Impact of respiratory syncytial virus in the United States

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What Is RSV?

RSV is a negative-sense, enveloped RNA virus.1 Two subgroups of RSV (A and B) have been identified, each with multiple genotypes. Both subgroups may circulate during annual RSV outbreaks; however, it has not been possible to associate either one of these subgroups with the occurrence of more severe RSV disease.2,3

Epidemiology of RSV

In addition to being the leading cause of upper and lower respiratory tract infections in infants and young children,4 RSV is the most common cause of bronchiolitis and pneumonia in children younger than one year of age.4 The peak incidence of RSV infection occurs in children aged 2–8 months,5 with over half of all children being infected with RSV by their first birthday.6 Although the majority of children develop mild upper respiratory tract disease during the initial RSV infection, the rate of RSV-associated lower respiratory tract infections appears to be increasing.7 According to the Centers for Disease Control and Prevention, between 25% and 40% of infants and young children show signs and symptoms of bronchiolitis or pneumonia during their initial RSV infection.1 Almost all children will experience at least one RSV infection by age two.6,8

Since infection with RSV does not result in permanent or lifelong immunity, reinfection is common...
and can occur throughout life. It has been found that antibody response to RSV is not sufficient to prevent subsequent reinfection. Repeat infections may occur during the same RSV season. Results of the Houston Family Study showed that reinfection rates varied between 50% for children age five and 75.9% in children in their second year of life. Similar rates of reinfection were observed in a later study, with results showing that 73% of patients were reinfected at least once during the 26 months following the first infection. In this study, 50% of children experienced three or more infections. Reinfections tended to be mild in normally healthy individuals.

**RSV-associated hospitalization.** Approximately 75,000–125,000 hospitalizations associated with RSV occur in the United States each year, and the majority of children hospitalized are under age six months. RSV bronchiolitis is the leading cause of hospitalization in children younger than one (Figure 1). RSV infection results in two to three times more pediatric hospitalizations compared with metapneumovirus, influenza virus, and parainfluenza virus. Results of two studies showed that the typical length of stay (LOS) for pediatric patients hospitalized due to RSV is three days. It had been found that risk factors for more severe disease were associated with significantly longer LOS in the hospital and pediatric intensive care unit (ICU) (Table 1).

Complications are common in infants hospitalized for RSV-associated bronchiolitis and pneumonia. In a study looking at the occurrence of complications in infants age one or younger who were hospitalized for bronchiolitis or pneumonia, 79% of infants had at least one complication, with 24% experiencing a serious complication. Complications associated with hospitalization for RSV included respiratory problems (60%), infectious complications (41%), electrolyte imbalance (19%), and cardiovascular problems (9%). Rates of complications were higher in infants with congenital heart disease (93%), other congenital abnormalities (90%), and former premature infants (87%) compared to those without risk factors (76%) for more severe disease. The presence of any complication was associated with a longer LOS in the hospital or pediatric ICU. Compared to infants with no complications, those with minor complications had a slightly longer average LOS in the hospital (1 day; p < 0.0001) and pediatric ICU (0.8 days; p = 0.016). A significantly longer LOS in the hospital (7.3 days; p < 0.0001) or pediatric ICU (6.5 days; p < 0.0001) was observed in infants with major complications compared to those with no complications.

**Mortality associated with RSV.** Although mortality from RSV has decreased over the last 20 years, RSV is still the leading cause of viral deaths in infants. The mortality associated with RSV infection is almost 10 times that of influenza in children less than one year of age. Approximately 500 deaths due to RSV occur annually in the U.S., with 80% of these deaths occurring in children younger than one (Figure 2).

**Long-term health consequences of RSV**

In addition to the immediate ef-
fects of infection, RSV is associated with an increased risk of respiratory complications in older children. Sigurs and colleagues\textsuperscript{16} looked at the long-term impact of RSV lower respiratory tract infections in a cohort of children who were hospitalized for RSV bronchiolitis during the first year of life. A higher frequency of wheezing disorder, clinical allergy, and allergic sensitization up to age seven was observed in the RSV bronchiolitis group compared with matched controls. It was hypothesized that these differences would continue, and another study\textsuperscript{17} demonstrated similar results up to age 13. In this study, the risk of wheezing was significantly higher at 13 years in the RSV bronchiolitis group compared with controls ($p < 0.001$). The authors concluded that severe RSV bronchiolitis in early infancy is a strong risk factor for the occurrence of allergic asthma in early adolescence. Another study\textsuperscript{18} found that RSV hospitalization in healthy pre-term infants (32–35 weeks gestational age) is associated with a significant increase in subsequent healthcare resource utilization such as hospitalization, in-hospital procedures, outpatients visits, respiratory therapy visits, special care unit visits, and physician consults.

**Economic impact of pediatric RSV infections**

RSV is a major cause of morbidity and mortality among infants and young children, resulting in substantial economic burden. Numerous studies have looked at the direct costs of RSV-related illnesses. In a 1998 study, the costs associated with one RSV hospital admission varied from $2025 to $166,375, with a mean cost of approximately $27,101.\textsuperscript{19} A later study looking at the annual costs of RSV found that RSV-associated hospitalizations totaled more than $1.1 billion.\textsuperscript{20} In addition to the considerable direct medical costs associated with hospitalization of infants infected with RSV, indirect costs place significant economic burden on the families of these children, in terms of out-of-pocket expenses. A study by Leader and colleagues\textsuperscript{21} quantified out-of-pocket costs associated with confirmed RSV hospitalization of infants who had not received RSV prophylaxis. The average out-of-pocket expenses totaled $214 for full-term infants and $644 for pre-term infants (born at 33–35 weeks gestational age).

Per admission, the total average economic burden was $2135 for full-term infants and $4517 for pre-term infants, which included the value of lost productivity. Results from this study\textsuperscript{22} showed that prematurity, which has been identified as a risk factor for severe disease, is associated with higher indirect costs. Similar results were observed in another study\textsuperscript{13} in relation to direct medical costs. The costs associated with hospital resource use were $3777 for infants with no risk factors; $7376 for premature infants; $11,335 for infants with congenital heart disease; and $13,241 for those with other congenital abnormalities. Compared to infants with no risk factors, the costs associated with those with risk factors for severe disease were significantly higher ($p < 0.0001$). Additionally, this study showed that the presence of any complication was associated with a significant increase in hospital resource use and costs: $3078 for infants with no complications versus $4899 for infants with any complication ($p < 0.0001$).

**RSV in adults**

Since lifelong immunity does not occur with RSV infection during childhood, this virus is also an important pathogen in adults, particularly in patients with impaired immunity and the elderly. The data
regarding RSV-associated disease burden are increasing. RSV infection in adults characteristically results in mild-to-moderate upper respiratory tract illness. One study found that 10–22% of adults visiting their primary care physician with respiratory symptoms were diagnosed with RSV positivity. In addition, RSV is being increasingly recognized as a cause of pneumonia, as well as exacerbations of cardiac disease and chronic pulmonary disease in adults.

Assessing the economic burden of RSV in the elderly, if approximately 2–9% of hospitalizations for pneumonia are caused by RSV infections, the estimated cost per hospitalization is $11,000, with an estimated annual cost of $150–$680 million.

Conclusion

RSV infection is associated with significant disease burden in infants and young children in terms of hospitalization, related complications, and even morbidity. RSV is also associated with an increased risk of respiratory complications in older children, and has been recognized as an important cause of pneumonia and exacerbations of chronic pulmonary disease in adults. The economic burden resulting from RSV disease is also substantial, with significantly higher costs seen in children with risk factors for severe disease and RSV-related complications, which increase hospital resource use.

References


