Protecting the Family to Protect the Child: Vaccination Strategy Guided by RSV Transmission Dynamics

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(See the major article by Munywoki et al on pages 1685–92.)

Respiratory syncytial virus (RSV) is the most important respiratory pathogen of childhood and also contributes to substantial morbidity and mortality in the elderly. It was recently estimated that as a single infectious agent, RSV is second only to malaria as a cause of death in children between 1 month and 1 year of age [1]. In addition, the global impact as an adult pathogen has a comparable level of morbidity and mortality as influenza in the frail elderly [2, 3]. Further demonstration that RSV is a ubiquitous global pathogen is now reported in the prospective family cohort study performed by Munywoki et al and reported in this issue of the Journal of Infectious Diseases [4]. More than 80% of households with children experienced an RSV infection within the 6-month surveillance period, and RSV was detected in 64% of study infants (defined as <1 year of age). In about 50% of households, more than one person was infected, and repeat infections in the same individual from homologous or heterologous RSV subtypes within the same season were documented. Thus, transmission within family units is common, and natural infection with RSV, especially in very young infants, does not provide solid immunity against reinfection. These data that were collected in rural Kenya are consistent with another household study performed more than 40 years ago in Rochester, New York, that reported 2 months of surveillance data [5]. Although it would be useful to have more data from different geographic and climatic settings, the congruity of these 2 studies suggests the likelihood that these results are a realistic reflection of how RSV is transmitted within family units globally. Importantly, the current study was prospective, employed active surveillance, and used modern diagnostic techniques such as polymerase chain reaction (PCR) and viral isolate sequencing to confirm temporal transmission patterns. The investigators showed that transmission of an infant’s first RSV infection was most often attributed to school-age children in the household.

This report exemplifies the importance of understanding the epidemiological details of how a contagious respiratory pathogen spreads within a community. Indeed, understanding transmission dynamics may be a key factor in defining strategies that can successfully protect infants from RSV infection. In addition to using this information to emphasize the importance of handwashing and avoiding large particle aerosol andomite transmission, it may be useful to ask how understanding transmission dynamics can inform vaccine development strategies. In particular, we should explore the potential target populations for RSV immunization.

Although there is no licensed vaccine for RSV prevention, there are several candidates in development, and at least 3 are currently being evaluated in clinical trials. One of the key decisions each developer has to make is which population should be targeted for vaccination to accomplish their objectives. Although considerations could range from market size to public health impact, or from reducing severe disease in young infants to reducing morbidity and mortality in the elderly, the primary objective of most vaccine developers has been to prevent or reduce disease severity in the very young infant. Peak age of hospitalization with RSV is between 2 and 3 months of age, and hospitalized infants are known to have a higher frequency of subsequent wheezing during childhood. Therefore, preventing severe RSV infection in young infants would not only have a direct benefit on primary disease but may also reduce the incidence of childhood asthma. This hope has resulted in a rare consensus among parents, clinicians, hospitals, public health officials, insurance companies, and marketing executives, who all agree that protecting this youngest age group is the top priority.
There are several major challenges, however, in effectively immunizing a child prior to 2 months of age. First, the logistics will be difficult. Most vaccine approaches require multiple immunizations, so the regimens would need to start near the time of birth. For some vector-based approaches and live-attenuated virus vaccines, it may be possible to immunize with a single dose, but still the window of time is small, and the evidence that natural infection with replicating virus does not provide solid immunity suggests there are other biological factors that must be considered [6]. Inducing effective immunity in the context of the developing immune system of the neonate is challenging. Although there are examples of successful neonatal immunization including BCG and hepatitis B, antigen presenting cells are known to improve over time in their capacity for antigen processing and costimulation, and the ability for B cells to promote somatic mutation to achieve affinity maturation of antibody responses is limited until 4–5 months of age. In addition, there is a relative Th2-bias of the adaptive immune response and a diminished ability to produce Type I and II interferons in neonates. These features of the neonatal immune response may limit the efficacy of vaccination. Another consideration is that maternally derived antibodies against RSV can help protect the infant from infection but may also dampen the endogenous response to neutralization-sensitive antigenic sites on viral surface glycoproteins and thus diminish vaccine immunogenicity. In addition to logistical and immunological factors that make implementation difficult and efficacy uncertain, there are other features of the neonate that may complicate the vaccine development pathway from a safety or regulatory perspective. One is that there are more idiosyncratic rare adverse events in the neonate including apnea that may be difficult to distinguish from vaccine-associated events. Also, the small airway of the neonate increases the likelihood of obstructive events and leaves a relatively small therapeutic window, especially for vaccines administered into the airway, or those that may initially increase the inflammatory response to subsequent infection. This may have been part of the pathogenesis of the enhanced disease syndrome associated with a formalin-inactivated whole virus vaccine tested in the 1960s, particularly evident in the youngest age group [7].

How can we solve the conundrum that the most important and vulnerable population to protect from RSV is also the least likely to achieve immunity from active vaccination? One approach is demonstrated by the efficacy of palivizumab (Synagis®) given passively to infants at high risk for severe RSV disease. This is a neutralizing monoclonal antibody directed to antigenic site II on the F glycoprotein of RSV. When sufficient neutralizing activity can be achieved in serum, there is a reduction in hospitalization [8] and wheezing [9] attributed to RSV during the first year of life. Therefore, immunizing pregnant women or women of childbearing age to significantly raise the level of neutralizing activity available for transplacental delivery to the fetus is also likely to reduce RSV disease burden. The data on transmission dynamics reported by Munywoki et al [4] in this issue provide support for an alternative approach to indirectly protect young infants by active vaccination of older siblings. As noted with pertussis vaccination [10], protecting the primary transmitters of RSV to young infants would be a targeted method of providing herd immunity within the family unit if not the community at large.

There are a number of other considerations that support the idea that achieving licensure for RSV vaccine products in children >6 months of age should be a primary goal for clinical development. In addition, to a large burden of medically attended lower respiratory infections, about 50% of RSV-related hospitalizations in children occur after 6 months of age, so immunizing this age group would have a significant direct benefit, as well as the indirect benefit for younger children. Roughly 70% of infants are still uninfected at 6 months of age, so immunizing at this time allows the majority of infants to be immunized first with the vaccine instead of natural infection and provides the opportunity to improve on naturally acquired immunity. If age of first infection can be delayed by immunizing older siblings, as suggested by the Munywoki et al article, there would be profound consequences not only on disease severity but on ability to vaccinate effectively, and to more often accomplish “primary” immunization by vaccination. By 6 months of age, maternal antibody has waned, maturation of immune functions has progressed, and the likelihood of idiosyncratic adverse events has diminished. Therefore, targeting infants older than 6 months would alleviate many of the efficacy and safety concerns associated with vaccinating very young infants.

There is evidence from studies on influenza that school age children are often transmitters to the elderly, and that vaccination of 5–16 year old children may be a more cost-effective approach to protecting the elderly from influenza than direct vaccination of the elderly population [11]. If school age children are, indeed, the most important transmitter population for RSV, as they have been shown to be for influenza, an additional booster immunizations could be administered at 5–10 years of age to sustain protection of older children, and it would not be unreasonable to expect a protective effect from RSV in the elderly as well as young infants. Once a substantial database for vaccine safety and efficacy in children >6 months of age is established, it would facilitate the gradual application of vaccine to younger age groups. By combining this strategy with maternal immunization, as now recommended for other respiratory pathogens including influenza and pertussis, one can envision protecting the very young infant from severe RSV disease by reducing transmission from outside the home and providing passive immunity from maternal
transfer, while working toward effective active vaccination strategies that could directly protect all age groups.

The study by Munywoki et al should signal the beginning of more intensive evaluation and modeling of RSV transmission dynamics that will be critical for informing strategic approaches for RSV vaccine development. The initial indications suggest that just as it may take a village to raise a child, it may be necessary to immunize a village to protect a child against RSV.

Notes

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References