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Respiratory Syncytial Virus Disease: Immunoprophylaxis Policy Review and Public Health Concerns in Preterm and Young Infants

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Abstract

Globally, respiratory syncytial virus (RSV) is a leading cause of hospitalization due to severe respiratory infections in infants of all gestational ages and children aged 5 years and younger, and it is associated with a substantial health care burden. Approximately, 1% to 3% of infants younger than 1 year are hospitalized with severe RSV disease in the United States. With no specific treatment or vaccine, palivizumab is the only licensed immunoprophylaxis for the prevention of severe RSV disease in high-risk pediatric populations, including infants born at or before 35 weeks' gestational age (wGA). In the United States, the American Academy of Pediatrics (AAP) periodically publishes its recommendation for the use of RSV immunoprophylaxis, which is largely followed by health care professionals and payers. In 2014, the AAP Committee on Infectious Diseases stopped recommending RSV immunoprophylaxis for otherwise healthy infants born at or after 29 wGA and stated that the RSV hospitalization rates in infants 29 to 34 wGA and full-term infants were similar. Several studies have demonstrated that a significant decline in palivizumab use following the AAP 2014 recommendations was accompanied by increases in rates of RSV hospitalization and disease severity and hospital costs in infants 29 to 34 wGA versus full-term infants. Despite the growing evidence demonstrating high RSV morbidity in infants 29 to 34 wGA, the AAP reaffirmed its 2014 policy in 2019. This article will discuss the critical roles and strategies of advocacy groups and nurses in providing the maximum protection with RSV immunoprophylaxis to all high-risk and label-eligible preterm infants.

Keywords

respiratory syncytial virus, premature infant, caregivers, palivizumab

Respiratory syncytial virus (RSV) belongs to the *Pneumovirus* family and was first isolated in 1956. It has two main antigenic strains, namely A and B, and multiple genotypes. Both RSV-A and RSV-B are known to circulate during seasonal outbreaks. RSV is very common, and it infects nearly every child by age 2. Infection with RSV does not provide lifelong immunity, and reinfections occur frequently (Hall, 2010; Piedimonte & Perez, 2014). The timing and duration of the RSV season varies by year and geographic location. In the United States, seasonal outbreaks typically occur between October and May, with median peaks in February. There is significant regional and local variability in the timing and duration of the RSV season owing to factors such as antigenic variations, sociodemographic factors, and RSV circulation among communities (Pavilack et al., 2018; Rose et al., 2018).

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RSV is primarily a human pathogen and is highly contagious. It is commonly spread through direct or indirect contact with infected secretions. RSV is capable of surviving for several hours on hard surfaces and for more than 30 minutes on hands. This in turn favors nosocomial infections and faster transmission between close contacts (American Academy of Pediatrics [AAP], 2018; Hall, 2010). The Centers for Disease Control and Prevention (CDC, 2018) recommends general measures such as frequent handwashing and respiratory hygiene to contain respiratory secretions and reduce disease transmission. RSV generally presents as a common cold-like illness, but in 20% to 30% of infants, it may progress to serious lower respiratory infection (LRI) characterized by nasal flaring, chest wall retractions, tachypnea, wheezing, hypoxemia, and respiratory failure. Pediatric populations at high risk of developing severe RSV infection include infants born prematurely and children with chronic lung disease of prematurity (CLDP), congenital heart disease (CHD), Down syndrome, immunodeficiency, airway or neuromuscular abnormalities, or cystic fibrosis (AAP, 2018; Hall, 2010; Piedimonte & Perez, 2014). In a retrospective analysis, Boyce et al. (2000) estimated that the risk of RSV hospitalization among premature infants (born before 36 weeks' gestational age, wGA) aged less than 6 months, children with CLDP, and children with CHD is approximately 2, 3, and 13 times higher, respectively, than the risk in full-term infants. Pathological factors underlying higher susceptibility of premature infants to severe respiratory infections than term infants include immature airways and relatively lower amounts of protective maternal antibodies (Piedimonte & Perez, 2014).

RSV Disease Burden

Globally, RSV accounted for more than 3 million hospitalizations and about 60,000 in-hospital deaths among children younger than 5 years in 2015. Although 99% of RSV mortality occurs in developing countries, RSV in developed countries is associated with substantial morbidity and health care utilization (Shi et al., 2017). In Western countries, including the United States, Canada, and European countries, RSV accounts for more than 60% of all LRI and more than 80% of viral LRI among young children. Moreover, in these countries, annual hospitalization rates per 1,000 due to RSV LRI range from 3.2 to 42.7 in infants younger than 1 year and 0.6 to 1.8 in children aged 1 to 4 years. On average, RSV LRI necessitates stays of up to 11 days in the hospital, and up to 12% of infants who are hospitalized because of RSV may require admission to the intensive care unit (ICU). Severity of RSV hospitalization, as measured by length of hospital stay and admission to the ICU, increases with earlier gestational age and younger chronologic age and further varies depending on the presence of other risk factors and geographic location. Besides premature birth and younger chronologic age, other sociodemographic risk factors commonly associated with the development of severe RSV include presence of siblings, birth occurring closer to RSV season, exposure to tobacco smoke, low birth weight, and lack of breast-feeding (Bont et al., 2016).

In the United States, RSV is the leading cause of hospitalization resulting from LRI such as bronchiolitis and pneumonia among infants younger than 1 year (Jain et al., 2015; Leader & Kohlhase, 2002). Severe RSV disease causes more than 57,000 hospitalizations and 2 million outpatient visits in children aged younger than 5 years and accounts for 20% of hospitalizations, 18% of emergency department visits, and 15% of all office visits caused by LRI (Hall et al., 2009). In addition, RSV LRI in childhood have been shown to be associated with the development of recurrent wheezing (in up to 50% of cases) and asthma later in life (Hall, 2010; Piedimonte & Perez, 2014). Overall, RSV LRI cause substantial short-term and long-term morbidity that is associated with significant health care utilization and financial burden.

Management of RSV Disease

Treatment of RSV is primarily symptomatic and includes adequate hydration, supplemental oxygen, airway clearance, and mechanical ventilation in severe cases of respiratory distress. Hypertonic saline, beta-adrenergic agonists, corticosteroids, and antibiotics for superinfection are among other agents that are used in clinical practice but not recommended by the AAP for the routine clinical management of RSV bronchiolitis (AAP, 2018).

Disease prevention is critical in managing RSV because there is no specific treatment or vaccine available for RSV disease (AAP, 2018; PATH, 2019). Palivizumab, a humanized, RSV F protein-targeting monoclonal antibody, is the only seasonal immunoprophylaxis approved by the Food and Drug Administration (FDA) for the prevention of severe RSV disease in premature infants (born at or before 35 wGA) aged 6 months or younger, children with CLDP who are 24 months of age or younger, and children with hemodynamically significant CHD who are 24 months of age or younger (MedImmune, LLC, 2014). The safety and efficacy of palivizumab were established through two randomized, placebo-controlled trials. In comparison with placebo, palivizumab reduced RSV hospitalization by 78% in infants born at or before 35 wGA and younger than 6 months ($p < .001$), by 39% in children with CLPD aged 24 months or younger ($p = .038$), and by 45% ($p = .003$) in children with CHD aged 24 months

or younger. Palivizumab was generally well tolerated, and occurrence of adverse events was similar to that observed in the placebo group (Feltes et al., 2003; The IMpact-RSV Study Group, 1998). Other studies have demonstrated the effectiveness of palivizumab in reducing the risk of severe RSV infection and its long-term complications such as wheezing (Blanken et al., 2013; Goldstein et al., 2017). This review discusses the impact of the changing policies and guidelines for RSV immunoprophylaxis on RSV disease burden among high-risk infants born at 29 to 34 wGA in the United States. In addition, the article presents strategies for clinicians, including nurse practitioners, to effectively identify high-risk infants and assist their families in gaining access to palivizumab, the only available RSV preventative agent.

Changes in the AAP Policy Guiding RSV Immunoprophylaxis

Policies and guidelines governing RSV immunoprophylaxis with palivizumab for high-risk pediatric populations differ between countries. In the United States, the AAP Committee on Infectious Diseases publishes clinical guidance for management of pediatric infectious diseases, including RSV immunoprophylaxis, every 5 years. The AAP revises its policy for RSV immunoprophylaxis based on published reports, expert opinion, and other factors such as the acquisition cost of palivizumab and its cost-effectiveness, changes in RSV seasonality, and mortality rates (American Academy of Pediatrics Committee on Infectious Diseases & Committee on Fetus and Newborn, 1998; American Academy of Pediatrics Committee on Infectious Diseases & American Academy of Pediatrics Bronchiolitis Guidelines Committee, 2014a; Goldstein et al., 2012).

In 1998, the AAP published its first policy statement with recommendations for palivizumab based on the IMpact-RSV clinical trial. It advised RSV immunoprophylaxis for all infants born at less than 32 wGA and infants 32 to 35 wGA with additional risk factors. The recommendations defined the usefulness of palivizumab for prevention of RSV disease in high-risk infants and children. In addition, the AAP recommended palivizumab for immunocompromised children, although this recommendation was not supported with randomized controlled trials (American Academy of Pediatrics Committee on Infectious Diseases & Committee on Fetus and Newborn, 1998). Since the approval of palivizumab in 1998, the AAP's recommendations for palivizumab use have evolved to become increasingly restrictive in contrast with the FDA-approved indications. From 2009 until 2014, the AAP supported RSV immunoprophylaxis for all infants born at less than 32 wGA and infants 32 to 34 wGA with additional risk factors (attending day care or having young sibling[s] in the household), and children with CLDP or CHD (Committee on Infectious Diseases, 2009).

In 2014, the AAP stopped recommending RSV immunoprophylaxis to otherwise healthy infants born at or after 29 wGA (Table 1). The AAP's rationale was that the risk of RSV hospitalization among infants born at 29 to 34 wGA was similar to that of term infants based on available evidence. However, the studies that were used to arrive at this conclusion did not have adequate power and were conducted during the prophylaxis era: the observed reduction in RSV risk could have been due to the effective control of severe RSV disease by palivizumab (American Academy of Pediatrics Committee on Infectious Diseases & American Academy of Pediatrics Bronchiolitis Guidelines Committee, 2014a; Yogev et al., 2015). Because palivizumab has been effective since its FDA approval in reducing the incidence of severe RSV disease, some clinicians caring for high-risk infants may not fully appreciate the significant impact of RSV in infants born at 29 to 34 wGA. As the AAP policy for RSV immunoprophylaxis became more restrictive, infants who previously would have received protection are now at an elevated risk for severe RSV disease (Goldstein et al., 2017; Pavilack et al., 2018).

Evidence Published Since the 2014 AAP Policy Change

Since the 2014 AAP policy change, clinical experts and advocacy groups have questioned the rationale for excluding high-risk infants born at or after 29 wGA. Multiple regional and national studies in the United States have analyzed the risk of RSV hospitalization that occurred in the RSV seasons after 2014 in infants 29 to 34 wGA relative to term infants. SENTINEL1, a large, observational, multicenter US study conducted in the 2014 to 2016 RSV seasons, analyzed the severity of RSV hospitalization occurring in infants 29 to 35 wGA who did not receive RSV immunoprophylaxis. The study reported that RSV hospitalization in infants 29 to 35 wGA without RSV immunoprophylaxis was often severe, and many required ICU admission (45%) and mechanical ventilation (19%). Severity of RSV illness and hospital charges further increased with younger chronologic age and earlier gestational age (Anderson et al., 2020).

Industry-sponsored studies based on large national databases (Truven Health MarketScan® and Optum Research Database) have shown that the prophylactic use of palivizumab decreased significantly in infants 29 to 34 wGA in RSV seasons after 2014. Kong et al. (2018) demonstrated that RSV hospitalization rates increased by 2.7 and 1.4 times in commercially and Medicaid-insured infants 29 to 34 wGA (aged less than 3 months), respectively, in the 2014 to 2015 versus 2013 to 2014

Table 1. Comparison of Palivizumab Label and the History of RSV Immunoprophylaxis Policies.

Condition	Palivizumab-approved label (MedImmune, LLC, 2014)	AAP 2014 and AAP 2019 guidance (AAP Committee on Infectious Diseases & AAP Bronchiolitis Guidelines Committee, 2014a; AAP Committee on Infectious Diseases & AAP Bronchiolitis Guidelines Committee, 2014b)	NPA 2018 guidelines (Goldstein et al., 2017)
Preterm	All infants born at or before 35 wGA and aged 6 months or younger at the start of RSV season	All infants born at less than 29wGA and aged younger than 12 months at the start of RSV season	All infants born at or before 28wGA and aged younger than 12 months at the start of RSV season All infants 29–32 wGA aged younger than 6 months at the start of RSV season All infants 33–35 wGA aged younger than 6 months at the start of RSV season with additional risk factors
BPD/CLDP	Children 24 months of age or younger at the start of RSV season who required additional medical support in past 6 months	All infants born at less than 32wGA and requiring oxygen for at least the first 28 days post-birth All those aged younger than 12 months at the start of RSV season All those aged 12–24 months at the start of RSV season requiring medications in past 6 months	Children aged younger than 24 months at the start of RSV season requiring additional medical support
HS-CHD	Children 24 months of age or younger at the start of RSV season	All children aged younger than 12 months at the start of RSV season	All children aged younger than 24 months at RSV season start, unless cardiology waiver is obtained

Note. AAP = American Academy of Pediatrics; BPD = bronchopulmonary dysplasia; CLDP = chronic lung disease of prematurity; HS-CHD = hemodynamically significant congenital heart disease; NPA = National Perinatal Association; RSV = respiratory syncytial virus; wGA = weeks' gestational age.

RSV seasons. Goldstein et al. (2018) reported that the relative risk of RSV hospitalization in infants 29 to 34 wGA versus term infants rose significantly (for both commercially, 2 times, and Medicaid-insured, 1.5 times, infants) in the RSV seasons after 2014 versus before. Krilov et al. (2020) observed a 55% increase in RSV hospitalization risk in infants 29 to 34 wGA compared with term infants in the 2014 to 2017 versus 2011 to 2014 RSV seasons. In addition, morbidity associated with RSV hospitalization as measured by length of stay, proportions requiring ICU admission and mechanical ventilation, and health care expenses also increased in infants 29 to 34 wGA after 2014 (Krilov et al., 2020). A summary of the evidence published following the 2014 policy change is shown in Table 2. Overall, the decline in RSV immunoprophylaxis after the 2014 AAP policy has resulted in an increase in RSV hospitalization and health care utilization and costs in infants 29 to 34 wGA, who have higher vulnerability to severe RSV infection than full-term infants.

Cost-Effectiveness of Palivizumab

The primary factor limiting the widespread use of palivizumab per approved label is its acquisition cost. Palivizumab is administered as a monthly intramuscular injection throughout the RSV season with the first dose given prior to the start of the season. Without factoring in Medicaid program discounts, it is estimated that the cost of palivizumab can range from $1,500 to $4,300 per monthly dose and $6,000 to $20,000 per child during one RSV season (4–5 doses). A significant portion of the children receiving immunoprophylaxis are covered by state Medicaid plans, although eligibility criteria for

Table 2. Summary of Evidence That Examined RSV Hospitalization in Infants 29–35 wGA After the 2014 AAP Policy Change.

Study (RSV seasons)	Study design	Major conclusions
Evidence showing increase in RSV morbidity after 2014		
Krilov et al. (2020) (2011–2014 vs. 2014–2017)	Retrospective observational study using Optum Research Database in infants 29–34 wGA	– RSV IP use decreased significantly – RSVH risk in infants 29–34 wGA vs. term infants increased by 55% – RSVH severity and cost also increased
Anderson et al. (2020); SENTINEL1 (2014–2016)	Large, multicenter, observational study in infants 29–35 wGA who did not receive RSV IP	– RSVH was often severe (required ICU admission and mechanical ventilation) and was associated with high hospital charges
Goldstein et al. (2018) (2012–2014 vs. 2014–2016)	Retrospective analysis using Truven MarketScan® Database in infants 29–34 wGA	– RSV IP use decreased significantly – RSVH risk in infants 29–34 wGA vs. term infants increased by up to two fold – Hospital costs also increased
Kong et al. (2018) (2013–2014 vs. 2014–2015)	Retrospective analysis using Truven MarketScan® Database in infants 29–34 wGA	– RSV IP use decreased significantly – RSVH risk in infants 29–34 wGA vs. term infants increased by up to 2.7-fold
Rajah et al. (2017) (2013–2014 vs. 2014–2015)	Retrospective study conducted at Nationwide Children's Hospital in infants 29–34 wGA	– Proportion of RSVH increased significantly – Severity and hospital charges also increased
Blake et al. (2017) (2012–2014 vs. 2014–2016)	Retrospective study conducted at Duke University Health System in infants born between 29 and less than 32wGA aged younger than 12 months	– RSV IP use decreased significantly – RSVH increased significantly
Evidence showing no increase in RSV morbidity after 2014		
Zembles et al. (2019) (2012–2014 vs. 2014–2017)	Retrospective regional study in infants 29–34 wGA	– RSVH rates and morbidity did not increase significantly
Farber (2017) (2012–2014 vs. 2014–2015)	Retrospective study using Texas Medicaid claims in infants 29–32 wGA	– RSVH rates did not increase significantly

Note. AAP = American Academy of Pediatrics; ICU = intensive care unit; IP = immunoprophylaxis; RSV = respiratory syncytial virus; RSVH = respiratory syncytial virus hospitalization; wGA = weeks' gestational age.

coverage vary from state to state (Olchanski et al., 2018). The cost-benefit and cost-effectiveness of palivizumab have been an unresolved debate for more than a decade. Blake et al. (2017) estimated that 20 infants must receive palivizumab (total cost of a course of palivizumab for 20 infants = $90,000, average cost per course per patient = $4,500) in order to prevent one RSV hospitalization (cost = $29,000). Other studies have reached varying conclusions regarding the cost-benefit of palivizumab and recommendations for RSV immunoprophylaxis in high-risk groups. In general, these studies are highly variable in their study design and epidemiology, which in turn, render them incomparable. Moreover, the acquisition cost of palivizumab and cost analyses vary depending on the payer versus societal perspective, insurance rebates, dosing regimen, and vial sharing (Mac et al., 2019).

RSV hospitalization often results in significant stress for both the affected infants and their caregivers (parents and family). In 2005, Leidy et al. examined patient and family distress associated with RSV hospitalization in premature infants and young children relative to an age-matched control group. The study reported that caregiver stress was substantial during and after hospitalization and persisted for up to 2 months post-discharge (Leidy et al., 2005). In a secondary analysis of SENTINEL1 data, Pokrzywinski et al. (2019) examined the self-rated caregiver stress associated with RSV hospitalization of infants 29 to 35 wGA aged <1 year. The study reported that caregiver stress persisted for at least 1 month following discharge and was accompanied by considerable loss of work productivity, financial impacts, anxiety, and strain on family routines and relationships (Pokrzywinski et al., 2019). These data

emphasize the indirect costs associated with RSV hospitalization, which should not be trivialized. Factoring in both the direct (hospital visits, RSV health care utilization, treatment cost) and indirect (treatment of long-term complications, caregiver burden, missed work) costs that accompany severe RSV disease may provide justification for the use of palivizumab in vulnerable high-risk infants and children (Goldstein et al., 2017).

Implications for Practice

Nurses are often the frontline advocates for patients and caregivers, who in turn, rely on them to help navigate their illness and the complex processes surrounding payer approval of therapies. Following the restriction of the AAP recommendations on RSV immunoprophylaxis in high-risk infants, multiple professional and parent organizations have mounted intensive and ongoing advocacy efforts to affect a revision in the AAP policy. Organizations and advocacy groups such as the National Association of Neonatal Nurses, National Association of Pediatric Nurse Practitioners, National Black Nurses Association, National Medical Association, Preemie Parent Alliance, National Coalition for Infant Health (an advocacy arm of the Alliance for Patient Access, a national network of health care practitioners dedicated to ensuring patient access to approved therapies and appropriate clinical care), and the National Perinatal Association (NPA) have been working collaboratively with pediatric clinicians (physicians, nurses, nurse practitioners), parents and caregivers, and communities to promote greater awareness of RSV disease and to gain access to RSV immunoprophylaxis for label-eligible high-risk infants. A timeline of policy and guideline changes and advocacy efforts by professional associations and patient support organizations since 2009 is shown in Table 3.

Clinicians, in collaboration with caregivers and legal equality groups (Legal Aid, Advocates for Basic Legal Equality™, n.d.), have successfully challenged treatment denials to obtain access to palivizumab. For clinicians managing the care of infants covered under a state Medicaid program or the Children's Health Insurance Program (CHIP), knowledge of the state's formulary process and the rebate programs within the state is a necessity. In general, formularies and drug rebate programs vary from state to state and may be based on contract terms with pharmaceutical companies, state funding levels, and internal data collection. Although Medicaid programs are required to comply with section 1927(d)(1) and (2) of the Social Security Act (The Social Security Act of 1935), states may subject a covered outpatient drug to prior authorization or exclude or restrict coverage if the prescribed use is not for a medically acceptable indication. Any denial by state Medicaid programs of palivizumab for indications listed in the FDA-approved label is considered to be noncompliant with this section of the Social Security Act. In practice, states that do not support palivizumab prophylaxis for infants 29 to 34 wGA may be excluding a therapy with well-established clinical efficacy and an acceptable safety profile (Goldstein et al., 2017; MedImmune, LLC, 2014).

Implications for Education and Research

Nurses play a critical role in raising awareness of the risk factors for severe RSV disease and the availability of preventative intervention with palivizumab. Families and caregivers of high-risk infants and children should be educated about the importance of adherence to RSV immunoprophylaxis for maximum benefit and general disease prevention practices such as good hand hygiene, avoiding overcrowded areas, and limiting exposure to tobacco smoke (AAP, 2018).

Understanding and identifying region-specific sociodemographic risk factors in moderate to late premature infants can empower clinicians and those prescribing palivizumab to appeal payer denial of RSV immunotherapy for suitable high-risk candidates. However, this process must begin well before the onset of the RSV season (Anderson et al., 2020). Published evidence should be used to guide prophylaxis decisions. It is imperative that all neonatal and pediatric clinicians maintain a broader understanding of the "state of the science" related to RSV disease and its morbidity in high-risk infants and young children.

Implications for Policy

Many pediatric clinicians, including physicians, nurses, and nurse practitioners who care for premature infants, were hoping for a revision of the 2014 AAP policy based on data demonstrating an increased risk of RSV hospitalization and severity in infants 29 to 34 wGA relative to full-term infants. However, the AAP reaffirmed its 2014 policy in 2019 without giving any additional explanation (AAP Committee on Infectious Diseases & AAP Bronchiolitis Guidelines Committee, 2014b). As a result, infants born between 29 and 34 wGA continue to have a gap in access to prophylactic therapy.

The NPA convened two separate expert panels to review the available evidence related to RSV morbidity and published a broader dosing guideline that aligns more closely with the approved indications for palivizumab. It recommended RSV immunoprophylaxis for all infants born at less than 32 wGA and infants 32 to 35wGA with risk factors, in addition to all children with CLDP or CHD aged younger than 2 years (Table 1; Goldstein et al., 2017). Alternate guidelines are a tool that clinicians and parents may use when therapy is

Table 3. Timeline of RSV Immunoprophylaxis Policy or Guideline Changes and Advocacy Efforts Since 2009.

Year	RSV immunoprophylaxis policy or guideline changes	Advocacy efforts in response to AAP policy changes
2009	AAP released its RSV immunoprophylaxis policy (AAP, 2009)	
		Health care professionals and the public petitioned the involvement of the CDC; the ACIP convened a work group to evaluate the issue (https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun10.pdf)
		NMA and NBNA issued *Consensus Panel Paper: Respiratory Syncytial Virus and African Americans* (Fall, 2010) requesting additional research to assess risk of severe RSV in high-risk infants (https://www.nbna.org/pressoct2010)
		NANN and NANNP began advocacy efforts on behalf of the nursing community; online petitions were presented to CDC ACIP on behalf of NANN/NANNP and NAPNAP (https://www.youtube.com/watch?v=hhZBnR2RqSc)
		NANN and NANNP requested that AAP convene a multidisciplinary work group to critically analyze this issue; NAPNAP and NBNA sent similar requests to the AAP Board of Directors (http://www.infanthealth.org/blog/2010/10/preemie-matters-oct-2010)
2011		The CDC ACIP RSV work group was disbanded (https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-feb11.pdf)
2012	AAP published its 2012 policy, with further restriction of RSV immunotherapy (AAP, 2012) NPA issued its 2012 guidelines for RSV Prevention (Goldstein et al., 2012)	
2013		The NMA and AAP held meeting and voiced the need to provide access of RSV immunoprophylaxis to all premature infants (January 2013) (https://cdn.ymaws.com/www.nmanet.org/resource/resmgr/Docs/RSV/RSV_Jan162013.pdf)
2014	AAP published its 2014 policy statement. RSV immunotherapy is not recommended for infants born at or after 29wGA (AAP, 2014)	AfPA launched advocacy outreach plan to increase RSV disease awareness (https://www.youtube.com/watch?v=pkUbV6HI11o&feature=emb_logo)
2015	NPA published its 2015 guidelines for RSV Prevention (Goldstein et al., 2014)	NCfIH launched RSV access key issue (http://www.infanthealth.org/rsv-1; https://instituteforpatientaccess.org/?s=RSV)
2018	NPA published its updated guidelines for RSV immunoprophylaxis with broader recommendations (Goldstein et al., 2017)	
2019	AAP reaffirmed its 2014 RSV policy without providing additional information (AAP, 2019)	

Note. AAP = American Academy of Pediatrics; ACIP = Advisory Committee on Immunization Practices; AfPA = Alliance for Patient Access; CDC = Centers for Disease Control and Prevention; NANN = National Association of Neonatal Nurses; NANNP = National Association of Neonatal Nurse Practitioners; NAPNAP = National Association of Pediatric Nurse Practitioners; NBNA = National Black Nurses Association; NCfIH = National Coalition for Infant Health; NMA = National Medical Association; NPA = National Perinatal Association; RSV = respiratory syncytial virus; wGA = weeks' gestational age.

denied by an insurance company or Medicaid program based on the infant's gestational age alone without considering other risk factors. Obtaining payer approval of a therapy can be a time-consuming process for both caregivers and clinicians; often the process takes so long that the patient may become infected with RSV and eventually be hospitalized. Until a vaccine or other cost-effective immunoprophylaxis becomes available, palivizumab should be made accessible to all label-eligible high-risk infants and children.

Conclusion

Even with modern medical advances, RSV hospitalization and morbidity continue to significantly affect high-risk infants and children and their caregivers. Despite the FDA approval of palivizumab, widespread immunoprophylaxis among eligible candidates is hampered by the drug's acquisition cost and AAP policy changes, which most payers use to determine reimbursement for palivizumab. As the AAP policy evolved and became more restrictive, infants 29 to 34 wGA were subjected to a suboptimal regimen that has led to increased RSV hospitalization and morbidity (Goldstein et al., 2017). It is important that clinicians, including nurses, use the most current and accurate evidence, collaborate with advocacy groups to provide the best available care to vulnerable infants 29 to 34 wGA, and assist caregivers in obtaining access to the only licensed RSV immunoprophylaxis.

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References

American Academy of Pediatrics Committee on Infectious Diseases & American Academy of Pediatrics Bronchiolitis Guidelines Committee. (2014a). Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. *Pediatrics*, *134*(2), e620–e638. https://doi.org/10.1542/peds.2014-1666

American Academy of Pediatrics Committee on Infectious Diseases & American Academy of Pediatrics Bronchiolitis Guidelines Committee. (2014b). Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. *Pediatrics*, *134*(2), 415–420. Reaffirmed February 2019. https://doi.org/10.1542/peds.2014-1665

American Academy of Pediatrics Committee on Infectious Diseases & Committee on Fetus and Newborn. (1998). Prevention of respiratory syncytial virus infections: indications for the use of palivizumab and update on the use of RSV-IGIV. *Pediatrics*, *102*(5), 1211–1216.

American Academy of Pediatrics. (2018). Respiratory syncytial virus. In L. K. Pickering, C. J. Baker, D. W. Kimberlin, & S. S. Long (Eds.), *Red book: 2018 Report of the Committee on Infectious Diseases* (31st ed., pp. 682–692).

Anderson, E. J., DeVincenzo, J. P., Simões, E. A. F., Krilov, L. R., Forbes, M. L., Pannaraj, P. S., Espinosa, C. M., Welliver, R. C., Wolkoff, L. I., Yogev, R., Checchia, P. A., Domachowske, J. B., Halasa, N., McBride, S. J., Kumar, V. R., McLaurin, K. K., Rizzo, C. P., & Ambrose, C. S. (2020). SENTINEL1: Two-season study of respiratory syncytial virus hospitalizations among U.S. infants born at 29 to 35 weeks' gestational age not receiving immunoprophylaxis. *American Journal of Perinatology*, *37*(4), 421–429. https://doi.org/10.1055/s-0039-1681014

Blake, S. M., Tanaka, D., Bendz, L. M., Staebler, S., & Brandon, D. (2017). Evaluation of the financial and health burden of infants at risk for respiratory syncytial virus. *Advances in Neonatal Care*, *17*(4), 292–298. https://doi.org/10.1097/ANC.0000000000000367

Blanken, M. O., Rovers, M. M., Molenaar, J. M., Winkler-Seinstra, P. L., Meijer, A., Kimpen, J. L., Louis Bont, M. D., & Dutch RSV Neonatal Network. (2013). Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. *New England Journal of Medicine, 368*(19), 1791–1799. https://doi.org/10.1056/NEJMoa1211917

Bont, L., Checchia, P. A., Fauroux, B., Figueras-Aloy, J., Manzoni, P., Paes, B., Simões, E. A., Carbonell-Estrany, X. (2016). Defining the epidemiology and burden of severe respiratory syncytial virus infection among infants and children in Western countries. *Infectious Diseases and Therapy, 5*(3), 271–298. https://doi.org/10.1007/s40121-016-0123-0

Boyce, T. G., Mellen, B. G., Mitchel, E. F., Jr., Wright, P. F., & Griffin, M. R. (2000). Rates of hospitalization for respiratory syncytial virus infection among children in Medicaid. *The Journal of Pediatrics, 137*(6), 865–870. https://doi.org/10.1067/mpd.2000.110531

Centers for Disease Control and Prevention (CDC). (2018, June 26). *RSV in infants and young children*. https://www.cdc.gov/rsv/high-risk/infants-young-children.html

Committee on Infectious Diseases. (2009). From the American Academy of Pediatrics: Policy statements – Modified recommendations for use of palivizumab for prevention of

respiratory syncytial virus infections. *Pediatrics, 124*(6), 1694–1701. https://doi.org/10.1542/peds.2009-2345

Farber, H. J. (2017). Impact of the 2014 American Academy of Pediatrics guidance on respiratory syncytial virus and bronchiolitis hospitalization rates for infants born prematurely. *The Journal of Pediatrics, 185*, 250. https://doi.org/10.1016/j.jpeds.2017.01.054

Feltes, T. F., Cabalka, A. K., Meissner, H. C., Piazza, F. M., Carlin, D. A., Top, F. H., Jr., Connor, E. M., Sondheimer, H. M., & Cardiac Synagis Study Group. (2003). Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. *The Journal of Pediatrics*, *143*(4), 532–540. https://doi.org/10.1067/S0022-3476(03)00454-2

Goldstein, M., Krilov, L. R., Fergie, J., McLaurin, K. K., Wade, S. W., Diakun, D., Lenhart, G. H., Bloomfield, A., & Kong, A. M. (2018). Respiratory syncytial virus hospitalizations among U.S. preterm infants compared with term infants before and after the 2014 American Academy of Pediatrics guidance on immunoprophylaxis: 2012–2016. *American Journal of Perinatology*, *35*(14), 1433–1442. https://doi.org/10.1055/s-0038-1660466

Goldstein, M., Merritt, A., Phillips, R., Martin, G., Hall, S., Yogev, R., & Spitzer, A. (2014). National Perinatal Association 2015 respiratory syncytial virus (RSV) prevention guideline. *Neonatology Today*, *9*(11), 1–11. https://www.neonatologytoday.net/newsletters/nt-nov14.pdf

Goldstein, M., Merritt, T. A., Phillips, R., & Sola, A. (2012). Respiratory syncytial virus (RSV) prevention 2012. *Neonatology Today, 7*(11), 1–7. https://www.neonatologytoday.net/newsletters/nt-nov12.pdf

Goldstein, M., Phillips, R., DeVincenzo, J. P., Krilov, L. R., Merritt, T. A., Yogev, R., Staebler, S., Kadri, M., Fergie, J. E., Schechter, M. S., Gorham, M., & Cherry, J. D. (2017). National Perinatal Association 2018 respiratory syncytial virus (RSV) prevention clinical practice guideline: An evidence-based interdisciplinary collaboration. *Neonatology Today*, *12*(10), 1–14. http://www.neonatologytoday.net/newsletters/nt-oct17.pdf

Hall, C. B. (2010). Respiratory syncytial virus. In G. L. Mandell, J. E. Bennett, & R. Dolin (Eds.), *Mandell, Douglas, and Bennett's principles and practice of infectious diseases* (7th ed., pp. 2207–2221). Churchill Livingstone/Elsevier.

Hall, C. B., Weinberg, G. A., Iwane, M. K., Blumkin, A. K., Edwards, K. M., Staat, M. A., Auinger, P., Griffin, M. R., Poehling, K. A., Erdman, D., Grijalva, C. G., Zhu, Y., & Szilagyi, P. (2009). The burden of respiratory syncytial virus infection in young children. *The New England Journal of Medicine*, *360*(6), 588–598. https://doi.org/10.1056/NEJMoa0804877

Jain, S., Williams, D. J., Arnold, S. R., Ampofo, K., Bramley, A. M., Reed, C., Stockmann, C., Anderson, E. J., Grijalva, C. G., Self, W. H., Zhu, Y., Patel, A., Hymas, W., Chappell, J. D., Kaufman, R. A., Kan, J. H., Dansie, D., Lenny, N., Hillyard, D. R., Haynes, L. M., & CDC EPIC Study Team. (2015). Community-acquired pneumonia requiring hospitalization among U.S. children. *The New England Journal of Medicine*, *372*(9), 835–845. https://doi.org/10.1056/NEJMoa1405870

Kong, A. M., Krilov, L. R., Fergie, J., Goldstein, M., Diakun, D., Wade, S. W., Pavilack, M., & McLaurin, K. K. (2018). The 2014–2015 national impact of the 2014 American Academy of Pediatrics guidance for respiratory syncytial virus immunoprophylaxis on preterm infants born in the United States. *American Journal of Perinatology*, *35*(2), 192–200. https://doi.org/10.1055/s-0037-1606352

Krilov, L. R., Fergie, J., Goldstein, M., & Brannman, L. (2020). Impact of the 2014 American Academy of Pediatrics immunoprophylaxis policy on the rate, severity, and cost of respiratory syncytial virus hospitalizations among preterm infants. *American Journal of Perinatology*, *37*(2), 174–183. https://doi.org/10.1055/s-0039-1694008

Leader, S., & Kohlhase, K. (2002). Respiratory syncytial virus-coded pediatric hospitalizations, 1997 to 1999. *The Pediatric Infectious Disease Journal*, *21*(7), 629–632.

Legal Aid, Advocates for Basic Legal Equality™. (n.d.). ABLE services. https://www.ablelaw.org/able-services

Leidy, N. K., Margolis, M. K., Marcin, J. P., Flynn, J. A., Frankel, L. R., Johnson, S., Langkamp, D., & Simoes, E. A. (2005). The impact of severe respiratory syncytial virus on the child, caregiver, and family during hospitalization and recovery. *Pediatrics*, *115*(6), 1536–1546. https://doi.org/10.1542/peds.2004-1149

Mac, S., Sumner, A., Duchesne-Belanger, S., Stirling, R., Tunis, M., & Sander, B. (2019). Cost-effectiveness of palivizumab for respiratory syncytial virus: a systematic review. *Pediatrics*, *143*(5), e20184064. https://doi.org/10.1542/peds.2018-4064

MedImmune, LLC. (2014). Synagis®: Full prescribing information.

Olchanski, N., Hansen, R. N., Pope, E., D'Cruz, B., Fergie, J., Goldstein, M., Krilov, L. R., McLaurin, K. K., Nabrit-Stephens, B., Oster, G., Schaecher, K., Shaya, F. T., Neumann, P. J., & Sullivan, S. D. (2018). Palivizumab prophylaxis for respiratory syncytial virus: examining the evidence around value. *Open Forum Infectious Diseases*, *5*(3), ofy031. https://doi.org/10.1093/ofid/ofy031

PATH. (2019). RSV vaccine and mAb snapshot—PATH vaccine resource library. https://path.org/resources/rsv-vaccine-and-mab-snapshot/

Pavilack, M., Clifford, R. A., Gonzales, T., Kong, A. M., Wade, S., & McLaurin, K. K. (2018). Trends in utilization of outpatient respiratory syncytial virus prophylaxis with palivizumab among Medicaid and commercially insured infants. *Infectious Diseases and Therapy*, *7*(1), 121–134. https://doi.org/10.1007/s40121-017-0178-6

Piedimonte, G., & Perez, M. K. (2014). Respiratory syncytial virus infection and bronchiolitis. *Pediatrics in Review*, *35*(12), 519–530. https://doi.org/10.1542/pir.35-12-519

Pokrzywinski, R. M., Swett, L. L., Pannaraj, P. S., Yi, J., Pavilack, M. S., Kumar, V. R., & McLaurin, K. K. (2019). Impact of respiratory syncytial virus-confirmed hospitalizations on caregivers of US preterm infants. *Clinical Pediatrics*, *58*(8), 837–850. https://doi.org/10.1177/0009922819843639

Rajah, B., Sanchez, P. J., Garcia-Maurino, C., Leber, A., Ramilo, O., & Mejias, A. (2017). Impact of the updated guidance for palivizumab prophylaxis against respiratory syncytial virus infection: A single center experience. *The Journal of Pediatrics*, *181*, 183–188.e1. https://doi.org/10.1016/j.jpeds.2016.10.074

Rose, E. B., Wheatley, A., Langley, G., Gerber, S., & Haynes, A. (2018). Respiratory syncytial virus seasonality – United States, 2014–2017. *Morbidity and Mortality Weekly Report*, *67*(2), 71–76. https://doi.org/10.15585/mmwr.mm6702a4

Shi, T., McAllister, D. A., O'Brien, K. L., Simoes, E. A. F., Madhi, S. A., Gessner, B. D., Polack, F. P., Balsells, E., Acacio, S., Aguayo, C., Alassani, I., Ali, A., Antonio, M., Awasthi, S., Awori, J. O., Azziz-Baumgartner, E., Baggett, H. C., Baillie, V. L., Balmaseda, A., Barahona, A., & RSV Epidemiology Network. (2017). Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: A systematic review and modelling study. *Lancet*, *390*(10098), 946–958. https://doi.org/10.1016/S0140-6736(17)30938-8

The IMpact-RSV Study Group. (1998). Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics*, *102*(3), 531–537. https://doi.org/10.1542/peds.102.3.531

The Social Security Act of 1935, 42 U.S.C. § 1927(d)(1) and (2). https://www.ssa.gov/OP_Home/ssact/title19/1935.htm

Yogev, R., Krilov, L. R., Fergie, J. E., & Weiner, L. B. (2015). Re-evaluating the new Committee on Infectious Diseases recommendations for palivizumab use in premature infants. *The Pediatric Infectious Disease Journal*, *34*(9), 958–960. https://doi.org/10.1097/INF.0000000000000808

Zembles, T. N, Bushee, G. M., & Willoughby, R. E. (2019). Impact of American Academy of Pediatrics palivizumab guidance for children ≥29 and <35 weeks of gestational age. *The Journal of Pediatrics*, *209*, 125–129. https://doi.org/10.1016/j.jpeds.2019.02.020

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