

RESPIRATORY SYNCYTIAL VIRUS: VIROLOGY, CLINICAL CHARACTERISTICS OF RSV DISEASE, AND EPIDEMIOLOGY*

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ABSTRACT

By age 2, nearly all children have been infected with respiratory syncytial virus (RSV), with 1% to 3% hospitalized because of the infection. The economic costs of RSV are also significant, at least \$9115 higher in the first year of life for infants hospitalized with RSV than for those who are not hospitalized. The regional seasonality of the disease enables specific geographic areas to identify key times for infection and time prophylaxis for high-risk children. Identifying the risk factors is also important. Recent studies find that levels of maternally transferred immunoglobulin antibodies predict the risk of severe RSV in preterm infants. Other risk factors include chronic lung disease, congenital heart disease, neuromuscular disease, and immune suppression. Even in full-term infants with no medical conditions, the risk of RSV-related hospitalization increases with the number of people in the home, seasonality of birth, attendance in day care, and cigarette smoke exposure. Utilizing verified risk factors together with the knowledge of the seasonality of RSV could provide an opportunity for more precise identification of infants who could benefit from RSV immunoprophylaxis.

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Respiratory syncytial virus (RSV) was first identified in the 1950s in chimpanzees with cold symptoms and coryza.¹ It was originally called “chimpanzee coryza agent”² until it was recovered from infants with lower respiratory illness and characterized by a syncytial cytopathogenic effect in tissue culture.¹ The virus, a single-stranded, nonsegmented RNA virus, is a member of *Paramyxoviridae*, the same virus family as parainfluenza viruses.^{3,4}

The virus recruits macrophages, lymphocytes, and neutrophils to the lungs, triggering an inflammatory process that results in the production of a thick mucus that blocks alveoli in the bronchioles. Given the small size of the bronchioles in infants, this leads to hyperinflation and, eventually, hypoxemia.^{5,6}

Clinical characteristics of RSV infection include upper respiratory infection marked by rhinorrhea and nasal congestion that lasts between 7 and 12 days. Between 6% and 83% of children overall are reinfect ed each year, demonstrating an inadequate immune response to the initial infection.⁷ By 2 years of age, nearly all children have been infected with RSV, and 1% to 3% are hospitalized because of the infection.⁸

Approximately 33% of children develop RSV bronchiolitis, a lower respiratory tract infection (LRTI) marked by a low-grade fever, coughing, and wheezing followed by dyspnea and severe tachypnea. In addition, apnea occurs in premature infants and, in some cases, in full-term, normal infants aged younger than 6 weeks. The risk of RSV LRTI may be related to respiratory control center maturity. It is associated with significantly higher rates of intubation and oxygen administration.⁷

BURDEN OF RSV

The global burden of RSV is significant. A recent meta-analysis suggests that up to 200 000 children

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aged younger than 5 years die worldwide each year because of RSV-related infections, with 33.8 million new RSV-associated acute LRTIs among children under age 5 (22% of all LRTI cases) each year. At least 3.4 million cases required hospital admission, and an estimated 66 000 to 199 000 of the children died, nearly all in developing countries.⁹

In the United States, RSV is the most common cause of hospitalization in infants aged younger than 1 year, associated with approximately 75 000 to 125 000 hospitalizations annually and accounting for 1 out of every 334 hospitalizations in children aged younger than 5 years.^{8,10,11} The virus is associated with approximately 17 000 all-cause deaths each year in the United States, including 3.3% of all deaths from pneumonia and influenza; 1% of all deaths from respiratory and circulatory deaths; and 0.8% of all-cause deaths. The majority of deaths occur in persons aged 65 years and older.¹²

Given the high rate of hospitalization, it is to be expected that medical costs related to RSV are significant. Indeed, a recent economic analysis found that infants with RSV LRTI had healthcare costs \$9115 higher in the first year of life than those without. Late preterm infants with an RSV hospitalization incurred costs \$21 977 higher ($P < .001$), and those with an outpatient RSV infection \$3898 higher ($P < .001$), than children without the infection.¹¹

SEASONALITY OF RSV

The incidence of RSV varies significantly based on

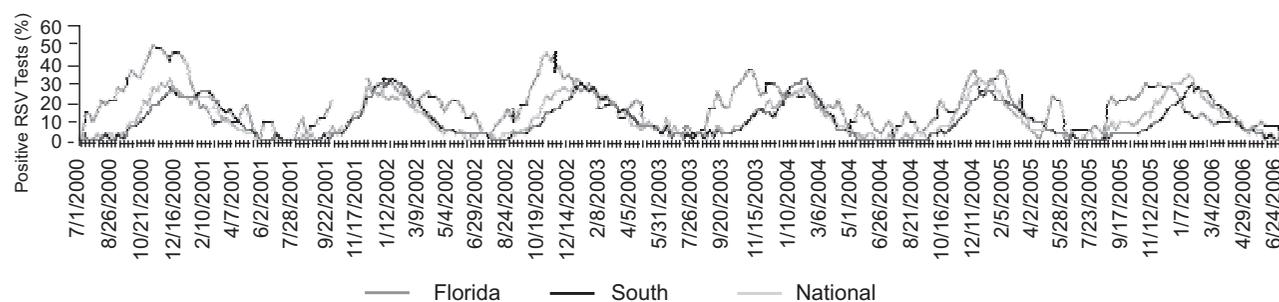
seasonality, with the majority of infections occurring in the fall and winter months and lasting an average of 6 months. However, there is wide geographic variation.

The Centers for Disease Control and Prevention finds that southern states typically demonstrate an earlier median season onset (week 47) and longer duration than other regions (16 weeks; Figure 1), with the Midwest demonstrating a much later median onset (week 1) with a shorter duration (13 weeks).^{13,14} In some states, such as Hawaii, infections continue throughout the year, with no clear peak,¹⁵ whereas in Colorado there appears to be a biennial pattern and small peaks occurring in alternate years.¹⁶ In addition, seasons appear to last longer in metropolitan areas than in rural areas, with approximately 50% of the United States experiencing 6-month seasons, 25% experiencing seasons of less than 4 months, and 25% experiencing seasons of more than 4 months.¹³

Geographic differences appear to be related to weather, particularly temperature increases and decreases, as well as rainfall. Demographic factors, such as overcrowding and population density, urban or rural location, also play a role in severity.¹⁷⁻¹⁹

Maternal antibody levels also are predictive of seasonality. A study using cord blood samples from the Danish National Birth cohort and data from a Danish RSV database on RSV hospitalizations in infants found lower levels of antibody titer predicted increased levels of RSV hospitalization for infants aged younger than 6 months for that season, with the RSV epidemic peaking shortly after the nadir of the

Figure 1. RSV Seasonality

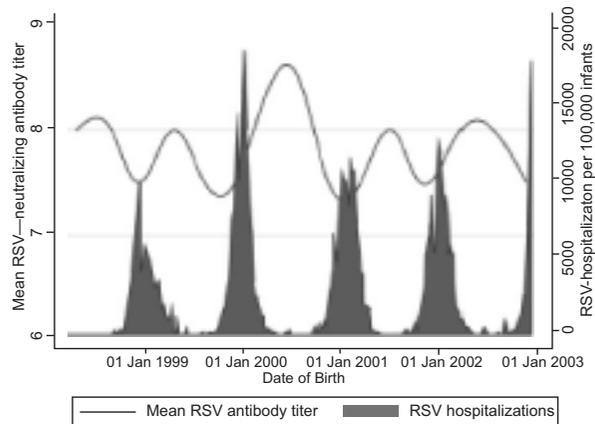


United States, South, and Florida RSV trends: percent positive by antigen detection—3-week running averages, July 2000 through June 2006.

RSV = respiratory syncytial virus.

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Figure 2. Maternally Derived RSV-Neutralizing Antibody and Hospitalization Risk



The titer of maternally derived RSV-neutralizing antibody in 457 cord blood samples from Danish infants born 1998–2003 and incidence of RSV hospitalization per 100 000 Danish infants younger than 6 months of age 1998–2003.

Note: The mean RSV antibody titer expressed to the log base 2 is presented by use of the cubic spline technique and based on 58 infants born in 1998, 92 infants in 1999, 112 infants in 2000, 110 infants in 2001, and 85 in 2002.

RSV = respiratory syncytial virus.

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mean antibody level.²⁰ The results suggest that infants with a higher exposure to RSV antibodies in utero were less likely to be hospitalized. It is possible, then, that immunizing pregnant women against RSV could reduce the incidence of RSV hospitalization among their infants.

There is also some evidence that maternally transferred immunoglobulin G (IgG) antibodies delay the first incidence of RSV infection and reduce its severity, with high titers inversely associated with incidence during the first year. Meanwhile, a lack of transfer of maternal RSV-neutralizing antibodies has been implicated in an increased risk of severe RSV in preterm infants (Figure 2).²⁰⁻²³

A greater understanding of the factors involved in the seasonality of RSV may eventually lead to the development of algorithms that can stratify risk and tailor prophylaxis to children in specific geographic areas.

RISKS CORRELATED WITH RSV-RELATED HOSPITALIZATION

Infants are more likely to be hospitalized with RSV if they are younger than 6 weeks old or premature;

have chronic lung disease (CLD), including bronchopulmonary dysplasia, cystic fibrosis, and diaphragmatic abnormalities; have congenital heart disease (CHD); are immune suppressed from transplant immunosuppressives or chemotherapy; or have neuromuscular disease.^{24,25} Approximately 3.5% of infants with underlying CLD and RSV die within 2 weeks of hospitalization.²⁶

Even premature infants without CLD have high hospitalization rates, ranging from 9% to 13%. Among those hospitalized with RSV, 28% to 34% are admitted to the pediatric intensive care unit and 7% to 22% require mechanical ventilation.²⁷ Premature lung development and reduced levels of lung function, low antibody levels, and modified airway development all contribute to this increased rate of hospitalization.²⁸⁻³²

Hispanics, Native Alaskans, and Native Americans also have a higher risk of hospitalization, as do males, likely because of shorter, narrower airways that contribute to bronchial obstruction.^{24,33} Other risk factors in normal infants include:

- Birth during the first half of the RSV season
- Crowding. Just as the risk of RSV itself increases among infants living in crowded, metropolitan areas, so, too, does the risk of hospitalization. Possible reasons for the correlation include higher viral load through interpersonal transmission, higher viral presence in crowded environments, and greater exposure to RSV in crowded households.²⁴
- Low socioeconomic status, which increases the risk up to 5-fold²⁴
- Attendance in group day care with 5 or more children. Case-control studies find the risk of RSV hospitalization may be more than 3 times higher in infants attending day care while other work demonstrates an increased risk if a sibling attends group day care^{34,35}
- Passive smoke exposure in utero and during infancy^{24,36}
- Altitude greater than 2500 meters. An analysis comparing hospitalization rates for children at 3 altitude categories (<1500 m; 1500–2500 m; and >2500 m) found that infants living at altitudes greater than 2500 m (high) were 33% more likely to be hospitalized (relative risk [RR]: 1.30; $P < .018$) than those at moderate elevation, with 1- to 4-year-old children exhibiting an 80% increase in their hospitalization rate (RR: 1.80;

$P < .001$).³⁷ Altitude can have numerous respiratory effects, including lower oxygen saturation values, nasal obstruction and impaired ciliary activity, and hypoxia-related pulmonary vasoconstriction.

Breast-feeding does not appear protective unless there are other risk factors.³⁸ It also appears that the protective effects of breast-feeding may be stronger in Hispanic than white infants. Other studies, however, show no benefit.³⁹⁻⁴¹

Much of the data on risk factors associated with RSV-related hospitalization come from 4 large, prospective trials: The Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC), a prospective, multicenter, cohort study conducted in 16 regions across Canada during 2 successive RSV seasons in which 1860 infants, including those with underlying congestive and/or lung disease, were followed for a mean of 104 days³⁹; the Spanish Factors that most Likely may lead to development of RSV-related respiratory Infection and subsequent hospital administration among Premature infants born 33 to 35 weeks gestational age study (FLIP), which also compared premature infants hospitalized for RSV with matched controls ($n = 186$ cases and 371 controls)⁴⁰; a follow-up to the FLIP trial that followed 5441 children over 2 RSV seasons⁴²; and a nested case-control Danish study that followed children from birth to 18 months ($n = 2564$ children with RSV and 12 816 controls).⁴¹ The Table depicts the risk factors identified in each study.³⁹⁻⁴²

PREDICTING RSV IN PRETERM INFANTS

Given the high cost of RSV prophylaxis, an algorithm that could identify high-risk infants with significant specificity and sensitivity could lead to significant reductions in morbidity, mortality, and cost. To that end, a robust European model for predicting which premature infants 33 to 35 weeks gestational age were at highest risk for hospitalization has been developed using data from Spain and Germany⁴³ and validated in studies from Denmark,⁴⁴ Italy,⁴⁵ and France.⁴⁵

The model assigns individual weights to the 7 most predictive factors from the FLIP study: birth ± 10 weeks from the beginning of the RSV season; birth weight; breastfed 2 or fewer months; number of siblings aged 2 years or older; number of family members with atopy; number of family members with wheez-

ing; and sex.⁴³⁻⁴⁷ It is currently being implemented in some countries to determine the most effective application of palivizumab in this population.

RSV AND WHEEZING/ASTHMA RISK

The long-term outcome of severe RSV is a very important issue. As demonstrated in the Danish study mentioned earlier, it is clear that an atopic background predisposes children to RSV. Infants between 6 and 12 months who wheeze infrequently have a nearly 2-fold increased risk of RSV hospitalization (odds ratio [OR], 2.7; 95% confidence interval [CI], 1.87–3.91), whereas those with recurrent wheezing have a nearly 12-fold increased risk (OR, 12.56; 95% CI, 8.23–19.15). Children between 12 and 18 months of age with infrequent wheezing have a 1.15 increased risk (OR, 2.15; 95% CI, 1.37–3.39), whereas those between 12 and 18 months with recurrent wheezing have a 6-fold increased risk (OR, 6.99; 95% CI, 4.34–11.23).⁴¹

The opposite is also true, in that children with mild RSV LRTI within the first 3 years of life have an increased risk for frequent wheeze up to 11 years ($P \leq .01$), although not at 13 years.⁴⁸ However, among a Swedish cohort hospitalized for RSV LRTI in the first year of life, the risk of wheeze was significantly higher at 13 years compared with controls ($P < .001$).^{49,50}

It appears that RSV LRTI may be the causative factor in the pulmonary sequelae (wheezing and/or asthma), given longitudinal studies demonstrating that children who have RSV LRTI at age younger than 3 years have recurrent wheezing rates 25% to 80% greater than controls 11 to 13 years later.^{48,50,51}

This raises the question of whether long-term pulmonary effects could be avoided with prophylactic measures to prevent RSV in high-risk infants. One small ($n = 13$ patients, 26 controls) follow-up trial to evaluate the long-term effects of RSV IgG prophylaxis on respiratory and allergic outcomes in children with CLD and/or chronic airway disease found that the treated children demonstrated a significantly better ratio of forced expiratory volume in 1 second to forced vital capacity ($P = .02$), had less atopy ($P < .04$), and were less likely to have missed school ($P = .006$), or have had an asthma attack ($P = .03$).⁵² However, large-scale, prospective studies are needed.

Such a trial has been conducted to examine the effect of palivizumab prophylaxis on wheezing.⁵³ This multinational, double-cohort design trial occurred at

27 sites. Preterm infants (≤ 35 weight gestational age) with no CLD or CHD were enrolled and randomized

to receive either palivizumab prophylaxis at age 6 months or younger or no prophylaxis, then followed

Table. Infant Characteristics Associated with RSV-Related Hospitalization

	PICNIC* ³⁹	FLIP-1† ⁴⁰	FLIP-2 ⁴²	DNBC (n = 2564) ⁴¹
Age at start of RSV season	3.95 mo (OR, 4.89; 95% CI, 2.57–9.29);	Absolute chronological age ≤ 10 wk at the onset of RSV season (OR, 3.95; 95% CI, 2.65–5.9)	Absolute chronological age ≤ 10 wk at the onset of RSV season (OR, 2.99; 95% CI, 2.23–4.01)	N/A
Breast-feeding	Not significant	Breast-feeding for ≤ 2 mo total (OR, 3.26; 95% CI, 1.96–5.42)	Not significant	Not significant
Siblings	Preschool-aged sibling(s) (OR, 2.76; 95% CI, 1.51–5.03)	Presence of ≥ 1 school-aged sibling (OR, 2.85; 95% CI, 1.88–4.33)	Presence of school-aged siblings or day care attendance (OR, 2.04; 95% CI, 1.53–2.74)	Presence of other children < 12 y of age (OR, 2.2; 95% CI, 1.97–2.45)
Crowding in home	> 5 people, counting the subject (OR, 1.79; 95% CI, 1.02–3.16)	≥ 4 residents and visitors at home (discounting school-aged siblings and the case/control him/herself) (OR, 1.91; 95% CI, 1.19–3.07)	Not significant	N/A
Sex	Male; (OR, 1.91; 95% CI, 1.1–3.31)	N/A	Not significant	Male (OR, 1.25; 95% CI, 1.14–1.37)
Birth weight	< 10 th percentile (OR, 2.19; 95% CI, 1.14–4.22)	Not significant	Not significant	N/A
Smoking	≥ 2 smokers in the home (OR, 1.87; 95% CI, 1.07–3.26)	Smoking during pregnancy (OR, 1.62; 95% CI, 1.08–2.42)	Maternal smoking during pregnancy (OR, 1.61; 95% CI, 1.16–2.25)	Maternal smoking during pregnancy (OR, 1.35; 95% CI, 1.2–1.52)
Day care attendance	OR, 12.32; 95% CI, 2.56–59.34	N/A	Not significant	OR, 1.4; 95% CI, 1.15–1.7
Family history	Family history of eczema (OR, 0.42; 95% CI, 0.18–0.996)	Family history of wheezing (OR, 1.9; 95% CI, 1.19–3.01)	Not significant	Maternal, physician-diagnosed asthma (OR, 1.77; 95% CI, 1.16–2.71)
Other				Risk of RSV as a result of wheezing/asthma <ul style="list-style-type: none"> • Infrequent between 6–12 mo (OR, 2.7; 95% CI, 1.87–3.91) • Infrequent between 12–18 mo (OR, 2.15; 95% CI, 1.37–3.39) • Recurrent between 6–12 mo (OR, 12.56; 95% CI, 8.23–19.15) • Recurrent between 12–18 mo (OR, 6.99; CI, 4.34–11.23)

*Included infants with congenital and/or lung disease; †Did not include infants with congenital and/or lung disease. CI = confidence interval; DNBC = Danish National Birth Cohort; FLIP = Factors that most Likely may lead to development of RSV-related respiratory Infection and subsequent hospital administration among Premature infants born 33–35 weeks gestational age; NA = not applicable; OR = odds ratio; PICNIC = The Pediatric Investigators Collaborative Network on Infections in Canada study; RSV = respiratory syncytial virus. Data from Law et al³⁹; Figueras-Aloy et al⁴⁰; Stensballe et al⁴¹; and Figueras-Aloy et al.⁴²

for 2 years. The outcome demonstrated a nearly 50% reduction in the number of children with physician-documented recurrent wheezing and in the incidence of wheezing. Similar effects were seen in the time-to-event analyses for both outcomes.

CONCLUSIONS

Approximately 33% of children with RSV develop LRTIs, with at least 3.5 million children under age 5 requiring hospitalization each year. Medical costs for RSV are significant, as is the mortality rate in developing countries. However, recent studies provide important information on the seasonality and risk factors associated with hospitalization of children with RSV. Among the most important risk factors are birth ± 10 weeks from the beginning of the RSV season; birth weight; number of siblings aged 2 years or older; number of family members with atopy; number of family members with wheezing; and sex.⁴³⁻⁴⁶

Information about the risk of hospitalization in children with RSV could be used to develop algorithms to determine which children are at highest risk of RSV complications and thus should be given immunoprophylaxis.

The ability of immunoprophylaxis to prevent wheezing and/or asthma in children who develop severe RSV is under study. Although it is clear that a family history of atopy increases the risk of RSV-related hospitalization, the data are still sparse as to any causative link between RSV and wheezing/asthma in the child. Nonetheless, some research suggests that immunoprophylaxis may reduce the risk of such long-term complications, although larger trials are required.

DISCUSSION

Dr Rich: Eric, we were talking briefly about the transition from neonatology care to pediatric care within the community. Are you noticing any issues with that as far as coordinating doses? When does the baby, a premature infant, move from neonatology care to community-based pediatric care? Is it just upon discharge, or does the neonatologist see the infant for some time?

Dr Simões: I think it varies by hospital and by site. Around the country, probably 80% or 90% of children go from the neonatal intensive care unit (NICU) to private practice, or to a pediatrician's care, whereas another 10% to 20% are still taken care of by follow-up neonatologists. Thus, there is definitely a place

where children fall through the cracks and, in fact, it happens quite often (ie, between discharge from the NICU, being seen in the private practice, and receiving prophylaxis). Thus, it is important to get the doses in, at least the first dose, before they leave the NICU.

Dr Lee: Do you have any recommendations about coordinating with the infant's health plan to get the pediatrician involved earlier so the hospital is not responsible for the cost of the drug? In some states, palivizumab is considered an outpatient drug by payors so hospitals do not get extra reimbursement just because we have treated with this very expensive drug.

Dr Simões: Consider putting RSV prophylaxis in the contract with the insurers. You know what proportion of your children is premature and who will need prophylaxis before discharge in the RSV season. Because giving prophylaxis means doing it correctly, in my opinion doing it correctly means you protect the child before they leave the NICU, especially during respiratory season.

Dr Lee: Such negotiations, for some reason, have not worked well in our hospital. I do not know if it is just our state being separated out as several TennCare organizations instead of Medicaid.

Dr Simões: In my opinion, immunoprophylaxis is part of the inpatient care. You treat your bone marrow patients. They get far more expensive drugs than palivizumab.

Dr Burgoyne: Those drugs are not coded as outpatient.

Dr Lee: That is the difference. Those drugs are considered inpatient drugs.

Dr Rich: When you have a patient in the NICU, even if you do give that first dose we find problems with the managed care organization getting involved so that the next dose is given on time. Any suggestions based on your experience working with that?

Dr Simões: I work with this all the time. If a newborn baby comes into the hospital for 3 months and the parents lose their insurance by the time the child leaves the hospital, that is the time when it is a problem. But if they have insurance, it is not a problem. The neonatologists coordinate with the pediatricians and then it goes more smoothly.

Dr Rich: Well, we have a problem getting that information in a timely enough manner to make that decision to approve continuation of doses. We may not hear about that until we get an emergency request because the

dose is “due today” and nobody bothered to go to the plan and say, “This infant is on RSV prophylaxis.”

Dr Buckley: We have tried to encourage discharge planners to make sure that if the infant got a dose of palivizumab that they are communicating and making sure that the child has a pediatrician and a follow-up appointment with the pediatrician prior to discharge. It is still not hugely successful, but we have tried. We also have tried to get the outpatient pediatrician who will be following the child throughout the season to initiate the prior authorization while the child is an inpatient but that did not work either.

Dr Rich: Let me ask another question. Let us assume we have started somebody on RSV prophylaxis in the community and he or she is hospitalized for something not related to RSV and the next dose comes due in the hospital. How are you handling that? Eric, are you giving the next dose in the hospital then and then trying to bill for it at that point?

Dr Simões: Yes, the hospital will not get reimbursed. So that is just the cost of doing business.

Dr Lee: We discourage using the hospital supply and we ask the caregiver of the patient to bring it in from their pediatrician’s office supply and we give it in the hospital.

Dr Simões: The other aspect is that probably 50% or 60% of children in Denver are getting their doses at home. In that case, we ask them to bring the dose in. But in other cases, we just bite the bullet and give it. We certainly do not send them home without protection.

REFERENCES

- Blount RE Jr, Morris JA, Savage RE. Recovery of cytopathogenic agent from chimpanzees with coryza. *Proc Soc Exp Biol Med.* 1956;92:544-549.
- Chanock R, Roizman B, Myers R. Recovery from infants with respiratory illness of a virus related to chimpanzee coryza agent (CCA). I. Isolation, properties and characterization. *Am J Hyg.* 1957;66:281-290.
- World Health Organization. Acute respiratory infections. Update September 2009. Available at: http://www.who.int/vaccine_research/diseases/ari/en/index3.html. Accessed June 1, 2010.
- Easton AJ, Domachowske JB, Rosenberg HF. Animal pneumoviruses: molecular genetics and pathogenesis. *Clin Microbiol Rev.* 2004;17:390-412.
- Peebles RS Jr, Graham BS. Pathogenesis of respiratory syncytial virus infection in the murine model. *Proc Am Thorac Soc.* 2005;2:110-115.
- Tripp RA, Oshansky C, Alvarez R. Cytokines and respiratory syncytial virus infection. *Proc Am Thorac Soc.* 2005;2:147-149.
- Tregoning JS, Schwarze J. Respiratory viral infections in infants: causes, clinical symptoms, virology, and immunology. *Clin Microbiol Rev.* 2010;23:74-98.
- 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.
- Nair H, Nokes DJ, Gessner BD, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. *Lancet.* 2010;375:1545-1555.
- Robinson RF. Impact of respiratory syncytial virus in the United States. *Am J Health Syst Pharm.* 2008;65(23 suppl 8):S3-S6.
- Stewart DL, Romero JR, Buysman EK, et al. Total healthcare costs in the US for preterm infants with respiratory syncytial virus lower respiratory infection in the first year of life requiring medical attention. *Curr Med Res Opin.* 2009;25:2795-2804.
- Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA.* 2003;289:179-186.
- Panozzo CA, Fowlkes AL, Anderson IJ. Variation in timing of respiratory syncytial virus outbreaks: lessons from national surveillance. *Pediatr Infect Dis J.* 2007;26(11 suppl):S41-S45.
- Light M, Bauman J, Mavunda K, et al. Correlation between respiratory syncytial virus (RSV) test data and hospitalization of children for RSV lower respiratory tract illness in Florida. *Pediatr Infect Dis J.* 2008;27:512-518.
- Yorita KL, Holman RC, Steiner CA, et al. Severe bronchiolitis and respiratory syncytial virus among young children in Hawaii. *Pediatr Infect Dis J.* 2007;26:1081-1088.
- Zachariah P, Shah S, Gao D, et al. Predictors of the duration of the respiratory syncytial virus season. *Pediatr Infect Dis J.* 2009;28:772-776.
- Noyola DE, Mandeville PB. Effect of climatological factors on respiratory syncytial virus epidemics. *Epidemiol Infect.* 2008;136:1328-1332.
- Stensballe LG, Devasundaram JK, Simões EA. Respiratory syncytial virus epidemics: the ups and downs of a seasonal virus. *Pediatr Infect Dis J.* 2003;22(2 suppl):S21-S32.
- Wilfret DA, Baker BT, Palavecino E, et al. Epidemiology of respiratory syncytial virus in various regions within North Carolina during multiple seasons. *N C Med J.* 2008;69:447-452.
- Stensballe LG, Ravn H, Kristensen K. Seasonal variation of maternally derived respiratory syncytial virus antibodies and association with infant hospitalizations for respiratory syncytial virus. *J Pediatr.* 2009;154:296-298.
- Roca A, Abacassamo F, Loscertales MP, et al. Prevalence of respiratory syncytial virus IgG antibodies in infants living in a rural area of Mozambique. *J Med Virol.* 2002;67:616-623.
- Wang EE, Law BJ, Robinson JL, et al. PICNIC (Pediatric Investigators Collaborative Network on Infections in Canada) study of the role of age and respiratory syncytial virus neutralizing antibody on respiratory syncytial virus ill-

- ness in patients with underlying heart or lung disease. *Pediatrics*. 1997;99:E9.
23. de Sierra TM, Kumar ML, Wasser TE, et al. Respiratory syncytial virus-specific immunoglobulins in preterm infants. *J Pediatr*. 1993;122(5 Pt 1):787-791.
 24. Simões EA. Environmental and demographic risk factors for respiratory syncytial virus lower respiratory tract disease. *J Pediatr*. 2003;143(5 suppl):S118-S126.
 25. Wilkesmann A, Ammann RA, Schildgen O, et al. Hospitalized children with respiratory syncytial virus infection and neuromuscular impairment face an increased risk of a complicated course. *Pediatr Infect Dis J*. 2007;26:485-491.
 26. Navas L, Wang E, de Carvalho V, et al. 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;121:348-354.
 27. Simões EA. Immunoprophylaxis of respiratory syncytial virus: global experience. *Respir Res*. 2002;3(suppl 1):S26-S33.
 28. Hall CB. Respiratory syncytial virus and parainfluenza virus. *N Engl J Med*. 2001;344:1917-1928.
 29. Friedrich L, Stein RT, Pitrez PM, et al. Reduced lung function in healthy preterm infants in the first months of life. *Am J Respir Crit Care Med*. 2006;173:442-447.
 30. Hoo AF, Dezateux C, Henschen M, et al. Development of airway function in infancy after preterm delivery. *J Pediatr*. 2002;141:652-658.
 31. Mansell AL, Driscoll JM, James LS. Pulmonary follow-up of moderately low birth weight infants with and without respiratory distress syndrome. *J Pediatr*. 1987;110:111-115.
 32. Yeung CY, Hobbs JR. Serum-gamma-G-globulin levels in normal premature, post-mature, and "small-for-dates" newborn babies. *Lancet*. 1968;1:1167-1170.
 33. Simões EA. Respiratory syncytial virus infection. *Lancet*. 1999;354:847-852.
 34. Anderson LJ, Parker RA, Strikas RA, et al. Day-care center attendance and hospitalization for lower respiratory tract illness. *Pediatrics*. 1988;82:300-308.
 35. Liese JG, Grill E, Fischer B, et al. Incidence and risk factors of respiratory syncytial virus-related hospitalizations in premature infants in Germany. *Eur J Pediatr*. 2003;162:230-236.
 36. Simões EA. Maternal smoking, asthma, and bronchiolitis: clear-cut association or equivocal evidence? *Pediatrics*. 2007;119:1210-1212.
 37. Choudhuri JA, Ogden LG, Ruttenber AJ, et al. Effect of altitude on hospitalizations for respiratory syncytial virus infection. *Pediatrics*. 2006;117:349-356.
 38. Holberg CJ, Wright AL, Martinez FD, et al. Risk factors for respiratory syncytial virus-associated lower respiratory illnesses in the first year of life. *Am J Epidemiol*. 1991;133:1135-1151.
 39. 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;23:806-814.
 40. Figueras-Aloy J, Carbonell-Estrany X, Quero J, et al. 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;23:815-820.
 41. Stensballe LG, Kristensen K, Simões EAF, et al. Atopic disposition, wheezing, and subsequent respiratory syncytial virus hospitalization in Danish children younger than 18 months: a nested case-control study. *Pediatrics*. 2006;118:e1360-e1368.
 42. Figueras-Aloy J, Carbonell-Estrany X, Quero-Jiménez J, et al. FLIP-2 study: risk factors linked to respiratory syncytial virus infection requiring hospitalization in premature infants born in Spain at a gestational age of 32 to 35 weeks. *Pediatr Infect Dis J*. 2008;27:788-793.
 43. Simões EA, Carbonell-Estrany X, Fullarton JR, et al. European risk factors' model to predict hospitalization of premature infants born 33-35 weeks' gestational age with respiratory syncytial virus: validation with Italian data. *J Matern Fetal Neonatal Med*. 2010 May 21. [Epub ahead of print]
 44. Stensballe LG, Fullarton JR, Carbonell-Estrany X, et al. Population based external validation of a European predictive model for respiratory syncytial virus hospitalization of premature infants born 33 to 35 weeks of gestational age. *Pediatr Infect Dis J*. 2010;29:374-376.
 45. Carbonell-Estrany X, Simões EA, Fullarton JR, et al. Validation of a model to predict hospitalization due to RSV of infants born at 33-35 weeks' gestation. *J Perinat Med*. 2010;38:411-417.
 46. Simões EA, Carbonell-Estrany X, Fullarton JR, et al. A predictive model for respiratory syncytial virus (RSV) hospitalisation of premature infants born at 33-35 weeks of gestational age, based on data from the Spanish FLIP Study. *Respir Res*. 2008;9:78.
 47. Colin AA, McEvoy C, Castile RG. Respiratory morbidity and lung function in preterm infants of 32 to 36 weeks' gestational age. *Pediatrics*. 2010;126:115-128.
 48. Stein RT, Sherrill D, Morgan WJ, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet*. 1999;354:541-545.
 49. Sigurs N, Bjarnason R, Sigurbergsson F, et al. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. *Am J Respir Crit Care Med*. 2000;161:1501-1507.
 50. Sigurs N, Gustafsson PM, Bjarnason R, et al. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. *Am J Respir Crit Care Med*. 2005;171:137-141.
 51. Henderson J, Hilliard TN, Sherriff A, et al. Hospitalization for RSV bronchiolitis before 12 months of age and subsequent asthma, atopy and wheeze: a longitudinal birth cohort study. *Pediatr Allergy Immunol*. 2005;16:386-392.
 52. Wenzel SE, Gibbs RL, Lehr MV, et al. Respiratory outcomes in high-risk children 7 to 10 years after prophylaxis with respiratory syncytial virus immune globulin. *Am J Med*. 2002;112:627-633.
 53. Simões EAF, Groothuis JR, Carbonell-Estrany X, et al. Palivizumab prophylaxis, respiratory syncytial virus, and subsequent recurrent wheezing. *J Pediatr*. 2007;151:34-42.