

Medical and Economic Impact of a Respiratory Syncytial Virus Outbreak

Michael L. Forbes, MD

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Summary

Respiratory syncytial virus (RSV) has emerged as a formidable pathogen akin to influenza, parainfluenza, and rhinovirus as causing significant life changing or life threatening infections. The most affected populations are the very young and the very old. Prophylaxis of RSV infection is safe and efficacious but the cost effectiveness of one available agent, palivizumab, is controversial.

Key Points

- Nearly all children (97.1 percent) have had at least one RSV infection episode by 24 months of age.
- RSV infection does not confer lasting immunity.
- RSV is the leading cause of hospitalization among infants in the United States.
- RSV infection can be fatal.
- Seasonal, annual outbreaks that vary in intensity occur across the country.
- South Florida, Tennessee, and Hawaii have year round infections.
- Several host factors and concomitant conditions predispose people to severe infections.
- The American Academy of Pediatrics has clinical bronchiolitis guidelines, which can be used to develop managed care policies for treatment and prophylaxis.
- Palivizumab has been shown to reduce hospitalization of children with chronic lung disease and hemodynamically significant congenital heart disease.
- The cost effectiveness of palivizumab is controversial but the data are incomplete.

RESPIRATORY SYNCYTIAL VIRUS (RSV) infection usually begins with a three-to-four day upper respiratory infection prodrome. Clinical features of RSV bronchiolitis include moderate tachypnea, low-grade fever (38° to 38.2°C), occasional otitis media, noisy tachypnea, perioral cyanosis, pallor, hypoxemic respiratory failure, and inconsolable distress. RSV-related apnea is not uncommon in vulnerable children because of immaturity of central respiratory centers and fatigue due to inefficient pulmonary mechanics.¹ In children, RSV bronchiolitis occurs in otherwise healthy infants within six months of life or those more than six months old with comorbidity. RSV infection primarily results in upper respiratory infections and sometimes lower airways disease including severe pneumonia. In vulnerable children and adults, it can be a fatal pathogen. Nearly all children (97.1 percent) have had at least one RSV infection episode by 24 months of age.²

The re-infection rate for RSV is high. About a third to three-quarters of the children followed each

year will be re-infected.² Some are in fact re-infected within the same season.² RSV infection does not confer lasting immunity.³

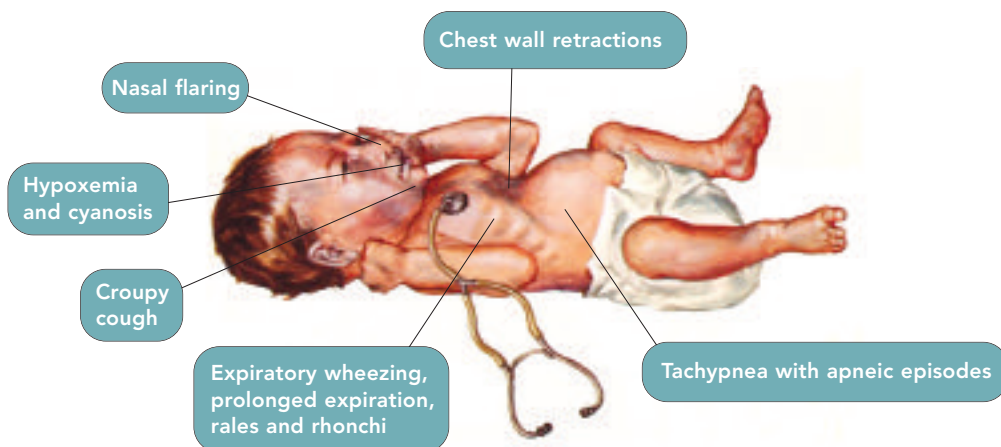
RSV is an RNA enveloped virus that is responsible for the destruction of respiratory membranes and the creation of multinucleated syncytial (Exhibit 2).⁴ Initially, infection was described in chimpanzees. It affects infants and young children worldwide, and there is a growing body of evidence that it also affects vulnerable adults as well. RSV is the leading cause of hospitalization among infants in the United States.⁵ Nearly 100,000 infants are hospitalized annually, which results in an estimated annual cost of \$300 million.

Throughout most of the United States, RSV produces an annual outbreak. These outbreaks vary in length from region to region and from season to season. Typically, the annual RSV outbreak begins in the fall and runs into spring. Year-round RSV disease has been reported in some southern states (South Florida, Tennessee, and Hawaii).⁶

Because the onset and duration of RSV seasons

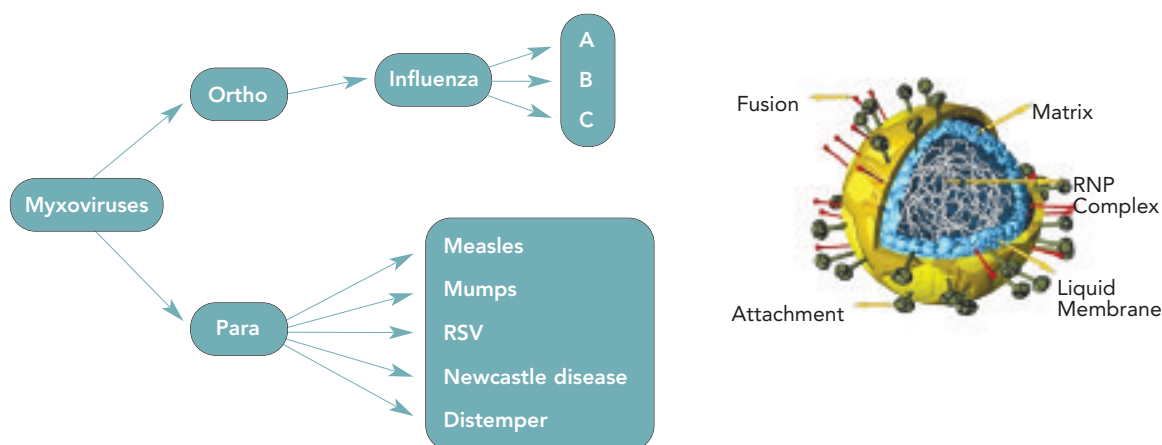
Exhibit 1: RSV Bronchiolitis: Who Gets Affected?

Usually otherwise healthy infants within 6 months of life of those >6 months old with comorbidity



(Adapted from Netter F. The Ciba Collection of Medical Illustrations. Vol. 7, Respiratory System. CIBA, 1979.)

Exhibit 2: RSV is a Member of a Common Family Mammalian Pathogens



Reference: 4

vary by year and location, local data are needed to accurately characterize the RSV season and to define timing of immunoprophylaxis.⁷ The CDC follows the RSV season trend nationally and has broken the country down into five regions (South, Midwest, Northwest, West, and Florida). Florida is carved out from the rest of the country because the RSV season begins in the middle of summer, peaks out, and almost seems to never go away. Areas of the country with year round disease pose a prophylaxis challenge for families and doctors as well as managed care managers.

A recently published ten-year study from Germany looking at year-round active surveillance found that the worst RSV seasons tend to be every other odd epidemiologic year.⁸ Thus the 07/08 season would

be worse than 08/09. In every other odd season, RSV came early and was severe.⁸ In the even years, it tended to come late and was not as severe.⁸ Similar data have been shown for the seasons in the United States.

The German study also showed that as the total number of RSV samples over time increased, the rate of positivity also increased.⁸ Thus the more samples gathered, the more data gained. It is worth identifying whether a child is really infected with RSV, rather than assuming infections are due to RSV.

The German study also found the rate of co-infection was about 12.5 percent.⁸ More than one organism infected one out of every eight children in the study. The authors suggest that maybe influenza, RSV, meta pneumoniae, and parainfluenza have enough molecular

Exhibit 3: Children at Increased Risk of Severe RSV Infection

Conditions	Pathophysiology
Premature birth	Altered airway anatomy Absence of maternal antibody
Chronic lung disease	Bronchial hyperresponsiveness Reduced lung reserve
Congenital heart disease	Pulmonary hypertension
Neuromuscular disease	Decreased respiratory muscle strength and endurance
Immune deficiency	Decreased host defense

References: 9,10

weaponry to cause disease as a single agent.⁸ Rhinovirus, adenovirus, and microplasma tend to be co-infectors but these are not the main reason for children's suffering. A population-based active surveillance, like the German study provides a much better idea of the epidemiology of these organisms.

The disease burden of RSV can be divided into two groups—acute and chronic. The acute impact includes medically attended upper and lower respiratory tract infections. It includes primary care physician visits, emergency department visits, acute hospitalizations,

ICU visits, and then mechanical ventilation.

Vulnerability to serious life-threatening or life-changing RSV infection is not universal. All patients are not all equally at risk. The very young, particularly pre-term infants, and the elderly, especially institutionalized elderly, are uniquely vulnerable to RSV. Also, there are biological elements that determine our vulnerability to RSV.

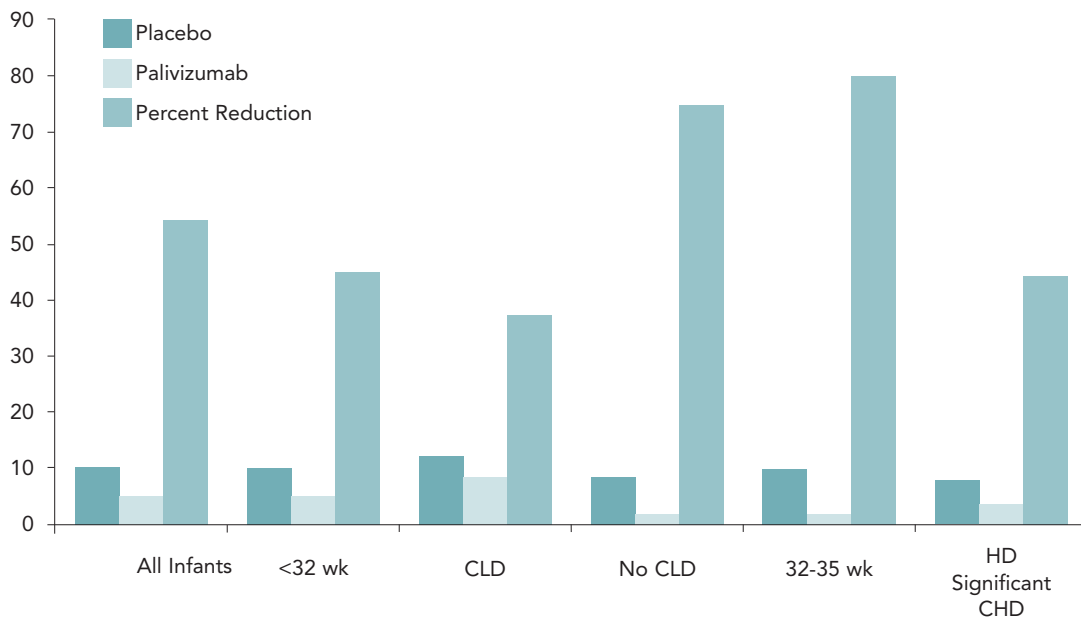
Exhibit 3 lists the conditions that predispose children to severe RSV infection.^{9,10} Pre-term infants are vulnerable because they have altered airway anatomy. They have an absence or a significant reduction of maternal antibodies. Infants with chronic lung disease are vulnerable because they have bronchial hyper-responsiveness. They also have reduced lung reserve. Children with the conditions listed in Exhibit 3 are the children who end up in the emergency room and ICU.

Several host factors that predispose children to severe RSV have been identified. These include low birth weight, in utero exposure to tobacco smoke, multiple birth, family history of wheezing or asthma, minimal breast-feeding, and young chronological age (<12 weeks) at season onset.¹¹⁻¹⁹

In the United States, there is a growing denominator of uniquely vulnerable children as younger preterm infants survive. From 1997 to 2002, RSV hospitalization rates among infants < one year of age increased by 25 percent and mean hospital charges for RSV increased by 39 percent.²⁰ Annual U.S. mortality due to RSV is estimated to be 500 infants and children.

In adults, RSV is second to influenza as a serious

Exhibit 4: Palivizumab Reduces RSV-Related Hospitalization Rates in Selected Populations



Reference: 33, 34

viral disease. Annually about 20 to 30 percent of adults will see a primary care provider, 9 percent will visit an emergency department, and 16 percent will be hospitalized for RSV.²¹ The adult mortality rate from RSV is 4 percent.²¹ It results in approximately 10,000 deaths in persons >65 each year.^{22,23}

Adults with chronic cardiac or pulmonary disease are prone to have severe RSV and have higher mortality, morbidity, and costs.^{21,24} Interestingly, persistent RSV may play a role in the progression of COPD.²⁵ RSV results in more airway inflammation and worsening pulmonary function tests in patients who are persistently positive for RSV.

The other aspect of RSV infection is the potential for chronic impact. Data suggests that once infants are infected, their lives are changed. They have higher health care utilization in the two years after initial infection.²⁶ RSV infection is associated with the later diagnosis of asthma and recurrent wheezing if a child was hospitalized for RSV when three or younger.²⁷⁻³⁰

Preventing RSV-related hospitalization appears to have long-term impact. A recently published small study showed that prophylaxis with RespiGam[®], RSV immune globulin, decreased the number of colds, asthma attacks, and school days missed over seven to 10 years.³¹ Urgent care visits and the rate of hospitalization was about the same whether kids received prophylaxis or not.

The American Academy of Pediatrics (AAP) has clinical bronchiolitis guidelines.³² These guidelines can be used to develop managed care policies for RSV treatment and prophylaxis. For acute outpatient or emergency room treatment, the guidelines recommend a carefully monitored trial of alpha- or beta-agonists. These should be discontinued if no improvement occurs. There are some children who will respond but most are non-responders. There is no evidence that a child hospitalized with RSV benefits from beta-agonist treatment. Supplemental oxygen is recommended if oxygen saturation consistently falls below 90 percent. This is stopped if oxygen saturation increases to 90 percent, if the patient is feeding again, and if they have minimal respiratory distress. As clinical improvement occurs, continuous pulse oximetry is not routinely needed. Chest physiotherapy, bronchodilators (other than alpha or beta agonists), ribavirin, nor corticosteroids should be used routinely. Antibacterial medications should be reserved for children with specific indications for the presence of bacterial infections.

The AAP guidelines state palivizumab (Synagis[™]) prophylaxis may be administered to children with chronic lung disease, a history of prematurity (<35 wks gestation) or with congenital heart disease. Five doses should be given starting in November or December. The exact schedule depends on the local RSV season.

Palivizumab, a humanized RSV monoclonal antibody, reduces hospitalization from the RSV infection in high-risk infants.³³ It also reduces hospitalization due to RSV in young children with hemodynamically significant congenital heart disease (Exhibit 4).^{33,34}

The estimated annual costs of this agent range from \$4,138 (child =3.3 kg) to \$8,401 (child 3.4 to 6.7 kg).³⁵ Because of the annual cost, cost effectiveness studies have been conducted examining RSV immunoprophylaxis with palivizumab. A retrospective Australian study concluded that RSV prophylaxis was not cost effective.³⁶ In another study, Stephens and colleagues found that giving four doses of palivizumab reduced overall drug costs by 20 percent and provided coverage for 94 percent of hospitalizations.³⁷

A United Kingdom review concluded that despite proven safety and efficacy of palivizumab, costs of administration were “far in excess of any likely savings achieved by reducing hospitalization rates”.³⁸ This review noted the probability of hospitalization would have to be > 31 percent for it to be a cost-effective alternative to no prophylaxis. The hospitalization rate for RSV is approximately 10 percent.

The experiences of Horizon/Mercy, a health care management company with about 280,000 members, including publicly insured enrollees (including Medicaid and New Jersey Family Care State Children’s Health Insurance Program), with a palivizumab prophylaxis policy has been published.^{39,40} Patients were eligible for prophylaxis if they met the AAP guidelines. The plan’s approval policy also stated it would be appropriate not to approve palivizumab if the only risk factors mentioned were considered additional risk factors (school-age siblings, multiple births, tobacco exposure, crowding at home, cyanotic congenital heart disease, history of apnea, apnea monitor, reactive airway disease, patent ductus arteriosus, GERD, or RSV last season). In the 2000 to 2001 RSV season, the plan approved 212 uses of prophylaxis and denied 79 with no RSV related hospitalizations. The plan saved \$474,000 by avoiding use in 79 patients. In the 2001 to 2002 season, 276 uses were approved and 152 were denied. Two RSV related hospitalizations occurred in the prophylaxis group and none in the denied group. This resulted in \$851,000 of avoided costs. The authors noted that their findings demonstrate that, by appropriate application of criteria for the use of palivizumab, a significant amount of money can be saved with no additional risk to the patients and no compromise in quality of care.

Cost efficacy analysis studies are moving towards incremental cost effectiveness ratios. This type of analysis tries to place a dollar value on incremental improvements in the quality of life. In the United

States, there's a wide range of what is accepted as cost effective changes in quality of life. Fifty to 200,000 U.S. dollars per year per quality adjusted life year (QALY) has been proposed as an acceptable limit. When the cost of conferring a single additional year of perfect life is more than \$50,000, decision-makers often conclude an intervention is in fact not cost effective.

Two such studies have been published examining palivizumab prophylaxis in high-risk children. One study examined the cost effectiveness of prophylaxis in preterm infants <35 weeks gestation, children with bronchopulmonary dysplasia, and children with congenital heart disease in the United Kingdom.⁴¹ The authors interpreted the asthma-RSV link hypothesis as causal to link today's dollars with asthma costs 20 years later. They concluded there was a 73 percent to 86 percent probability that the palivizumab incremental cost effectiveness ratio (ICER) was acceptable for children with prematurity or bronchopulmonary dysplasia and a 98 percent probability the palivizumab ICER was acceptable for children with hemodynamically significant congenital heart disease. They also concluded that the positive clinical and economic benefits may persist beyond one RSV season.

In a hypothetical cohort of infants born at 26 to 32 weeks gestational age, Elhassan and colleagues concluded that the ICER for palivizumab prophylaxis is not cost-effective by today's standards unless asthma-related morbidity is considered.⁴² The ICER appeared more favorable when RSV related asthma morbidity was assumed to be high.

Safety and efficacy in reducing hospitalization in studied infants is well established but palivizumab's cost efficacy remains incompletely analyzed. Overall, there is a 55 percent relative reduction ($p = 0.00004$) in RSV related hospitalizations compared to unprophylaxed controls.⁴³ Safety and efficacy of palivizumab has been established in preterm and term infants. Discontinuation due to adverse effects is rare (0.3 percent).³³ No current data has assessed the true individual or societal costs of RSV disease. The short-term reduction of impact on families is unmeasured. Additionally, the potential benefit of reduction of long term consequences (e.g. physician diagnosed asthma) of infant viral infections remains incompletely understood.⁴⁴ There is mounting evidence that suggests a link between viral infections in infancy and the development of chronic, clinically significant wheezing and physician diagnosed asthma. Mortality from RSV infection is low, even in high-risk groups. Mortality-focused cost effective analysis is, therefore, incomplete. In all the studies published to date, the cost of prophylaxis is greater than the cost savings associated with reduced hospitalization.

In addition to prophylaxis in appropriate patients, there are other important measures to decrease the

spread of RSV. Prevention of transmission of RSV in the health care setting is especially important. Hand decontamination is the most important step in preventing nosocomial spread of RSV. Alcohol-based rubs are preferred for hand decontamination. Clinicians should educate personnel and families about hand sanitation. Additionally, new mothers should be educated about the benefits of breastfeeding to reduce the likelihood of lower respiratory tract infections.

Conclusion

RSV is a significant pathogen causing predictable morbidity and mortality but not all patients are equally at risk. While a small component of the national population, vulnerable children represent a high resource use sub-group and a preventative strategy beyond hand washing and isolation is in order. Prevention begins with deliberate hand washing and minimizing exposure of the uniquely vulnerable patient. Palivizumab has been shown to reduce hospitalization of children with prematurity, chronic lung disease, and hemodynamically significant congenital heart disease. More investigation is warranted to determine the usefulness, if any, of palivizumab in kids with cardiopulmonary and/or neurological conditions that elevate their risk of hospitalization and its associated morbidity. More viral and bacteriology epidemiology data to fully assess the disease burden caused by RSV in the adult population is needed. **JMCM**

Michael L. Forbes, MD, is a board certified pediatric intensivist in the Division of Critical Care Medicine at the Children's Hospital Medical Center in Akron, OH.

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