

Respiratory Syncytial Virus: Pathogenesis and Disease Burden

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ABSTRACT: Although respiratory syncytial virus (RSV) was first described more than 50 years ago, RSV remains a cause of significant disease burden in infants and young children—especially those who are born prematurely or who have certain underlying diagnoses. Lower respiratory tract infections (LRTIs) develop in a significant percentage of patients who become infected with RSV, often resulting in hospitalization. Around 20% of premature infants are hospitalized with RSV-associated illness; in North America, about 1% of children hospitalized with RSV disease die. In addition, infants who have RSV LRTIs may experience pulmonary sequelae, including wheezing and asthma, that can last until adolescence.

Respiratory syncytial virus (RSV) can cause an array of respiratory diseases, such as bronchiolitis and pneumonia, and it has been linked to chronic wheezing and asthma. Each year, infection with RSV causes up to 126,300 hospitalizations of infants in the United States,¹ and the worldwide mortality associated with RSV infection has been estimated as being as high as 1 million per year.² Although nearly all children are likely to be infected with RSV at some point within their first 2 years, certain groups of infants are at significantly increased risk for serious infection and associated complications.

In this article, I review the pertinent facts about the virus—its history, structure, mode of transmission, and seasonal nature—as well as the clinical course of RSV infection, in-

cluding its pathology and pathophysiology, associated morbidity and mortality, hospital course, and costs. I then discuss in depth which patients are at particular risk for RSV infection, the reasons for this heightened risk, and the long-term impact of serious RSV infection.

NATURE OF RSV

RSV was first isolated in 1956,³ when it was described as a cause of coryza in chimpanzees. RSV infection in children was first diagnosed a year later in hospitalized patients with lower respiratory tract infections (LRTIs).⁴ The first documented outbreak of RSV in a neonatal intensive care unit (NICU) occurred in 1964.⁵

Structure of the virus. There are several glycoproteins on the surface of RSV. The 2 most significant of these are the F (fusion) protein and the G (attachment) protein.⁶ The F protein, which seems to be the more stable of the two, mediates cell-to-cell fusion of RSV and the formation of syncytia.⁷ The G protein is responsible for attachment to respiratory cells.⁸ Although both the F and G glycoproteins are major targets of neutralizing antibodies, the F protein elicits a particularly powerful antibody response.⁹ Moreover, antibodies against this particular glycoprotein protect against the 2 broad serological subtypes of RSV (A and B). For these reasons, the F protein has been the target of efforts to develop antibodies for the prevention of RSV infection.^{7,10}

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Transmission. RSV is shed in nasopharyngeal secretions; infected patients can shed significant amounts of the virus for up to 21 days.¹¹ RSV can survive on non-porous surfaces, such as countertops or crib rails, for up to 7 hours; on porous surfaces, such as clothing, for up to 4 hours; and on skin for up to 1 hour.¹² RSV enters the body through the mucosal surfaces of the mouth, nose, and conjunctivae. The ability of the virus to enter via the conjunctivae plays a significant role in its transmission. This stems from the fact that health care personnel typically don gowns, gloves, and masks when working in a nursery in which patients with RSV infection have been isolated; however, they less commonly put on goggles. Thus, if a physician or nurse accidentally rubs his or her eye while working with infected infants then later has contact with an infant who is not infected and rubs the eye again, RSV may be transmitted.

In a study by Hall and colleagues,¹² 3 groups of volunteers were put in rooms with patients infected with RSV. Those in the first group were instructed to simply sit in the room and not touch anything;

those in the second group were instructed to touch various surfaces; and those in the third group were asked to hold the infected infants. RSV infection subsequently developed in none of the volunteers in the first group, in 40% of those in the second group, and in 71% of those in the third group (**Figure 1**). This study demonstrated that RSV is not an airborne pathogen.

The transmissibility of RSV in NICUs was historically a significant health care burden: in the 1970s, RSV infection developed in 45% of infants who were hospitalized in the NICU during RSV season for longer than 1 week, and the risk of an RSV infection was even higher among patients who had congenital heart disease; were premature; had chronic lung disease, leukemia, or bone marrow transplants; or were elderly.^{13,14} Understanding how RSV is transmitted is the first step to controlling infection; infection rates have been significantly reduced through the imposition of appropriate control measures.

Seasonality. RSV infection is seasonal in nature the world over. Although the timing of the RSV season varies with latitude and climate, it

typically occurs at the same time every year. In the United States, the season runs from winter into spring and lasts from 2 to 5 months—usually from November through March (although it can start in October and last as late as April). In more northern parts of the country, the RSV season tends to be shorter than it is further south.

In other countries with a temperate climate, such as the Netherlands, Belgium, and the United Kingdom, RSV season also tends to run from November through March. The season in the southern hemisphere occurs at the opposite time of year. In countries with a tropical climate, such as Indonesia, RSV season typically coincides with the rainy season.

The predictability of the RSV season in the United States is shown in the graph in **Figure 2**, which is based on data collected by the CDC on RSV epidemics.¹⁵ The CDC monitors RSV infections through weekly reports from selected centers (public health laboratories, hospitals, and clinics) on the number of specimens that are tested for RSV and the number of these specimens that test positive. An RSV epidemic is defined as occurring when more than 50% of the reporting centers detect RSV once or more in 2 consecutive weeks or when more than 10% of the specimens tested during the surveillance week are positive for RSV.

The morbidity and mortality that occur during an RSV epidemic are significant and dramatic. During an epidemic, RSV is the principal cause of hospitalizations for LRTIs. Although infections with other viruses (eg, influenza A, influenza B, parainfluenza, adenovirus) also tend to peak during the winter, at the time of an RSV epidemic, the number of hospitalizations for RSV-associated infections typically exceeds those caused by all other

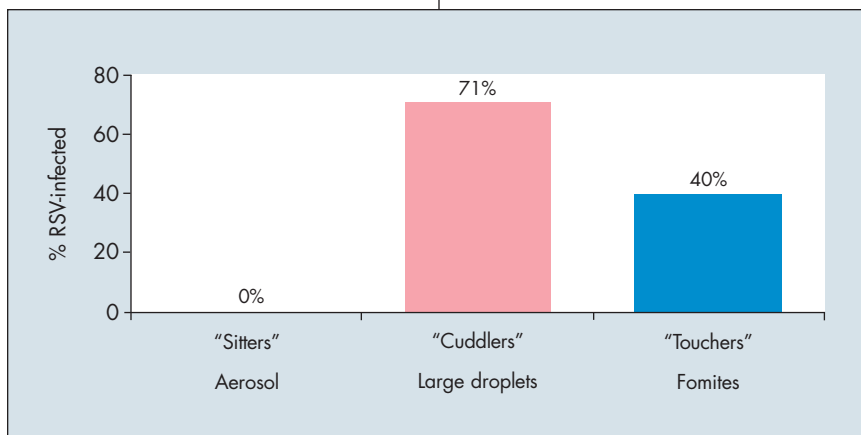


Figure 1 – This graph shows the relative likelihood of infection with respiratory syncytial virus with 3 different types of exposure: sitting in the same room with an infected infant but at a distance from him and without touching anything (“sitters”); sitting in the same room with an infected infant and touching various surfaces (“touchers”); and actually holding an infected infant (“cuddlers”).
(Data from Hall et al. *J Infect Dis.* 1980.¹²)

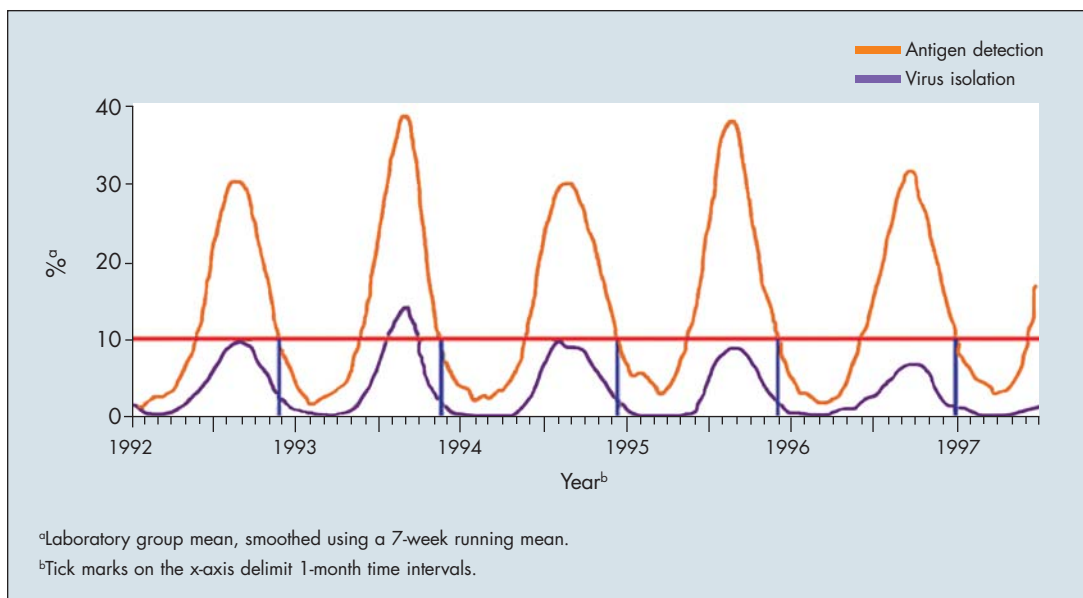


Figure 2 – This graph shows the percentage of specimens that tested positive (using 2 different confirmation methods) for respiratory syncytial virus (RSV) in the United States each week from July 1992 through November 1997; it demonstrates the predictability and consistency of the RSV season.¹⁵

viruses (Figure 3).¹⁶ In addition, infant mortality from LRTIs closely parallels RSV epidemic activity.¹⁷

CLINICAL COURSE OF RSV INFECTION

Epidemiology. By age 1 year, 50% of children will have had an RSV infection, and by age 2 years, virtually all children will have been infected with RSV. Because infection does not confer long-lasting immunity, as with diphtheria or pertussis, reinfection with RSV is common. By age 2 years, 50% of children will have had 2 or more RSV infections.

RSV causes 40% to 49% of cases of bronchiolitis, up to 44% of cases of outpatient pneumonia, and up to 63% of cases of inpatient pneumonia.

Clinical manifestations. Uncomplicated RSV infection presents with rhinorrhea, cough, and fever. However, a significant number of these infections progress to LRTIs. The clinical presentation of an RSV-associated LRTI includes chest wall retractions, nasal flaring, tachypnea, sometimes cyanosis, and wheezing and rhonchi

on auscultation. Neonates, especially those in the NICU, may present with apnea.

Pathology and pathophysiology. RSV infection causes epithelial necrosis of the bronchioles with sloughing of necrotic debris, mononuclear infiltrates in peribronchiolar tissue with edema of the submucosa, and hypersecretion of mucus. These effects produce bronchoconstriction leading to airway obstruction. Turbulent airflow in narrow airways is the cause of the wheezing heard in RSV bronchiolitis. Because the airways in premature and young infants are already relatively narrow, the risk of respiratory symptoms from RSV infection is increased in these populations.

RSV-associated hospitalizations. As many as 126,300 infants in the United States are hospitalized each year for RSV-associated bronchiolitis or pneumonia,¹ and estimates of annual mortality in US infants and children attributed to RSV range from 200¹ to more than 2700.¹⁸ In North America and Europe, RSV-associated hospitalizations involve

primarily infants younger than 1 year¹⁹⁻²¹; in developing countries, however, older children are often hospitalized as well.

Among otherwise healthy children, between 0.5% and 2% are hospitalized each year for RSV infection.²² However, hospitalization rates are significantly increased in various groups of high-risk children. In an analysis of 9 studies of children under age 2 years who had chronic lung disease or bronchopulmonary dysplasia (BPD), the weighted mean hospitalization rate for RSV infection was approximately 17%.^{20,23-30} An analysis of studies of infants born at less than 36 weeks' gestation showed a weighted mean hospitalization rate of almost 9%.^{24,27,29,31-35}

A study by Boyce and colleagues²⁶ has shown that, of the risk factors for severe RSV infection, BPD is associated with the highest rate of RSV hospitalization, followed by congenital heart disease and prematurity. Among infants younger than 1 year, the number of RSV-associated hospitalizations per 1000 children-

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Positive tests (n)

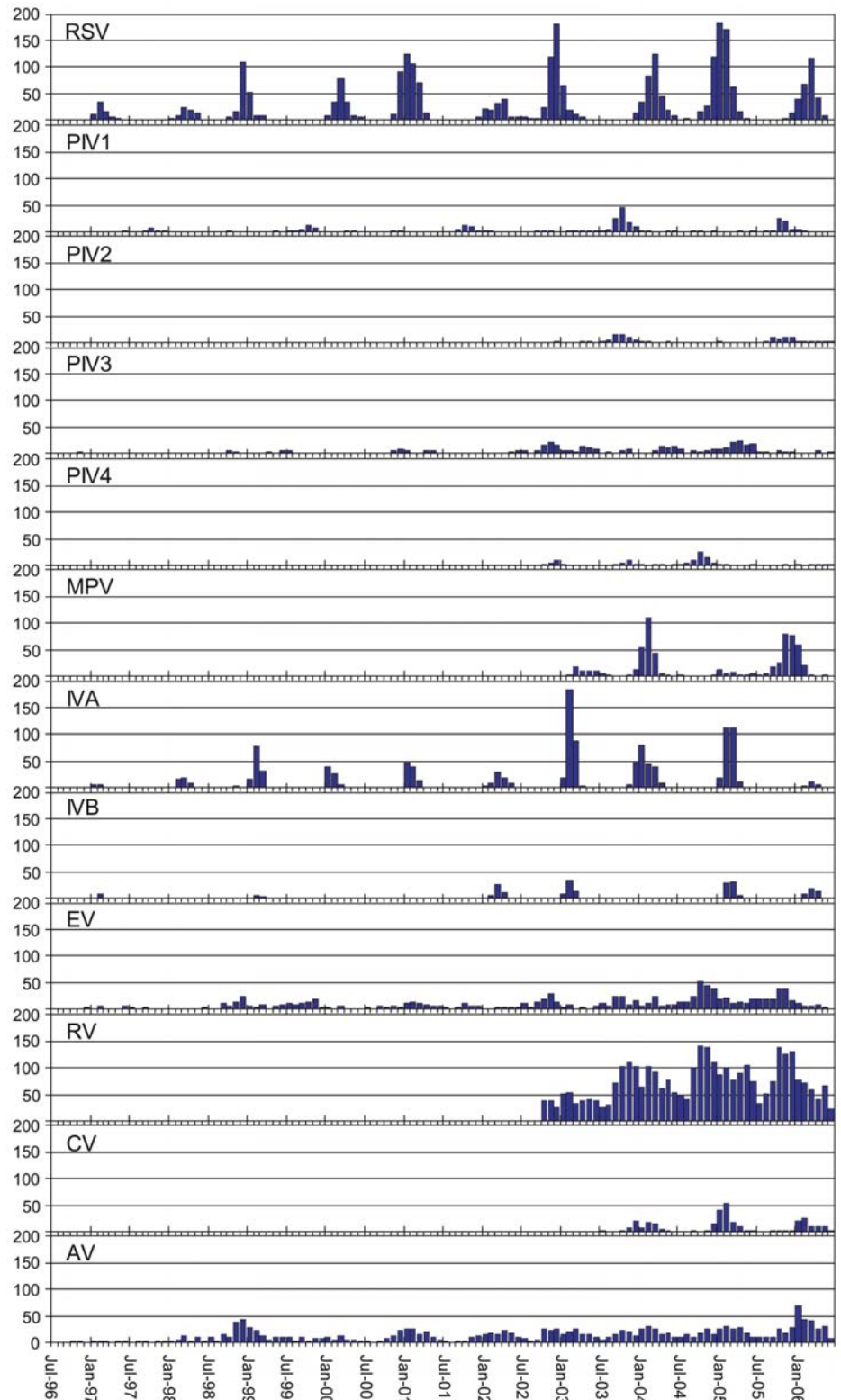


Figure 3 – These graphs show the monthly incidence of 12 common pathogens identified in nasopharyngeal aspirates obtained from German children aged birth to 16 years in whom a lower respiratory infection or complicated acute respiratory infection had been diagnosed (data are shown for the 10-year period July 1996 through June 2006 for all pathogens except rhinoviruses, for which data are shown from October 2002 onwards, and coronaviruses, for which data are shown from April 2003 onwards). At the height of RSV infection epidemics, the number of positive tests for RSV generally surpassed the number of positive results for any other pathogen.

(From Weigl et al. *Eur J Pediatr.* 2007.¹⁶)

years was 388.4 among those with BPD, 92.2 among those with congenital heart disease, and 65.9 among those born between 29 and 32 weeks' gestation. Moreover, by age 2 years, the only children with any substantial persistent risk of hospitalization for RSV infection were those with BPD.

Hospital stays for RSV LRTIs are frequently lengthy. Many factors are involved in determining the duration of such stays, including the presence of an underlying diagnosis (eg, prematurity, congenital heart disease, chronic lung disease) and local practice in the area where the hospital is located. In Canada, the length of an RSV-associated hospital stay ranges from 4.6 to 6.7 days for otherwise healthy patients and from 8.6 to 11.8 days for patients with another diagnosis.³⁶ In Europe, RSV-associated stays range in length from 4 to 9 days.³⁷

In addition, hospitalization for many children who are admitted for an RSV LRTI—especially those with an underlying diagnosis—may involve time in the ICU and/or the need for ventilation. A study by Arnold and colleagues¹⁹ showed that children hospitalized with an RSV LRTI who also had underlying lung disease (eg, cystic fibrosis, chronic lung disease of prematurity, recurrent aspiration) spent between 4 and 11 days in the ICU and between 3.5 and 14 days on ventilation.

Morbidity and mortality. Between 20% and 40% of RSV infections result in LRTI. The vast majority of patients with an RSV LRTI seek medical care, and between 0.5% and 2% of previously healthy patients with an RSV LRTI are hospitalized.²² In North America, approximately 1% (between 0.1% and 2%) of children hospitalized with RSV infection die; the mortality rate among high-risk children is even greater—3% to 4% of those hospitalized.³⁸ Worldwide, because of poorer quality health care in many areas, RSV-related mortality is

far higher—between 600,000 and 1 million deaths per year of children younger than 5 years.²

In the United States, the children at greatest risk for death from RSV infection are those who were infants with very low birth weight (less than 1500 g) or low birth weight (1500 to 2499 g). Their risks of death are, respectively, about 5 times and 2.5 times that of healthy weight infants born at term.³⁹

Cost of RSV infection. Data on the costs associated with RSV infection are difficult to come by. The best available data come from Canada and are about 15 years old. However, while the specific numbers may be somewhat out-of-date, the apportionment of costs they show is noteworthy. About 62% of total costs were related to hospital care; nearly 40% of the annual cost of RSV infection was attributable to outpatient care (including physician services, loss of homemaker wages, travel, and so on).⁴⁰

WHICH PATIENTS ARE AT GREATEST RISK—AND WHY

The risk of severe RSV infection is highest in the following 5 groups of infants:

- Those with chronic lung disease.
- Those with cystic fibrosis.
- Those with cardiac disease.
- Those with neuromuscular disorders.
- Those who are immune-deficient.
- Those who were born prematurely.

Of these groups, preterm infants are at greatest risk. In the United States, nearly 300,000 infants are born at less than 36 weeks' gestation each year, and more than 76,000 at less than 32 weeks' gestation.⁴¹ Depending on the study cited, premature infants account for 12%²⁶ to 27%⁴² of all RSV-associated hospitalizations. Thus, approximately 20% of premature infants are hospitalized for RSV infection.

Reasons underlying increased risk. The reasons for the increased risk vary among the different at-risk

populations. Infants with chronic lung disease or cystic fibrosis have hyper-responsive airways and reduced lung capacity. Those with cardiac disease often have pulmonary vascular changes that lead to hyperresponsiveness, or increased pulmonary blood flow that could result in pulmonary hypertension, or pulmonary edema. Infants with neuromuscular disorders have decreased respiratory muscle strength and endurance, and those with immune deficiency have a decreased host response and impaired ability to eliminate the virus.

In premature infants, the increased risk can be attributed to underdeveloped lungs, an immature immune system, and incomplete transfer of maternal antibody. Lung volume, lung weight, and alveolar diameters are all substantially reduced in infants born at 30 weeks' gestation compared with those born at full term.⁴³ When airways are smaller, the risk that a small change—such as that caused by RSV infection—will result in significant respiratory problems is increased. (Of note, the severity of RSV-associated respiratory illness in hospitalized preterm infants born between 32 and 35 weeks' gestation has been shown to be similar to that seen in those born at less than 32 weeks' gestation: length of hospital stay, risk of needing supplemental oxygen and/or ventilation, and risk of transfer to the ICU were roughly the same in both groups.⁴⁴)

Although women typically transmit antibody to their babies throughout pregnancy, the majority is transmitted at the end of gestation. Thus, a preterm infant will not receive the “full dose” of maternal antibody. **Figure 4** shows the reduced levels of postnatal IgG seen in infants born at 25 to 28 weeks' gestation and at 29 to 32 weeks' gestation compared with the levels in full-term infants.

Other factors associated with increased risk. In addition to the in-

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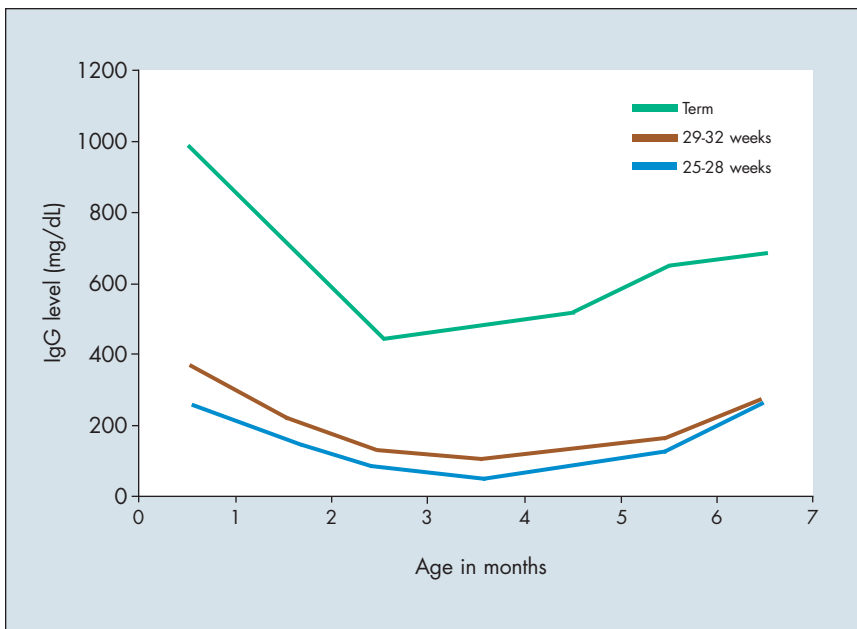


Figure 4 – Postnatal levels of IgG are significantly lower in preterm infants than in full-term infants. (Data from Ballow et al. *Pediatr Res.* 1986.⁵⁰)

creased risk of severe RSV infection seen in the 5 groups of infants listed above, a number of other factors can raise the risk still further. These include the following, which have been documented in episodic observational studies:

- Overcrowding.^{29,45}
- Use of gas rather than electricity for cooking.²⁹
- Day care attendance.⁴⁰
- School-aged siblings.⁴⁶
- Two or more children sharing a bedroom.^{23,45}
- Multiple births⁴⁵ (although this may be more a result of prematurity).
- Passive smoke exposure^{23,46} (although this is currently being debated by the American Academy of Pediatrics).
- Birth in the 6 months before the start of RSV season.³⁵

LONG-TERM IMPACT OF RSV INFECTION

RSV infection is a significant cause of morbidity among infants and young children. It also appears to be associated with increased mor-

bidity years after the at-risk period has passed. A 1999 study by Stein and colleagues,⁴⁷ published in *The Lancet*, showed that the risk of recurrent wheezing developing later in childhood was significantly greater in children who had LRTIs caused by RSV before age 3 than in children who did not have an early LRTI. In addition, it showed that the risk of wheezing later in childhood was greater in children who had an early LRTI caused by RSV than in those who had an LRTI caused by parainfluenza virus. The increased risk of wheezing was seen at ages 6, 8, 11, and 13 years.

Similar findings are seen in the work of Sigurs and colleagues.^{48,49} These researchers compared rates of wheezing and asthma in children who had been hospitalized with RSV infections in the first year of life with rates in those who had not been hospitalized. The children who had been hospitalized with an RSV infection were significantly more likely to have wheezing or asthma than were those who had not been hospitalized—and

this was true at ages 3 and 7 years as well as at age 1 year.

CONCLUSION

The disease burden of RSV infection is indeed great. RSV is the cause of significant morbidity and mortality in infants and young children—especially those born prematurely—and of ongoing morbidity in older children who have had early severe infections. However, there are a number of effective strategies physicians can use to help reduce this burden: frequent hand washing; isolation of infected patients from ill contacts; avoidance of second-hand smoke, day care, and crowds during RSV season; the cohorting of hospitalized patients with RSV infection; and passive immunoprophylaxis of high-risk infants. The second article in this supplement will discuss these and other preventive strategies at greater depth. ■

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