TECHNICAL REPORT

American Academy of Pediatrics

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Palivizumab Prophylaxis in Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection

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Guidance from the American Academy of Pediatrics (AAP) for the use of palivizumab prophylaxis against respiratory syncytial virus (RSV) was first published in a policy statement in 1998. AAP recommendations have been updated periodically to reflect the most recent literature regarding children at greatest risk of severe RSV disease. Since the last update in 2014, which refined prophylaxis guidance to focus on those children at greatest risk, data have become available regarding the seasonality of RSV circulation, the incidence and risk factors associated with bronchiolitis hospitalizations, and the potential effects of the implementation of prophylaxis recommendations on hospitalization rates of children with RSV infection. This technical report summarizes the literature review by the Committee on Infectious Diseases, supporting the reaffirmation of the 2014 AAP policy statement on palivizumab prophylaxis among infants and young children at increased risk of hospitalization for RSV infection. Review of publications since 2014 did not support a change in recommendations for palivizumab prophylaxis and continues to endorse the guidance provided in the 2021 *Red Book*.

INTRODUCTION

Palivizumab (Synagis, Sobi, Inc, United States), is a humanized mouse immunoglobulin G1 (IgG1 κ) monoclonal antibody produced by recombinant DNA technology. The antibody is directed against a conserved epitope, site II of the prefusion and postfusion (F) protein of respiratory syncytial virus (RSV) and demonstrates both neutralizing and fusion inhibitory activity.[1,2] The antibody consists of 2 heavy chains and 2 light chains; 95% of the amino acid sequences (framework) are of

abstract

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FINANCIAL/CONFLICT OF INTEREST DISCLOSURE: Dr Munoz has disclosed data safety monitoring board relationships with Pfizer and Moderna for RSV vaccine, a data safety monitor board relationship with Moderna for vaccines inclusive of RSV and COVID-19, and consultant relationships with Sanofi and Aztra-Zeneca for RSV monoclonal antibody products. Her consultant (Continued)

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human origin, and 5% (antigen binding sites) are of mouse origin. After intramuscular administration, palivizumab is distributed hematogenously throughout the body, including the lower respiratory tract. When RSV encounters palivizumab in the lower respiratory tract, antibody binds to F protein and prevents the structural conformational change that is necessary for fusion of the viral RSV envelope with the plasma membrane of the respiratory epithelial cell.[3] Without fusion, the virus is unable to enter the cell and unable to replicate. In addition, palivizumab prevents cell-to-cell fusion of RSV-infected cells.[3]

BACKGROUND

Palivizumab was licensed by the US Food and Drug Administration (FDA) in June 1998, largely on the basis of results of the IMpact-RSV trial conducted during the 1996 to 1997 RSV season. This randomized, placebo-controlled, double-blind trial involved 1502 infants and young children born preterm (at or before 35 weeks' gestation), some of whom had chronic lung disease (CLD) of prematurity.[4] The IMpact-RSV trial demonstrated a RSV hospitalization rate of 10.6% in the placebo arm and 4.8% among infants who received prophylaxis, an absolute reduction of 5.8% in RSV hospitalizations ($P < .001$), and relative risk reduction of 54.7%.[4] A second randomized, placebo-controlled, double-blind trial conducted from 1998 to 2002 enrolled 1287 children with hemodynamically significant congenital heart disease (CHD).[5] This trial evaluated the safety and efficacy of palivizumab prophylaxis and demonstrated an RSV hospitalization rate of 9.7% in the placebo arm and 5.3% among recipients of palivizumab prophylaxis, an absolute reduction in the RSV hospitalization rate of 4.4% ($P < .003$), with relative risk reduction of 45.3%. Palivizumab was found to be safe and well tolerated in both of these studies. No placebo-controlled trials assessing the efficacy of palivizumab prophylaxis have been conducted in other high-risk subgroups.

Palivizumab was licensed for the prevention of severe lower respiratory tract disease in pediatric patients at increased risk of severe RSV disease.[1] Recommendations from the American Academy of Pediatrics (AAP) for use of prophylaxis have evolved since licensure of palivizumab as additional information has become available.

The AAP policy statement and accompanying technical report for palivizumab prophylaxis is updated periodically to reflect the ongoing assessment by the Committee on Infectious Diseases (COID) of peer-reviewed publications as data become available. This technical report supports the 2014 policy statement (reaffirmed in 2019)[6] and the guidance provided in the 2021 *Red Book*.[7] The scientific literature published since 2014 was reviewed to offer guidance on the most appropriate use of palivizumab prophylaxis. Current guidance is risk-stratified, targeting infants at greatest risk of severe disease and most likely to benefit from prophylaxis. The goal of this updated technical report is to present the results of the COID's review of the available literature supporting recommendations for palivizumab use for infants and young children who are most likely to derive benefit from RSV prophylaxis with this agent. Following the review, COID determined that the data support a reaffirmation of the currently published policy statement.

It is important to note that indications contained in a package label reflect data from clinical trials conducted by the sponsor and submitted to the FDA for drug licensure. The FDA does not issue guidelines or recommendations for drug use. The palivizumab package insert states "Synagis is indicated for the prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease."[1] In the absence of a specific definition of "high risk" by the FDA, the AAP has endeavored, since palivizumab was first licensed, to provide more precise guidance for determining those at increased risk.[6–10] The same is true with this updated review.

ADMINISTRATION

Palivizumab is administered intramuscularly at a dosage of 15 mg/kg once a month. The drug is packaged in single-dose liquid solution vials at 50 mg/0.5 mL and 100 mg/1.0 mL and does not contain preservative. A vial cannot be stored once it is opened, so a vial-sharing scheme is important to minimize wastage. Anaphylaxis has occurred following palivizumab administration after initial exposure or re-exposure, with some cases of severe hypersensitivity reactions also reported.[1]

RSV IMMUNOPROPHYLAXIS AND VACCINE ADMINISTRATION

Palivizumab does not interfere with the immune response to live or inactivated vaccines.[11] The childhood immunization schedule should be followed for all children, regardless of palivizumab use.[1]

GUIDANCE FOR PALIVIZUMAB PROPHYLAXIS

Burden of RSV Disease

RSV is a leading cause of respiratory disease in the United States and remains an important cause of hospitalization in the first months of life. It is estimated that nearly 58 000 children in the first few years of life are hospitalized annually because of RSV infection, with RSV being the most common pathogen identified in children less than 5 years of age hospitalized for community acquired pneumonia in a prospective study.[12,13] Infants in the second month after birth (1–2 months of age) have the highest RSV hospitalization rate (25.1 per 1000, 95% confidence interval [CI]: 21.1–29.3), a rate that is almost

twice that of the next highest risk group (infants in the first month after birth).[14,15] However, retrospective analyses using national databases and the *International Classification of Diseases, Ninth Revision* (ICD-9) discharge diagnoses have shown considerable variation in estimates of annual hospitalization rates attributable to RSV for infants.[16–19] Prospective population-based studies of laboratory-confirmed cases demonstrate that RSV hospitalization rates are approximately half the rates reported in retrospective studies.[12,14,20,21]

Approximately 2.1 million children younger than 2 years seek medical care as outpatients for RSV infection annually in the United States. The majority of these visits occur in the pediatric practice setting (approximately 1.6 million) with an estimated 472 000 visits to the Emergency Department for RSV infection per year.[22] Outpatient visits among RSV-infected children exceed the number of outpatient visits attributable to influenza infection by more than twofold.[22] One study of acute respiratory infection in children younger than 8 years estimated children from birth through 23 months of age experienced overall emergency department visits attributable to RSV infection at a rate of 64.4 per 1000 (95% CI: 45.4–91.3) compared with a rate of 15.0 per 1000 (95% CI: 4.4–50.6) among influenza-infected children (27% had received influenza vaccine) during 2 respiratory virus seasons between 2003 and 2005.[23]

Preterm Infants Without CLD

In 2017, 3.86 million births were reported in the United States, 9.9% of which were preterm infants born at less than 37 weeks' gestation.[24] Infants born at less than 28 weeks' gestation accounted for 0.7% of the annual birth cohort.[24] Moderate to late preterm infants born from 32 weeks 0 days to 36 weeks 6 days gestation represented approximately 8.3% of the birth cohort.[24]

Beginning with the first AAP statement in 1998, the high cost of palivizumab was considered by the COID, leading to attempts to identify risk factors for RSV hospitalization among the large number of moderate to late preterm infants born from 32 weeks 0 days to 35 weeks' gestation.[8] The New Vaccine Surveillance Network (NVSN), sponsored by the Centers for Disease Control and Prevention (CDC), conducted prospective population-based surveillance studies from 3 geographically diverse locations in the United States for young children hospitalized with laboratory-confirmed RSV respiratory illness. One study conducted during the RSV seasons from 2000 through 2005 used multiple logistic-regression analyses and found that only young chronologic age and premature birth were significantly correlated with risk of hospitalization for RSV illness.[14] In this study, some of the previously reported potential risk factors, including siblings in the household and child care attendance, were not associated with a significantly increased risk of RSV hospitalization.[14] The association between preterm birth and increased risk of severe illness was not specific for RSV.[12]

In addition, prior data from the NVSN revealed that for all preterm infants (<37 weeks' gestation), the RSV hospitalization rate was 4.6 per 1000 children less than 24 months of age. This was not significantly different from the hospitalization rate for term infants, which was 5.3 per 1000 children (Table 1).[14] Rates were derived from 132 085 children born during the study period, among whom 2149 were hospitalized with acute respiratory illness, and 559 of the hospitalized children had laboratory-confirmed RSV (Table 1). Infants born at <30 weeks' gestation experienced a higher RSV hospitalization rate (18.7 per 1000 children) than early preterm infants (30–33 weeks), although the small number of infants born before 30 weeks' gestation limits the generalizability of these data.[14] Late preterm infants (34–36 weeks' gestation) were hospitalized at a significantly lower rate than term infants for RSV infection.[14]

An analysis of Tennessee Medicaid data for children younger than 3 years conducted from July 1989 to June 1993 (preimmunoprophylaxis era) included 248 652 child-years of follow-up. The retrospective cohort analysis was conducted to determine RSV hospitalization rates among infants with different degrees of prematurity and other comorbidities.[25] Within each age group, preterm infants had similar rates of RSV hospitalization, regardless of the degree of prematurity (Table 2). In this analysis, preterm infants with CLD were categorized separately to reduce confounding.

A historical cohort analysis from Rochester, New York, reported on RSV hospitalization rates among 1029 consecutive preterm infants born before or at 32 weeks' gestation during a 5-year period.[26] The RSV hospitalization rate increased with decreasing gestational age, with a significantly increased rate at ≤28 weeks' gestation (Table 3). Among infants born at or before 26 weeks' gestation, the risk of RSV-associated hospitalization was 13.9% versus 4.4% among children hospitalized at >30 to 32 weeks' gestation. Although the point estimate for the proportion hospitalized was higher, there was no statistically significant difference in RSV hospitalization rates between infants with gestational ages of >28 to 30 weeks and infants with gestational ages of >30 to 32 weeks.

A retrospective cohort study of infants enrolled in Medicaid in Texas and Florida between 1999 and 2004 examined RSV hospitalization rates in moderately preterm infants 32 to 34 weeks' gestation.[27] Less than 20% of each cohort received palivizumab prophylaxis. In Florida, 71 (3.1%) of the moderately preterm infants were hospitalized compared with 1246 (1.5%) of term infants, and in Texas 164 (4.5%) of the moderately preterm infants were hospitalized compared with 3815 (2.5%) of

TABLE 1 Average RSV Hospitalization Rates Among Children Younger Than 24 Months (2000–2005)[14] and (2015–2016)[15] Seasons

	2000–2005		2015–2016		
Children <24 mo	*N*[a]	RSV Hospitalization Rate per 1000 (95% CI)	*N*[d]	RSV Hospitalization Rate per 1000 95% CI	Rate Ratio[e] (95% CI)
All infants regardless of gestational age	559[b]	5.2 (4.8–5.7)	1043	6.3 (5.9–6.7)	NA
All term infants (≥37 wk gestation)	479	5.3 (4.9–5.8)	881	5.8 (5.4–6.3)	Ref.
All preterm infants (<37 wk gestation)	56	4.6 (3.4–5.8)	162	9.6 (8.1–11.1)	**1.6 (1.3–2.0)**
≥35 wk gestation (2000–2005); >35–37 wk gestation (2015–2016)	494	5.1 (4.7–5.5)	70	7.4 (5.8–9.2)	1.3 (1.0[f]–1.6)
32–34 wk gestation	23	6.9 (4.3–10.1)	50	11.3 (8.1–14.6)	**1.9 (1.4–2.5)**
29–31 wk gestation	6	6.3 (2.0–12.4)	18	13.8 (8.1–20.8)	**2.4 (1.3–3.5)**
<29 wk gestation	12	19.3 (8.4–34.0)	19	15.4 (7.3–24.3)	**2.6 (1.3–4.1)**
All very preterm (<30 wk gestation)	15[c]	18.7 (10.0–30.0)	NA	NA	NA

NA, not applicable.
[a] Among 2149 enrolled hospitalized children from a birth cohort of 132 085 children.
[b] The total of 559 children hospitalized with RSV includes 24 whose gestational age could not be verified.
[c] Personal communication, Geoffrey A. Weinberg, MD.
[d] Total eligible children <60 mo; *n* = 4716, tested with conclusive result for RSV: 2969 (RSV positive *n* = 1043, 35%), (RSV negative *n* = 1926, 65%); (162 infants that tested positive were preterm [18%], median GA 34 wk), and 21 (2%) received palivizumab during the 2015 to 2016 season. Five preterm infants (1%) had no gestational age available.
[e] Rate ratio during the 2015 to 2016 season only compared with reference group of term infants. Statistically significant in bold.
[f] Lower confidence limit <1.00 (0.99).

term infants. Palivizumab prophylaxis was associated with decreased hospitalization in moderately preterm infants in Texas but not in Florida. The risk of RSV hospitalization in moderately preterm infants was similar to 1-month-old term infants by 4.2 months in Florida (95% CI: 2.5–5.7) and by 4.5 months in Texas (95% CI: 2.8–6.4).[27]

Prior data regarding the risk of RSV hospitalization have not supported a benefit from prophylaxis for most preterm infants. In large cohort studies of moderately preterm infants, (32–34 weeks of gestational age), the majority of whom did not receive palivizumab, 2.5% to 4.9% required hospitalization for RSV infection during the RSV season, indicating that more than 95% did not require hospitalization.[27] The rate of hospitalization among infants ≥35 weeks' gestation (5.1 per 1000) was not different than the rate for term infants (5.3 per 1000) (Table 1). The hospitalization rate of infants ≥30 weeks to 35 weeks' gestation indicated a slight increase in risk, compared with term infants (Tables 1–3). Data concerning host or environmental risk factors for hospitalization in preterm infants without CLD or CHD are inconsistent, with the exception of age younger than 3 months at the start of the RSV season, which has been associated with an increased risk of hospitalization.[14]

Based upon the data consistently demonstrating the greatest increase in risk for hospitalization is in preterm infants born before 29 weeks 0 days gestation (hospitalization rates 2–4 times higher than later preterm infants) (Tables 1–3), the consensus of the COID and the Bronchiolitis Guidelines Committee in the 2014 Technical Report and Policy Statement was that consideration of palivizumab prophylaxis in infants without other indications, whose gestational age was less than 29 weeks (28 weeks, 6 days or less), was most consistent with the evidence.

Additional data have become available since the 2014 recommendations were published, with several studies comparing RSV hospitalization rates from before and after the policy update. In an industry-sponsored report utilizing the Truven Health Market-Scan Commercial and Multi-State Medicaid database, RSV hospitalization was

TABLE 2 RSV Hospitalizations per 1000 Children From >248 000 Child-Years of Follow-up from 1989 to 1993[26]

Age Stratum or Risk vGroup	0 to <6 mo old	6 to <12 mo old	12 to <24 mo old	IRR (95% CI) for 0 to <6 mo	Adjusted IRR (95% CI) for first 12 mo
Low-risk infants	44.1	15.0	3.7	Comparator	Comparator
Infants with CHD	120.8	63.5	18.2	2.7 (2.2–3.4)	2.8 (2.3–3.3)
Infants with CLD	562.5	214.3	73.4	12.8 (9.3–17.2)	10.7 (8.4–13.6)
≤28 wk gestation	93.8	46.1	30.0	2.1 (1.4–3.1)	2.4 (1.8–3.3)
29 to <33 wk gestation	81.8	50.0	8.4	1.9 (1.4–2.4)	2.2 (1.8–2.7)
33 to <36 wk gestation	79.8	34.5	10.8	1.8 (1.5–2.1)	1.8 (1.6–2.1)
Other condition[a]	122.3	55.2	24.1	2.8 (2.5–3.1)	2.3 (2.1–2.6)

[a] Asthma, cystic fibrosis, cancer, HIV infection, immunodeficiency, steroid therapy, chronic renal disease, diabetes mellitus, congenital anomalies of the respiratory tract, respiratory distress syndrome.

TABLE 3 RSV Hospitalizations Among 1029 Infants Born at or Before 32 Weeks' Gestation[27]

Gestational Age, Weeks	No. of Infants	No. of RSV Admissions	% Admitted	*P* Versus 30–32 Weeks' Gestation
≤26	165	23	13.9	<.001
27–28	171	17	9.9	.007
>28–30	240	18	7.5	.12
>30–32	453	20	4.4	Comparator
Total	1029	78	7.6	—

Study included RSV seasons 1992 through 1996 with 1029 consecutive premature infants born at 32 wk gestation or earlier surviving to discharge from the birth hospitalization.

identified by *International Classification of Diseases, Ninth Revision* (ICD-9 CM) Clinical Modification diagnostic codes.[28] Infants less than 3 months of age born preterm at 29 to <35 weeks' gestation but without other comorbidities had a RSV hospitalization rate that was 2.65 to 1.41 times greater in the year after the change in recommendations compared with the prior year in the commercially insured and Medicaid insured infants, respectively. However, the RSV hospitalization rate was not consistently significantly different between the 2 time periods in preterm infants 3 to <6 months of age or when the cohort was further divided into 2-week gestational age subgroups, despite an absolute decline of 6% to 39% in the use of palivizumab. A later study from the same group of investigators utilizing the Truven Health Market-Scan database compared RSV hospitalization rates in infants born at 29 to <35 weeks' gestation without other comorbidities from 2 years before to 2 years after the guideline change.[29] The preterm population included in the analyses was less than 6 months of age and comprised 3% to 3.5% of the infants in the database. There was a significant decrease in the use of palivizumab across the 2 time periods. The risk of RSV hospitalizations in preterm infants was greater than term infants in all years analyzed and increased by 46% to 100% in Medicaid and commercially insured infants compared with full term infants in 2014 to 2016. The rate of RSV hospitalization decreased for full term newborns from 10% to 28% over the same period. The increased risk of RSV hospitalizations in preterm infants was directly correlated with the degree of prematurity. An update to this study covering the time period 2011 to 2017 and including infants under 6 months of age from 29 to <35 weeks' gestational age at birth confirmed the significant decline in the use of palivizumab after 2014.[30] The point estimate of the RSV hospitalization rate generally increased in the combined 2014 to 2017 seasons compared with the prior 3 years. However, this was not consistent and the 95% CI overlapped in several of the comparison groups (Fig 1). The adjusted risk of RSV hospitalization in the preterm population was significantly higher than the term population after the policy change except in infants born at 29 to 30 weeks' gestation and commercially insured.

Two additional industry sponsored studies have been published. The first examined claims for RSV hospitalization from the Optum Research Database from 2011 to 2017 for infants under 6 months of age utilizing the ICD-9/10 CM diagnosis and procedure codes.[31] Although the data set included 517 223 eligible infants, 22% could not be included in the analyses because of missing gestational age information. Palivizumab usage significantly decreased in the cohort from the 3 years before to the 3 years after the 2014 AAP guidance change. Hospitalization rates for otherwise healthy preterm infants 29 to <35 weeks' gestational age significantly increased from 2.1 to 3.1 hospitalizations per 100 infant seasons across the 2 time periods in unadjusted analyses ($P = .02$). The rate for term infants did not change over the 2 time periods. Multivariable modeling of rate ratios with adjustment for covariates showed that the risk of hospitalization in the preterm group compared with the term group significantly increased across the 2 time periods. When the data were broken down by chronological age, the preterm group less than 3 months of age continued to have a significantly higher unadjusted hospitalization rate ratio across the 2 time periods. However, the unadjusted rate ratio was not different between the 2 time periods in preterm infants from 3 to <6 months of age. Hospitalization rates were not further broken down by 2 week gestational age groups so that differential risk based upon gestational age could not be determined.

The second study used the Pediatric Health Information System (PHIS) database to perform a historical, observational cohort study of RSV hospitalization in infants less than 6 months of age from 2010 to 2017, again using ICD-9/10 CM diagnosis and procedure codes.[32] The PHIS data set is limited to affiliated children's hospitals and is not a nationally representative data set. RSV hospitalizations were identified in 67 570 infants but only 22 937 infants could be categorized by gestational age. The proportion of RSV hospitalizations for infants in the 29 to <34 weeks' gestational age group significantly increased after 2014 from 8.7% to 14.2% ($P < .0001$).

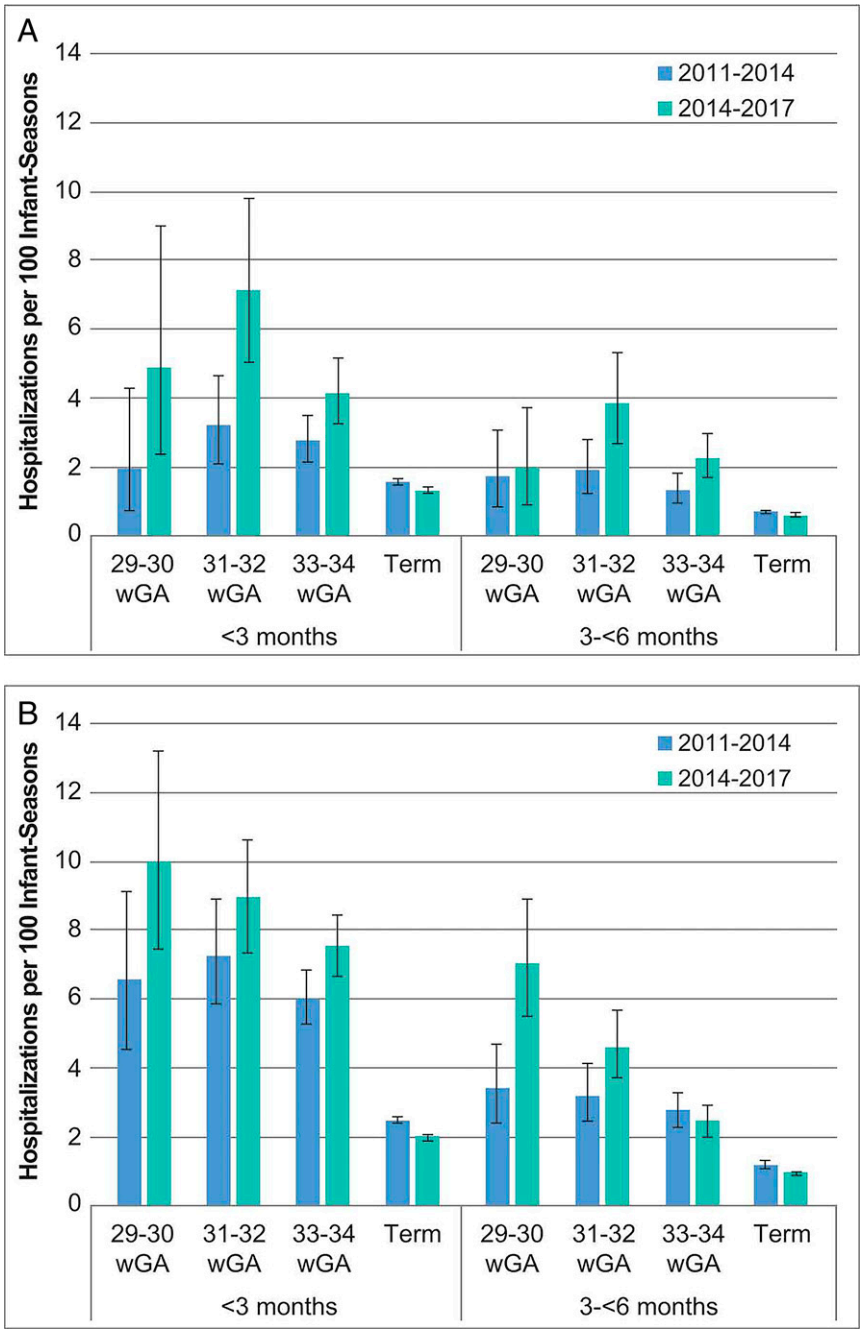

FIGURE 1

RSV hospitalization rates with 95% CIs for 2011 through 2014 and 2014 through 2017 RSV seasons by gestational age (wGA) among infants with (A) commercial or (B) Medicaid insurance. From Fergie J, Goldstein M, Krilov LR, Wade SW, Kong AM, Lance Brannman L. Update on respiratory syncytial virus hospitalizations among U.S. preterm and term infants before and after the 2014 American Academy of Pediatrics policy on immunoprophylaxis: 2011–2017. *Human Vaccines and Immunotherapeutics*, 2021;17(5): 1536–1545, DOI: 10.1080/21645515.2020.1822134.

A separate report utilizing data from Medicaid Managed Care programs in Texas found that infants born at 29 to <33 weeks' gestation who had received palivizumab had a decreased rate of RSV hospitalization (3.1%) compared with those born at 29 to <33 weeks' gestation who did not receive palivizumab (5.0%).[33] However, an increased rate of hospitalization with bronchiolitis not because of RSV (3.3% vs 1.9%) was also noted in the infants who received palivizumab, offsetting the decrease in hospital days because of RSV infection. The protective effect of palivizumab on RSV hospitalization was accounted for mostly by those infants who had received

80% to 100% of the recommended doses. Data from a single region of Canada over a 3 year period did not find a difference in RSV associated hospital visits between infants born at 29 to 31 and 6/7 weeks' gestation who received approval to receive palivizumab based upon a risk score and those that did not receive approval.[34]

A single-center study compared hospitalization rates for laboratory-confirmed RSV infection in children less than 24 months of age from the 2 years before to the 1 year after the guideline change.[35] No significant difference was found between the 2 periods in RSV hospitalization rate despite more than a 50% drop in the use of palivizumab. Subsequent single center studies focusing on infants born at ≥29 to <35 weeks' gestation with confirmed RSV infection also did not find significant increases in the percentage or number of overall hospitalizations comparing the years before and after the change in recommendations.[36,37] One of these studies included results from 3 seasons after the guideline change. The data from this report highlighted the variability in yearly RSV hospitalization rates and the necessity of examining multiple years of follow-up.

A recent study from the NVSN examined RSV hospitalization rates at 7 centers during 1 season (2015–2016) in 1043 infants and children less than 5 years of age. This study confirmed that RSV hospitalization rates were greatest in the youngest infants with the highest rate identified in 1 month old infants (25.1 per 1000, 95% CI: 21.1–29.3).[15] RSV hospitalization rates were higher overall for preterm infants (<37 weeks' gestation), 9.6 per 1000, 95% CI: 8.1–11.1, than infants born at term, 5.8 per 1000, 95% CI: 5.4–6.3, among infants <24 months of age. Half of all hospitalizations occurred in infants less than 6 months of age. There were only 37 infants <32 weeks' gestational age and less than 24 months of age included in this report, comprising 4% of RSV hospitalizations in the cohort. Five infants were 29 to <32 weeks' gestational age and less than 6 months of age at the time of hospitalization. Because of small numbers of subjects in the lower gestational age groups, no conclusions were drawn regarding differences in RSV hospitalization rates among the different groups of premature infants or between those of different chronological ages. Infants of 32 to 34 weeks, 29 to 31 weeks, and those less than 29 weeks' gestational age all had hospitalization rates higher than the total group of term infants less than 24 months of age (Table 1). Palivizumab use was reported in 2% of the cohort, whereas 21% of enrolled children had a chronic comorbid condition, including 11.2% with chronic lung disease, 4.4% with congenital heart disease, 4.1% with neurologic or neuromuscular disease, and 1.2% with an immunosuppressive condition. Infants with comorbid conditions were not evaluated separately in this study. As such, the impact of prematurity alone on RSV hospitalization rates in this cohort is not available. The hospitalization rates varied significantly across the 7 centers and rates reported for each group of premature infants did not exceed the highest rate reported, that for all 1 month old infants, a group for which RSV prophylaxis is not recommended.

A population-based real-world effectiveness study of RSV immunoprophylaxis was performed in infants <12 months of age born from 1996 to 2008 and enrolled in the Kaiser Permanente Northern California integrated health care delivery system.[38] The outcome was a diagnosis of bronchiolitis as assigned by the ICD-9 codes. To avoid confounding by indication, analyses were limited to infants who had received at least 1 dose of RSV immunoprophylaxis. RSV immunoprophylaxis was associated with a decreased risk of hospitalization for bronchiolitis during the 30 days after administration (incidence rate ratio [IRR] = 0.65, 95% CI: 0.46–0.93). Adjusted analyses also showed a decreased risk of hospitalization for bronchiolitis in the 30 day protected period for infants with prior receipt of immunoprophylaxis in the same season (adjusted hazard ratio 0.49, 95% CI: 0.28–0.88). The largest risk reduction for bronchiolitis hospitalization was found in infants with chronic lung disease (IRR = 0.48, 95% CI: 0.25–0.94). No significant reduction in risk of hospitalization for bronchiolitis was identified in premature infants <29 weeks' gestation or those from 29 to 31 weeks' gestational age.[38] As the time span of this study included the use of RSV immune globulin and palivizumab, sensitivity analyses were performed and showed consistent results when the cohort was limited to infants born after 1998 who should have received only palivizumab, and the protective period of immunoprophylaxis was extended to 35 days after administration. When the 2014 guidance recommendations were applied to the data set, the risk of bronchiolitis hospitalization was not significantly decreased among infants who received prophylaxis and would continue to be eligible for palivizumab prophylaxis.[38] The risk was also not significantly decreased among infants who received prophylaxis but who would no longer be eligible.

In summary, data generated before 2014 demonstrated a substantial increase in the risk of RSV hospitalization in preterm infants born at less than 29 weeks' gestation compared with other preterm and term infants. These data were instrumental in the development of the 2014 AAP guidelines. Since that time, industry-sponsored database studies comparing hospitalization rates in infants younger than 6 months from before 2014 to 1 to 3 years later have been published. These studies have generally shown an increased rate of hospitalization for preterm infants born at 29 to <35 weeks' gestation compared with term infants after the 2014 guidance change. Data were most consistent for the youngest infants, especially those from 0 to 3 months of age. Several single-center

studies analyzing 1 to 3 years of RSV hospitalizations after 2014 have not shown consistent increases in hospitalization for preterm infants born at 29 to <35 weeks' gestation. Additionally, these studies highlighted the variability in RSV hospitalizations across seasons. Prospective data from the New Vaccine Surveillance Network from the single 2015 to 2016 season reported hospitalization rates for preterm and term infants younger than 24 months. These data showed increased rates of RSV hospitalization for most preterm groups compared with term infants. However, small numbers of preterm infants were included in the study, hospitalization rates were inconsistent across sites, and infants with comorbid conditions, such as chronic lung disease of prematurity, were not analyzed separately. After a thorough review of all the data, the consensus among COID members was that there was a lack of consistent and robust evidence that would require a change in policy for preterm infants without chronic lung disease.

Preterm Infants With CLD

Multiple studies have documented that infants and young children with CLD have increased rates of RSV hospitalization.[24,25] These elevated rates are sustained through the second year of life compared with healthy term infants at 1 month of age, the group of healthy infants at highest risk of RSV hospitalization, for whom immunoprophylaxis is not recommended.[39,40] Results from the IMpact-RSV trial evaluating all preterm infants with CLD (n = 762 randomized preterm infants) demonstrated that the RSV hospitalization rate among placebo recipients was 12.8% and 7.9% among palivizumab recipients (P = .038).[4] Recent industry sponsored retrospective analyses of state and national databases utilizing ICD-9-CM discharge diagnoses have demonstrated a decrease in RSV hospitalization in infants with CLD from 1997 to 2012, occurring simultaneously with the introduction and use of palivizumab.[41,42] These studies are put forward as further indirect evidence of palivizumab efficacy in preventing hospitalization in this group of infants and are consistent with other published data. Additionally, data from the Canadian RSV Evaluation Study of Palivizumab (CARESS) demonstrated that children with CLD receiving palivizumab in their second year of life had a similar risk of hospitalization due to RSV infection as infants with CLD receiving palivizumab in the first year of life (hazard ratio 1.1, 95% CI: 0.4–2.9), further supporting the current recommendation.[43]

Infants With Hemodynamically Significant CHD

Palivizumab is recommended for infants with hemodynamically significant congenital heart disease during their first RSV season. The results of an industry-funded, multicenter, randomized, double-blind, placebo-controlled trial of palivizumab prophylaxis among 1287 children (639 palivizumab recipients, 648 placebo recipients) younger than 24 months with hemodynamically significant CHD was published in 2003.[5] Results from this study demonstrated a reduction in RSV hospitalization rates of 44% (9.7% among placebo recipients and 5.3% among palivizumab recipients; P = .003).[5] The reduction in the number of RSV hospitalizations between the 2 study groups was 29 fewer RSV hospitalizations among palivizumab recipients during the 4 years of the study.[5] Prophylaxis with palivizumab appeared to have less benefit among cyanotic children than among acyanotic children. Among children in the cyanotic group, there were 23 fewer RSV hospitalizations per 1000 palivizumab recipients (7.9% versus 5.6%, P = .285). Among children in the acyanotic group, there were 68 fewer RSV hospitalizations per 1000 prophylaxis recipients (11.8% vs 5.0%; P = .003). Despite enrolling 1287 subjects, the trial did not have sufficient power to detect statistically significant differences among subgroups of children with different cardiac lesions.

A retrospective analysis of the effect of palivizumab prophylaxis on RSV hospitalizations among children with hemodynamically significant CHD was conducted in California. The authors estimated a statewide 19% reduction in RSV hospitalization between 2000 and 2002 (preprophylaxis era) and 2004 to 2006 (prophylaxis era) after the licensure of palivizumab for children with CHD. The authors concluded that in the state of California, 7 fewer RSV hospitalizations per year occurred among children younger than 2 years with hemodynamically significant CHD following recommendations for palivizumab prophylaxis in this group.[44]

More recent studies describe lower rates of RSV hospitalizations among patients with hemodynamically significant CHD (2% to 3%) who do not receive prophylaxis compared with the 9.7% rate reported in the placebo arm of the 2003 study.[45–48] Nevertheless, the effectiveness of palivizumab prophylaxis in reducing RSV-related hospitalizations among infants with CHD continues to be supported by recent observational studies from countries[40,48–51] with variable prophylaxis recommendations, particularly among patients with cyanotic heart disease[49,52] in the first year of life.

A retrospective analysis of children younger than 3 years (248 652 child-years) in the Tennessee Medicaid program reported that the RSV hospitalization rate for children with CHD in the second year of life (18.2 per 1000) was less than half the hospitalization rate for low-risk infants in the first 5 months after birth (44.1 per 1000), a group for whom palivizumab prophylaxis is not recommended[25] (Table 2). Another retrospective large database study using the US National Inpatient Sample from 1997 to 2013 concluded that certain CHD (Ebstein's anomaly, transposition of the great arteries, aortic stenosis, heterotaxia, and aortic arch anomalies) could be associated with an elevated relative risk for RSV associated

mortality, and various complex congenital heart diseases could be associated with an elevated relative risk for RSV hospitalization in the second year of life (12–23 months) compared with children without CHD.[53] However, Walpert et al reported no change in outcomes (length of stay, rate of admission to the ICU, or hospital mortality) or direct costs for children 13 to 24 months of age with CHD after the implementation of the 2014 AAP palivizumab prophylaxis guidelines.[54]

Children With Anatomic Pulmonary Abnormalities or Neuromuscular Disorders

The risk of RSV hospitalization is not well defined in children with neuromuscular disorders that impair the ability to clear secretions from the upper airway because of ineffective cough, recurrent gastroesophageal tract reflux, pulmonary malformations, tracheoesophageal fistula, upper airway conditions, or conditions requiring tracheostomy.

Studies suggest children and infants with neuromuscular disease who are hospitalized with RSV infection tend to be older compared with other groups of patients hospitalized with RSV infection and are more likely to have preexisting immunity to RSV.[55,56] This may reflect the progressive nature of neuromuscular disease, with susceptibility to respiratory tract disease increasing with age. Children with medically complex conditions or anatomic anomalies, including neuromuscular disorders, congenital diaphragmatic hernia, and those who require tracheotomy or ventilatory support, might experience more frequent and prolonged hospitalizations for respiratory infections, including RSV.[57–62]

Immunocompromised Children

Population-based data are not available on the incidence or severity of RSV disease among children who receive solid organ transplants (SOTs) or hematopoietic stem cell transplants (HSCTs), children who receive chemotherapy, or children who are immunocompromised because of other conditions. Progression of RSV infection from upper to lower respiratory tract disease depends on the specific abnormalities in the immunocompromised host's immune response attributable to the underlying disease or to treatment.

RSV infection in immunocompromised children and adults can progress to respiratory failure and death.[63,64] Lymphopenia has been recognized as a risk factor for disease progression in several studies of immunocompromised patients. One study in adults noted that progression of RSV illness to lower respiratory tract disease did not occur in patients with a lymphocyte count greater than 1000 cells/mm^3 at time of onset of upper respiratory tract infection.[65] An absolute lymphocyte count of 100 cells/mm^3 or less at the time of RSV upper tract infection was associated with progression to lower respiratory tract disease. In contrast to lymphopenia, analysis of antibody concentration in these adult HSCT recipients indicated no correlation between preexisting anti-RSV antibody concentration and progression from upper to lower respiratory tract disease.[65]

A retrospective report from one institution described 58 immunocompromised children with RSV infection between 1997 and 2005.[66] Sixty five percent of the RSV-infected children were managed as outpatients. No deaths occurred among 28 children infected with RSV who were receiving chemotherapy for acute lymphoblastic leukemia or among 11 immunosuppressed SOT recipients. Five of 58 patients with lower respiratory tract infection died (8.6%), including 4 children who were allogeneic HSCT recipients and 1 child with severe combined immunodeficiency. One of the deaths occurred in a 10-year-old child, and a second death occurred in a child with *Aspergillus* species coinfection. Profound lymphopenia ($<$100 cells/mm^3) was associated with progression to lower respiratory tract disease.[66]

Another single center retrospective report noted 5 deaths among 117 RSV-infected, immunocompromised patients between 2006 and 2011 (2 with severe combined immunodeficiency, 1 with uncharacterized immunodeficiency, 1 with chronic granulomatous disease, 1 SOT recipient).[67] The deaths occurred in children who presented with community-acquired RSV lower respiratory tract infection. No deaths occurred among children who were HSCT recipients or those with leukemia or lymphoma.

A retrospective review of RSV infections in children with cancer was conducted from 1998 to 2009.[68] Among 57 patients, 37% experienced progression to lower respiratory tract disease. Three patients died of respiratory failure within 60 days of RSV diagnosis (1 had concomitant bacteremia and fungemia and 1 had concomitant herpes simplex pneumonia).

In a review of 208 viral respiratory infections among 166 patients over a 13-year period who received HSCTs, SOTs, or chemotherapy for malignancy, RSV infection accounted for 43% of the infections.[69] The mean and median ages of patients at the time of infection were 6.1 years and 4.3 years, with a range of 2 months to 21 years of age. Death occurred in 17 (8%) patients with viral respiratory infection, including 6 of 88 (7%) RSV-infected children who received allogeneic HSCTs or SOTs. No infection resulted in death among patients who received chemotherapy, despite being severely immunosuppressed. Mortality and morbidity did not have a statistically significant correlation with the degree of immune suppression.

A retrospective cohort study of 2554 pediatric liver transplant recipients identified through the PHIS database from 2004 to 2012 concluded that in the first

2 years posttransplant, liver transplant recipients are hospitalized at a significantly higher rate than children of the same age in the general population because of RSV infections.[70] In this study, 135 (5.3%) patients had 158 cases of RSV after transplantation, 26 occurred during the transplant hospitalization and 112 occurred in the first year after transplantation (median 0.5 years post), for a hospitalization rate of 4.0% in the first year post-transplant. This rate was higher than for the majority of vaccine preventable diseases included in the study. The median age at infection was 2.2 years. Transplant hospitalizations complicated by RSV were significantly longer, more expensive, and associated with higher rejection rates. Predictors for hospitalization for RSV identified by multivariate analyses included age younger than 2 years ($P < .001$) and multivisceral organ recipient ($P = .04$). An additional study utilizing the PHIS database from 2003 to 2018 found that RSV was also the most common cause of hospitalization among pediatric heart transplant recipients.[71]

Other risk factors for a poor outcome after RSV infection in an immunosuppressed host include age younger than 2 years, presence of lower respiratory tract symptoms at presentation (particularly in the absence of symptoms of upper respiratory infection), corticosteroid therapy, and lymphopenia. Underlying diagnosis, degree of immune suppression, RSV load in bronchoalveolar lavage, or specific humoral immunity to RSV have not been found to correlate with outcome.[72,73] This inability to correlate degree of immunosuppression with disease severity indicates an incomplete understanding of the immune response to viral respiratory infections in the immunocompromised host.

Antibody-based therapy for prophylaxis or treatment, including immune globulin and palivizumab, have not been associated with improved outcome in HSCT recipients.[74] Results from randomized, placebo controlled trials of adjunctive immunoglobulin therapy among SOT patients are not available. No change in RSV incidence was reported among HSCT patients during the 2015 to 2016 season, after implementation of the 2014 palivizumab guidelines.[75] No data are available to suggest benefit from immunoprophylaxis among immunocompromised patients, and practices vary nationwide.[76–78] Further research is required before definitive recommendations can be made for the use of palivizumab in this heterogeneous group of children.

Children With Down Syndrome

Several factors appear to place children with Down syndrome at increased risk of RSV lower respiratory tract disease compared with children without Down syndrome.[79–82] CHD, with or without pulmonary hypertension, occurs in approximately 45% of children with Down syndrome, and lesions include atrioventricular canal, ventricular septal defect, patent ductus arteriosus, and tetralogy of Fallot.[73] Anatomic abnormalities of the upper or lower respiratory tract, muscle dystonia, and intrinsic immune dysfunction may contribute to viral respiratory disease in this population.

One population-based cohort study over an 11-year period in Colorado reported a statewide total of 85 RSV hospitalizations among 680 children with Down syndrome during their first 2 years of life. Concurrent risk factors were present in 35 of the 85 (41%) hospitalized children, indicating they would have qualified for prophylaxis for other reasons. RSV hospitalization rates were 67 per 1000 child years for children with Down syndrome and other risk factors, 42 per 1000 child years for children with Down syndrome without cardiopulmonary disease, and 12 per 1000 child years for children in a control group.[82] These data suggest an estimated overall 7.7 RSV admissions per year (85 admissions over 11 years) in the state of Colorado for children with Down syndrome. Using these figures, 4.6 RSV hospitalizations per year occur among children with Down syndrome without concurrent factors (50 admissions in 11 years) in Colorado. Assuming a 55% reduction in hospitalization, approximately 2 to 3 hospitalizations per year might have been avoided from prophylaxis administered to 680 children. Although children with Down syndrome were more likely to experience a temperature $>100.4^{\circ}$ F, the median length of stay for children younger than 1 year of age with Down syndrome was 4 days, and for children without Down syndrome, the median was 3 days. No deaths were reported in this study.[82] These data suggest children with Down syndrome have a slightly higher hospitalization rate, but the absolute number of RSV hospitalizations is small, and a number of children with Down syndrome are at increased risk because of qualifying heart disease or other factors.

Another report described 39 of 395 (9.9%) children with Down syndrome hospitalized because of RSV infection in the first 2 years of life.[81] Among hospitalized children, 38% had hemodynamically significant heart disease. This study had insufficient power to differentiate among subgroups, meaning the increased RSV hospitalization rate may have been explained by concurrent risk factors and not Down syndrome.[81] Another study of 41 children with Down syndrome hospitalized with RSV infection noted that 51% had underlying CHD.[79] An additional report of 222 children with Down syndrome hospitalized with RSV infection noted the mean age of hospitalized children (1.3 years; range, 0–6.1 years) was significantly older than the age of children hospitalized with RSV who did not have Down syndrome. A similar finding was noted in the Colorado report, with a mean age of 9.6 months at admission for RSV infected patients with Down syndrome and

no other risk factors. In this study, the age range for hospitalization extended through 17 years.[82]

A recent meta-analysis of 5 articles published between 1995 and 2017 suggested Down syndrome as an independent risk factor for RSV hospitalization for children <2 years, with a 6.8 fold increased risk (95% CI: 5.4–6.7) when compared with unaffected children, but the meta-analysis was limited by a small number of included studies and potential confounding because of additional comorbidities.[83] In Japan, where routine prophylaxis has been given to patients with Down syndrome since 2013, independent of other risk factors, overall RSV hospitalizations were less frequent in patients receiving prophylaxis (4.2%) compared with those without prophylaxis (6%) (odds ratio: 0.41; 95% CI: 0.18–0.92; $P = .03$), but this effect was not evaluated separately among those with and without comorbidites.[84] A more recent study utilizing a nationwide inpatient database and interrupted time series analysis did not find evidence of a decrease in RSV associated hospitalizations in children with Down syndrome in Japan after the change in policy.[85] There is a need for more studies to determine the role of RSV prophylaxis in the first year of life in children with Down syndrome without other recognized risk factors for severe RSV disease, such as congenital heart disease, chronic lung disease, airway clearance issues, or prematurity (<29 weeks' gestation).[80,82]

Children With Cystic Fibrosis

Available studies indicate RSV hospitalization in children with cystic fibrosis is uncommon and the incidence is unlikely to be different from children without cystic fibrosis. Evidence to support a benefit from palivizumab prophylaxis in patients with cystic fibrosis is not available.[86–88]

A randomized clinical trial with palivizumab prophylaxis included 186 children with cystic fibrosis from 40 centers. One subject in the untreated group and 1 subject in the palivizumab group were hospitalized for RSV infection.[89] Although this study was not powered for efficacy, no clinically meaningful differences in outcome between the 2 groups were reported. At the 12-month follow-up, there was no significant difference between the treated and untreated groups in number of *Pseudomonas* colonizations or change in weight-to height ratio. A case-control study of palivizumab in 75 children with cystic fibrosis noted a possible trend toward a potential clinical benefit of palivizumab prophylaxis, but the difference was not statistically significant.[87]

A large Danish study of RSV hospitalizations occurring between 1997 and 2003 in children with chronic medical conditions identified 72 children with cystic fibrosis.[90] There were 13 RSV-related hospitalizations, which resulted in an adjusted incidence rate ratio for risk of RSV hospitalization of 4.32 (95% CI: 2.42–7.71). The geometric mean ratio for duration of RSV hospitalization in these children with cystic fibrosis was 1.3 days (95% CI: 0.81–2.11 days).

Two recent reviews[91,92] of RSV infection in infants with cystic fibrosis (CF) acknowledged that infants with cystic fibrosis may have a slightly increased risk for hospitalization with RSV. However, both reports stated there is insufficient evidence related to safety and efficacy in infants with cystic fibrosis to support a recommendation for palivizumab prophylaxis.[91,92] A survey of cystic fibrosis center directors published in 2008 noted that palivizumab prophylaxis is not the standard of care for patients with cystic fibrosis.[93] A report based on the CF foundation registry concluded that receipt of palivizumab in the first 2 years of life was not associated with improved long-term outcomes (pulmonary function, annual risk of hospitalization, or time to first positive sputum culture) among 1588 (of 4267) children treated from 2008 to 2015 in the United States.[94] Conversely, a Canadian registry study conducted from 2005 to 2016 found a similar incidence of RSV hospitalization in CF children compared with children with established indications, suggesting that CF children may be at similar risk as those who receive prophylaxis for other indications, and in a small study from the same group, children with CF who received palivizumab had shorter length of hospitalization compared with untreated CF children.[95,96] The disparate results from these reports do not currently support a recommendation for palivizumab prophylaxis in infants with CF.

Discontinuation of Palivizumab Prophylaxis Among Children Who Experience Breakthrough RSV Infection or Hospitalization

RSV is classified into subgroups A and B, based on antigenic differences in the surface G glycoprotein. Subgroups are classified further into genotypes based on genetic analysis. The ability of RSV to cause reinfections throughout life is likely attributable both to strain variability and to an immune response that does not fully protect against subsequent infection. Reinfections with both heterologous and homologous strains occur. More than 1 RSV strain may circulate concurrently in a community. However, repeat RSV hospitalizations during 1 season are rare.[97]

One study identified 726 RSV lower respiratory tract infections among 1560 children younger than 5 years over 8 successive RSV seasons in an outpatient setting.[98] Only 1 instance of repeat RSV infection occurred during the same season. Furthermore, it is well established that repeat RSV infections are associated with less severe clinical illness than the initial RSV infection.[99,100]

In the blinded and randomized clinical trial that involved 1287 children younger than 24 months with hemodynamically significant CHD, a total of 5 readmissions for a second RSV hospitalization occurred (a rate of less than 0.5%). Three of 648 children in the placebo group and 2 of 639 children who received palivizumab had more than 1 RSV hospitalization over 4 years.[5]

In a Dutch trial of 429 preterm infants randomized to receive either palivizumab prophylaxis or placebo between April 2008 and December 2010, infants were followed for recurrent wheezing. No RSV reinfections were detected in either group, again indicating that repeat RSV infections in the same year seldom occur.[101]

Use of Palivizumab in the Second Year of Life

The majority of RSV hospitalizations occur during the first year of life. A prospective population-based surveillance study of 5067 children younger than 5 years evaluated 564 children hospitalized with laboratory-confirmed RSV infection. Among the children hospitalized with RSV infection, 75% were younger than 12 months. Less than 20% of all pediatric RSV hospitalizations occurred during the second year of life.[12]

Limited safety data and no efficacy data are available regarding palivizumab prophylaxis in the second year of life.[102,103] Regardless of the presence or absence of comorbidities, RSV hospitalization rates decline during the second RSV season for all children.[14,25] Despite this decrease, the rate of RSV hospitalization in the second year of life in children with chronic lung disease remains high.[39,40–42] Therefore, palivizumab prophylaxis is recommended for a second RSV season in children with chronic lung disease who continue to require medical therapy (see above). Palivizumab may also be considered for use in children less than 2 years of age with cardiac transplantation during the RSV season.

Lack of Therapeutic Efficacy of Palivizumab

Controlled studies have demonstrated that monoclonal antibodies have no therapeutic benefit in the treatment of RSV-infected children. One randomized study determined that intravenous palivizumab administered to RSV-infected and intubated infants reduced the RSV viral load in the lower respiratory tract but had no effect on RSV concentration in the upper respiratory tract.[104] Despite a reduction in viral load in the lower respiratory tract, no difference in disease severity was found between palivizumab recipients and placebo recipients. A recent Cochrane systematic review of 7 randomized controlled trials comparing the therapeutic use of RSV immunoglobulins, palivizumab, or motavizumab versus placebo in 486 hospitalized infants found no impact on mortality, length of hospital stay, or severity of illness.[105] No effect on mortality was observed in another study of patients with hematologic diseases treated with palivizumab from 2007 to 2016.[106]

Prevention of Health Care–Associated RSV Disease

Strict infection control practices, including restriction of visitors to the NICU during respiratory virus season, has been shown to decrease health care–associated RSV disease. Evidence does not support the use of palivizumab among hospitalized preterm infants to prevent health care–associated spread of RSV.[107,108] If an RSV outbreak occurs in a high-risk unit (eg, pediatric, NICU, or HSCT unit), primary emphasis should be placed on proper infection control practices, especially hand hygiene. No rigorous data exist to support palivizumab use in controlling outbreaks of neonatal health care–associated disease. Further, rehospitalization rates for RSV infection do not differ among infants who receive inpatient palivizumab prophylaxis while in the NICU compared with those who initiate prophylaxis at hospital discharge.[109] Although health care–associated RSV infection is rare, patients with underlying conditions that meet criteria for palivizumab prophylaxis and require prolonged hospitalization may benefit from continuation of administration of prophylaxis when hospitalized during the RSV season, in addition to strict infection control practices to reduce the risk of infection.[110]

CONSIDERATIONS AFFECTING REVISION OF GUIDANCE

Risk Factors for RSV Hospitalization

Overall, approximately 2% to 3% of infants in the first 12 months of life are hospitalized with RSV infection each year in the United States. Children with certain comorbidities are at increased risk of severe RSV disease relative to children without these comorbidities.[12,25] Chronologic age is the single most important risk factor for RSV hospitalization on the basis of the observation that more than 58% to 64% of pediatric RSV hospitalizations occur in the first 5 months after birth.[12,14,25] Most of these hospitalizations occur in the first 90 days after birth.[14,27,111] Certain subgroups of infants with comorbidities, such as prematurity, CLD, or hemodynamically significant CHD, have increased risks for RSV hospitalization, although the degree of risk varies among studies.[16,112] The risk of RSV hospitalization associated with most other risk factors has been difficult to determine because of low rates of occurrence. Most host and environmental factors increase the risk for RSV hospitalization by only a small magnitude, so their contribution to overall disease burden is limited.[113] In addition, these factors are not identified consistently from study to study. These inconsistencies likely reflect variation in practice patterns in different countries, variation in living conditions and climate, variation in health care coverage, yearly variation in disease severity, and incompletely

understood genetic factors. Differences in study design may also contribute to these inconsistencies.

Reported host risk factors of limited and variable impact include: congenital malformations, congenital airway anomaly, neuromuscular impairment, birth weight, sex, lack of breastfeeding, duration of breastfeeding, cord serum anti-RSV antibody concentration, small for gestational age, Down syndrome, epilepsy, cord blood vitamin D concentration, family history of atopy, viral load, malnutrition, and singletons versus multiple birth subjects. Environmental risk factors of limited and variable impact include: environmental pollution, crowded living conditions, living at increased altitude, meteorological conditions, malnutrition, low parental education, low socioeconomic status, child care attendance, size of child care facility, month of birth, smoke exposure, maternal smoking during pregnancy, and proximity to hospital care.[12,16,25,55,56,81,90,112,114–128] One publication suggested that malformations of the urinary tract increase the risk of RSV hospitalization.[90]

Multiple logistic-regression analyses of data from the 4-year population-based prospective study found that of the evaluated risk factors (male sex, child care attendance, smoke exposure, lack of breastfeeding, and other children in the house), only preterm birth and young chronologic age independently correlated with more severe RSV disease after adjusting for other covariates.[12]

RSV Seasonality

RSV epidemiology has been globally impacted by the coronavirus disease 2019 pandemic with decreased cases noted in the traditional fall and winter seasons beginning in 2020. Alternatively, substantial circulation of RSV was identified during the spring, summer, and fall of 2021 and 2022 in different regions of the United States. It is unknown if or when the typical seasonality will return. In the United States from July 2014 through July 2017, the median time of the year for RSV onset was mid-October with the season lasting 31 weeks until early May.[129] The median national peak occurred in early February. The national onset occurred 1 week later, and season duration decreased by 1 week by excluding Florida and Hawaii from these data. The onsets for the 2014 to 2017 seasons were approximately 2 weeks earlier than the 2012 to 2014 seasons. However, the 2014 to 2017 reports were based on polymerase chain reaction data, whereas prior reports were based on antigen data. This necessitated the use of different statistical methods for determining the RSV seasons, and thus the apparent earlier and lengthened seasons are thought to be artificial and a result of the change in methodology.

Florida has historically had a different seasonality than the rest of the United States, and because of its northern latitude, Alaska may experience a longer RSV season (see later discussions for each).[130,131] In addition, based on antigen testing, RSV circulation patterns appeared to differ in Hawaii compared with other states in the same region. However, there were too few laboratories consistently reporting polymerase chain reaction data to report state level data with confidence. Because 5 monthly doses of palivizumab at 15 mg/kg per dose will provide more than 6 months of serum palivizumab concentrations above the desired serum concentration for most infants, administration of more than 5 monthly doses is not recommended within the continental United States during a typical RSV season.[132] Children who qualify for 5 monthly doses of palivizumab prophylaxis should receive the first dose at the time of onset of the RSV season. For qualifying infants born during the RSV season, fewer than 5 doses will be needed to provide protection until the RSV season ends in their region (maximum of 5 doses). A small number of sporadic RSV hospitalizations occur before or after the main season in many areas of the United States,[113,133] but maximum benefit from prophylaxis is derived during the peak of the season and not when the incidence of RSV hospitalization is low.

Prophylaxis for American Indian and Alaska Native Children and Timing of Palivizumab Initiation

Hospitalization rates for RSV disease and all causes of bronchiolitis are higher in American Indian and Alaska Native (AI/AN) infants and children than in the general US child population of the same ages.[134,135] An average annual RSV hospitalization rate of 22.1 per 1000 AI/AN infants was reported from 2009 to 2011 compared with 16.6 per 1000 in the general US infant population.[134] The highest RSV hospitalization rates were identified among American Indian infants in the Southwest region (25.4 per 1000) and Alaska (43.1 per 1000).[134] Bronchiolitis hospitalization rates during the same time period were 59.0 per 1000 in Southwest American Indian and 68.2 per 1000 Alaska Native infants with the average general US infant population rate of 26.1 per 1000.[134] Variability in hospitalization rates between communities within a region has also been identified. Alaska Native Yupik Eskimo infants in the southwestern Alaska Yukon-Kuskokwim Delta (YKD) area experienced RSV hospitalization rates 3 times higher than the general population of US infants with an average annual rate of 63.3 per 1000 from 2005 to 2012.[136] Infants living on the Navajo and White Mountain Apache reservations in the Southwest region had annual average RSV hospitalization rates from 1997 to 2000 of 78.1 and 164.3 per 1000, respectively.[137] Additionally, prolonged RSV circulation was previously demonstrated in the YKD area of Alaska with more recent data showing a shortening of the season, similar to the typical general US season.[136]

Social determinants of health have been associated with high rates of hospitalization because of lower respiratory

tract infections in American Indian/Alaska Native infants and children.[135,136] RSV hospitalization rates in the YKD area were higher in communities with a greater percentage of families lacking complete plumbing, having more than 1.5 persons per room, and living below the poverty rate by multivariate analyses.[136] Hospitalization rates were also higher in communities located closer to the regional hospital and with a larger population. An intervention to improve indoor air quality through home remediation and education has been shown to decrease respiratory symptoms reported by parents and outpatient visits for lower respiratory tract infections for high risk Alaska Native children.[138]

Prior research supports the use of RSV prophylaxis in AI/AN infants. A retrospective study comparing RSV hospitalization rates in Alaska Native children in the 3 years before the use of palivizumab (1993–1998) to 3 years after routine use (1998–2001) showed a significant decrease in RSV hospitalization rates (risk ratio: 0.34; 95% CI: 0.17–0.68).[139] One randomized controlled trial of motavizumab for RSV prevention in healthy term American Indian infants in the southwest United States has been reported.[140] Motavizumab, an IgG1 humanized monoclonal antibody designed for greater affinity to RSV than palivizumab, was studied in clinical trials but never proceeded to licensure. In American Indian infants, motavizumab use was associated with an 87% relative reduction in RSV hospitalization compared with placebo.

Utilizing local RSV epidemiology in Alaska, statewide recommendations are published outlining the selection of infants eligible for prophylaxis.[141] These recommendations may differ from the remainder of the United States. Clinicians may wish to use RSV surveillance data generated by the state of Alaska to assist in determining onset and end of the RSV season for appropriate timing of palivizumab administration.[142] Additionally, the selection of infants eligible for prophylaxis in select American Indian populations with a high burden of RSV disease may differ from the remainder of the United States for infants in the first year of life.

Timing of Prophylaxis for the State of Florida

Variation in the onset and offset of the RSV season in different regions of Florida may affect the timing of palivizumab administration. Season onset can be determined in real time by identifying the first week of 2 consecutive weeks that RSV molecular assay test positivity is 3% or greater or antigen detection positivity is 10% or greater.[129,143] Florida Department of Health data may be used to determine the appropriate timing for administration of the first dose of palivizumab for qualifying infants. Despite varying onset and offset dates of the RSV season in different regions of Florida, a maximum of 5 monthly doses of palivizumab will be adequate for qualifying infants for most RSV seasons in Florida. Even if the first of 5 monthly doses is administered in July, protective serum concentrations of palivizumab will be present for most infants and young children for at least 6 months and likely into February.

Pharmacokinetics of Palivizumab

A threshold protective serum palivizumab concentration in humans has not been established. On the basis of studies of palivizumab prophylaxis in the cotton rat model, serum concentrations of 25 to 30 mcg/mL produced a mean reduction in pulmonary RSV concentrations of 99% (2 $\log_{10}$).[144,145] Because of the reliability of the cotton rat model to predict results in humans, this serum concentration became the target trough concentration in the randomized clinical trials.[4,5] The package label states that "palivizumab serum concentrations of greater than or equal to 40 mcg/mL have been shown to reduce pulmonary RSV replication in the cotton rat model of RSV infection by 100 fold."[1]

Palivizumab pharmacokinetic data published by the manufacturer in 2012 demonstrate that after 5 monthly doses, serum concentrations of palivizumab remain at or above protective levels for most children for at least 6 months (>24 weeks).[132] There is seldom justification to administer more than 5 doses within the continental United States. These data were derived from a computer model based on 22 clinical trials.

Weight dosing at 15 mg/kg resulted in similar palivizumab concentrations in healthy term infants as well as preterm infants.[132]

Mortality Rates Among Hospitalized Children With RSV Infection

Findings from 2 national databases (PHIS data for 2000 to 2011 and the Health Cost and Utilization Project Kids' Inpatient Database [KID] for 2000, 2003, 2006, and 2009) showed that mortality rates associated with hospitalization in infants with RSV infection were lower than previously estimated. The KID data sets from more than 4000 hospitals in 44 states identified 550 deaths (9 deaths per 10 000 admissions, whereas the PHIS data set from 44 children's hospitals identified 671 deaths from 2000 to 2011 [25.4 deaths per 10 000 admissions, $P < .001$]). When limited to infants with a primary diagnosis of RSV, the KID data set estimated 42 annual deaths (3.0 deaths per 10 000 admissions) and the PHIS data set showed a decreasing trend, with mortality peaking in 2002 and 2003 at 14.0 deaths per 10 000 admissions, decreasing to 4.0 per 10 000 admissions by 2011. The majority of deaths in both data sets were in infants with either complex chronic conditions or other acute conditions such as sepsis.[146,147] Approximately 40 deaths per year in the United States associated with RSV

infection were identified in children under age 5 years in death certificate data from 2005 to 2016 with steady yearly rates over that time period.[148,149]

An industry-sponsored meta-analysis of published reports of fatality rates attributable to RSV infection in children suggested higher rates of death based on estimates from earlier years, likely because supportive care received in intensive care units was less effective in earlier years.[150]

A statistically significant reduction in RSV mortality has not been demonstrated in any randomized clinical trial with palivizumab. Thus, inclusion of mortality reduction or life years saved is difficult to justify in a cost analysis of palivizumab prophylaxis.

Palivizumab-Resistant Isolates

Palivizumab binds to a highly conserved epitope (pre and postfusion F site II) on the extracellular domain of the mature F protein that encompasses amino acids 262 to 275. After antibody binding, viral entry into the respiratory epithelial cell is blocked, as is cell-to-cell fusion of infected cells.[3] RSV escape mutants resistant to palivizumab have been isolated from about 5% of children hospitalized with breakthrough RSV infection while receiving monthly palivizumab prophylaxis.[1,111,151–156] RSV isolates resistant to palivizumab contain mutations in codons encoding the amino acids between 262 and 276 of the F protein. Amino acid sequence variations outside antigenic site II do not appear to confer palivizumab resistance.

Effect of Palivizumab Prophylaxis on Subsequent Wheezing

Several studies have documented that infants hospitalized with viral lower airway disease are more likely to experience recurrent wheezing compared with infants who do not experience severe bronchiolitis.[98,157–161]

A double-blind placebo-controlled trial conducted in the Netherlands addressed palivizumab prophylaxis and recurrent wheezing.[101] Parent-reported wheezing in otherwise healthy late preterm infants during the first year of life was evaluated in 214 infants who received monthly prophylaxis with palivizumab compared with 215 infants who received placebo. During the first year of life, infants and young children in the placebo group experienced 2309 days with wheezing from a total 51 726 patient days (4.5%), whereas those in the palivizumab group had 930 days of wheezing out of 53 075 patient days (1.8%; $P = .01$). This represents an absolute 2.7 fewer days of wheezing per 100 patient days (17.5 wheezing days per 1000 days versus 44.6 wheezing days per 1000 days or 27.1 fewer wheezing days per 1000 days) among infants who received monthly palivizumab in contrast to those who did not receive prophylaxis.[101] Reliance on patient reporting of wheezing was identified as a potential limitation. The wheezing episodes were not medically attended events but parent-reported wheezing of unknown severity.[101] The proportion of infants using bronchodilators in the placebo group was 23% and 13% among palivizumab recipients.

Investigators followed the infants enrolled in this trial through 6 years of age and assessed forced expiratory volume in 0.5 seconds and 2 diagnostic versions of asthma: parent-reported current asthma versus physician-diagnosed asthma.[162] They achieved a 92% follow-up rate for their sample, and forced expiratory volume in 0.5 seconds × percentage predicted values were the same in the RSV prevention group (89.1% [SD 10.6]) and placebo group (90.1% [11.1]). The proportion of children with current physician-diagnosed asthma was also similar between the RSV prevention group (19 [10.3%] of 185) and placebo group (18 [9.9%] of 182). Both of these outcomes had nonsignificant absolute risk reduction values favoring placebo. Parent-reported current asthma rates did differ between groups (ARR 9.9%; 95% CI: 2.2, 17.6) favoring prophylaxis, but this was a nonblinded study. The authors concluded that RSV prevention from immunoprophylaxis did not have a major effect on asthma or lung function at 6 years of age.

One additional randomized, double-blind, placebo-controlled trial employed motavizumab in healthy Native American children born at 36 weeks and followed through 3 years of age for recurrent wheezing illness.[141] This trial failed to demonstrate any effect on prevention of medically attended episodes of wheezing from ages 1 to 3 years. Investigators randomized 2127 infants from the Navajo and Apache Nations to receive either motavizumab (1417) or placebo (710). A statistically significant reduction in severe RSV infections was observed in the motavizumab group (11% RSV hospitalization rate among placebo recipients versus 2% RSV hospitalization rate among motavizumab recipients, $P < .0001$). No effect on rates of medically attended wheezing in children aged 1 to 3 years (190 [14.9%] of participants randomly assigned to receive motavizumab vs 90 [14.0%] participants randomly assigned to receive placebo) was found. Thus, results from 2 high quality randomized trials did not suggest that avoidance of severe RSV infection with monthly immunoprophylaxis is associated with a subsequent reduction in asthma among populations of young children at moderate risk of asthma.

Cost Analyses

Financial stewardship is a concept that acknowledges a physician's responsibility to advocate "for a just and cost-effective distribution of finite resources."[163,164] Use of noncost-effective interventions contributes to maladies within the health care system, including significant deficits, lower quality of care, and inequitable access to

health care.[165] A number of economic analyses from different countries have evaluated immunoprophylaxis use in different age groups among children with varying comorbidities and from both the payer and the societal perspective.[166] Economic evaluations sponsored by the manufacturer of palivizumab suggest cost neutrality or even cost savings.[167–177] In contrast, analyses conducted by independent investigators consistently demonstrate the cost of palivizumab prophylaxis far exceeds the economic benefit of hospital avoidance, even among infants at highest risk.[26,27,44,47,124,166,178–189]

A recent meta-analysis identified 28 economic analyses of palivizumab in a multitude of patient populations and noted there were barriers to drawing definitive conclusions on the economic value of the drug.[190] Study estimates ranged from concluding a cost savings exists to an incremental cost-effectiveness ratio of $2 526 203 per quality-adjusted life year. Typical cut points for concluding cost effectiveness are $50 000 to $100 000 USD per quality-adjusted life year. Furthermore, from a sensitivity analysis standpoint, the major variable driving cost effectiveness models for palivizumab is the inclusion of a mortality benefit. No mortality benefit has been shown to exist for palivizumab in the randomized trials as mortality because of RSV is exceptionally low in the developed world. Models that do not ascribe a mortality benefit to palivizumab generally do not result in incremental cost-effectiveness ratios falling within a cost-effective range regardless of the population studied.

Cost was considered during deliberations by the COID and the Bronchiolitis Guidelines Committee but the final guidance as presented in the accompanying policy statements is driven by the limited clinical benefit derived from palivizumab prophylaxis.

The American College of Physicians Clinical Guidelines Committee outlines principles to help clinicians define high-value health care by considering key concepts: benefits, harms, and cost of the intervention; downstream costs that occur as a result of the intervention; and the incremental cost-effectiveness ratio.[191] On the basis of these principles, the minimal clinical reduction in RSV hospitalizations and reduction in parent-reported wheezing episodes associated with palivizumab prophylaxis do not justify the cost. Although some RSV hospitalizations may be severe and prolonged, the majority of hospitalizations last 2 to 3 days. The high cost of palivizumab prophylaxis becomes a cost-inefficient way to prevent a limited number of short hospitalizations and a small number of longer hospital stays, especially in the absence of evidence of significant long-term benefit and no measurable effect on mortality.[191]

Health expenditures should not be based only on cost and benefit but rather on the assessment of the benefit of the intervention relative to the expenditure. High-cost interventions may be appropriate if highly beneficial.[191] Because the high cost of palivizumab prophylaxis is associated with minimal health benefit, this intervention cannot be considered high-value health care for any group of infants.

Control Measures

A critical aspect of RSV prevention among all infants is education of parents and other caregivers about the importance of decreasing exposure to and transmission of RSV and other viral respiratory infections. For all infants, particularly those that are high risk, preventive measures include limiting, where feasible, exposure to contagious settings (eg, large group child care) and emphasis on hand and cough hygiene in all settings, including the home and the NICU, especially during periods when contacts of children at high risk have respiratory tract infections. For all children, the importance of breastfeeding, avoidance of crowds, avoidance of tobacco or other smoke exposure, including secondhand and thirdhand exposure, and immunization of household contacts with influenza and pertussis vaccines and eligible contacts with coronavirus disease 2019 vaccine, should be emphasized.

Future Research and Possibilities

Continued research examining RSV hospitalization rates in all groups of children thought to be at increased risk is needed. The effect of immunoprophylaxis on medically attended outpatient visits should also be evaluated.

Investigation of other types of passive immunoprophylaxis is ongoing. Nirsevimab (MEDI8897, AztraZeneca/Medimmune/Sanofi-Pasteur) is a recombinant human monoclonal antibody derived from human B cells that targets a unique antigenic site (site "zero") on the prefusion RSV F protein. It is a much more potent inhibitor of RSV than palivizumab in vitro and has a substantially longer half-life, allowing for a single intramuscular dose for the entire RSV season. An initial study of nirsevimab in premature infants from 29 to <35 weeks' gestation demonstrated a 70.1% (95% CI: 52.3–81.2) lower incidence of medically attended lower respiratory tract infections in the treated population.[192] The product is currently in Phase 3 trials and is being studied for potential use in all infants for prevention of RSV disease in their first season.[193]

MK-1654 (Merck & Co Inc, Kenilworth, NJ), is also an extended half-life monoclonal antibody directed against an antigenic site (site IV) present in both the pre and postfusion forms of the RSV F protein, and is currently in Phase 3 clinical trials and intended to be used in both term and preterm infants.[194,195]

Development of safe and effective RSV vaccines remains a high priority.[196–199] Prevention of RSV in infants and young children may be possible by active infant

immunization, by passive transplacental transfer of antibodies after maternal vaccination, or a combination of both. Numerous candidate vaccines are currently in development (https://www.path.org/resources/rsv-vaccine-and-mab-snapshot/). Progress has been achieved with live-attenuated and chimeric intranasal vaccines, as well as vector-based vaccines for infants and young children, several of which are in Phase 1 and 2 clinical trials.[200–202] Ensuring adequate attenuation while maintaining immunogenicity remains a challenge. Early experience with a formalin-inactivated whole virus vaccine resulted in enhanced RSV disease in young children in the 1960s and has complicated development of inactivated RSV vaccines.[196,203] New protein-based RSV vaccines are aimed mainly for use in adults, and target antigenic sites in the prefusion configuration of the F protein.[204–207] A viral-like particle vaccine based on the F-protein was the first to be evaluated in a large global Phase 3 clinical trial in pregnant women, after demonstrating the potential to offer passive protection for young children through the first months of life in the Phase 2 trial.[203,208–210] Unfortunately, the vaccine failed to meet its prespecified primary outcome of preventing medically attended RSV disease in infants.[211] However, active development of 1 other vaccine for maternal immunization is ongoing, with interim analysis results demonstrating safety, immunogenicity, and efficient transplacental transfer of antibody to the newborn.[212] Lastly, new technologies allowing the production of nucleic acid vaccines with specific antigenic targets may allow for the development of effective RSV vaccines for infants, alone or in combination with other common pediatric respiratory viruses.[207]

Effective antiviral agents for the treatment of RSV are needed. Ribavirin was licensed in 1986 and remains the only FDA-licensed antiviral agent for therapy but seldom is used because of limited efficacy, cumbersome delivery (aerosol), and high cost.[7] Interest continues in developing more broadly effective antiviral agents including fusion inhibitors and replication inhibitors.[213–217]

Multiple studies have demonstrated an association between social determinants of health and hospitalization rates for bronchiolitis, RSV, and lower respiratory tract infections in infants and children in Europe, New Zealand, and North America including the American Indian and Alaska Native Populations.[136,218–222] Specific measures of social vulnerability, such as crowding, unemployment, and estimates of poverty as well as the maternal characteristics of younger age, addiction, mental health concerns, and involvement with the criminal justice system, have been identified in these reports. Further research examining these associations may identify additional groups of infants that would benefit from prophylaxis due to high rates of RSV hospitalization and impact policy.

SUMMARY

The vast majority of RSV hospitalizations occur among healthy term infants. Prematurity is an important risk factor for severe RSV disease, and among preterm infants, those born at less than 29 weeks of gestation have one of the highest risks of severe morbidity and hospitalization from RSV, despite the use of palivizumab. After a thorough review, the COID members agreed that there were data supporting an increased rate of RSV hospitalizations in preterm infants born at >29 weeks' gestation compared with term infants following the 2014 change in AAP guidance. The data were strongest for infants less than 3 months of age but were not consistent across all studies. Small sample sizes and varying methodology precludes comparisons across publications. Likewise, no currently published data are available that would allow for a direct comparison between RSV hospitalization rates in preterm infants and healthy, term, 1-month-old infants, a group believed to be at high risk of hospitalization and for whom RSV prophylaxis is not currently recommended. An increase in RSV associated mortality associated with the guidance change has not been reported from well conducted reviews and was not found in the original randomized controlled trials. Additionally, real world effectiveness studies do not support a major impact of palivizumab use on otherwise healthy preterm infants.

Based upon the inconsistent changes in RSV hospitalization in preterm infants reported after 2014, the absence of an effect on mortality, the minimal benefit provided by palivizumab, and the notable predominance of RSV hospitalizations among healthy term infants for whom prophylaxis is not recommended, the consensus among COID members was that the evidence was insufficient to warrant a change in policy regarding the use of palivizumab in otherwise healthy preterm infants. The COID members also agreed that the current evidence continues to support the AAP 2014 policy regarding infants with chronic lung disease, congenital heart disease, Down syndrome, immunocompromising conditions, anatomic pulmonary abnormalities or neuromuscular disorders, and cystic fibrosis.

Immunoprophylaxis with palivizumab remains an option for children at high risk, as outlined in the 2014 AAP policy statement.[6] Several new options for the prevention of severe RSV in all infants, including term and preterm, are under active evaluation, with the possibility of substantially impacting the recommendations for RSV prophylaxis in the near future.

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ABBREVIATIONS

AAP: American Academy of Pediatrics
CDC: Centers for Disease Control and Prevention
CHD: congenital heart disease
CI: confidence interval
CLD: chronic lung disease
COID: Committee on Infectious Diseases
FDA: US Food and Drug Administration
HSCT: hematopoietic stem cell transplant
KID: Kids' Inpatient Database
NVSN: New Vaccine Surveillance Network
PHIS: Pediatric Health Information System
RSV: respiratory syncytial virus
SOT: solid organ transplant

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