A Systematic Review of Compliance with Palivizumab Administration for RSV Immunoprophylaxis

Michael P. Frogel, MD; Dan L. Stewart, MD; Michael Hoopes, PharmD;
Ancilla W. Fernandes, PhD; and Parthiv J. Mahadevia, MD, MPH

ABSTRACT

BACKGROUND: Respiratory syncytial virus (RSV) is a leading cause of lower respiratory tract infection (LRTI) in infants and young children, accounting for approximately 75,000-125,000 hospitalizations per year. It is estimated that in 2000, RSV infection accounted for 1.7 million office visits, 402,000 emergency room visits, and 236,000 hospital outpatient visits per year for children younger than 5 years of age. Palivizumab, a humanized monoclonal antibody directed against RSV, is the only immunoprophylaxis therapy approved by the FDA for prevention of serious lower respiratory tract disease caused by RSV in infants (up to 2 years of age) who meet 1 or more of the following criteria for high risk: (a) gestational age up to 35 weeks; (b) diagnosis of chronic lung disease (CLD, formerly bronchopulmonary dysplasia [BPD]); or (c) diagnosis of cyanotic or complex congenital heart disease. The RSV season typically occurs between November and March but may vary by region. During the period of our review, depending on local duration of the RSV season, infants usually required 5 monthly (every 28-30 days) intramuscular injections of palivizumab. Infants born in the middle of the season received their palivizumab doses from the time of birth to the end of the season and, therefore, may have required less than 5 doses. It is unclear if compliance with monthly doses is a problem and whether noncompliance increases the risk of RSV hospitalizations in routine clinical practice.

OBJECTIVES: To (a) identify and describe compliance rates and the factors that influence parental compliance with immunoprophylaxis regimens, (b) review intervention programs and describe those that have been associated with increased compliance, and (c) summarize the association of compliance with RSV hospitalization rates.

METHODS: An electronic literature search was conducted using journal databases, including Ovid, Current Contents, Embase, Medline In-Process & Other Non-Indexed Citations; Ovid Medline, PubMed, and Web of Science; and an abstract database, Medical Intelligence Solution, for citations through April 2008. Specific search terms used were *palivizumab* with *patient compliance*, *patient adherence*, or *patient persistence*.

RESULTS: Twenty-five articles and abstracts met the inclusion criteria. Available studies were mostly retrospective or observational prospective. Compliance, defined in various ways across the studies, varied between 25% and 100%, and 12 studies identified some of the factors related to noncompliance. Compliance generally was lower among Medicaid patients, African American patients, and other minorities. Ten studies (3 manuscripts and 7 abstracts) investigated the association of administration of prophylaxis through monthly home visits by a health professional with parental compliance with therapy. Most of the home-based programs were associated with higher compliance rates compared with clinic or office programs. Rates as high as 94% and 64% were achieved when Medicaid infants and infants of minority descent, respectively, received their doses through a home health program. When these infants received their doses at a clinic or

office, depending on the definition of compliance, rates were 61%-100% for Medicaid infants and 44% for infants of minority descent. Reminder telephone calls to parents or caregivers, comprehensive multidisciplinary programs that included extensive counseling of parents, calendars with sticker reminders, and education in the language native to parents also were associated with increased compliance, although statistical significance was reported in only 1 study. Several studies recommended educating parents on the benefits of RSV prophylaxis, alleviating transportation and language difficulties, recognizing cultural differences and biases, and clarifying misperception of RSV illness severity. Home health programs had lower rates of RSV hospitalizations than office-based programs in 3 analyses conducted in 2 studies. In 4 other abstracts, the rates of RSV hospitalization for home health programs and office-based administration did not significantly differ. In a large, 4-season, prospective outcome study, compliant infants had lower RSV hospitalization rates than those who were not compliant under one definition of compliance (doses within 35-day intervals). RSV hospitalization rates were not significantly different using another definition of compliance (receipt of anticipated doses, expected vs. observed rates). In a large survey of 10,390 infants identified from pharmacy dispensing records, RSV hospitalization rates were 1.4% in the compliant group versus 3.1% in the noncompliant group (OR=2.2, 95% CI=1.4-3.5, $P<0.001$). Adjustment for confounding was not reported in these studies.

CONCLUSION: Medicaid and minority infants were less likely to receive scheduled palivizumab doses. Home-based programs for the administration of palivizumab have been investigated more than other interventions and are associated with improved compliance compared with office-based administration. Compliance with dosing, in general, was associated with lower RSV hospitalization rates. However, these strategies should be further investigated using well-designed studies.

J Manag Care Pharm. 2010;16(1):46-58

Copyright© 2010, Academy of Managed Care Pharmacy. All rights reserved.

What is already known about this subject

- Respiratory syncytial virus (RSV) is a leading cause of hospitalization among infants and young children accounting for approximately 75,000-125,000 hospitalizations per year. In 2000 in the United States, RSV infection accounted for an estimated 1.7 million office visits, 402,000 emergency room visits, and 236,000 hospital outpatient visits for children younger than 5 years. Although the mortality rate in patients with RSV LRTI hospitalization is less than 1% overall, children with heart and lung disease have significantly higher mortality rates (3.4% and 3.5%, respectively).
- Palivizumab, approved by the FDA in 1998, remains the only therapy for prevention of severe RSV disease in high-risk infants.

Note: This article is the subject of an editorial that appears on pages 59-66 of this issue.

What is already known about this subject (continued)

- Two randomized controlled trials (RCTs) have investigated the efficacy of palivizumab in reducing RSV-associated hospitalizations. During the 1996-1997 RSV season, for children with either prematurity up to 35 weeks gestation or bronchopulmonary dysplasia/chronic lung disease (BPD/CLD), palivizumab compared with placebo reduced RSV-associated hospitalizations for both those without BPD/CLD (78% reduction: 8.1% vs. 1.8%, $P<0.001$) and those with BPD/CLD (39% reduction: 12.8% vs. 7.9%, $P=0.038$). In the second RCT, RSV-associated hospitalizations were reduced by 45% for palivizumab versus placebo (9.7% vs. 5.3%, $P=0.003$) for children aged 24 months or younger with hemodynamically significant congenital heart disease in 4 RSV seasons from 1998-1999 through 2001-2002.
- Palivizumab has a mean half-life of approximately 20 days and is dosed in monthly (28-30 days) intramuscular injections of 15 milligrams per kilogram during the RSV season.
- The American Academy of Pediatrics promulgated new recommendations for RSV prophylaxis in September 2009.

What this review adds

- Rates of compliance with RSV prophylaxis range from 25% to 100% and are more variable than those observed in clinical trials (92% and 93%).
- Compliance rates tend to be lower in infants enrolled in Medicaid and in minority groups, ranging between 44% and 100% using office- or clinic-based administration. Home health programs have been associated with better compliance rates, ranging from 64% to 94%, in these groups.
- Other factors that negatively affect compliance include limited access to care, parental perception of limited benefits with prophylaxis, transportation problems, and language difficulties. Interventions aimed at eliminating these barriers should be investigated further using well-designed studies.
- Home-based programs for the administration of palivizumab have been investigated more than other interventions and are associated with improved compliance compared with office-based administration. Compliance with dosing, in general, was associated with lower RSV hospitalization rates. However, these strategies should be further investigated using well-designed studies.

Respiratory syncytial virus (RSV) infection is a leading cause of lower respiratory tract infection (LRTI) in infants and young children.¹⁻⁴ RSV-related illnesses account for approximately 75,000-125,000 hospitalizations per year.⁴ Furthermore, RSV was associated with a mortality rate of 5.3 per 100,000 person-years for infants younger than 1 year of age due to respiratory and circulatory causes from the 1990-1991 through 1998-1999 annual respiratory illness seasons (July through June).⁵ Although the mortality rate in patients hospitalized with RSV LRTI is less than 1% overall,⁶ children with heart and lung

disease have significantly higher mortality rates (3.4% and 3.5%, respectively).⁷ A study by Paramore et al. (2004) estimated that in 2000, RSV infection accounted for 1.7 million office visits, 402,000 emergency room visits, and 236,000 hospital outpatient visits per year for children younger than 5 years of age in the United States.⁸

The economic costs of RSV LRTIs are high. Premature infants (up to 35 weeks gestational age), including those with chronic lung disease (CLD, formerly bronchopulmonary dysplasia [BPD]), infants with cyanotic or complex congenital heart disease, and those with severe neurologic or airway problems, are particularly vulnerable to developing severe LRTIs, requiring frequent hospitalizations.^{1,6,9-13} In Horn and Smout's study of 304 infants hospitalized for bronchiolitis or RSV pneumonia at 9 children's hospitals from 1995-1996, rates of intensive care unit (ICU) admission were 31.3% overall, as high as 48.4% in infants born at 33-35 weeks gestational age ($n=31$), and 39.3% in those born at up to 32 weeks gestational age ($n=28$).¹⁴ Intubation was required in 16.4% overall, 38.7% of those born at 33-35 weeks gestational age, and 21.4% of those born at up to 32 weeks gestational age. In the subgroup born at up to 35 weeks gestational age, mean ICU length of stay was 5.8-7.7 days, and mean hospital stay was 6.8-8.4 days.¹⁴

Estimates of the cost of RSV-related hospitalization vary. Using data from a large managed care organization, Joffe et al. (1999)¹⁵ calculated the mean cost of a hospitalization for RSV as \$8,502 in 1995 dollars, but Robbins et al. (1998)¹⁶ calculated a higher "plausible estimate" of \$15,000-\$25,000 per RSV hospital admission. A more recent poster abstract report estimated the mean cost of RSV hospitalization, in 2007 dollars, to be \$9,014 in full-term infants ($n=1,983$), \$13,876 in infants born at less than 33 weeks gestational age ($n=46$), and \$18,403 in infants born at 33-36 weeks gestational age ($n=149$).¹⁷ In addition, although a significant association has been shown between RSV infection in childhood and long-term development of subsequent asthma and recurrent wheezing, a systematic review of the literature suggested that further studies are needed to confirm this association.¹⁸

No completely effective treatment for RSV LRTI exists, and attempts at developing a vaccine have proven unsuccessful thus far. Palivizumab (Synagis; MedImmune, Gaithersburg, MD), a humanized monoclonal antibody directed against the F protein of RSV, is the only immunoprophylaxis therapy available that is approved by the U.S. Food and Drug Administration (FDA) for the prevention of serious lower respiratory tract disease caused by RSV in pediatric patients at high risk of RSV disease.¹⁹ During the time of our review, palivizumab dosing usually consisted of 5 monthly (28-30 days) intramuscular injections of 15 milligrams per kilogram (mg per kg) administered during the RSV season,¹⁹ which typically occurs between November and March, but may vary by region.²⁰ Because infants born during the RSV season receive their palivizumab doses from the time of birth, infants included in the studies covered by this review may have required less than 5 doses.

The efficacy of palivizumab in reducing the incidence of lower respiratory tract disease is well established. In clinical studies, palivizumab has been shown to reduce the overall incidence of RSV-associated hospitalizations in high-risk pre-term infants and those with CLD and congenital heart disease (CHD) compared with placebo.^{19,21,22} In the pivotal licensure study, significant reductions in RSV-associated hospitalizations were observed in premature children up to 35 weeks gestation in comparison with placebo, both among those without BPD/CLD (78% reduction: 8.1% vs. 1.8%, $P < 0.001$) and those with BPD/CLD (39% reduction: 12.8% vs. 7.9%, $P = 0.038$), with an overall reduction of 55% (10.6% vs. 4.8%, $P < 0.001$).²¹ The most common adverse events, occurring at least 1% more frequently in palivizumab-treated versus control patients, were upper respiratory infection, otitis media, fever, and rhinitis.^{19,21} In comparison with placebo, palivizumab reduced RSV-associated hospitalizations by 45% (9.7% vs. 5.3%, $P = 0.003$) in infants and young children with hemodynamically significant CHD.²²

The Palivizumab Outcomes Registry was a prospective observational registry designed to collect data on the demographics, clinical characteristics, and outcomes of infants who received palivizumab for prophylaxis of RSV in the United States from 2000 to 2004.²³ Data collected in this registry and in several other observational post-marketing studies provided further evidence regarding the effectiveness of palivizumab in preventing serious RSV disease leading to hospitalization.²³⁻²⁹ Rates of RSV hospitalization were as low as 0.7% among prophylaxed infants during the most recent RSV season (2003-2004) in the Palivizumab Outcomes Registry.²³

Because of this evidence supporting the benefits of palivizumab immunoprophylaxis, 2006 recommendations by the American Academy of Pediatrics (AAP) guidelines (Red Book) for the use of palivizumab were as follows: (a) palivizumab prophylaxis should be considered for infants and children younger than 24 months of age with CLD of prematurity who required medical therapy for CLD (supplemental oxygen, bronchodilator, or diuretic or corticosteroid therapy) within 6 months before the start of the RSV season; (b) infants born at 32 weeks of gestation or earlier may benefit from RSV prophylaxis, even if they do not have CLD; (c) children who are 24 months of age or younger with hemodynamically significant cyanotic and acyanotic CHD will benefit from palivizumab prophylaxis, with the greatest likelihood of benefit in those who are receiving medication to control congestive heart failure or have either moderate to severe pulmonary hypertension or cyanotic heart disease; and (d) most experts recommend that among infants born at 32-35 weeks gestation, prophylaxis should be reserved for those at greatest risk of severe infection (i.e., 2 or more risk factors, such as child care attendance, school-aged siblings, exposure to environmental air pollutants, congenital abnormalities of the airways, or severe neuromuscular disease) and who are younger than 6 months of age at the start of the RSV season (Appendix).¹³ During the period

of this review, the 1998, 2003, and 2006 recommendations were applicable.^{13,30,31} New AAP recommendations for immunoprophylaxis with palivizumab were published in September 2009.³²

A study of North Carolina Medicaid enrollees during the 2002-2003 RSV season estimated a mean per patient seasonal cost for a group of infants immunoprophylaxed with palivizumab to be \$5,117, including the costs of the drug and of treatment for RSV.³³ Given the high costs of palivizumab, compliance could be an important issue to payers. Frequently, managed care organizations spend significant time and effort to prior authorize requests for palivizumab to ensure that high-risk infants receive prophylaxis.³⁴ Once prior authorization is obtained, compliance with the prescribed regimen is needed to maintain protection throughout the season. Thus, noncompliance diminishes the value of the expense already incurred for previously administered palivizumab doses and could result in hospitalization and higher costs.

Because palivizumab has a mean half-life of approximately 20 days, monthly injections are recommended during the RSV season.¹⁹ Palivizumab serum concentrations of at least 40 micrograms per milliliter (ug per mL) have been shown to reduce pulmonary RSV replication in the cotton rat model of RSV infection by 100-fold.¹⁹ Monthly intramuscular doses of 15 mg per kg in pediatric patients younger than 24 months of age achieved mean (SD) 30-day trough serum drug concentrations of 37 (21) ug per mL after the first injection, 57 (41) ug per mL after the second injection, 68 (51) ug per mL after the third injection, and 72 (50) ug per mL after the fourth injection.¹⁹

Understanding the characteristics of the noncompliant infant, the consequences of noncompliance, and interventions that potentially increase compliance should be useful to managed care decision makers. This literature review (a) identifies and describes compliance rates and the factors that influence parental compliance with palivizumab immunoprophylaxis regimens, (b) reviews intervention programs and describes those that have been associated with increasing compliance, and (c) summarizes the impact of compliance with the recommended regimen of palivizumab immunoprophylaxis on RSV hospitalization rates.

Methods

An electronic literature search was conducted using journal databases, including Ovid (BIOSIS, 1993-April 2008), Current Contents (1997-April 2008), Embase (1980-April 2008), Medline In-Process & Other Non-Indexed Citations; Ovid Medline (1950-April 2008), PubMed (1950-April 2008), Web of Science (1986-April 2008); and an abstract database, Medical Intelligence Solution (1998-April 2008). The search of abstract and journal databases combined the term *palivizumab* (or its synonyms) with the terms *patient compliance to therapy*, *patient adherence to therapy*, or *patient persistence with therapy*. For Ovid and Web of Science, the term *patient cooperation* was also used to make the search more comprehensive. The following inclusion criteria were

FIGURE 1 Flowchart for Study Selection^a

^aInclusion criteria were focus on palivizumab use and compliance with therapy, articles uploaded until April 2008, and articles written in English.

applied to the search: focus on palivizumab use and compliance with therapy, articles uploaded until April 2008, and articles written in English. Exclusion criteria were as follows: abstracts/articles not related to palivizumab (e.g., respiratory syncytial virus immune globulin intravenous [RespiGam]), those focusing on provider compliance with guidelines or other topics, those not reporting compliance rates, and those reporting use of palivizumab primarily in populations not currently indicated for prophylaxis.

A total of 116 articles and abstracts were reviewed for topic significance (Figure 1). Initially, 67 articles and abstracts met the inclusion criteria. In the second review cycle, duplicate articles and abstracts and multiple reports of the same data were excluded; for these studies, the most recent report with the most comprehensive data was used. Of 34 articles and abstracts that met the inclusion criteria in the second review cycle, 9 were rejected because their focus was on provider compliance with guidelines or on off-label use or because they did not provide information relevant to the scope of this review (remaining articles, n=25). All authors performed screening in each review cycle independently and met to discuss and reach final agreement

on included and excluded abstracts and articles.

Data from different studies selected were summarized into the following categories to help understand the literature available: (a) characteristics of compliant versus noncompliant infants (12 studies); (b) home-based versus office or clinic care (10 studies); (c) programs to improve compliance (6 studies); and (d) impact of compliance on RSV hospitalizations (2 studies). Some studies provided information that fit more than 1 category.

Results

A total of 25 articles and abstracts were identified as relevant to compliance with palivizumab.^{23,35-58} Of these, 8 involved retrospective review of data,³⁵⁻⁴² 11 were prospective,^{23,43-52} 4 involved surveys,⁵³⁻⁵⁶ and 2 involved a review of data retrospectively combined with a follow-up call/interview.^{57,58} A total of 8 studies were peer-reviewed articles,^{23,39,43,47,48,52,53,56} 1 was a letter to the editor,⁴² and the remaining 16 were meeting abstracts.^{35-38,40,41,44-46,49-51,54,55,57,58}

Compliance was defined in various ways across studies. In 11 studies,^{37,40,42,43,47-49,52-55} infants who received all recommended palivizumab doses were considered compliant. In 1

study, compliance was defined as receipt of at least 80% of recommended doses.³⁸ In 5 studies,^{45,46,51,57,58} the definition of compliance was based on appropriate intervals (21-35 days) between doses, whereas 6 studies defined compliance as receipt of all palivizumab doses and/or as receipt of doses at appropriate intervals.^{23,35,36,39,44,56} In studies that used number of doses to define compliance, the actual number of injections given at the appropriate time was compared with the projected number of injections an infant should receive. Infants and young children who did not receive the projected number of doses were considered noncompliant. Some abstracts did not adequately describe their definition of compliance, presumably due to space restriction.^{41,50} Nevertheless, the information contained in these abstracts regarding compliance rates before and after specific interventions is included in this review. Overall compliance rates varied from as low as 25% to as high as 100%.^{40,55} The compliance rates of patients in clinical studies involved in palivizumab licensure were 92% and 93%.^{21,22} Thus, compliance in routine practice was more variable.

Characteristics of Compliant and Noncompliant Infants

Twelve studies explored factors positively and negatively associated with compliance to immunoprophylaxis with palivizumab.^{35,42,44-48,53-56,58} A program in which telephone interviews (n=123) were conducted using a quantitative questionnaire revealed that compliance was significantly higher in nonsmoking families (79.8% vs. 47.4%, $P=0.003$, odds ratio [OR]=4.38, 95% confidence interval [CI]=1.59-12.20) and in families that did not have an infant with previous RSV infection (75.7% vs. 33.3%, $P=0.022$, OR=6.25, 95% CI=1.08-35.71).⁵⁸ A retrospective review of records (n=650) from a variety of prophylaxis administration sites reported noncompliance rates of 70% for physician offices, 26% for day health centers, 12% for pulmonologists' offices, 11% for outpatient clinics, and 9% for at-home administration of palivizumab by a visiting nurse. The authors concluded that compliance with an RSV prophylaxis program was greater in a more specialized setting.³⁵

Medicaid enrollment was associated with noncompliance with the recommended regimen. A large number of infants in the Palivizumab Outcomes Registry (47% of 19,474) were enrolled in Medicaid.⁴⁴ When risk factors and compliance with therapy were compared in infants enrolled in Medicaid with other insurance coverage, a higher proportion of infants enrolled in Medicaid were found to be noncompliant (22% vs. 15%, $P<0.001$) when the number of doses received was compared with the number of doses anticipated, irrespective of duration between doses. When the definition of noncompliance accounted for between-dose duration exceeding 35 days, the rates of noncompliance for Medicaid and other coverage, respectively, were 37% versus 24% ($P<0.001$).⁴⁴ Langkamp et al. (2001; 2002) also reported lower compliance in a subgroup of Medicaid patients compared with patients in the sample overall evaluated over 2 RSV seasons

(1999-2000: overall compliance 78% vs. Medicaid subgroup 68%; 2000-2001: overall compliance 79% vs. Medicaid subgroup 68%).^{54,55} However, the authors reported neither the subgroup sizes nor the statistical significance of these differences.

In a study reported by Romero et al. (2004), among infants of minority descent (African American, Hispanic, Asian, Pacific Islander, Native American or other/mixed ethnicity) who constituted 45.5% (n=2,862 of 6,291) of the Palivizumab Outcomes Registry cases observed during the 2002-2003 RSV season, 45% received their doses on average every 30 days compared with 62% of Caucasian infants ($P<0.001$).⁴⁵ During the 2002-2003 season, only 52% of the 994 African American infants enrolled in the Registry, the majority (74%) of whom were covered by Medicaid, received all palivizumab doses within an average of 30 days, according to Gelfand et al. (2004).⁴⁶

Parental perception of the benefits of immunoprophylaxis is an important consideration when designing interventional programs to enhance compliance. Langkamp and Hlavin (2001) reported the results of a survey mailed to 385 families (211 completed questionnaires) of high-risk infants (i.e., infants who had been discharged from a neonatal ICU or who had CLD not associated with prematurity) who were eligible to receive prophylaxis in 1998-1999. The strongest predictor of compliance was the parents' perception that palivizumab would protect their infant from RSV.⁵³ A total of 78% of infants received all of their doses; 67% of parents in the compliant group answered that they believed palivizumab would protect their infant "a great deal" against RSV, compared with 48% of parents in the noncompliant group ($P=0.04$). Langkamp et al. (2001; 2002) reported that parental perception continued to have an influence on compliance rates over the next 2 seasons of 1999-2000 and 2000-2001.^{54,55} Parents who thought that palivizumab would protect their child against RSV infection "some" or "a lot" (believers) were more likely to be compliant than those who thought it would protect "not at all" or "a little" (skeptics)—88% compliance among believers versus 53% among skeptics ($P<0.001$) in 2000-2001⁵⁴ and 85% compliance among believers versus 18% among skeptics ($P<0.001$) in 1999-2000.⁵⁵

Lack of transportation was also a barrier to compliance. In the 1998-1999 season, 85% of parents in the compliant group versus only 65% in the noncompliant group reported that they had no difficulty with transportation ($P=0.004$).⁵³ In addition, parents of Medicaid children who were worried about their infant being infected with RSV were more likely to be compliant than less worried parents (OR=6.62, 95% CI=1.22-35.97, $P=0.03$). Langkamp and Hlavin concluded that parental education emphasizing the benefits of palivizumab immunoprophylaxis may influence compliance and that advice from primary care providers, such as the 2-page letter provided to parents in the Langkamp and Hlavin study, may play an important role in improving compliance.⁵³

Results of some studies carried out outside the United States may be applicable to some U.S. populations. In a multicenter,

prospective study involving 118 Italian pediatric centers in which 4,859 children were recruited, Macagno (2005) showed that compliance with palivizumab prophylaxis was low in children starting the program in October and November but increased over the course of the season.⁴⁷ This finding suggests that Italians perceived the risk of RSV infection mainly during the peak of the outbreak. The number of expected doses in this study was 8,328, and the actual doses administered were 4,881, which can be estimated as an overall compliance rate of 58.6%.⁴⁷ A similar prospective surveillance study repeated the following year revealed that compliance with immunoprophylaxis was relatively stable for a limited period of the RSV season, between December and March, with a decrease after February. Compliance progressively decreased from the first to the last dose. The overall compliance rate for this study was reported to be 66.1%.⁴⁸

Language barriers also may influence compliance. Pignotti et al. (2006) conducted a survey among the parents of 216 infants receiving RSV prophylaxis.⁵⁶ Over a 4-year period involving 4 cohorts of high-risk infants, the overall compliance rate with all doses was 87%, and the strongest factor affecting poor compliance was being foreign-born or a non-native speaker ($P < 0.01$).⁵⁶ A palivizumab outpatient prophylaxis program was carried out in a tertiary level neonatal intensive care unit in Italy.⁴² Retrospective analysis of medical records and recorded demographic data for 156 high-risk infants, of whom 16 were foreign-born, revealed that the compliance rate with all doses during 3 respiratory seasons was 86% overall, compared with 56% among foreign parents. The strongest predictor for poor compliance was being foreign-born and speaking a non-native language ($P < 0.01$).⁴² Though these studies reported data collected outside the United States, the findings may be applicable to U.S. patients of minority origin.⁴⁵

Overall, barriers that influence or predict noncompliance with the recommended regimen of RSV prophylaxis were found to be parental smoking, Medicaid enrollment, lower parental expectations for the benefits of RSV prophylaxis, lack of transportation, and language difficulties.

Home-Based Versus Office/Clinic Care

Ten studies have assessed the impact of an at-home intervention program on compliance and outcomes from documented RSV disease.^{23,36-39,43,45,51,54,55} Three of these, only 1 of which assessed a large patient sample, were presented as full manuscripts and 7 as meeting abstracts (Table 1). Home interventions consist of monthly visits by a professional from a home health care agency for administration of palivizumab at the patient's home. However, an exact description of the program was not always provided. These studies were performed using retrospective medical record review. Exceptions were the Palivizumab Outcomes Registry analyses^{23,45} and the study by Golombek et al. (2004),⁵¹ which used prospective observational designs. All of the studies compared home health patients with clinic/office patients in the same

RSV season except Hand et al. (2008), who used a pre-intervention versus post-intervention comparison.³⁹ Sample size, when reported, varied from 41 to 17,641 in groups being compared. Two studies^{54,55} did not report the sample size for the home or the clinic/office group and compared 3 groups: outpatient clinic, home, and primary care physician office. Therefore, P values reported correspond to a 3-group comparison. Also, 1 study had a sample size of less than 50 per group.⁴³ Nine of the 10 studies were single-center studies that followed infants from a particular local hospital, the geographic location of which was mentioned only in 2 reports (Newark, Delaware,⁴³ and Bronx, New York³⁹). One study involved 256 pediatric sites located throughout the United States (41 states and the District of Columbia).²³

All 10 studies reported data on primarily high-risk infants with Medicaid patients in 4 of them. Data from the Palivizumab Outcomes Registry were reported for all patients available at follow-up and for the Medicaid subgroup.²³ One study reported data on minority infants,⁴⁵ and 1 reported data on urban inner-city infants.³⁸ Definitions of compliance were based on total number of doses, doses given on schedule, or doses within 35 days of previous dose.^{23,36-39,43,45,51,54,55} Compliance rates at clinic or office sites ranged from 36%⁴³ to 100%,⁵⁵ as compared with home health rates, which ranged from 64%⁴⁵ to 96.9%.⁵¹ For Medicaid patients, the compliance rates for clinic or office ranged from 53%⁵⁴ to 100%,⁵⁵ whereas home health compliance rates ranged from 75%²³ to 94%.⁵⁴ In one study, minority patients had a compliance rate of 44% at the clinic/office setting and 64% at the home setting ($P < 0.001$).⁴⁵ In another study, the rates for urban inner-city patients were 83.3% for clinic/office setting and 96.2% for home setting ($P = 0.012$, calculated using a Fisher's exact test).³⁸ Most comparisons found significantly better compliance rates with home health programs as compared with clinic/office programs^{23,36-39,43,45,51,54} except the 2001 Langkamp study in which 1 of the clinic groups had higher compliance than the home health group.⁵⁵

When the association between RSV hospitalization and administration site was investigated, patients who received all doses of palivizumab at home had lower RSV hospitalization rates than did clinic/office patients in the Palivizumab Outcomes Registry study (overall: 0.4% vs. 1.2%, $P = 0.014$; Medicaid: 0.6% vs. 1.6%, $P = 0.02$)²³ and a lower mean number of all-cause hospitalizations per patient during the RSV season in a 2008 study by Hand et al. (0.35 vs. 1.01, $P = 0.001$).³⁹ However, in 4 studies, the differences in RSV hospitalization rates for clinic/office and home health care were not significant.^{36-38,51} Note that 1 study did not specify whether the hospitalization rate reported during the RSV season was attributable to documented RSV hospitalizations.³⁹ These studies did not report any multivariate analyses to control for potential confounders. Although the data from these studies suggest better compliance in home-based programs, well-designed studies would help further establish this relationship.

A Systematic Review of Compliance with Palivizumab Administration for RSV Immunoprophylaxis

TABLE 1 Compliance with Recommended Regimen of RSV Prophylaxis and Hospitalization Rates—At-Home Versus Clinic or Office Administration of Palivizumab

Source	Design	Definition of Compliance	Population	Clinic or Office Program			Home Health Program			Compliance Rate	RSV Hospitalization Rate
				N	Compliance Rate (%)	RSV Hospitalization Rate (%)	N	Compliance Rate (%)	RSV Hospitalization Rate (%)	P Value	P Value
Peer-reviewed studies (n = 3)											
Frogel et al., 2008 ²³	Observational prospective over 4 RSV seasons (registry)	All anticipated doses or more	Primarily high-risk infants	17,641	81	1.2 (overall)	1,226	88	0.4 (overall)	<0.001	0.014
		All doses within 35 days	Primarily high-risk infants	17,641	69		1,226	76		<0.001	
		All anticipated doses or more	Primarily high-risk Medicaid infants	8,070	76	1.6 (overall)	858	90	0.6 (overall)	<0.001	0.02
		All doses within 35 days	Primarily high-risk Medicaid infants	8,070	61		858	75		<0.001	
Paul et al., 2002 ⁴³	Retrospective	All scheduled doses administered	Discharged from special care nursery, met AAP criteria ^a	41	36	Not reported	32	67	Not reported	0.02	
Hand et al., 2008 ^{39,b}	Retrospective	Projected doses within 35 days	Medicaid, neonatal clinic patients, met AAP criteria ^a	109	61.6	1.01 ^b	127	81.8	0.35 ^b	<0.001	0.001
Poster abstracts (n = 7)											
Chua et al., 2008 ³⁶	Retrospective	Doses on schedule	Discharged from NICU, met AAP criteria ^a	1,041	69	0.29	1,549	82	0.39	<0.001	NS
Chua et al., 2007 ³⁷	Retrospective	Monthly doses during RSV season	Discharged from NICU, met AAP criteria ^a	676	91	0.74	618	95	0.16	<0.001	NS ^c
Golombek et al., 2004 ⁵¹	Prospective	Doses given on schedule	Met AAP criteria ^a	1,487	89.2	2.01	4,881	96.9	1.3	<0.001	NS
Langkamp and Hlavin, 2002 ^{54,d}	Retrospective	All doses	High-risk Medicaid infants ^c	Not reported	53 CCH/79 PMD	Not reported	Not reported	94	Not reported	<0.001	
Langkamp et al., 2001 ^{55,d}	Retrospective	All doses	High-risk Medicaid infants ^c	Not reported	62 CCH/100 PMD	Not reported	Not reported	80	Not reported	<0.005	
Romero et al., 2004 ⁴⁵	Observational prospective (registry)	Doses every 30 days	Primarily high-risk minority infants	2,561	44	Not reported	164	64	Not reported	<0.001	
Srinivasan and Srinivasan, 2007 ³⁸	Retrospective	80% of doses administered	High-risk urban inner-city infants	72	83.3	2.8	80	96.2	1.3	0.012 ^c	NS ^c

^aRefers to the AAP criteria for the administration of palivizumab that were in effect at the time that the present study was conducted.

^bPatients in this study were from 2 different birth cohorts in 2 different RSV seasons. Hospitalization results represent mean number of all-cause hospitalizations per patient during the RSV season.

^cP values were not presented in the original paper but were calculated by the authors of the present study based on a 2-sided Fisher's exact test.

^dBecause these studies compared 3 groups instead of 2, this P value corresponds to a 3-group comparison.

^eThe study report indicates that for privately insured patients in the study sample, site of administration was not significantly associated with compliance; however, no numeric details were reported for this comparison.

AAP = American Academy of Pediatrics; CCH = outpatient clinic at children's hospital; NICU = neonatal intensive care unit; NS = not statistically significant; PMD = primary care physician's office; RSV = respiratory syncytial virus.

TABLE 2 Results of Interventions

Source	Programs	Before		After	
		n	Compliance Rate (%)	n	Compliance Rate (%)
<i>Studies measuring compliance rates</i>					
Pignotti et al., 2004 ⁴²	Letter to non-native parents and their physicians explaining risks of RSV infection and benefits of prophylaxis	Not reported ^a	80.0	Not reported	88.0
Awaida et al., 2005 ⁵⁰	Reminder telephone calls to parents or caregivers	89	64.0	89	92.0
Roberts et al., 2006 ⁴⁰	Comprehensive multidisciplinary RSV prophylaxis program <ul style="list-style-type: none"> • Extensive counseling of parents • Reminder telephone calls to parents • Calendars with stickers given to parents • Tracking chart in nursing medication room 	24	25.0 ^b	31	71.0 ^b
Singleton et al., 2006 ⁵²	Training of community health aides for at-home administration of RSV prophylaxis in a remote region of Alaska	111	74.0	68	90.4
Blais et al., 2004 ⁴¹	Staff outreach program <ul style="list-style-type: none"> • Timely home visits • Monthly assessments • RSV prevention education 			900	99.5
<i>Study measuring compliance defined as mean number of doses received</i>		n	Average seasonal doses	n	Average seasonal doses
Frogel and Nerwen, 2005 ⁴⁹	Coordinated neonatal/general pediatric practice program Increase in at-home administration rate of palivizumab (some or all doses) from 5% to 58%	61	3.6	92	5.6

^aAuthors reported a total n of 16 families over 3 RSV seasons.

^bP = 0.005.

RSV = respiratory syncytial virus.

Programs to Improve Compliance

Six studies reported impact of an intervention program on compliance (Table 2).^{40-42,49,50,52} Five of these used pre-intervention versus post-intervention comparisons,^{40,42,49,50,52} whereas 1 reported only post-intervention data.⁴¹ One study analyzed the association of pharmacy intervention with compliance.⁵⁰ Sample sizes, when provided, ranged from 24 to 900. Studies were mostly observational with retrospective assessment of data via records or survey. None used a randomized design or contemporaneous comparison group. Interventions included simple telephone reminders to parents or caregivers,⁵⁰ multidisciplinary programs involving counseling, reminder telephone calls on the day prior to the appointment, and nurses tracking charts.⁴⁰ Complete definitions of interventions and compliance were not always present. All studies reported increased compliance rates but only Roberts et al. (2006) reported statistical testing.⁴⁰ When a comprehensive multidisciplinary program that included counseling, tracking charts, and reminder telephone calls was implemented, the contribution of each individual approach to the overall improvement in compliance rate was not analyzed.⁴⁰

Interventions to address language and socioeconomic levels were associated with improvements in compliance. When Pignotti et al. used language translators, together with a letter explaining to non-native parents and their physicians the risks of RSV infection and the benefits of prophylaxis, compliance rates increased from 80% to 88% over 2 RSV seasons.⁴² Pignotti et al.

reported in a letter to the editor that use of nonmedical language translators in the absence of the letter was unhelpful in promoting compliance.⁴² In a study by Awaida et al. (2005) in a pharmacy department setting, reminder telephone calls to parents were associated with an increase in compliance from 64% to 92%.⁵⁰

Another intervention was the development of a coordinated neonatal/general pediatric RSV bronchiolitis/pneumonia prevention program. A total of 493 high-risk infants were enrolled over 6 RSV seasons.⁴⁹ In the first season (Fall 1998-Spring 1999), patients averaged 3.6 doses, whereas in the sixth season (Fall 2003-Spring 2004), patients averaged 5.6 doses. The percentage of patients receiving some or all doses at home increased from 5% to 58% over this time. Blais et al. (2004) reported that a unique home care-based model that included monthly skilled pediatric nurse visits, monthly assessments, and RSV prevention education resulted in a RSV hospitalization rate of 1.42%, with a compliance rate of 99.5%; however, only post-intervention results were reported.⁴¹

A new procedure involving extensive counseling of parents, reminder telephone calls, calendars with reminder stickers, and tracking charts in the nursing medication rooms was used to improve compliance in a hospital-based clinic.⁴⁰ Results showed that an increased percentage of infants (71%) received the appropriate number of injections after implementation of the new interventions compared with 25% before the new interventions ($P = 0.005$).⁴⁰

RSV hospitalization rates among high-risk premature infants decreased after palivizumab introduction in the Yukon Kuskokwim Delta region of Alaska.⁵² However, compliance with monthly injections remained low because prophylaxis was administered at the Delta regional hospital that was not easily accessible to or from the village by patients' families or a visiting nurse. During the 2003-2004 RSV season, a pilot project was conducted to train certified community health aides to administer palivizumab. Compliance was measured by comparing the actual number of injections administered with the projected numbers, based on month of administration. Following implementation of the pilot project, 90.4% of projected doses were administered, compared with 74% in previous years.⁵²

Impact of Compliance on RSV Hospitalizations

In a study by Berger et al. (2003), palivizumab use was assessed in 10,390 infants based on dispensing records for a pharmacy benefits management company that provided follow-up telephone contact to ensure the prescribed dose was administered.⁵⁷ A total of 9,675 (93.1%) of 10,390 infants were found to be compliant, defined as having no more than 35 days between shipment of doses. RSV hospitalization rates were 1.4% in the compliant group versus 3.1% in the noncompliant group (OR=2.2, 95% CI=1.4-3.5, $P<0.001$).⁵⁷

The Palivizumab Outcomes Registry provided an opportunity to characterize the patterns and scope of palivizumab administration in a cross section of infants in the United States and to correlate compliance with scheduled injections with RSV hospitalization outcomes.²³ Over a 4-year study period, compliance as defined by number of expected doses was not significantly associated with RSV hospitalization in the registry. However, using a different definition of compliance—receipt of all doses within 35 days of the previous dose—odds of RSV hospitalization were significantly lower for those who were compliant (OR=0.70, 95% CI=0.54-0.91; RSV hospitalization rates in compliant vs. non-compliant infants were 1.16% vs. 1.65%, respectively, $P=0.007$).²³ This study also reported a significant association between RSV hospitalization and number of injections in compliant patients (i.e., those who received all doses within 35 days of the previous dose) with a greater number of hospitalizations observed among infants with a lower number of injections ($P<0.001$). In another analysis of this study, Medicaid patients had higher non-compliance rates defined as receipt of all anticipated doses (22% Medicaid vs. 15% non-Medicaid) and doses within 35 days (37% Medicaid vs. 24% non-Medicaid; both comparisons $P<0.001$) compared with non-Medicaid patients. Medicaid patients had higher RSV hospitalization rates compared with non-Medicaid patients (1.6% vs. 0.9%, $P<0.001$).⁴⁴

Discussion

Our review indicated that compliance with immunoprophylaxis is variable and is suboptimal in certain patient subgroups, such as infants with Medicaid coverage,^{23,44} African Americans,⁴⁶ and

other minority populations.⁴⁵ Several factors were associated with noncompliance, including Medicaid enrollment and minority race,^{23,44-46} lower parental expectations about the benefits of RSV prophylaxis,^{54,55} lack of transportation,⁵³ language difficulties,^{42,56} and socioeconomic level.⁵⁰ Despite the progress that has been made in reducing hospitalization rates, infants whose parents are noncompliant with palivizumab continue to have hospitalization rates that are unacceptably high. Studies by Frogel et al. (2008) and Berger et al., examining compliance and RSV hospitalization rates, suggested that improved compliance, defined as receipt of all doses within 35 days of the previous dose, was associated with a reduced risk of RSV hospitalization, consistent with the clinical efficacy of palivizumab.^{23,57} For example, Berger et al. found that compliant patients had a hospitalization rate of 1.4% compared with 3.1% in noncompliant infants.⁵⁷ However, these studies did not report controlling for confounding variables.

Lack of access to the site of administration was one of the most important barriers to compliance. An at-home immunoprophylaxis program was associated with improved compliance in patients across different subgroups.^{23,36-39,43,45,51,54} When a home-based program including monthly assessments and education about RSV prevention was introduced, compliance rates as high as 99.5% were reported by Blais et al.⁴¹ Compliance rates were also higher among Medicaid patients who received palivizumab at home versus in a clinic setting (90% and 76%, respectively).²³ Furthermore, there was a general increase in number of doses received when the proportion of patients receiving some or all doses at home increased over 6 seasons at a coordinated neonatal/general pediatric practice program.⁴⁹ Training of community health aides for at-home administration of RSV prophylaxis was associated with an increase in compliance in a pilot project conducted in villages of the Yukon Kuskokwim Delta region of Alaska.⁵² Although these studies strengthen the evidence in favor of a home-based program for palivizumab administration, weaknesses in study methodology limit the degree to which definitive conclusions can be drawn from study results.

Based on these studies, a home-based program to administer RSV immunoprophylaxis could be a key component in ensuring compliance during the RSV season. Most barriers that affect compliance could be overcome, providing greater opportunity to educate parents or caregivers on the risks of RSV disease and the benefits of prophylaxis. Furthermore, a home-based delivery system might offer some additional benefit of decreasing exposure of the infant to pathogens, including RSV, in the clinic or office setting.³⁹ RSV can survive for several hours on many surfaces and may thus infect a susceptible host.⁵⁹

Other intervention strategies have been tested, some of which resulted in a greater improvement in compliance rates than others. Reminder telephone calls to parents/caregivers were associated with an increase in compliance from 64% to 92%, providing another promising alternative.⁵⁰ A comparative analysis of the financial implications of such programs should reveal the most cost-effective and realistic program. Some of the characteristics

of the noncompliant infant identified in the reviewed studies should be used to develop intervention strategies for each particular group of patients to promote optimal compliance. These interventions could include patient reminder telephone calls, multilingual call centers, or focused patient education efforts that target those demonstrating such a need.

Much of the literature examined in this review reported that a home care strategy for administration of palivizumab, by offering consistent delivery of medication and ongoing parent/caregiver education, was associated with better compliance with therapy. The support services provided by specialty pharmacies are now widely used to streamline the drug distribution, delivery, and management process in ways that engage patients in their care.⁶⁰ Our search did not reveal any study that assessed the effect of timely delivery by specialty pharmacies on compliance. However, it is possible that some of the studies did use specialty pharmacies for drug delivery but did not report it. This should be an interesting and important avenue to explore.

Many programs described in this review involved multiple interventions, and most studies did not measure the impact of individual interventions. Therefore, individual strategies to improve compliance with therapy require further study using adequate sample sizes and research designs, predefined outcomes, and standardized definitions and methods for evaluating outcomes. In the interim, interventions such as home-based health care could be helpful to high-risk patients and especially certain subgroups with suboptimal compliance, such as Medicaid recipients. The financial implications of home-based health care represent an interesting avenue to explore but are not within the scope of this review.

Limitations

First, this review identified several important limitations in the available research literature. Different studies varied slightly in their definitions of compliance, making it difficult to compare outcomes across studies. Much of the data originated from meeting abstracts that provided limited information about each study, including details about interventions and methods. Other shortcomings in the literature include deficient study designs, non-standardized outcomes, inadequate sample sizes, and absence of statistical testing, making it difficult to draw definitive conclusions. These limitations may affect the degree to which findings are applicable in clinical situations; however, the studies described here provided information that could potentially be considered in decision making.

Second, our search was based on the keyword palivizumab together with the terms *compliance*, *adherence*, or *persistence*. This search may have missed some articles whose primary focus was not compliance or palivizumab; it may have also missed articles that did not use these exact terms as keywords but reported results relevant to this study. Future studies should attempt to correct these limitations.

Conclusion

This systematic literature review emphasizes that compliance with immunoprophylaxis to prevent RSV LRTI can be variable and is suboptimal in certain subgroups. A number of strategies to improve compliance have been tried. The most investigated strategy was an at-home program of palivizumab administration. By eliminating most barriers to compliance, this strategy offered consistent delivery of palivizumab and ongoing parent/caregiver education. Furthermore, it was associated with a significant decrease in hospitalization rates in 2 of 6 studies. Compliance in general is associated with decreased hospitalization rates. Early identification of infants at risk for poor compliance could help in tailoring intervention programs specifically aimed at improving compliance and ultimately patients' outcomes.

Authors

MICHAEL P. FROGEL, MD, is Associate Professor of Pediatrics, Albert Einstein College of Medicine, and Chief of General Pediatrics, Schneider Children's Hospital, New Hyde Park, New York. DAN L. STEWART, MD, is Professor of Pediatrics, Kosair Children's Hospital, Louisville, Kentucky. MICHAEL HOOPES, PharmD, is Director, Medical Information; ANCILLA W. FERNANDES, PhD, is Associate Director, Health Outcomes and Pharmacoeconomics; and PARTHIV J. MAHADEVIA, MD, MPH, is Senior Director, Health Outcomes and Pharmacoeconomics, MedImmune, LLC, Gaithersburg, Maryland.

AUTHOR CORRESPONDENCE: Michael P. Frogel, MD, Schneider Children's Hospital, Division of General Pediatrics, 410 Lakeville Rd., Ste. 108, New Hyde Park, NY 11042. Tel.: 516.465.4377; E-mail: frogel@lij.edu.

DISCLOSURES

The authors wish to acknowledge writing support provided by Jacqueline Lanoix, PhD, from Physicians World, a division of KnowledgePoint360 Group, LLC, funded by MedImmune, LLC; editorial support provided by Jan Markind, PharmD, Christina Valentine-Leary, Kelly Mann, and Keeley Sankey from StemScientific, another division of KnowledgePoint360 Group, LLC, also funded by MedImmune, LLC; and coordination and documentation assistance provided by Vicky Barnhart, an employee of MedImmune, LLC.

Funding for this study was provided by MedImmune, LLC, a manufacturer of palivizumab. Hoopes, Fernandes, and Mahadevia are employees of MedImmune, LLC. Frogel and Stewart serve as consultants to MedImmune, LLC, and Frogel has participated as a member of MedImmune advisory boards.

Concept and design were primarily the work of Fernandes, Frogel, and Hoopes. Data collection was performed primarily by Fernandes, Frogel, and Stewart; and data interpretation was performed primarily by Fernandes, Frogel, Hoopes, and Stewart. The manuscript was written primarily by Frogel, Mahadevia, and Fernandes, with the assistance of Lanoix, and revised primarily by Frogel, Fernandes, and Mahadevia.

REFERENCES

1. Leader S, Kohlhasse K. Recent trends in severe respiratory syncytial virus (RSV) among US infants, 1997 to 2000. *J Pediatr*. 2003;143(5 Suppl):S127-32.
2. Leader S, Kohlhasse K. Respiratory syncytial virus-coded pediatric hospitalizations, 1997 to 1999. *Pediatr Infect Dis J*. 2002;21(7):629-32.
3. Centers for Disease Control and Prevention (CDC). Bronchiolitis-associated outpatient visits and hospitalizations among American Indian and Alaska Native children—United States, 1990-2000. *Morb Mortal Wkly Report*. 2003;52(30):707-10. Available at: www.cdc.gov/mmwr/preview/mmwrhtml/mm5230a5.htm. Accessed December 4, 2009.
4. Shay DK, Holman RC, Newman RD, et al. Bronchiolitis-associated hospitalizations among US children, 1980-1996. *JAMA*. 1999;282(15):1440-46. Available at: <http://jama.ama-assn.org/cgi/reprint/282/15/1440>. Accessed October 30, 2009.
5. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA*. 2003;289(2):179-86. Available at: <http://jama.ama-assn.org/cgi/content/full/289/2/179>. Accessed December 4, 2009.
6. Wang EE, Law BJ, Stephens D. Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) prospective study of risk factors and outcomes in patients hospitalized with respiratory syncytial viral lower respiratory tract infection. *J Pediatr*. 1995;126(2):212-19.
7. Navas L, Wang E, de Carvalho V, Robinson J. Improved outcome of respiratory syncytial virus infection in a high-risk hospitalized population of Canadian children. Pediatric Investigators Collaborative Network on Infections in Canada. *J Pediatr*. 1992;121(3):348-54.
8. Paramore LC, Ciuryla V, Ciesla G, Liu L. Economic impact of respiratory syncytial virus-related illness in the US: an analysis of national databases. *Pharmacoeconomics*. 2004;22(5):275-84.
9. MacDonald NE, Hall CB, Suffin SC, et al. Respiratory syncytial viral infection in infants with congenital heart disease. *N Engl J Med*. 1982;307(7):397-400.
10. Figueras-Aloy J, Carbonell-Estrany X, Quero J. Case-control study of the risk factors linked to respiratory syncytial virus infection requiring hospitalization in premature infants born at a gestational age of 33-35 weeks in Spain. *Pediatr Infect Dis J*. 2004;23(9):815-20.
11. Law BJ, Langley JM, Allen U, et al. The Pediatric Investigators Collaborative Network on infections in Canada study of predictors of hospitalization for respiratory syncytial virus infection for infants born at 33 through 35 completed weeks of gestation. *Pediatr Infect Dis J*. 2004;23(9):806-14.
12. Carbonell-Estrany X, Quero J, Bustos G, et al. Rehospitalization because of respiratory syncytial virus infection in premature infants younger than 33 weeks of gestation: a prospective study. IRIS Study Group. *Pediatr Infect Dis J*. 2000;19(7):592-97.
13. American Academy of Pediatrics Subcommittee on Diagnosis and Management of Bronchiolitis. Diagnosis and management of bronchiolitis. *Pediatrics*. 2006;118(4):1774-93. Available at: <http://pediatrics.aappublications.org/cgi/reprint/118/4/1774>. Accessed December 4, 2009.
14. Horn SD, Smout RJ. Effect of prematurity on respiratory syncytial virus hospital resource use and outcomes. *J Pediatr*. 2003;143(5 Suppl):S133-41.
15. Joffe S, Ray GT, Escobar GJ, et al. Cost-effectiveness of respiratory syncytial virus prophylaxis among preterm infants. *Pediatrics*. 1999;104(3 Pt 1):419-27.
16. Robbins JM, Tilford JM, Jacobs RF, et al. A number-needed-to-treat analysis of the use of respiratory syncytial virus immune globulin to prevent hospitalization. *Arch Pediatr Adolesc Med*. 1998;152(4):358-66. Available at: <http://archpedi.ama-assn.org/cgi/reprint/152/4/358.pdf>. Accessed December 4, 2009.
17. Forbes ML, Hall CB, Jackson A, et al. Cost and resource utilization of respiratory syncytial virus (RSV) or winter unspecified bronchiolitis or pneumonia (UBP) hospitalizations during the first year of life among late-preterm and full-term infants. Poster presented at: ISPOR 14th Annual International Meeting; May 16-20, 2009; Orlando, FL.
18. Pérez-Yarza EG, Moreno A, Lázaro P, et al. The association between respiratory syncytial virus infection and the development of childhood asthma: a systematic review of the literature. *Pediatr Infect Dis J*. 2007;26(8):733-39.
19. Synagis (palivizumab). Full prescribing information. MedImmune, LLC; Gaithersburg, MD: 2008. Available at: http://www.medimmune.com/pdf/products/synagis_pi.pdf. Accessed December 4, 2009.
20. Mullins JA, LaMonte AC, Bresee JS, Anderson LJ. Substantial variability in community respiratory syncytial virus season timing. *Pediatr Infect Dis J*. 2003;22(10):857-62.
21. The IMPact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics*. 1998;102(3 Pt 1):531-37.
22. Feltes TF, Cabalka AK, Meissner HC, et al. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. *J Pediatr*. 2003;143(4):532-40.
23. Frogel M, Nerwen C, Cohen A, et al. Prevention of hospitalization due to respiratory syncytial virus: results from the Palivizumab Outcomes Registry. *J Perinatol*. 2008;28(7):511-17.
24. Parnes C, Guillermin J, Habersang R, et al. Palivizumab prophylaxis of respiratory syncytial virus disease in 2000-2001: results from the Palivizumab Outcomes Registry. *Pediatr Pulmonol*. 2003;35(6):484-89.
25. Romero JR. Palivizumab prophylaxis of respiratory syncytial virus disease from 1998 to 2002: results from four years of palivizumab usage. *Pediatr Infect Dis J*. 2003;22(2 Suppl):S46-54.
26. Sorrentino M, Powers T. Effectiveness of palivizumab: evaluation of outcomes from the 1998 to 1999 respiratory syncytial virus season. The Palivizumab Outcomes Study Group. *Pediatr Infect Dis J*. 2000;19(11):1068-71.
27. Cohen SA, Zanni R, Cohen A, et al. Palivizumab use in subjects with congenital heart disease: results from the 2000-2004 Palivizumab Outcomes Registry. *Pediatr Cardiol*. 2007;29(2):382-87.
28. Cohen AH, Sorrentino M, Powers T. Effectiveness of palivizumab for preventing serious RSV disease. *J Respi Dis*. 2000;2(Suppl):S30-32.
29. Pedraz C, Carbonell-Estrany X, Figueras-Aloy J, Quero J; IRIS Study Group. Effect of palivizumab prophylaxis in decreasing respiratory syncytial virus hospitalizations in premature infants. *Pediatr Infect Dis J*. 2003;22(9):823-87.
30. American Academy of Pediatrics Committee on Infectious Diseases and Committee of Fetus and Newborn. Prevention of respiratory syncytial virus infections: indications for the use of palivizumab and update on the use of RSV-IGIV. *Pediatrics*. 1998;102(5):1211-16.
31. American Academy of Pediatrics. Respiratory syncytial virus. In: Pickering LK, ed. *Red Book: 2003 Report of the Committee on Infectious Diseases*. 26th edition. Elk Grove Village, IL: American Academy of Pediatrics; 2003:523-28.
32. Committee on Infectious Diseases. From the American Academy of Pediatrics: Policy statements—Modified recommendations for use of palivizumab for prevention of respiratory syncytial virus infections. *Pediatrics*. 2009;124(6):169-701. Available at: <http://pediatrics.aappublications.org/cgi/reprint/peds.2009-2345v1>. Accessed December 4, 2009.
33. Wegner S, Vann JJ, Liu G, et al. Direct cost analyses of palivizumab treatment in a cohort of at-risk children: evidence from the North Carolina Medicaid Program. *Pediatrics*. 2004;114(6):1612-19.

34. BlueCross BlueShield of Illinois. Prior Authorization: Synagis (palivizumab). Available at: <http://www.bcbsil.com/provider/pdf/synagis.pdf>. Accessed December 4, 2009.
35. Hughes S, Springer L, Kehoe K. Multiple treatment sites effect on RSV prophylaxis compliance [abstract P1312E]. Poster presented at: 39th Annual Meeting of the American Society of Health-System Pharmacists Midyear Clinical Meeting and Exhibits; December 5-9, 2004; Orlando, FL.
36. Chua CO, Mercado VV, Golombek SG. Compliance with palivizumab prophylaxis for respiratory syncytial virus in a home-care based program [abstract 253]. Poster presented at: 118th Annual Meeting of the American Pediatric Society/77th Annual Meeting for the Society for Pediatric Research; May 3, 2008; Honolulu, HI.
37. Chua CO, Mercado VV, Siegel M, et al. Compliance with RSV prophylaxis: a comparison between office and home settings [abstract 160775]. Poster presented at: 135th Annual Meeting and Exposition of the American Public Health Association (APHA); November 3-7, 2007; Washington, DC.
38. Srinivasan G, Srinivasan HB. Compliance with RSV prophylaxis in an urban inner-city population [abstract 6280.9]. Poster presented at: 117th Annual Meeting of the American Pediatric Society/76th Annual Meeting for the Society for Pediatric Research and the 2007 Annual Meeting of the American Society of Pediatric Hematology/Oncology; May 3-6, 2007; Toronto, Canada.
39. Hand IL, Noble L, Geiss D, Shotkin A. Respiratory syncytial virus immunoprophylaxis in an urban population: a comparison of delivery strategies and outcomes. *Pediatr Infect Dis J*. 2008;27(2):175-76.
40. Roberts JR, Martinez J, White S, et al. Improving compliance for respiratory syncytial virus prophylaxis [abstract 279]. Poster presented at: Southern Regional Meeting of the American Federation for Medical Research; March 3-5, 2006; Atlanta, GA.
41. Blais LR, Williams LB, Lamoureux VA. A novel home-care based program for palivizumab prophylaxis reduces RSV hospitalizations [abstract 3343]. Poster presented at: 114th Annual Meeting of the American Pediatric Society/73rd Annual Meeting of the Society for Pediatric Research; May 1, 2004; San Francisco, CA.
42. Pignotti MS, Indolfi G, Donzelli G. Factors impacting compliance with palivizumab prophylaxis. *Pediatr Infect Dis J*. 2004;23(2):186-87.
43. Paul DA, Leef KH, Chidekel A, et al. Home delivery of palivizumab: outcomes and compliance in regional preterm infants. *Del Med J*. 2002;74(1):11-15.
44. Frogel MP, Nerwen C, Boron M, et al. Impact of Medicaid insurance status among 19,474 infants given RSV monoclonal antibody prophylaxis [abstract 889]. Poster presented at: 115th Annual Meeting of the American Pediatric Society and 74th Annual Meeting of the Society for Pediatric Research together with the American Society of Pediatric Hematology/Oncology, the American Society of Pediatric Nephrology, the Lawson Wilkins Pediatric Endocrine Society, and the Pediatric Infectious Disease Society; May 14-17, 2005; Washington, DC.
45. Romero J, Cohen A, Boron M, et al. Respiratory syncytial virus (RSV) prophylaxis in minority populations; results from the Palivizumab Outcomes Registry 2002-2003 [abstract 1344]. Poster presented at: 114th Annual Meeting of the American Pediatric Society/73rd Annual Meeting of the Society for Pediatric Research; May 1-4, 2004; San Francisco, CA.
46. Gelfandl A, Cohen A, Boron M, Rankin M. RSV prophylaxis in African American children; results from the Palivizumab Outcomes Registry 2002-2003 [abstract 2944]. Poster presented at: 100th International Conference of the American Thoracic Society; May 21-24, 2004; Orlando, FL.
47. Macagno F, Previeni (Prevenzione del Virus respiratorio sinciziale: Epidemiologica Nazionale Italiana) Investigators. Main results of a national multicenter study assessing the compliance of pediatric centers to Italian Society of Neonatology recommendations on prevention of respiratory syncytial virus infection. *Pediatr Med Chir*. 2005;27(3-4):70-77.
48. Macagno F, Previeni (Prevenzione del Virus respiratorio sinciziale: Epidemiologica Nazionale Italiana) Investigators. Compliance of pediatric centers to Italian Society of Neonatology recommendations on prevention of respiratory syncytial virus infection: results of the second season of the Previeni Study. *Ped Med Chir*. 2005;27(3-4):78-87.
49. Frogel MP, Nerwen C. Six year experience with a coordinated neonatal and general pediatric practice palivizumab program that increases compliance and prevents RSV hospitalizations of high-risk infants [abstract 3128]. Poster presented at: 115th Annual Meeting of the American Pediatric Society and 74th Annual Meeting of the Society for Pediatric Research together with the American Society of Pediatric Hematology/Oncology, the American Society of Pediatric Nephrology, the Lawson Wilkins Pediatric Endocrine Society, and the Pediatric Infectious Disease Society; May 14, 2005; Washington, DC.
50. Awaida L, Roupret J, Prot-Labarthe S, et al. Evaluation of palivizumab compliance in paediatric patients and impact of patient education: a two year experience [abstract EDU-222]. Poster presented at: European Society of Clinical Pharmacy 5th Spring Conference on Clinical Pharmacy: Integrating Research, Education and Clinical Practice; May 25-28, 2005; Stockholm, Sweden.
51. Golombek SG, Berning K, Berning F. Benefits of an in-home palivizumab prophylaxis program: Three-year results. *Pediatr Res*. 2004;55(Suppl S, Pt 24):542A. Poster presented at: 114th Annual Meeting of the American Pediatric Society/73rd Annual Meeting of the Society for Pediatric Research; May 1-4, 2004; San Francisco, CA.
52. Singleton RJ, Bruden D, Brooks L, et al. Closer to home: Local care improves compliance with RSV prophylaxis in high-risk infants. *Int J Circumpolar Health*. 2006;65(1):4-7.
53. Langkamp DL, Hlavin SM. Factors predicting compliance with palivizumab in high-risk infants. *Am J Perinatol*. 2001;18(6):345-52.
54. Langkamp DL, Hlavin SM. Improving compliance with palivizumab. *Pediatr Res*. 2002;51(4 Pt 2):297A. Poster presented at: American Pediatric Society/Society for Pediatric Research Annual Meeting; May 4-7, 2002; Baltimore, MD.
55. Langkamp DL, Hlavin SM, Bowen M. Compliance with palivizumab. *Pediatr Res*. 2001;49(4 Pt 2):238A. Poster presented at: American Pediatric Society/Society for Pediatric Research/Ambulatory Pediatric Association Annual Meeting; April 27-May 1, 2001; Baltimore, MD.
56. Pignotti MS, Catarzi S, Donzelli G. A 4-year survey on palivizumab respiratory syncytial virus (RSV) prophylaxis: How can compliance be improved? *J Matern Fetal Neonatal Med*. 2006;19(4):221-24.
57. Berger J, Fensterheim L, O'Rourke J, et al. The importance of Synagis compliance in preventing hospitalizations [abstract]. *Pediatr Res*. 2003;53(4 Pt 2):468A-9.
58. Mitchell I, Xu J, Johnson D, et al. Compliance study on respiratory syncytial virus (RSV) prevention program [abstract 4745]. Poster presented at: 100th International Conference of the American Thoracic Society; May 21-26, 2004; Orlando, FL.
59. Hall CB. Nosocomial respiratory syncytial virus infections: the "Cold War" has not ended. *Clin Infect Dis*. 2000;31(2):590-96.
60. Suchanek D. The rise and role of specialty pharmacy. *Biotechnology Healthcare*. October 2005. Alliance for Health Reform. Available at: <http://www.allhealth.org/BriefingMaterials/BiotechHealthcareSpecialtyPharmacies-416.pdf>. Accessed December 5, 2009.

APPENDIX Summary of the 2006 AAP Guidelines for RSV Prophylaxis^a

^aAAP, 2006.¹³ New guidelines were promulgated in September 2009.³²

^bAge at start of RSV season.

^cRisk factors: child care attendance, school-age siblings, exposure to environmental air pollutants, congenital abnormalities of the airways, or severe neuromuscular disease.

^dThose most likely to benefit include infants receiving medication to control congestive heart failure, with moderate to severe pulmonary hypertension, or with cyanotic heart disease.

^eMedical therapy for CLD—supplemental oxygen, bronchodilator, or diuretic or corticosteroid therapy.

AAP=American Academy of Pediatrics; CHD=congenital heart disease; CLD=chronic lung disease; GA=gestational age; RSV=respiratory syncytial virus.