Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract infection (LRTI) in infants and young children, accounting for upwards of 130,000 hospitalizations per year in children <5 years of age in the United States. Globally, RSV is responsible for an estimated 3.4 million hospitalizations per year in children <5 years of age. Although all infants are at risk for severe RSV LRTI, increased risk has been demonstrated in preterm infants aged <6 months and those with other health conditions, such as chronic lung disease of prematurity and hemodynamically significant congenital heart disease. On the basis of the demonstration of decreased RSV hospitalizations in these groups in which the anti-RSV monoclonal antibody palivizumab was administered during RSV season compared with placebo, they have been the primary target for RSV immunoprophylaxis (IP) with palivizumab since its US Food and Drug Administration approval in 1998, although even 20 years after its licensure optimal indications for palivizumab remain uncertain for these infants. In small studies, researchers have additionally suggested possible long-term benefits of RSV immunoprophylaxis in decreasing subsequent wheezing episodes, but this observation is far from conclusive and is not presently part of the consideration for RSV immunoprophylaxis.

Other smaller groups of infants and children are also likely at increased risk for severe RSV disease, including those with cystic fibrosis (CF). Using the CF Foundation Patient Registry, Somayaji et al recently provided evidence supporting a significant association between pulmonary exacerbations and RSV infection in children with CF. Because of lower numbers of such children, large prospective placebo-controlled trials of RSV immunoprophylaxis in infants and children with CF are lacking. On the basis of the concern for severe disease in this group, however, current American Academy of Pediatric guidelines recommend RSV immunoprophylaxis for infants with CF in the first year of life with evidence of chronic lung disease and/or nutritional compromise and for those <24 months of age with evidence of severe pulmonary disease and/or weight-for-length <10th percentile.

In this issue of Pediatrics, Fink et al used the CF Foundation Patient Registry to assess the potential longer-term impact of RSV immunoprophylaxis administered to infants and children with CF in the first 2 years of life compared with infants not receiving prophylaxis in a retrospective analysis of data from 2008 to 2016. They were unable to demonstrate differences in (1) annualized forced expiratory volume in 1 second percentage predicted during the year they turned seven, (2) time to first positive Pseudomonas aeruginosa...
culture result, or (3) age-specific number of pulmonary exacerbation hospitalizations or other pulmonary complications over the first 7 years of life. As the authors note, there are limitations to the analyses on the basis of incomplete data and exclusion of cases. Additionally, the possible short-term benefits of RSV immunoprophylaxis were not addressed in their analyses. Larger numbers of cases with stratification by age at receipt of palivizumab (especially <6 months of age at onset of receipt of palivizumab) might also be necessary to detect benefit.

Fortunately, recent developments in RSV research offer promise for improved prevention and treatment of severe RSV infection for all infants, including such high-risk groups in the foreseeable future. Recognition of the potent immunogenicity of the RSV prefusion protein and identification of a highly neutralization-sensitive epitope (antigenic site θ) as well as other targets for potent neutralizing antibodies has led to a surge in development of RSV vaccine candidates. Presently, there are ~60 vaccine candidates in preclinical and clinical trials, including a number in Phase 2 to 3 clinical trials. Additionally, a monoclonal antibody targeting this antigenic site θ and modified at the fragment crystallizable (Fc) receptor to provide a half-life of 4 to 5 months, which could enable prophylaxis with a single dose for the RSV season, is also leading to development of a number of antiviral agents for potential treatment of RSV infection. Such advances should not only lead to a decrease in the morbidity of RSV disease but also provide tools for better understanding of the short-term and long-term impacts of RSV LRTI in different at-risk populations.

**ABBREVIATIONS**

CF: cystic fibrosis  
LRTI: lower respiratory tract infection  
RSV: respiratory syncytial virus

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Respiratory Syncytial Virus Immunoprophylaxis: Issues in Short-term and Longer-term Impact
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