



COMMENTARY

The Role of Immunoprophylaxis in the Reduction of Disease Attributable to Respiratory Syncytial Virus

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Respiratory syncytial virus (RSV) is an RNA virus that infects human respiratory epithelial cells and causes annual outbreaks of respiratory tract disease among infants and young children as well as recurrent infections throughout life. Annual outbreaks of RSV disease are attributable to first-time infection in susceptible infants, to reinfection in children and adults with waning or incomplete immunity, and to infection by viral genotypes with sufficient antigenic variation to avoid innate and acquired immunity. In industrialized countries, few infectious diseases have a greater effect on the health of young children than does lower respiratory tract disease caused by RSV. By 2 years of age, almost all children will experience an RSV infection and approximately 50% will be infected twice.¹ Results from the New Vaccine Surveillance Network (a Centers for Disease Control and Prevention (CDC)-sponsored prospective, population-based surveillance program) define the burden of RSV disease in children less than 5 years of age.² An estimated 2 million children require medical care because of RSV infection, and approximately 57 500 children younger than 5 years are hospitalized annually. The major

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burden of RSV disease occurs among previously healthy infants and children whose susceptibility to severe RSV illness cannot be predicted through the use of risk factors.

Protection against RSV infection is mediated by serum antibody, secretory antibody, cytotoxic T lymphocytes, and innate immune responses. A vaccine offers the greatest promise for control of RSV disease, but vaccine development has been slowed by concerns about safety (enhancement of naturally occurring disease), the limited ability of infants to mount an immune response to RSV glycoprotein antigens, and the presence of maternal neutralizing antibody, which may attenuate an active immune response. Passive immunization with either a hyperimmune globulin or a monoclonal antibody preparation has been demonstrated in randomized, placebo-controlled trials to reduce the risk of hospitalization caused by RSV.³⁻⁷ The annual rate of hospitalization attributable to RSV infection among young infants in selected high-risk groups who do not receive immunoprophylaxis is approximately 10% to 15%, which is approximately 5 times higher than the hospitalization rate among non-high-risk infants.³⁻⁷ Results from 2 randomized, placebo-controlled trials involving 2789 infants and children with prematurity, chronic lung disease, or congenital heart disease who received palivizumab prophylaxis demonstrate a reduction in RSV hospitalization rates of between 39% and 78% in different groups.^{6,7}

Decisions regarding use of a medical intervention should include consideration of both benefit and cost and recognize that dollars spent on one intervention will not be available for other important interventions. A single dose of palivizumab costs about as much as the total cost of all vaccines received by one child from birth through 18 years of age. The revised recommendations for use of palivizumab presented in the 2009 American Academy of Pediatrics (AAP) policy statement are designed to balance both benefit and cost of this expensive

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intervention.⁸ A number of economic analyses of palivizumab prophylaxis have been published.⁹⁻¹⁴ Results demonstrate that the increased cost associated with palivizumab prophylaxis far exceeds the cost savings from reduced hospitalizations. No effect on subsequent reactive airway disease or asthma rates has been demonstrated from palivizumab prophylaxis in a prospective, randomized trial. Even when a possible effect on quality of life is considered in the cost analysis, cost savings from a reduction in asthma cannot be demonstrated.¹³ The increase in cost associated with palivizumab use is not offset by a reduction in mortality rates, because neither of the 2 clinical trials with palivizumab (and none of the 3 trials with RSV hyperimmune globulin) demonstrated a statistically significant reduction in mortality rates.³⁻⁷

In the IMpact-RSV trial, the number needed to treat with palivizumab to prevent one hospitalization among infants in the 32 to 35 weeks' gestational age group without chronic lung disease based on a 78% reduction (8.1% versus 1.8%, placebo versus active drug) in hospitalization was 15.9.^{6,15} Thus, the cost of prophylaxis to prevent one RSV hospitalization in this gestational age cohort was approximately \$95 000 (\$6000 cost of prophylaxis per infant per season x 15.9 infants).¹⁵ The cost saving per RSV hospitalization avoided typically is less than \$10 000, meaning the net cost of preventing one RSV hospitalization was approximately \$85 000.¹⁵ This is a crude figure, because it does not include additional costs, such as administration fees or drug wastage. It also does not include additional potential savings such as a reduction in outpatient visits or avoidance of indirect costs associated with hospitalization. Nonetheless, the overriding conclusion is that palivizumab prophylaxis results in a substantial increase in cost, a very small increase in quality adjusted life-years as a result of decreased hospitalizations, and no reduction in mortality. No national guidelines have been established to

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determine a value for prevention of one RSV hospitalization, but the cost of palivizumab prophylaxis is high relative to the benefit derived.

Given the large number of infants who require prophylaxis to prevent one hospitalization, it would be desirable to identify infants most likely to experience severe RSV disease. The ability to target prophylaxis at infants who are at greatest risk of intensive care admission or need for mechanical ventilation or prolonged hospitalization would represent optimal use of this intervention. Unfortunately, published studies do not enable identification of those infants at greatest risk of increased morbidity or mortality. Although numerous risk factors for hospitalization have been identified, such factors either are found inconsistently or have a minimal effect on the risk of hospitalization (less than two- to fourfold).¹⁶⁻²³ Because of this uncertainty, other countries, including Canada, rarely recommend palivizumab prophylaxis for infants born in the 32 to 35 weeks' gestational age category.

In an effort to simplify the guidelines and to optimize prophylaxis for infants in the 32 weeks, 0 days' through 34 weeks, 6 days' gestational age cohort, the 2009 AAP recommendations have been broadened to include a larger number of infants during the period of greatest risk. The most consistently identified risk factor for RSV hospitalization among infants is chronologic age less than 90 days.¹⁶⁻²³ Once a child exceeds 90 days of age, the risk of RSV hospitalization declines. Using the 2009 AAP recommendations, infants born 3 months before or during the RSV season require only 1 of 2 epidemiologic factors to qualify for prophylaxis:

1. presence of an older sibling or child younger than 5 years living in the same household; or
2. attendance at child care.

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Among published studies, these are the 2 most consistently identified risk factors for acquisition of RSV infection by preterm infants. The greatest cost benefit from palivizumab prophylaxis will occur during the period of greatest risk of hospitalization, and the least cost benefit will occur when the risk of hospitalization is lowest. Thus, current recommendations are directed at identifying infants who are most likely to acquire an RSV infection during the time period when the risk of hospitalization is greatest.

Prophylaxis continues to be recommended in some cases in which supporting evidence is limited and the benefit of prophylaxis may be modest. It is hoped that additional data will become available to assist in revising future guidelines for the following:

- Efficacy of prophylaxis during a second RSV season (the number needed to treat to prevent one hospitalization is likely be high);
- Continued prophylaxis after an infant is hospitalized with a breakthrough RSV infection (second RSV hospitalizations in the same year are rare);
- Evidence of benefit in immunocompromised infants (solid organ or hematopoietic stem cell transplant recipients, HIV-infected infants, and children with other primary or secondary immune deficiencies); and
- Evidence demonstrating that avoidance of RSV infection with palivizumab prophylaxis in cystic fibrosis patients prevents deterioration of pulmonary function.

The package insert for palivizumab states that “Synagis is indicated for prevention of serious lower respiratory tract disease caused by RSV in pediatric patients at high risk of RSV disease” and states that “infants should continue to receive monthly doses throughout the RSV season.”²⁴ This statement is based on the design of the IMPact-RSV trial. In an attempt to maximize benefit and minimize cost, recommendations from the AAP, starting with the initial

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recommendation published in November 1998, have urged use of palivizumab prophylaxis in a fashion that is more restrictive than what is proposed in the package insert. Differences between licensure of a product by the Food and Drug Administration and recommendations from the AAP and CDC for use of a product have occurred in the past, as demonstrated by 2 recent examples. The conjugated meningococcal vaccine (MCV4) is licensed by the FDA for use in children starting at 2 years of age. However, both the AAP and CDC do not recommend routine use of this vaccine before 11 years of age on the basis of considerations of epidemiology of disease, vaccine effectiveness, safety, and cost benefit.²⁵ The recent change in recommendations for postexposure prophylaxis following a suspected rabies exposure by the AAP and the CDC from 5 doses to 4 doses of rabies vaccine, despite the FDA licensure for 5 doses as stated in the package insert, represents another example of a recommendation that differs from the package insert.²⁶ A package insert reflects the inclusion and exclusion criteria used in the clinical trial data submitted by the manufacturer to the FDA. The indications in the package insert do not represent a recommendation by the FDA.

The most recent 2009 AAP recommendations for RSV prophylaxis continue to strive to reach the objective of maximal benefit at minimal cost and to provide pediatricians with reasonable recommendations for use. Hopefully, additional data will be published in the peer-reviewed literature that will enable further clarification of the most appropriate use of this compound as well as the anticipated second-generation product currently under review by the FDA.²⁷

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