Respiratory Syncytial Virus

Preventing Respiratory Syncytial Virus Infection—Where Is the Vaccine?

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Since 2005, several new vaccines have been approved by the US Food and Drug Administration (FDA). These additions to the universal childhood immunization schedule now include vaccines to protect against rotavirus gastroenteritis, human papillomavirus infection, meningococcal infection, and pertussis in adolescents and adults. While the individual and public health benefits of these efforts are proven, intuitive, and progressive, healthcare providers are left wondering why we still do not have a safe and effective respiratory syncytial virus (RSV) vaccine. RSV disease is a prime target for vaccine development because RSV infection is ubiquitous. Nearly all affected children are infected before their second birthday, and between 1 and 3% will require hospitalization. The primary risk factors for the development of serious RSV infection include prematurity, chronic lung disease, and hemodynamically significant congenital heart disease. Secondary risk factors include low birthweight, multiple gestations (twins, etc.), young siblings in the same household, day-care attendance, and male gender. Term infants born with low cord blood RSV-neutralizing antibody titters are known to develop RSV infection earlier in life, presumably due to the lack of protective maternally transmitted antibodies.

RSV bronchiolitis is the single most common reason for infant hospitalization in the US with approximately 126,000 RSV-related admissions and 500 deaths annually, costing our healthcare system in excess of $1 billion. Hospitalization is necessary for infants who develop hypoxemia secondary to lower respiratory tract RSV infection. Young infants are also prone to develop RSV-associated periodic breathing and apnea. Even when hospitalized, care is supportive as highly effective treatment interventions have yet to be identified. While infants with risk factors for serious RSV infection can be followed, and in many cases identified to receive RSV prophylaxis, many of the infant hospitalizations still occur in previously healthy term infants. Preventing RSV infection with a safe and effective vaccine would reduce infant morbidity and mortality and save healthcare dollars.

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What is being done to prevent RSV disease in 2007? Can we expect to add an RSV vaccine to our universal infant immunization schedule? Despite decades of intense research, a safe and effective RSV vaccine that can be given to young infants has remained elusive. Perhaps the single most important concern is that vaccination may exacerbate naturally occurring RSV infections, a phenomenon witnessed when an inactivated RSV vaccine was administered in clinical trials during the 1960s. A second major obstacle to the development of an effective vaccine is that RSV infection itself, even in its most severe form, elicits only incomplete immunoprotection. A true surrogate of immunity simply does not exist. Moreover, a successful RSV vaccine will need to protect against the two divergent RSV groups: A and B.

A Success Story

The first attempt at preventing RSV disease using a passive immunization strategy was the use of a polyclonal antibody preparation called RSV-immunoglobulin intravenous (IGIV), marketed as RespiGam™. RSV-IGIV is derived from plasma obtained from selected human donors with high-titer anti-RSV neutralizing activity. Although effective at reducing the rate of severe RSV disease in some high-risk infants, a major disadvantage was the need to administer the product as large-volume infusions. A landmark study showed that RSV-IGIV was effective in preventing RSV hospitalizations and serious disease in premature infants with or without chronic lung disease of prematurity, but a similar study carried out in infants with congenital heart disease found no evidence to support RSV-IGIV as safe in that high-risk population. With advances in neutralizing monoclonal antibody technology, the production of the polyclonal RespiGam product was halted, and it is no longer commercially available.

The successful development and implementation of palivizumab (Synagis®), a humanized monoclonal antibody that recognizes an RSV F-protein epitope, offered significant advantages over RSV-IGIV. Palivizumab can be administered at one-fiftieth the dose of RSV-IGIV (15mg/kg) as monthly intramuscular injections instead of intravenous infusions. Palivizumab reduces RSV hospitalizations by 55% in premature infants with or without chronic lung disease of prematurity, and by 45% in children with hemodynamically significant heart disease. High-risk infants who receive monthly injections of palivizumab during the RSV season are less likely to develop serious RSV infection, but there remains room for improvement. First, breakthrough infection is known to occur. Second, not all high-risk infants receive prophylaxis. Third, the time from neonatal intensive care unit discharge of a high-risk infant to receipt of the first dose, even during the RSV season, is on average 28 days. Finally, as the product is a monoclonal antibody, protection is short-lived, resulting in only short-term protection.
Anti-RSV monoclonal antibodies that bind RSV with higher affinity than palivizumab are currently under investigation. The product closest to the market is another monoclonal antibody, motavizumab (Numax®), which is in the final stages of several phase III clinical trials involving high-risk premature infants and infants with chronic lung disease of prematurity and congenital heart disease. In premature infants, motavizumab was tested head to head against palivizumab. The newer monoclonal antibody showed a further 26% reduction in serious RSV-related disease compared with palivizumab, with a further 52% reduction in RSV-related outpatient, medically attended lower respiratory tract infections. An FDA biologic license application was filed by the manufacturer, Medimmune, in 2007. Currently, passive immunoprotection with anti-RSV monoclonal antibodies is reserved for high-risk infants only. Given the epidemiology of RSV disease, the single most cost-effective method of prevention is likely to be universal infant immunization with a vaccine that induces active, durable immunity. Candidate formulations include both subunit and live-attenuated RSV vaccines.

The History of the Vaccine

The first RSV vaccine was developed in the 1960s as a whole-virus formalin-inactivated preparation. Rather than preventing disease, this vaccine preparation resulted in an unpredicted aberrant immune response to natural RSV infection, a phenomenon now referred to as ‘disease enhancement.’ The vaccine-enhanced disease associated with the formalin-inactivated RSV vaccine understandably slowed RSV vaccine development, but the recent evolution of newer vaccine production techniques has permitted alternative vaccination strategies to move forward.

During the 1990s, the focus of RSV vaccine development was on subunit vaccines. These vaccine candidates contained only one to three target proteins from the virus. The underlying concept was that these vaccines may have the potential to induce neutralizing antibody responses without eliciting vaccine-enhanced disease. Purified RSV F-protein (PPF) was shown to be immunogenic and safe in children in clinical studies and was studied through several iterations (PPF-1, PPF-2, and PPF-3). A phase III study of PPF-3 in 298 children with cystic fibrosis was disappointing because, although it showed the F-protein vaccine to be safe and immunogenic, it was not effective at preventing RSV infection. A subunit RSV vaccine containing the F, G, and M proteins has been found to be immunogenic in adults, but antibody titers waned after only one year. One fusion protein candidate, BBG2Na, consisting of a conserved portion of the G protein (G2Na) fused to the albumin-binding region (BB) of staphylococcal protein G, is immunogenic in animals, but human trials were halted because of the unexpected development of a purpura in some vaccine trial enrollees.

The development and study of live-attenuated RSV vaccines has also received significant attention. Traditional techniques used to develop these experimental strains of RSV vaccine include serial passage in tissue culture and chemical mutagenesis. Neuerer techniques that take advantage of molecular genetics now allow for the introduction of targeted mutations that will theoretically permit the development of a new battery of vaccine candidates.

Before recombinant RSV vaccine candidates became available, the best-studied vaccines were cold-passaged temperature-sensitive (cpts) mutants. Cpts RSV viruses are capable of growing to high titers at the permissive temperature of 32°C (in vitro), but are replication-incompetent at core (lung) temperature of 37°C, similar to the licensed live-attenuated influenza nasal vaccine. Sequence analysis of complete genomes of several cpts RSV strains, and subsequent testing in animal models of recombinant viruses, revealed specific mutations in attenuating RSV-encoded proteins. The first vaccine candidate to be tested extensively was a cpts RSV mutant known as cpts 248/404. Compared with an earlier, similar vaccine candidate (cpts 248/955), cpts 248/404 replicated less effectively in seronegative children and older infants, and could be evaluated in infants as young as one to two months of age. In this younger population, the vaccine virus had residual virulence producing symptoms of mild upper respiratory infection. It did seem to provide protection against subsequent challenge with the RSV vaccine strain and showed promise in preventing wild-type RSV infection.

Later, additional mutations were added to this virus backbone and the resulting vaccine was re-tested in adults, children, and infants. Additional attenuating mutations, including a mis-sense mutation and complete deletion of the virus small hydrophobic (SH) gene, were included to produce two new vaccine candidates, rA2cp248/404/1030ASH and rA2cp248/404/45SH. The deletion of the SH gene was attenuating in isolation, but did not appear to confer additional attenuation when added to the cpts 248/404 backbone. Furthermore, because cpts 248/404 induced significant upper respiratory congestion in infants, rA2cp248/404/45SH was not tested in infants as it was considered unlikely to be sufficiently attenuated. Most recently, the reverse genetics approach has allowed the creation of chimeric live-attenuated vaccines containing elements from more than one virus. The most advanced chimeric vaccine candidate is a combination RSV-parainfluenza type-3 vaccine. This new vaccine (MEDI-534) has already undergone phase I trials in adult volunteers, and phase I–II trials began in infants in the summer of 2007.

Given the obstacles to RSV vaccine development, a licensed RSV vaccine will not be available for some time, but the ability to refine live virus vaccine candidates using the available technology should facilitate progress. ■

5. The Impact-RSV study group, Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants, Pediatrics, 1998;102(3 Pt 1):531–7.