE related to the study drug was similar between the two groups. 34 cost-effectiveness and/or cost-utility studies were included. The cost-effectiveness of PAL prophylaxis depends on the consumption of resources taken into account by the study authors, and on the cost-effectiveness threshold set by the healthcare sector in each country. Authors conclude that the SR evidences supports PAL prophylaxis for reducing RSV-mediated hospitalizations for LTRI in children with chronic lung disease, congenital heart disease, or those born preterm. However, the authors state that "[r]esults from economic evaluations of palivizumab prophylaxis are inconsistent across studies, ranging from highly cost-effective to not cost-effective, implying that economic findings must be interpreted with caution."

Table 1. Systematic Reviews

Other Systematic Reviews		
Kua et al, 2017[26] Systematic Review of the Safety and Efficacy of Palivizumab among Infants and Young Children with Cystic Fibrosis	**Objective—** efficacy assessment of PAL prophylaxis in reducing RSV hospitalizations in children with cystic fibrosis younger than 2 years old **Literature searched through** January 2017 for RCTs, and non-randomized controlled trials (e.g. before and after studies, prospective observational studies,	Studies selected included 10 total: 2 before-and-after studies, 6 cohort studies (3 prospective and 3 retrospective), 1 cross-sectional survey, and 1 RCT. 4 of these were in the US (**1 RCT [Cohen et al 2005]**, 2 retrospective studies, 1 prospective study) ▪ There are inconsistent findings among observational studies with regard to the reduction of RSV hospitalizations in the CF pediatric population. Moreover in some cohort studies, the systematic review authors were not able to determine whether studies adjusted and/or controlled for pertinent known risk factors of RSV infection among treatment groups. ▪ The RCT by Cohen et al, did not find a significant difference between the PAL and no prophylaxis group for the outcomes of RSV hospitalization, death during 6 months of follow up. ▪ More well designed RCT studies are need to investigate this study question.
Manikam et al, 2016[33]	**Objective—** efficacy assessment for RSV prophylaxis in reducing RSV hospitalizations in children with down syndrome younger than 2 years old **Literature searched through** February 2015 for all study types except for case series and case reports	Authors identified one prospective cohort study (Yi et al, 2014)[34] which included 532 Canadian children < 2 years old with Down's syndrome that were provided palivizumab prophylaxis for 2 RSV seasons. This cohort was compared to 233 Dutch children with Down's syndrome who did not receive immunoprophylaxis. Overall, the palivizumab group had a 3.6-fold reduction in the adjusted risk (adjusted incidence rate ratio 3.63, 95% confidence interval: 1.52–8.67) of RSV-related hospitalizations compared to the untreated group, however, no significant differences were found between treated and untreated children with no risk factors (hemodynamically significant CHD, CLD, multisystem anomalies, prematurity, and insignificant CHD).[34]

Abbreviations: CF, cystic fibrosis; LRTI, lower respiratory tract infection; PAL, palivizumab; RCT; randomized controlled trial; RSV, respiratory syncytial virus

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