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EDITORIAL

# Burden of respiratory syncytial virus infection in young children

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## Abstract

Respiratory syncytial virus (RSV) is the most frequent and important cause of lower respiratory tract infection in infants and children. It is a seasonal virus, with peak rates of infection occurring annually in the cold season in temperate climates, and in the rainy season, as temperatures fall, in tropical climates. High risk groups for severe RSV disease include infants below six mo of age, premature infants with or without chronic lung disease, infants with hemodynamically significant congenital heart disease, infants with immunodeficiency or cystic fibrosis, and infants with neuromuscular diseases. Mortality rates associated with RSV infection are generally low in previous healthy infants (below 1%), but increase significantly in children with underlying chronic conditions and comorbidities. Following early RSV lower respiratory tract infection, some patients experience recurrent episodes of wheezing mimicking early childhood asthma with persistence of lung function abnormalities until adolescence. There is currently no RSV vaccine available, but promising candidate vaccines are in development. Palivizumab, a monoclonal RSV antibody that is the only tool for immunoprophylaxis in high-risk infants, lowers the burden of RSV infection in certain carefully selected patient groups.



**Key words:** Children; Epidemiology; Infant; Palivizumab; Respiratory syncytial virus; Respiratory tract infection; Risk factors; Vaccine

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## INTRODUCTION

Respiratory syncytial virus (RSV) is the most frequent and important cause of lower respiratory tract infection in infants and children. Fifty to 90% of hospitalizations for bronchiolitis, 5% to 40% of those for pneumonia, and 10% to 30% of those for tracheobronchitis are caused by RSV[1]. Substantial increases in the number of admissions for RSV bronchiolitis (up to 126 300 hospitalizations and 500 deaths annually) have been documented in North America[2]. In Canada, inpatient care of RSV illness costs $18 million US dollars annually, accounting for 62% of the total cost of this disease[1]. The magnitude of the costs is understandable, because virtually all children become

infected with RSV within two years after birth, and one percent requires hospitalization[3].

## RISK FACTORS AND PATIENTS' GROUPS AT HIGH RISK FOR SEVERE RSV INFECTION

High risk groups for severe RSV disease include infants below six mo of age, premature infants with or without chronic lung disease [bronchopulmonary dysplasia- (BPD)], infants with hemodynamically significant congenital heart disease (CHD), infants with immunodeficiency or cystic fibrosis, and infants with neuromuscular diseases[4-6]. There is no particular age-group that is not at risk for RSV infection, but certain risk factors have been implicated in more severe disease: low socioeconomic status, crowded living conditions, indoor smoke pollution, a family history of asthma or atopy, and, perhaps, infection with the A subgroup of RSV[4]. Preterm infants with or without BPD and infants with CHD are known to be at increased risk for hospitalization, including admission to an intensive care unit, ventilatory support, or prolonged supplemental oxygen[7-9].

## EPIDEMIOLOGY OF RSV INFECTIONS

The year-to-year and seasonal variations in RSV activity are key aspects of RSV epidemiology. RSV is a seasonal virus, with peak rates of infection occurring annually in the cold season in temperate climates, and in the rainy season, as temperatures fall, in tropical climates[4]. In Europe, RSV related re-hospitalizations of preterm infants show a seasonal distribution mainly during the winter and spring months, from October to May, and peaking between December/January and March[10].

## MORTALITY AND CASE-FATALITY RATES IN INFANTS AND CHILDREN ASSOCIATED WITH RSV INFECTION

Mortality rates associated with RSV infection are generally low in previous healthy infants (below 1%), but increase significantly in children with BPD and CHD. Navas *et al*[11] noted a three times higher rate in children with cardiac (3.4%) and lung disease (3.5%), and an increased rate in the CHD subgroup with pulmonary hypertension (9.4%). MacDonald *et al*[12] reported an even higher mortality rate associated with CHD (37%): up to 73% in infants with CHD and pulmonary hypertension. Despite a significant decrease in mortality over the last decades, pulmonary hypertension remains a significant risk factor for morbidity and mortality in these patients[13]. Sampalis[14] reported an increased mortality rate of 8.1% in a cohort of 2415 preterm infants of 32 to 35 wk gestational age hospitalized for RSV infection, compared with a rate of 1.6% in 20 254 matched controls. Another smaller study[15] including 135 children ventilated mechanically due to bronchiolitis, demonstrated a comparable high mortality rate of 8.9% in preterm infants (four of 45 infants). Recently, case-fatality rates related to RSV infection have been systematically summarized, which included 36 studies, and are depicted in Table 1 categorized by comorbidities[16].

**Table 1 Rates of respiratory syncytial virus-related case-fatality by comorbidity[16]**

| Comorbidity | RSV case-fatality rate range (%) |
|---|---|
| Chronic lung disease | 3.5-23 |
| Congenital heart disease | 2-37 |
| Premature infants (≤ 36 wk of gestational age) | 0-6.1 |
| Nosocomial RSV infection | 0-12.2 |
| Intensive care support | 1.1 -33 |
| No comorbidity or risk factors | < 1 |
| Mixed population or undefined risk factors | 0-5.9 |

RSV: Respiratory syncytial virus.

## BURDEN OF RSV DISEASE

In 2005, a WHO founded meta-analysis estimated that 33.8 (95%CI: 19.3-46.2) million new episodes of RSV-associated acute lower respiratory tract infections occurred worldwide in children younger than 5 years (22% of all respiratory tract episodes), with at least 3.4 (2.8-4.3) million episodes representing severe RSV-associated respiratory tract infections necessitating hospital admission. The authors[17] estimated that 66 000-199 000 children younger than 5 years died from RSV associated respiratory tract infection in 2005, with 99% of these deaths occurring in developing countries. Incidence and mortality might vary substantially from year to year in any one setting. Reflecting these data, RSV is the most common cause of childhood acute lower respiratory tract infections and a major cause of admission to hospital because of severe respiratory tract infection. Mortality data suggest that RSV is an important cause of death in childhood from acute lower respiratory tract infections, after pneumococcal pneumonia and *Haemophilus influenzae* type b. The authors[17] concluded that the development of novel prevention and treatment strategies should be accelerated as a priority.

## POST- RSV WHEEZING DISORDER

Another phenomenon following early RSV lower respiratory tract infection is recurrent episodes of wheezing mimicking early childhood asthma during childhood. The prevalence of respiratory symptoms appears to diminish over the first years of life[18], but recent studies observed either reactive airway disease[19] or lung function abnormality[20] persisting until adolescence.

## RSV VACCINE

There is currently no RSV vaccine available. In the 1960s,

a formalin-inactivated RSV (FI-RSV) vaccine trial led to exacerbated disease upon natural infection of immunized children, including two deaths. The causes involved in the disastrous results of these vaccine trials are still unclear, but they remain the engine for searching new avenues to develop a safe vaccine that can provide long-term protection against this important pathogen[21]. A recent report from the Seventh International RSV symposium held in Rotterdam, the Netherlands, from December 2-5, 2010 and published in Vaccine[21] summarized the most recent activities in the field of RSV vaccine trials. Two vaccination approaches, a live attenuated recombinant RSV and bivalent vectored RSV/HPIV3, and one promising recombinant virus (MedImmune: Medi-559: A2cp248/404/1030SH), containing a set of five mutations from biological viruses, are currently being tested in infants of 1-3 mo of age. New recombinant virus candidates are being developed lacking non-essential RSV genes (NS1, M2-2). PIV3-vectored vaccines containing the RSV F and/or G genes are also in development. A different approach, using a Sendai virus (SeV)-based RSV vaccine, was presented from the St. Jude's Children's Research Hospital, Memphis, United States. The SeV platform is being developed for hPIV1 and a combination of hPIV1 and RSV. SeV parent virus proved to be well tolerated in adults and children. An SeV-RSV-F recombinant vaccine induced neutralizing antibodies against several A and B virus isolates and conferred long-term protection against RSV challenge in cotton rats. A virosomal RSV vaccine candidate containing the reconstituted viral envelope with or without a co-incorporated TLR-2 ligand Pam3CSK4 was successfully tested in cotton rats. Another approach employing gene-based replication-defective vaccine vectors induced responses strongly increasing the potency of antibody-mediated protection. Heterologous rAd-(RSV)-F vaccinations improved the neutralizing antibody response in mice and rhesus monkey models. A single Ad5-F vaccination conferred long-term protection on cotton rats against RSV. Venezuelan equine encephalitis virus (VEE) is a positive stranded RNA virus that infects rodents, horses and humans. The VEE replicon vaccine is based on a non-replicating particle with additional attenuating mutations in envelope viral proteins that induces high antigen expression levels from self replicating RNA. The vaccine induces high humoral, mucosal and T cell responses and has good potential as a vaccine, as shown by a successful phase I trial for CMV.

A safe and efficacious vaccine for RSV will require "re-education" of the host immune response against RSV to prevent vaccine-enhanced or severe RSV disease[22].

## PALIVIZUMAB FOR RSV PROPHYLAXIS

In 1997, a humanized murine monoclonal antibody was developed and called palivizumab. Palivizumab recognizes a conserved neutralizing epitope at the "A" region on the F glycoprotein of RSV[23]. RSV isolates were collected at eight US sites from 458 infants hospitalized for RSV disease (1998-2002), and palivizumab bound to all 371 evaluable RSV isolates, including 25 from active-palivizumab recipients. Thus, the epitope appeared to be highly conserved, even in infants receiving prophylaxis with palivizumab[24]. Effects of palivizumab on viral load have been demonstrated in nasal[25] and tracheal aspirates[26] in premature infants below 2 years of age. A phase Ⅰ/Ⅱ study of the safety, tolerance, immunogenicity and pharmacokinetics of repeat intravenous doses of palivizumab in premature infants (≤ 35 wk of gestation, ≤ 6 mo of age) and infants with BPD (≤ 24 mo of age) successfully tested palivizumab in 62 participants receiving 3, 10 or 15 mg/kg palivizumab or 0.9% saline as placebo every 30 d for up to five doses[27]. With repeated dosing every 30 d, the mean trough concentrations were maintained above 40 μg/mL (the dose found to be protective against RSV in the cotton rat model) for the 15 mg/kg palivizumab dose group.

In a randomized, placebo controlled (palivizumab: placebo = 2:1), double-blind, multicenter phase Ⅲ trial including 139 centers in the United States, Canada, and the United Kingdom, 1,502 children with history of prematurity (≤ 35 wk of gestation, ≤ 6 mo of age) or BPD (≤ 24 mo of age, requiring medical treatment within the past 6 mo for their chronic lung disease) were included during the 1996 to 1997 RSV season to receive 5 monthly (every 30 d) injections of either 15 mg/kg palivizumab or an equivalent volume of placebo intramuscularly[28]. Children were followed for 150 d for the primary endpoint hospitalization due to RSV infection. Ninety-nine percent of the children in both groups completed the study protocol and 93% received all five scheduled injections. Palivizumab prophylaxis resulted in an overall 55% reduction in hospitalization as a result of RSV infection.

An RSV vaccine is not in sight; therefore, palivizumab will continue to be used in high-risk infants. Guidelines for the use of palivizumab have been developed by each country on the basis of the recommendations of the American Academy of Pediatrics[29]. In cases of neuromuscular disease, immune deficiency syndromes, cystic fibrosis and other chronic pulmonary diseases of infancy, evidence of severe courses of RSV disease has been observed but studies on the prophylactic use of palivizumab are still pending for these indications. A new MEDI-524 monoclonal antibody (motavizumab) demonstrated a significantly higher binding to RSV by microneutralization test *in vitro*, a significant reduction of RSV titers in the cotton rat model, and, when given 24 h before RSV inoculation, significantly decreased lung RSV RNA loads at 5 and 28 d after RSV inoculation in mice[30,31]. Results of a large head-to-head randomized, clinical trial of palivizumab *vs* motavizumab in high risk infants showed that motavizumab demonstrated noninferiority in the primary end point, with a 26% relative reduction of RSV hospitalizations compared with palivizumab, and superior efficacy in the secondary endpoint, with a 50% relative reduction of RSV-specific lower respiratory tract infection requiring medical outpatient treatment[32].

## PHARMACOECONOMIC EVALUATIONS OF PALIVIZUMAB

Using the tool of quality-adjusted life years (QALY), pharmacoeconomic analyses from our RSV study group suggest that palivizumab is cost-effective for prophylaxis in high-risk infants compared with no prophylaxis[10,33]. Using this economic model, country-specific cost-effectiveness analyses can provide helpful information for health insurance companies. A comparison to costs per QALY of other medical treatments and interventions might be useful. The threshold costs per QALY depend on the health care system of each country and cannot be generalized as $50 000. Undoubtedly, the costs of palivizumab are high, but RSV-related health care costs and the costs of neonatal intensive care medicine in this particular high-risk population are no less high.

## CONCLUSION

Until the widespread delivery of an effective RSV vaccine, measures such as promotion of health-service use, provision of regular oxygen supplies at health centres and hospitals, and immunoprophylaxis with monoclonal antibodies (when appropriate and affordable) can be expected to substantially reduce morbidity and mortality associated with RSV disease[17].

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