Community-acquired Respiratory Infections in Young Children With Congenital Heart Diseases in the Palivizumab Era

The Spanish 4-Season Civic Epidemiologic Study

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Introduction: To investigate the epidemiology of acute respiratory tract infections (ARIs) in children younger than 24 months old with hemodynamically significant congenital heart diseases. Primary aim: incidence of hospital admission due to ARI. Secondary aims: risk factors, etiologic agents, clinical outcomes, and usefulness of preventive measures.

Patients and Methods: Prospective, multicenter, epidemiologic study conducted in 57 Spanish hospitals covering four 7-month seasons (2004–2008).

Results: A total of 2613 patients were eligible for the study. Three hundred fifty-four patients (13.5%) (95% confidence interval: 12.3–14.9) required a total of 453 hospital admissions. Clinical diagnoses: bronchiolitis (54.1%), upper respiratory tract infection (21%), pneumonia (19.9%), and others (17.4%). Median length of hospital stay: 7.0 days. No etiologic agent was identified in two-thirds of the patients. In the remaining patients either a single agent (26.8%) or polymicrobial infection (5%) was identified. Respiratory syncytial virus (RSV) was the agent that was most commonly found (3.8% specific hospitalization rate). Children receiving adequate RSV prophylaxis (90.5%) had a 58.2% (95% confidence interval: 37.6–78.3) reduction in RSV hospitalization. Risk factors for admission included malnourishment, infant age, male gender, chromosome alterations, wheezing, inadequate RSV prophylaxis fulfillment, and siblings <11 years of age. Pediatric intensive care unit care was required in 21.8% of the admissions and 9 patients (0.34%) died.

Conclusions: Hospital admission rate and severity of ARI remain as important issues in hemodynamically significant congenital heart disease patients. The strict fulfillment of prophylactic recommendations against RSV is the only protective factor that can be modulated to decrease the ARI hospital admission rate.

Key Words: respiratory infections, congenital heart diseases, RSV, palivizumab, vaccines

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Respiratory syncytial virus (RSV) infection remains the most important etiologic agent of lower respiratory tract infection in young children. Special populations known to be at high risk for severe RSV disease include premature infants, infants with bronchopulmonary dysplasia, infants with hemodynamically significant congenital heart disease (HSCHD), or immunocompromised individuals.[1–3]

Congenital heart diseases (CHDs) limit the infant's ability to increase cardiac output, and oxygen delivery can be severely limited. The development of RSV pneumonitis impairs oxygen uptake and increases the work of breathing in these infants with compromised cardiac reserve. Under such conditions infants are at significant risk of developing respiratory or cardiac failure and may require prompt institution of ventilator support. Because infants with serious CHD may deteriorate rapidly after the onset of RSV infection, hospital admission for close observation and monitoring is recommended.[4–6]

There is no specific treatment for RSV infection and therapy is essentially supportive, so prophylaxis is the best strategy against RSV disease. Passive immunization with monoclonal antibodies provides protection against severe RSV infection and significantly reduces hospitalizations in high-risk children.[7] The current use of RSV immune prophylaxis in HSCHD as well as its adherence to recommendations and efficacy in broad population-based studies is not well known.

The primary aim of the present study was to determine the frequency of hospital admission due to acute respiratory tract infections (ARIs) during 4 consecutive 7-month (fall through spring) seasons in children younger than 24 months old with HSCHD. Secondary aims include evaluation of risk factors, identification of etiologic agents, clinical outcome, and usefulness of preventive measures.

PATIENTS AND METHODS

Study Design

The study was a prospective, multicenter, epidemiologic study conducted in 57 hospitals throughout Spain covering four 7-month seasons (fall through spring), from October 1 to April 30, during 4 consecutive years (2004–2008).

Study Population

The population enrolled in the study included patients of ≤24 months of age diagnosed with HSCHD. Exclusion criteria included patients with non-HSCHD, HIV-infected patients, participation in a clinical study during the 3 months before study entry and finally, patients that developed ARIs while being admitted in the hospital due to any other reason (ie, cardiac surgery postoperative period). Parental/legal guardian written informed consent was required before inclusion of each child in the study. The trial was conducted following the guidelines of the local ethical review board in accordance with Good Clinical Practices and the tenets of the Declaration of Helsinki.

Data Collection

A total of 16 principal investigators (pediatric cardiologists in reference hospitals) participated in the study. Each investigator had associated collaborators (n = 41) in the surrounding referring hospitals. Data were collected in 2 visits: (1) Baseline visit: during

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this visit informed consent was obtained and socio-sanitary risk factors were also collected; (2) Final visit: during this visit the physician checked if there had been hospital admissions due to ARI during the study period. Data were obtained from the discharge reports or from the medical records in those cases in which admission took place in one of the participating centers.

Sample Size

According to the birthrate information from the Spanish Institute of Statistics, in the period between 2004 and 2007 a total of 1,896,426 births were registered in Spain. Based on the known incidence rate of CHD (8 per million), it was estimated that a maximum of 15,171 would present any CHD, and of those, 3793 subjects (25%) would present hemodynamically significant disease.[8] Therefore, in the study period the potential number of eligible patients would be 3793. The participating hospitals together with the collaborating centers covered all the public centers with pediatric cardiac surgery and managed most of the hemodynamically severe CHD.

Outcomes

Primary Outcome

The primary outcome was the incidence of hospital admission due to ARI during October 1 to April 30 in 4 consecutive seasons (2004–2005, 2005–2006, 2006–2007, and 2007–2008) of children ≤24 months of age with HSCHD. The definition of HSCHD given by the Spanish Society of Pediatric Cardiology was used.[9] The following data were collected during the admissions: date and duration of hospital stay; diagnosis: clinical and microbiologic, severity of the disease (pediatric intensive care unit [PICU] admission, associated complications); therapies: oxygen requirement, mechanical ventilation, extracorporeal membrane oxygenation; death and date of death. Microbiologic data collection was based on local clinical practice. Standard microbiologic procedures were used for pathogen identification whenever samples were collected.

Secondary Outcomes

Risk factors and the usefulness of preventive measures were evaluated. The following data were collected at baseline and final visits: gender, date of birth, gestational age and birth weight, current weight and weight changes during the follow-up; extent of malnourishment (weight below <3 percentile) was calculated using the standardized Spanish growth charts[10]; type of feeding: breast-feeding or formula, number of siblings <11 years of age that attended school or daycare, attendance to daycare, smoking habits at home, parental education level; type of heart disease: cyanotic, noncyanotic, treatment received for cardiac disease, cardiac surgery or interventions before and during the follow-up period; comorbidities: syndromes/chromosome alterations (Down syndrome, 22q11 deletion); associated respiratory disease: wheezing, anatomic modifications of the aerial tract; immunosuppression: pharmacologic, congenital; and finally data regarding vaccine/immunoprophylaxis schedule fulfillment for RSV, *Haemophilus influenzae*, *Streptococcus pneumoniae*, and influenza according to the Spanish Societies of Cardiology and Pediatric Guidelines. Complete prophylaxis included the following groups of patients: Patients that had received 5 or more doses; patients that had received the same number of doses than visits; patient enrolled in November and had received 4 or more doses; patient enrolled in December and had received 3 or more doses; patient enrolled in January and had received 2 or more doses; patient enrolled in February and had received one or more doses; all patients that were enrolled in April. Incomplete prophylaxis included the remaining patients.[11,12] Immunoprophylaxis consisted of one injection every 28 days during the high risk period, that depending on the geographic area, ranged from October to February.

Statistical Analysis

Continuous variables were described using the mean, median, standard deviation, range and 25 and 75 percentile and were analyzed using the Student *t* test or the nonparametric Mann-Whitney *U* test. Categorical variables were described as frequency and percentage and were analyzed using the χ^2 test. Predictive risk factors for ARI hospital admission were identified using a multivariate model. The clinical effect of the immunoprophylaxis was analyzed by comparison of the patients that required hospital admission versus those that did not require hospital admission. All the comparisons were performed using the χ^2 test.

In all the statistical tests a level of 0.05 of significance was applied. The R statistical program, version 2.5.1, was used for all statistical analyses.

RESULTS

Patient Characteristics

During the 4 consecutive seasons, a total of 3717 patients were evaluated; of those, 2613 (667 during the first season, 540 during the second season, 757 during the third season, and 649 during the fourth season) patients were eligible for the study. Patients were excluded for the analysis if they had been included in the prior studied season. There were 1465 boys and 1147 girls, with a mean age of 6.72 months (86.3% less than 12 month) at the first visit. The mean gestational age was 38.3 weeks (range, 25.0–43.0) and 427 (16.4%) children were premature. The mean birth weight was 2.9429 g (range, 580–5.140), being the mean weight at enrolment of 6041.7 g (46.5% less than 3 percentile). A total of 1356 patients had undergone some type of cardiac intervention (51.9%). The mean follow-up was 142.5 days (63% included in October and November). With regard to immunizations/vaccines, Figure 1 summarizes the fulfillment of prophylactic recommendations during the 4 study periods.

Hospital Admissions

The summary of all baseline patients′ characteristics of those patients that required hospital admission versus those that were not admitted are depicted in Fig, Supplemental Digital Content 1, http://links.lww.com/INF/A563. Three hundred and fifty-four patients (13.5%) (95% confidence interval [95% CI]: 12.3–14.9) required a total of 453 hospital admissions. Clinical diagnoses for admission: bronchiolitis (54.1%); upper respiratory tract infection (21%); pneumonia (19.9%); others (17.4%). The median length of hospital stay was 7 days (interquartile range, 4–11 days). Fig, Supplemental Digital Content 2, http://links.lww.com/INF/A564 displays the monthly patient admissions because of ARI throughout the 4 study seasons. In two-thirds of the patients (n = 301, 68.2%) no etiologic agent was identified. In the remaining 31.8% of the patients a single agent was found in 118 patients (26.8%) and polymicrobial infection was diagnosed in 22 patients (5%). Table 1 summarizes the results of the microbiologic studies. The most common etiologic agent identified was RSV (102 admissions; 3.8% specific admission rate). During the admission, a total of 322 patients (71.56%) required oxygen therapy (median duration, 5.0 days). A total of 86 patients required PICU admission, with a total of 98 admissions (21.8% of total hospital admissions). The median length of PICU stay of 6 days (interquartile range, 3–11 days). Of those, 38 patients (8.52%) required mechanical ventilation (median duration, 7.0 days). A total of 41 (9.2%) patients experienced complications that included pulmonary hypertension (n = 17, 3.8%), pleural effusion (n = 8, 1.8%), and respiratory distress syndrome

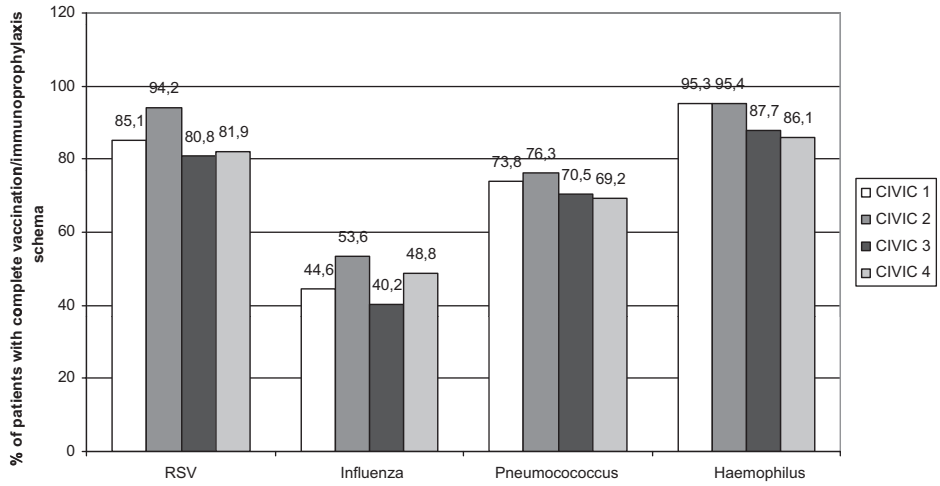

FIGURE 1. Description of prophylactic measurements accomplished during the 4 seasons of the study.

TABLE 1. Microbiologic Studies Conducted and Etiologic Identifications in 2613 Admissions

Pathogens	Test Performed (n, %)	Positive (n, %)
Virus		
RSV	221, 62.4%	102, 22.5%
Others (adenovirus, influenza, parainfluenza)	62, 17.4%	13, 2.9%
Chickenpox	11, 3.1%	2, 0.4%
Bacteria		
S. pneumoniae	95, 26.8%	12, 2.6%
H. influenzae	85, 24.0%	13, 2.9%
Staphylococcus spp.	84, 23.7%	1, 0.2%
Pseudomonas spp.	84, 23.9%	13, 2.9%
Fungi	17, 4.7%	5, 1.1%

TABLE 2. Protective and Risk Factors Associated With Hospital Admission Due to Acute Respiratory Tract Infections and Respiratory Syncytial Virus

Risk Factors	OR (95% CI) for ARI	OR (95% CI) for RSV
Wheezing	3.09 (2.05–4.66)	3.04 (1.56–5.94)
Chromosome alterations		
22q11 deletion	2.84 (1.38–5.84)	3.11 (1.02–9.49)
Trisomy 21	1.97 (1.45–2.70)	2.12 (1.28–3.52)
Presence of siblings <11 years of age	1.85 (1.35–2.54)	—
Inadequate RSV prophylaxis	1.77 (1.23–2.53)	2.48 (1.45–4.26)
Prematurity	1.31 (0.97–1.76)	1.76 (1.10–2.83)
Protective factors:		
Weight ≥3 percentile	0.75 (0.58–0.97)	—
Gender (girl)	0.70 (0.55–0.89)	—
Age >12 mo	0.41 (0.27–0.62)	0.18 (0.07–0.52)

OR indicates odds ratio; CI, confidence interval; ARI, acute respiratory tract infection; RSV, respiratory syncytial virus.

(n = 11, 2.5%). And 21 patients (4.7%) experienced sequela: 12 (2.7%) respiratory, 11 (2.5%) cardiac, 5 (1.1%) digestive, or 3 (0.7%) other. A total of 9 patients died due to respiratory illness while being admitted in the hospital that corresponds to 0.34% of the global number of children enrolled in the study and 1.98% of those patients that required hospital admission.

As shown in Table 2, among the risk factors associated with hospital admission due to ARI were as follows: wheezing (odds ratio [OR]: 3.09, 95% CI: 2.05–4.66), chromosome alterations, 22q11 deletion (OR: 2.84, 95% CI: 1.38–5.84) and trisomy 21 (OR: 1.97, 95% CI: 1.45–2.70), the presence of siblings <11 years of age (OR: 1.85, 95% CI: 1.35–2.54), and the inadequate RSV prophylaxis (OR: 1.77, 95% CI: 1.23–2.53). Conversely, the protective factors against ARI hospital admission included: weight ≥3 percentile (OR: 0.75, 95% CI: 0.58–0.97), female gender (OR: 0.70, 95% CI: 0.55–0.89), and age >12 months (OR: 0.41, 95% CI: 0.27–0.62). In addition, none of the cardiologic variables (cyanotic vs. noncyanotic CHD, previous surgeries) were classified as risk factors.

RSV Infection

RSV was the most common etiologic agent found in children that required hospital admission resulting from ARI. A total of 96 patients (61 boys and 35 girls) required hospital admission resulting from RSV infection, with a specific admission rate of 3.8%. RSV was identified in 102 admissions, representing 27.1% of total (95% CI: 22.9%–31.8%). Children who received adequate RSV prophylaxis (n = 2.366, 90.5%) compared with those that did not (n = 247, 9.5%) had a lower RSV hospital admission rate: 3.3% versus 7.9%, (RR: 2.37, 95% CI: 1.46–3.85, $P < 0.01$). The median length of hospital stay of children with RSV infection was 7 days (interquartile range, 5–17). A total of 31 admissions (30.4%) required PICU admittance, with a median PICU stay of 10.0 days (interquartile range, 5–18 days).

By multivariate analysis (Table 2), the variables that were identified as risk factors for RSV hospital admission were the following: immunodeficiencies (OR: 5.87, 95% CI: 1.97–17.54), wheezing (OR: 3.04, 95% CI: 1.56–5.94), 22q11 deletion (OR: 3.11, 95% CI: 1.02–9.49), inadequate RSV immunoprophylaxis (OR: 2.48, 95% CI: 1.45–4.26), trisomy 21 (OR: 2.12, 95% CI: 1.28–3.52), and prematurity (OR: 1.76, 95% CI: 1.10–2.83). The variable that was recognized as a protective factor for RSV hospital admission was age >12 months at study entry (OR: 0.18, 95% CI: 0.07–0.52).

DISCUSSION

The present study describes the incidence of hospital admissions due to acute respiratory infections in patients with CHD

throughout 4 consecutive 7-month (autumn through spring) periods (2004–2008) in Spain. The hospital admission rate (13.5%) had a similar pattern within the 4 study periods. Nevertheless, a seasonal peak was observed during the winter months (December and January). That is in agreement with the peak observed during winter in temperate climates for respiratory virus infections, including RSV.[13]

Pre-existing disease/comorbidity, in particular, multiple pre-existing diseases and cardiac anomaly, are associated with a significantly higher risk of death from severe RSV infection.[14] We believe that this is the first prospective study conducted to determine the hospital admission rate associated with ARI in CHD patients during 4 consecutive seasons. Prior studies have included epidemiologic data of ARIs in children less than 2 years old but none of them has focused on CHD patients.[15]

The first important conclusion from the present study is that the variables that increased susceptibility to ARI and worsen the hospital admission were not related to the type of cardiopathy. Among such variables was, in first place, undernourishment, that is very common in CHD (present in near half of our patients) and predispose children to respiratory infections in general.[16,17] Another variable that increased susceptibility was the presence of chromosome alterations such as trisomy 21 and 22q11 deletion. Multiple immunologic disturbances are commonly observed in individuals with chromosomal abnormalities.[18] The presence of young siblings among the household, an infant age at the time of the study, and female gender were also associated with an increased risk of hospital admission in CHD children with ARI. Finally, the presence of wheezing and an inadequate (incomplete) RSV immunoprophylaxis were also classified as risk factors for hospital admission.

Prophylaxis with palivizumab has been shown to be clinically effective for reducing the risk of serious lower respiratory tract infections caused by RSV infection and requiring hospitalization in high risk children.[19] The results of the Palivizumab Outcomes Registry conducted between 2000 and 2004 showed a very low rate of hospital admissions (1.9%) among children with CHD who had received RSV prophylaxis, corresponding to a 45% (95% CI: 23%–67%) reduction in RSV hospitalizations.[8,20,21] In the present study, children receiving adequate prophylaxis had a 58.2% (95% CI: 37.6–78.33) relative reduction in RSV hospitalization.

We did not perform cost-effectiveness analyses. Although children >12 months of age and older who received prophylaxis were protected from hospital admission (global OR, 0.41 and RSV OR, 0.27), the low percentage (13.6%) of such patients included in this subgroup minimized the importance of this finding when considering this outcome from a cost-effectiveness point of view.[22]

With regard to microbial identification, no etiologic agent was identified in almost two-thirds of the cases. In clinical practice, except for RSV diagnosis, the number of microbiologic tests that are performed for other etiologic agents is very limited and therefore in a high percentage of the cases no microbiologic agent is identified. In those cases that the etiologic agent was identified, RSV was the most prevalent organism. The percentage of microbiologic studies conducted to identify the etiologic agent was evaluated for RSV, standard for bacteria, and low for virus. The low rate of detection of influenza virus is in agreement with previous reports conducted in children.[23]

The rates of complete vaccination/immunoprophylaxis varied significantly: while high rates were observed for RSV (range, 80.8%–94.2%), *Haemophilus* (range, 86.1%–95.4%) and *Pneumococcus* (range, 69.2%–76.3%), significantly lower levels were recorded for influenza virus (range, 40.2%–53.6%).

It is important to note that children who received adequate RSV prophylaxis, which is the only known risk factor that can be easily modulated, had a lower hospital admission rate compared with those that did not. Appropriate RSV immunoprophylaxis improves the outcome of some CHD patients who develop an ARI.[24]

Among the limitations of the study include the theoretical determination of the study population, as well as the pool analysis of the outcomes collected from several hospitals, each one following their own clinical guidelines. Thus, the lack of central laboratory testing may have limited the consistency of the microbiologic tests used for ARI diagnosis. Another factor to consider is the recruitment of patients; whereas at the University hospitals patients were recruited by a cardiologist, and therefore, only the most severe cases were included in the study. In other smaller hospitals recruitment was performed by pediatricians and therefore probably not only severe cases but also milder cases were enrolled. It is important to note that nosocomial as well as postcardiac surgery infections were not included in the analysis. Prevention of RSV infection through the establishment of complete immunoprophylaxis schemes as well as a tight collaboration between primary physicians and hospital specialists might diminish the impact of infections in CHD children.

APPENDIX

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REFERENCES

1. Berger TM, Aebi C, Duppenthaler A, et al; the Swiss Pediatric Surveillance Unit. Prospective population-based study of RSV-related intermediate care and intensive care unit admissions in Switzerland over a 4-year period (2001–2005). *Infection*. 2009;37:109–116.
2. Hall CB. Respiratory syncitial virus and parainfluenza virus. *N Engl J Med*. 2001;344:1917–1928.
3. Glezen WP, Greenberg SB, Atmar RL, et al. Impact of respiratory virus infections on persons with chronic underlying conditions. *JAMA*. 2000;283: 499–505.
4. Hall CB, Weinberg GA, Iwane MK, et al. The burden of respiratory Syncytial virus infection in young children. *N Engl J Med*. 2009;360:588–598.
5. MacDonald NE, Hall CB, Suffin SC, et al. Respiratory syncytial viral infection in children with congenital heart diseases. *N Engl J Med*. 1982; 397:397–400.
6. Fixler DE. Respiratory syncytial virus infection in children with congenital heart disease: a review. *Pediatr Cardiol*. 1996;17:163–168.
7. 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;28:511–517.
8. Feltes TF, Cabalka AK, Meissner HC, et al. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodinamically significant congenital heart disease. *J Infect Dis*. 2003;143:532–540.
9. Sociedad Española de Cardiología Pediátrica y Cardiopatías Congénitas. Available at: http://www.secardioped.org/.

10. Tablas de crecimiento (estudios longitudinal y transversal) del instituto de investigación sobre crecimiento y desarrollo Fundación Faustino Obergozo Eizaguirre, María Díaz de Haro, 10 bis. 48013 Bilbao. Available at: http://www. Aepap.org/informat/index.htm.
11. Suárez Cabrera P, Malo Concepción P, Maroto E, et al. Recomendaciones para la prevención de la infección por virus respiratorio sincitial en pacientes con cardiopatía congénita. Sociedad Española de Cardiología Pediátrica y Cardiopatías Congénitas 2003. Available at: http://www.secardiped.org/pdfs/profilaxis-virus-vrs.pdf.
12. Comité Asesor de vacunas de la Asociación Española de Pediatría. Calendario de vacunación de la Asociación Española de Pediatría. *An Pediatr (Barc).* 2007;66:62–69.
13. Centers for Disease Control and Prevention (CDC). Brief report: respiratory syncytial virus activity—United States, July 2006-November 2007. *Morb Mortal Wkly Rep.* 2007;56:1263–1265.
14. Thorburn K. Pre-existing disease is associated with a significantly higher risk of death in severe respiratory syncytial virus infection. *Arch Dis Child*. 2009;94:99–103.
15. Lee JT, Chang LY, Wand LC, et al. Epidemiology of respiratory syncytial virus infection in northern Taiwan, 2001–2005—seasonality, clinical characteristics, and disease burden. *J Microbiol Immnunol Infect*. 2007;40:293–301.
16. Vaiyanathan B, Nair SB, Sundaram KR, et al. Malnutrition in children with congenital heart disease (CHD) determinants and short term impact of corrective intervention. *Indian Pediatr*. 2008;45:541–546.
17. Keusch GT. Nutritional effects on response of children in developing countries to respiratory tract pathogens: implications for vaccine development. *Rev Infect Dis*. 1991;6:S486–S491.
18. Cuadrado E, Barrena MJ. Immune dysfunction in Down's syndrome: primary immune deficiency or early senescence of the immune system? *Clin Immunol Immunopathol*. 1996;78:209–214.
19. Meissner HC, Rennels MB, Long SS, et al. Immunoprophylaxis with Respigam. *Pediatrics*. 2003;112:548–552.
20. Cohen SA, Zanni R, Cohen A, et al. Palivizumab use in subjects with congenital heart disease: results form the 2000–2004 palivizumab outcomes registry. *Pediatr Cardiol*. 2008;29:382–387.
21. Wang D, Cummins C, Bayliss S, et al. Immnunoprophylaxis against respiratory syncital virus (RSV) with palivizumab in children: a systematic review and economic evaluation. *Health Technol Assess.* 2008;12:iii, ix–x,1–86.
22. Geskey JM, Thomas NJ, Brummel GL. Palivimumab in congenital heart disease: should international guidelines be revised? *Expert Opin Biol Ther*. 2007;7:1615–1620.
23. Iskander M, Booy R, Lambert S. The burden of influenza in children. *Curr Opin Infect Dis*. 2007;20:259–263.
24. Chávez-Bueno S, Mejías A, Merryman RA, et al. Intravenous palivizumab and ribavirin combination for respiratory syncytial virus disease in high-risk pediatric patients. *Pediatr Infect Dis J*. 2007;26:1089–1093.