



## TECHNICAL REPORT

# Updated Guidance for Palivizumab Prophylaxis Among Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection

## abstract

FREE

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. Guidance initially was based on the result from a single randomized, placebo-controlled clinical trial conducted in 1996–1997 describing an overall reduction in RSV hospitalization rate from 10.6% among placebo recipients to 4.8% among children who received prophylaxis. The results of a second randomized, placebo-controlled trial of children with hemodynamically significant heart disease were published in 2003 and revealed a reduction in RSV hospitalization rate from 9.7% in control subjects to 5.3% among prophylaxis recipients. Because no additional controlled trials regarding efficacy were published, AAP guidance has been updated periodically to reflect the most recent literature regarding children at greatest risk of severe disease. Since the last update in 2012, new data have become available regarding the seasonality of RSV circulation, palivizumab pharmacokinetics, the changing incidence of bronchiolitis hospitalizations, the effects of gestational age and other risk factors on RSV hospitalization rates, the mortality of children hospitalized with RSV infection, and the effect of prophylaxis on wheezing and palivizumab-resistant RSV isolates. These data enable further refinement of AAP guidance to most clearly focus on those children at greatest risk. *Pediatrics* 2014;134:e620–e638

Palivizumab is a humanized mouse immunoglobulin (IgG1) monoclonal antibody produced by recombinant DNA technology. The antibody is directed against a conserved epitope of the A antigenic site of the fusion (F) protein of respiratory syncytial virus (RSV) and demonstrates both neutralizing and fusion inhibitory activity.<sup>1</sup> The antibody consists of 2 heavy chains and 2 light chains; 95% of the amino acid sequences (framework) are of 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

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RSV, respiratory syncytial virus, palivizumab, bronchiolitis, infants and young children, chronic lung disease, congenital heart disease

**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  
QALY—quality-adjusted life year  
RSV—respiratory syncytial virus  
SOT—solid organ transplant

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The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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conformational change that is necessary for fusion of the viral RSV envelope with the plasma membrane of the respiratory epithelial cell.<sup>2</sup> 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.<sup>2</sup>

## 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 1996–1997 RSV season. This randomized, placebo-controlled, double-blind trial involved 1501 infants and young children born preterm (at or before 35 weeks' gestation), some of whom had chronic lung disease (CLD) of prematurity.<sup>3</sup> The IMpact-RSV trial demonstrated an RSV hospitalization rate of 10.6% in the placebo arm and 4.8% among high-risk infants who received prophylaxis, a reduction of 5.8% in RSV hospitalizations ( $P < .001$ ).<sup>3</sup> A second randomized, double-blind, placebo-controlled trial conducted from 1998 to 2002 enrolled 1287 children with hemodynamically significant congenital heart disease (CHD).<sup>4</sup> This cardiac trial evaluated both 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, a reduction in the RSV hospitalization rate of 4.4% ( $P < .003$ ). No additional placebo-controlled trials regarding the efficacy of palivizumab prophylaxis in any other subgroup have been published.

Palivizumab was licensed for the prevention of severe lower respiratory tract disease in pediatric patients at increased risk of severe RSV disease.<sup>1</sup> Recommendations from the American Academy of Pediatrics (AAP) for use of prophylaxis have evolved since licensure

of palivizumab as additional information has become available.

In addition, peer-reviewed data have been published since preparation of the most recent guidance in 2012.<sup>5</sup> This technical report reviews the newer and older scientific literature to offer guidance on the most appropriate use of palivizumab prophylaxis, as published in the accompanying policy statement.<sup>6</sup> Current guidance is risk stratified, targeting infants at greatest risk of severe disease and most likely to benefit from prophylaxis on the basis of evaluation of the published literature. Therefore, not all infants enrolled in the 2 randomized trials are included in the current guidance. Twenty-one AAP sections and committees plus groups outside the AAP have contributed to and concur with the updated guidance presented in the accompanying policy statement.

AAP guidance regarding the use of palivizumab was first published in a policy statement<sup>7</sup> in 1998 and subsequently was revised in a 2003 policy statement,<sup>8</sup> the 2006 *Red Book*,<sup>9</sup> a 2009 policy statement,<sup>10</sup> and most recently in the 2012 *Red Book*.<sup>5</sup> The AAP guidance for palivizumab prophylaxis is being updated at this time to reflect the ongoing assessment by the Committee on Infectious Diseases (COID) of peer-reviewed publications, as exemplified in the following areas:

- Data regarding palivizumab pharmacokinetics<sup>11</sup>;
- Data on the seasonality of RSV circulation<sup>12,13</sup>;
- Data on overall declining incidence of hospitalizations for bronchiolitis in the United States<sup>14</sup>;
- Data demonstrating that mortality rates in children hospitalized with laboratory-confirmed RSV are lower than previously estimated<sup>15</sup>;
- Data demonstrating a statistically significant but clinically minimal

reduction of wheezing episodes among recipients of palivizumab prophylaxis<sup>16,17</sup>;

- Reports indicating little benefit of palivizumab prophylaxis among patients with cystic fibrosis or Down syndrome<sup>18–20</sup>;
- Reports describing palivizumab resistant RSV isolates from hospitalized patients who receive prophylaxis<sup>21–23</sup>; and
- Independently conducted cost analyses demonstrating a high cost versus limited benefit from palivizumab prophylaxis.<sup>24,25</sup>

In addition, the complexity of the current guidance has resulted in lack of prophylaxis for some children who qualify, whereas other children who do not qualify receive prophylaxis that may not be indicated.<sup>26,27</sup> The goal of this updated guidance is to present more clearly the COID recommendations for palivizumab use for infants and young children who are most likely to derive benefit from prophylaxis and, in the process, to simplify guidance for pediatricians and other clinicians.

It is important to note that using the same aggregate data, prophylaxis guidelines from other countries such as the United Kingdom are more restrictive than AAP guidance for the United States, and no evidence of excess morbidity has been observed.<sup>28,29</sup>

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 inserts states "Synagis is indicated for the prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease."<sup>1</sup> 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.<sup>5,7,8,10</sup> The same is true with this revision.

## 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 waste. Anaphylaxis has occurred after palivizumab administration after initial exposure or reexposure, with some cases of severe hypersensitivity reactions reported.<sup>1</sup>

## RSV IMMUNOPROPHYLAXIS AND VACCINE ADMINISTRATION

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

## GUIDANCE FOR PALIVIZUMAB PROPHYLAXIS

### Burden of RSV Disease

In the United States, RSV remains an important cause of hospitalization in the first months of life. Retrospective analyses using national databases and *International Classification of Diseases, Ninth Revision* discharge diagnoses have shown considerable variation in estimates of annual hospitalization rates attributable to RSV for infants.<sup>30–33</sup> More recent prospective population-based studies of laboratory confirmed cases demonstrate that RSV hospitalization rates are approximately half the rates reported in retrospective studies, yet rates remain high.<sup>14,34–36</sup>

It is estimated that approximately 2.1 million children younger than 5 years

require medical care as inpatients or as outpatients for RSV infection annually. Among outpatients, 60% (1.3 million) are 2 through 5 years of age, and the remaining 40% are between birth and 2 years of age.<sup>35</sup> Approximately 25% of RSV-infected children younger than 5 years are assessed and treated in an emergency department, and approximately 70% are assessed and treated in a pediatric office. It is estimated that each year, nearly 58 000 children in the first few years of life are hospitalized because of RSV infection.<sup>35</sup> Infants in the second month after birth have the highest RSV hospitalization rate, a rate that is almost twice that of the next highest risk group (infants in the first month after birth).<sup>34</sup>

### Preterm Infants Without CLD

In 2012, 3.95 million births were reported in the United States. Preterm infants (singleton and multiple births) born at less than 37 weeks' gestation represented 11.6% of all births.<sup>37</sup> Preterm births of infants at less than 28 weeks' gestation accounted for 0.7% of the annual birth cohort.<sup>37</sup> Infants born from 32 weeks to 35 weeks' gestation represented approximately 9% of the birth cohort.

Beginning with the first AAP statement in 1998,<sup>7</sup> the high cost of palivizumab influenced recommendations for use by the COID, leading to attempts to identify risk factors for RSV hospitalization among the large number of moderately preterm infants. The New Vaccine Surveillance Network (NVSN), sponsored by the Centers for Disease Control and Prevention (CDC) was a prospective population-based surveillance program from 3 geographically diverse locations in the United States for young children hospitalized with laboratory-confirmed RSV respiratory illness. Several studies were published summarizing data from the NVSN. One

conducted during the RSV seasons from 2000 through 2005 using multiple logistic-regression analyses of data revealed that 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.<sup>34</sup> In this study, only young chronologic age was significantly correlated with risk of hospitalization for RSV illness. The association between preterm birth and increased risk of severe illness was not specific for RSV.<sup>35</sup>

In addition, data from the NVSN study revealed that for all preterm infants (<37 weeks' gestation), the RSV hospitalization rate was 4.6/1000 children, which was not significantly different from the hospitalization rate for term infants, which was 5.3/1000 children (Table 1).<sup>34</sup> 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 (18.7/1000 children) than early preterm infants (30–33 weeks),<sup>34</sup> although the small number of infants born before 30 weeks' gestation limits the generalizability of this data. Late preterm infants were hospitalized significantly less often than term infants for RSV infection.<sup>34</sup>

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.<sup>38</sup> Within each age group, preterm infants had similar

**TABLE 1** Average RSV Hospitalization Rates Among Children Younger Than 24 Months (2000–2005)<sup>34</sup>

Children <24 mo	N <sup>a</sup>	RSV Hospitalization Rate/1000	95% CI
All infants regardless of gestational age	559 <sup>b</sup>	5.2	4.8–5.7
All term infants (≥37 wk gestation)	479	5.3	4.9–5.8
All preterm infants (<37 wk gestation)	56	4.6	3.4–5.8
≥35 wk gestation	494	5.1	4.7–5.5
32–34 wk gestation	23	6.9	4.3–10.1
29–31 wk gestation	6	6.3	2.0–12.4
<29 wk gestation	12	19.3	8.4–34.0
All very preterm (<30 wk gestation)	15 <sup>c</sup>	18.7	10.0–30.0

<sup>a</sup> Among 2149 enrolled hospitalized children from a birth cohort of 132 085 children.

<sup>b</sup> The total of 559 children hospitalized with RSV includes 24 whose gestational age could not be verified.

<sup>c</sup> Personal communication, Geoffrey A. Weinberg, MD.

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.<sup>39</sup> The RSV hospitalization rate increased with decreasing gestational age, with a breakpoint at ≤28 weeks' gestation (Table 3). Among infants born at or before 26 weeks' gestation, the risk of RSV-associated hospitalization was 13.9% vs 4.4% among children hospitalized at >30 to 32 weeks' gestation. There was not a 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.<sup>40</sup> 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 preterm infants were hospitalized compared with 3815 (2.5%) of 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% confidence interval [CI], 2.5–5.7) and by 4.5 months in Texas (95% CI, 2.8–6.4).<sup>40</sup>

Choosing an appropriate cutoff for gestational age for which palivizumab prophylaxis may be considered for preterm infants without other indications is challenging. Data consistently

demonstrate the greatest increase in risk for hospitalization is in preterm infants born before 29 weeks' gestation. These infants have hospitalization rates 2 to 4 times higher than later preterm infants (Tables 1, 2, and 3). The consensus of the COID and the Bronchiolitis Guidelines Committee is that palivizumab prophylaxis may be considered for infants, without other indications, whose gestational age is less than 29 weeks (28 weeks, 6 days or fewer). The available data do not support universal recommendations for palivizumab prophylaxis for preterm infants born at or after 29 weeks' gestation.

Data regarding the risk of RSV hospitalization for most preterm infants do not support a benefit from prophylaxis. In recent large cohort studies of moderately preterm infants, 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.<sup>40</sup> The rate of hospitalization among infants ≥35 weeks' gestation (5.1/1000) was no different than the rate for term infants (5.3/1000; Table 1). The hospitalization rate of infants ≥30 weeks to 35 weeks' gestation indicate only a slight increase in risk (less than twofold; Tables 1, 2, and 3). Data concerning host or environmental risk factors for hospitalization in preterm infants without CLD or CHD are inconsistent, with the exception of age

**TABLE 2** RSV Hospitalizations per 1000 Children From >248 000 Child-Years of Follow-up<sup>38</sup>

Age Stratum/Risk Group	0 to <6 mo	6 to <12 mo	12 to <24 mo	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 <sup>a</sup>	122.3	55.2	24.1	2.8 (2.5–3.1)	2.3 (2.1–2.6)

IRR, incidence rate ratio.

<sup>a</sup> Asthma, cystic fibrosis, cancer, HIV infection, immunodeficiency, steroid therapy, chronic renal disease, diabetes mellitus, congenital anomalies of the respiratory tract, or respiratory distress syndrome.

**TABLE 3** RSV Hospitalizations Among 1029 Infants Born at or Before 32 Weeks' Gestation<sup>39</sup>

Gestational Age, wk	No. of Infants	No. of RSV Admissions	% Admitted	<i>P</i> vs 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	Not applicable

younger than 3 months at the start of the RSV season, which has been associated with an increased risk of hospitalization.<sup>34</sup>

For all infants, particularly those who are preterm, the environment should be optimized to prevent RSV and other viral respiratory infections by offering breast milk feeds, immunizing household contacts with influenza vaccine, practicing hand and cough hygiene, and by avoiding tobacco or other smoke exposure and attendance in large group child care during the first winter season, whenever possible.

#### Preterm Infants With CLD

Studies have documented that infants and young children with CLD have increased rates of RSV hospitalization.<sup>38,39</sup> 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 ( $P = .038$ ).<sup>3</sup>

#### Infants With Hemodynamically Significant CHD

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.<sup>4</sup> Results from this study demonstrated a reduction in RSV hospitalization rates of 4.4% (9.7% among placebo recipients and 5.3% among palivizumab recipients;

$P = .003$ ).<sup>4</sup> 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.<sup>4</sup> 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% vs 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 and 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.<sup>41</sup>

Other investigators describe rates of RSV hospitalizations among patients with hemodynamically significant CHD (2%–3%) who do not receive pro-

phylaxis as lower than the 9.7% rate reported in the placebo arm of the cardiac study.<sup>42–46</sup> As the rate of RSV hospitalization decreases among children who do not receive prophylaxis, the cost to prevent 1 hospitalization with prophylaxis increases.

A retrospective analysis of children younger than 3 years (248 652 child-years) in the Tennessee Medicaid program revealed that the RSV hospitalization rate for children with CHD in the second year of life (18.2/1000) was less than half the hospitalization rate for low-risk infants in the first 5 months after birth (44.1/1000), a group for whom palivizumab prophylaxis is not recommended<sup>38</sup> (Table 2). Thus, prophylaxis is not recommended during the second year of life.

#### Children With Anatomic Pulmonary Abnormalities or Neuromuscular Disorder

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.<sup>47,48</sup> This may reflect the progressive nature of neuromuscular disease, with susceptibility to respiratory disease tract increasing with age.

#### 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 virulence of the RSV strain, as well as specific abnormalities in the immunocompromised host's immune response attributable to the underlying disease or to chemotherapy.

RSV infection in immunocompromised children and adults can progress to respiratory failure and death.<sup>49,50</sup> 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 to lower respiratory tract disease did not occur in patients with a lymphocyte count greater than 1000 cells/mm<sup>3</sup> at time of onset of upper respiratory tract infection.<sup>51</sup> An absolute lymphocyte count of 100 cells/mm<sup>3</sup> 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.<sup>51</sup>

A retrospective report from 1 institution described 58 immunocompromised children with RSV infection between 1997 and 2005.<sup>52</sup> 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 immune deficiency. 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<sup>3</sup>) was associated with progression to lower respiratory tract disease.<sup>52</sup>

Another retrospective report from 1 institution 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, and 1 SOT recipient).<sup>53</sup> 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 third retrospective review of RSV infections in children with cancer was conducted from 1998 to 2009.<sup>54</sup> 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.<sup>55</sup> 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%) of 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.

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 varying degrees of 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.<sup>56</sup> This inability to correlate degree of immunosuppression with disease severity indicates an incomplete understanding of the immune response to viral respiratory infections in an immunocompromised host.

Antibody-based treatments, including immune globulin and palivizumab, have not been associated with improved outcome in HSCT recipients.<sup>57</sup> No data are available to suggest benefit from immunoprophylaxis among immunocompromised patients, and practices vary nationwide.<sup>58,59</sup> 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 than children without Down syndrome.<sup>18,19,60,61</sup> 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. 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 revealed 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 67/1000 child-years for children with Down syndrome and other risk factors, 42/1000 child-years for children with Down syndrome without cardiopulmonary disease, and 12/1000 child-years for children in a control group.<sup>61</sup> These data suggest an estimated overall 7.7 RSV admissions per year (85 admissions per 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 per 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 >38°C, the median duration 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.<sup>61</sup> 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.<sup>60</sup> 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.<sup>60</sup> Another study of 41 children with Down syndrome hospitalized with RSV infection noted that 51% had underlying CHD.<sup>18</sup> 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.<sup>61</sup> RSV prophylaxis for the first year of life would have limited effect on RSV hospitalization for children with Down syndrome without other risk factors for RSV.<sup>19,61</sup>

### Children With Cystic Fibrosis

Available studies indicate the incidence of RSV hospitalization in children with cystic fibrosis is uncommon and 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.<sup>20,62,63</sup>

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.<sup>64</sup> 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.<sup>62</sup>

A large study of RSV hospitalizations occurring between 1997 and 2003 in Danish children with chronic medical conditions identified 72 children with cystic fibrosis.<sup>65</sup> 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<sup>20,66</sup> of RSV infection in infants with cystic fibrosis acknowledged that infants with cystic fibrosis may have a slightly increased risk for hospitalization with RSV. However, they both stated that there is insufficient evidence related to safety and efficacy in infants with cystic fibrosis to support a recommendation of palivizumab prophylaxis.<sup>20,66</sup> 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.<sup>67</sup>

### Discontinuation of Palivizumab Prophylaxis Among Children Who Experience Breakthrough RSV 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 likely

is 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.

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.<sup>68</sup> 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.<sup>69,70</sup>

In the blinded and randomized cardiac 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.<sup>4</sup>

In the Dutch trial of 429 preterm infants randomly assigned 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.<sup>16</sup>

### Use of Palivizumab in the Second 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.<sup>35</sup>

Limited safety data and no efficacy data are available regarding palivizumab prophylaxis in the second year of life.<sup>71,72</sup> Regardless of the presence or absence of comorbidities, RSV hospitalization rates decline during the second RSV season for all children.<sup>34,38</sup> In a retrospective cohort study conducted over 4 years and involving 248 652 child-years, RSV hospitalization rates in the second year of life for children with comorbidities were lower than the rate for healthy term infants in the first 12 months of life, a group for whom prophylaxis is not recommended<sup>38</sup> (Table 2).

### 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, intubated infants reduced the RSV viral load in the lower respiratory tract but had no effect on RSV concentration in the upper respiratory tract.<sup>73</sup> 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 phase 2 therapeutic trial involving 118 hospitalized, RSV infected infants evaluated the outcome among recipients of intravenous motavizumab at 30 mg/kg or at 100 mg/kg compared with placebo.<sup>74</sup> Motavizumab is an investigational monoclonal antibody with enhanced potency relative to palivizumab. No significant effect on RSV viral load in the upper respiratory tract was detected among motavizumab recipients. No difference in duration of hospitalization, requirement for supplemental oxygen, ICU admission, or need for mechanical ventilation between groups was detected.

### Prevention of Health Care-Associated RSV Disease

Strict infection-control practices, including restriction of visitors to the neonatal ICU during respiratory virus season, will 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.<sup>75,76</sup> If an RSV outbreak occurs in a high-risk unit (eg, pediatric or neonatal ICU 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 health care-associated disease. Further, hospitalization rates for RSV infection do not differ among infants who receive inpatient palivizumab prophylaxis while in the neonatal ICU compared with those who initiate prophylaxis at hospital discharge.<sup>77</sup>

## 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.<sup>35,38</sup> 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.<sup>34,35,38</sup> Most of these hospitalizations occur in the first 90 days after birth.<sup>22,34,40</sup> 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.<sup>30,78</sup> 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.<sup>79</sup> 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 contribute to these differences.

Reported host risk factors of limited (inconsistent) impact include the following: congenital malformations, congenital airway anomaly, neuromuscular impairment, birth weight, gender, 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, multiple births, and singletons versus multiple birth subjects. Environmental risk factors of limited (variable) impact include the following: environmental pollution, crowded living conditions, living at increased altitude, meteorological conditions, 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.<sup>30,35,38,47,48,60,65,78,80–94</sup> One publication suggested that malformations of the urinary tract increase the risk of RSV hospitalization.<sup>65</sup>

Multiple logistic-regression analyses of data from the 4-year population-based prospective study revealed that

of the evaluated risk factors (male gender, 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.<sup>35</sup>

### **RSV Seasonality**

During the 6 RSV seasons from July 2007 to January 2013, the median duration of the RSV season ranged from 13 to 23 weeks, with median peak activity from mid-December to early February, with the exception of Florida and Alaska (see later discussions for each).<sup>12,13</sup> Within the 10 Health and Human Services Regions, in the few regions when the RSV season began in October, the season ended in March or early April. In regions where the RSV season began in November or December, the season ended by April or early May. 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.<sup>11</sup> 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,<sup>79,95</sup> 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 Alaska Native/American Indian Children and Timing of Palivizumab Initiation**

Hospitalization rates for all causes of bronchiolitis as high as 484 to 590/1000 infants have been described in isolated Inuit populations.<sup>96–99</sup> Alaska Native infants in southwestern Alaska experience higher RSV hospitalization rates and a longer RSV season. On the basis of the epidemiology of RSV in Alaska, particularly in remote regions, the selection of infants eligible for prophylaxis 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.<sup>100</sup>

Two published studies have documented a bronchiolitis hospitalization rate in Navajo populations that was 91.3 to 96.3/1000 infants younger than 1 year.<sup>101,102</sup> This rate was similar to those seen with high-risk groups, such as infants born preterm and those with CLD. There are no data on efficacy of palivizumab in this population. However, if local data support a high burden of RSV disease in select American Indian populations, selection of infants eligible for prophylaxis 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. 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. More than 5 monthly doses are not recommended, despite the detection of a small number of cases of RSV infection outside this time window. A small number of sporadic RSV hospitalizations occur before or after the main season in many areas of the United States, but maximum benefit from prophylaxis is derived during the peak of the season and not when the incidence of RSV hospitalization is low.

### Pharmacokinetics of Palivizumab

A threshold protective serum palivizumab concentration in humans has not been established. On the basis of studies of palivizumab prophylaxis with the cotton rat, serum concentrations of 25 to 30 mcg/mL produced a mean reduction in pulmonary RSV concentrations of 99% (2 log<sub>10</sub>).<sup>103,104</sup> 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.<sup>3,4</sup> The package label states “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.”<sup>1</sup>

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).<sup>11</sup> 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.<sup>11</sup>

### Race and Sex

Data from the NVSN demonstrate that the overall rate of RSV hospitalization does not differ between African American and white children younger than 24 months of age (5.4/1000 for African American children and 4.7/1000 for white children).<sup>34</sup> Among infants younger than 6 months, RSV hospitalization rates for African American and white children were not significantly different.<sup>34</sup> Another report from NVSN evaluated 564 children hospitalized with RSV infection. Neither race nor ethnic group was found to be an independent risk factor for hospitalization.<sup>35</sup> A third CDC report revealed rates of RSV coded illness in African American and white children to be similar at 5.3/1000 (95% CI, 3.7–6.9/1000) and 5.3/1000 (95% CI, 4.3–6.3/1000), respectively.<sup>35</sup> Hospitalization rates did not differ during the years of this study (1997–1999 and 2004–2006) by African American or white race. In this study, hospitalization rates for RSV-coded illness were 7.5/1000 boys (95% CI, 5.9–9.1) and 5.9/1000 girls (95% CI, 4.5–7.3).

Another population-based study evaluated racial disparities between African American and white children who were hospitalized because of RSV infection in 3 large United States counties.<sup>105</sup> No disparity was found in any county for any of the 7 years studied among children in the first 12 months of life or between infants 0 to 2 months or infants 3 to 5 months of age. Because of small numbers, reliable estimates for other race groups are not available.<sup>35</sup> RSV hospitalization

rates among boys exceed that of girls in some, but not all studies.<sup>34,35</sup>

### Mortality Rates Among Hospitalized Children With RSV Infection

Using 2 national databases (the Pediatric Health Information System [PHIS] data for 2004–2011 and the Health Cost and Utilization Project Kids' Inpatient Database [KID] for 2009), mortality rates associated with hospitalized infants with RSV infection were lower than previously estimated. The PHIS data set from 44 children's hospitals identified 33 deaths per year (13.7 deaths/10 000 RSV admissions during the RSV season), but only 8.5 deaths/10 000 admissions were coded with RSV as the primary diagnosis, suggesting that other comorbidities were involved. In the KID data set from more than 4000 hospitals in 44 states, RSV was estimated to account for 121 deaths annually in the United States (9/10 000 RSV admissions) with 84 deaths per year occurring during the typical RSV season. In addition, as suggested by the PHIS database, nearly 80% of deaths occurred in children with complex chronic medical conditions. The mean age at time of death was 7.5 months for infants in the PHIS data set and 6.2 months in the KID data set.<sup>15</sup>

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.<sup>106</sup>

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

## Motavizumab

Motavizumab is a second-generation monoclonal antibody that differs from palivizumab by 13 amino acids. Motavizumab was developed by affinity maturation of the complementarity determining regions of palivizumab to improve binding affinity to F protein. In cell culture, motavizumab has approximately 10-fold greater neutralizing activity than palivizumab against RSV clinical isolates of both A and B subtypes.<sup>107</sup> Unlike palivizumab, motavizumab may reduce RSV viral load in the upper respiratory tract, as well as the lower respiratory tract.<sup>108</sup>

Data from several clinical trials, including a noninferiority trial between palivizumab and motavizumab, were submitted to the FDA as part of the licensing application for motavizumab.<sup>109–111</sup> In August 2010, the FDA rejected the license application for motavizumab. Among a number of concerns noted by the FDA was lack of greater clinical efficacy from motavizumab and a threefold increase in hypersensitivity reactions among motavizumab recipients relative to palivizumab recipients.<sup>107,109,112</sup> Methodologic concerns were raised by the FDA in regard to laboratory testing procedures and geographic variation in results from the noninferiority trial. Specifically, the generalizability of the main study finding was uncertain, because the results of the primary end point differed when stratified by geographic location. The results did not reach the noninferiority threshold for the northern hemisphere, where approximately 90% of subjects were enrolled.<sup>107</sup>

The overall RSV hospitalization rate was 4.8% among palivizumab recipients in the Impact-RSV trial compared with a 1.9% RSV hospitalization rate among palivizumab recipients in the palivizumab-motavizumab noninferiority trial. It was concluded that the non-

inferiority trial may have been conducted in a population with less comorbidity than the Impact-RSV study. The FDA requested an additional clinical trial to support a satisfactory risk–benefit profile in populations for which prophylaxis is being considered.<sup>107</sup>

RSV-specific outpatient medically attended lower respiratory tract infections were reported to be significantly lower among motavizumab recipients relative to palivizumab recipients in the noninferiority trial. However, this outcome was determined in a subset of patients from selected study sites, making the risk of bias high, as noted in the FDA report.<sup>107</sup>

Outpatient visits among RSV-infected children exceed the number of outpatient visits attributable to influenza infection by more than twofold.<sup>113</sup> 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 64.4/1000 (95% CI, 45.4–91.3) compared with a rate of 15.0/1000 (95% CI, 4.4–50.6) among influenza-infected children (27% had received influenza vaccine) during 2 respiratory virus seasons between 2003 and 2005.<sup>113</sup> The impact of immunoprophylaxis on outpatient medically attended events attributable to RSV infection is an important consideration but remains unknown because of lack of evaluation in a rigorous, controlled fashion.

## Palivizumab-Resistant Isolates

Palivizumab and motavizumab bind to a highly conserved epitope (antigenic site A) 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.<sup>2</sup> RSV escape mutants resistant

to palivizumab have been isolated from approximately 5% of children hospitalized with breakthrough RSV infection while receiving monthly palivizumab prophylaxis.<sup>1, 21,22,23,114</sup> RSV isolates resistant to palivizumab contain mutations in codons encoding the amino acids between 262 and 275 of the F protein. Amino acid sequence variations outside antigenic site A do not appear to confer palivizumab resistance.

## Effect of Palivizumab Prophylaxis on Subsequent Wheezing

Numerous 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.<sup>68,115–119</sup> The possible effect of avoidance of RSV lower respiratory tract infection early in life with palivizumab prophylaxis on recurrent wheezing was addressed in 3 industry-sponsored studies.<sup>16,17,120</sup>

One trial among preterm infants without CLD describes physician-diagnosed recurrent wheezing in 8% of prophylaxis recipients and in 16% of the control group. This trial was conducted at 27 sites, and the patients were followed for up to 24 months. Participants were not prospectively randomized, the groups were not balanced for birth weight, degree of prematurity or known RSV risk factors, and families were not blinded to study medication, making the results of uncertain significance.<sup>120</sup>

A nonrandomized observational report from Japan compared the incidence of wheezing between 349 preterm infants (33–35 weeks' gestation) who received palivizumab prophylaxis in the first 6 months of life with 95 infants who did not receive prophylaxis. The primary end point of the study was physician-diagnosed wheezing during

a 3-year follow-up. Twenty-two of 345 infants (6.4%) who received immunoprophylaxis experienced wheezing, whereas 18 of 95 infants (18.9%) who did not receive prophylaxis developed recurrent wheezing ( $P < .001$ ) during the 3-year follow-up period.<sup>17</sup> No difference in hospitalization rates attributable to respiratory disease between the 2 groups was found. Concerns with this study design include the lack of randomization and blinding and the absence of standardized enrollment criteria at the 52 participating sites, each of which may have led to enrollment bias, and no information was provided on the severity of the wheezing episodes. In addition, a history of smokers in the household and family history of allergy was significantly more common in the untreated group.

A double-blind placebo-controlled trial conducted in the Netherlands addressed palivizumab prophylaxis and recurrent wheezing using a different study design.<sup>16</sup> Parent-reported wheezing in 429 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 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/1000 days vs 44.6 wheezing days/1000 days or 27.1 fewer wheezing days/1000 days) among infants who received monthly palivizumab in contrast to those who did not receive prophylaxis.<sup>16</sup> Reliance on parent reporting of wheezing was identified as a potential limitation. The wheezing episodes were not

medically attended events but parent-reported wheezing of unknown severity.<sup>16</sup> The proportion of infants using bronchodilators in the placebo group was 23% and 13% among palivizumab recipients.

### 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."<sup>121,122</sup> Use of noncost-effective interventions contribute to maladies within the health care system, including huge deficits, lower quality of care, and inequitable access to health care.<sup>123</sup> Financial stewardship has become an essential component of successful reform of the existing health care system.

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.<sup>24</sup> Economic evaluations sponsored by the manufacturer of palivizumab suggest cost neutrality or even cost savings.<sup>124–134</sup> 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.<sup>24,25,39–42,46,90,135–143</sup> Variation in results are explained by differences in study methodology and different base case assumptions used in the model, such as incidence of RSV hospitalization for different risk groups, effectiveness of prophylaxis in reducing hospitalization rate by risk group, estimates of cost of prophylaxis and RSV hospitalizations avoided, number of doses administered, estimated age and weight of infants, and inclusion of a theoretical benefit on mortality reduction.

The CDC has recommended quality-adjusted life years (QALYs) saved as an optimal approach to evaluate the benefit of an intervention. One analysis using this methodology for hypothetical cohorts of infants without CLD born at 26 to 32 weeks' gestation revealed the incremental cost-effectiveness ratio to be greater than \$200 000 per QALY saved for all gestational ages, a figure not considered to be cost-effective.<sup>135</sup>

An economic analysis funded by the manufacturer of palivizumab and published in the *Journal of Medical Economics* also examined incremental cost-effectiveness ratios per QALY gained in 4 groups of preterm infants without CLD and revealed the cost of treatment with palivizumab for infants 32 to 35 weeks' gestation with  $\leq 1$  risk factor was \$464 476, using an average cost for palivizumab for private and public payers. Medicaid discounts were reported to have resulted in an "approximate 40% reduction in palivizumab cost for approximately 60% of palivizumab recipients."<sup>129</sup> Nonetheless, in most state Medicaid programs, palivizumab is one of the most costly medication expenditures.

Cost was considered during deliberations by the COID and the Bronchiolitis Guidelines Committee, but the final guidance as presented in the accompanying Policy Statement 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 finally, the incremental cost-effectiveness ratio.<sup>144</sup> On the basis of these principles, the minimal clinical reduction in RSV hospitalizations and reduction in wheezing

episodes associated with palivizumab prophylaxis are not of sufficient clinical and societal importance to justify the cost. Although some RSV hospitalizations may be severe and prolonged, the majority of hospitalizations generally last 2 to 3 days. The high cost of palivizumab prophylaxis becomes a cost-inefficient way to prevent a few short hospitalization stays 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.<sup>144</sup>

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.<sup>144</sup> Because the high cost of palivizumab prophylaxis is associated with minimal health benefit, this intervention cannot be considered as 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. Preventive measures include limiting, where feasible, exposure to contagious settings (eg, child care centers) and emphasis on hand hygiene in all settings, including the home and the neonatal ICU, especially during periods when contacts of children at high risk have respiratory tract infections. For all children, the importance of breastfeeding, avoidance of crowds, and absence of exposure to tobacco smoke, including second-hand and third-hand exposure, should be emphasized.

### Future Possibilities

Continued evaluation of the impact of palivizumab prophylaxis should include other groups considered to be

at increased risk of disease to evaluate reductions in RSV hospitalizations, as well as the effect of prophylaxis on medically attended outpatient visits.

Investigation of other types of passive immunoprophylaxis including anti-G monoclonal antibodies, should continue not only in prophylaxis but in treatment studies to modulate RSV disease severity.<sup>145</sup> Modification of the Fc fragment of the motavizumab molecule appears to prolong the half-life and theoretically may enable administration of fewer doses of motavizumab per season, although an increased risk of adverse effects remains a concern.<sup>107,146</sup> Nanobodies are antibody-derived proteins consisting of functional heavy-chain antibodies that lack light chains and were initially found in camels and llamas. Nanobodies directed against the RSV fusion protein have demonstrated RSV-neutralizing activity in experimental models.<sup>147</sup>

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.<sup>5</sup> Interest continues in developing more broadly effective antiviral agents including fusion inhibitors and small interfering RNA.<sup>148,149</sup>

Development of a safe and effective RSV vaccine remains a high priority.<sup>150–153</sup> Progress has been achieved with live-attenuated intranasal vaccines,<sup>154</sup> but 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, which has complicated development of inactivated RSV vaccines.<sup>150,155</sup> The demonstration of the effectiveness of passive prophylaxis with an anti-F monoclonal provides reassurance that antibody to the F protein is protective. New

subunit vaccines and particularly vaccines directed against the F protein administered intramuscularly or intranasally continue to be explored.<sup>150,155</sup> A vaccine against a “prefusion” configuration of the F protein may offer increased efficacy with less risk of disease enhancement.<sup>156</sup> F protein viral-like particle vaccines administered during the latter half of pregnancy might offer passive protection for young children through the first months of life.<sup>157,158</sup>

### SUMMARY

The vast majority of RSV hospitalizations occur among healthy term infants. Immunoprophylaxis remains an option for a very small number of children, but palivizumab immunoprophylaxis will continue to have only a minimal effect on the burden of RSV disease. Effort should be made to avoid prophylaxis among infants and young children who do not qualify for prophylaxis, as outlined in the accompanying AAP policy statement.<sup>6</sup>

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## LIAISONS

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## STAFF

Caryn Davidson, MA

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COMMITTEE ON INFECTIOUS DISEASES and BRONCHIOLITIS GUIDELINES COMMITTEE

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