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Vaccines against respiratory syncytial virus: The time has finally come

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ABSTRACT

Respiratory syncytial virus causes a significant public health burden, particularly in very young infants and the frail elderly. The legacy of enhanced RSV disease (ERD) from a whole formalin-inactivated RSV vaccine, and the complex biology of the virus and the neonate have delayed the development of effective vaccines. However, new insights into factors associated with ERD and breakthroughs in understanding the antigenic structure of the fusion (F) glycoprotein have increased optimism that vaccine development is possible. This has led to investment of time and resources by industry, regulatory authorities, governments, and nonprofit organizations to develop the infrastructure needed to make the advanced clinical development of RSV vaccine candidates a reality.

1. Epidemiology

Respiratory syncytial virus (RSV) is the most common cause of hospitalization in children under 5 years of age [1]. In developing countries RSV also causes substantial mortality in children under 1 year of age [2]. All children are infected by the age of 3 and people are repeatedly infected throughout life [3]. In otherwise healthy children over 5 years of age and in adults, RSV typically causes an upper respiratory syndrome sometimes complicated by sinusitis and otitis media [4,5]. In individuals with T cell deficiencies like Severe Combined Immunodeficiency (SCID) or following allogenic bone marrow transplantation or lung transplantation, RSV can cause a life-threatening progressive pneumonia [6,7]. In addition, RSV infection in the frail elderly is associated with excess mortality at frequencies comparable to influenza virus infection [8]. Infections tend to be seasonal in temperate climates, but in tropical climates can be detected throughout the year [9].

Approximately 20 per 1000 infants less than six months of age are hospitalized with severe RSV illness, and in the institutionalized elderly about 1–2 per 1000 [1,8,10,11]. Hospitalized children have a higher frequency of wheezing during childhood than their counterparts with milder disease. This predisposition to wheezing subsides during adolescence [12,13]. In children prophylactically treated with palivizumab (a neutralizing monoclonal antibody specific for antigenic site II on the RSV fusion glycoprotein) the frequency of subsequent wheezing is diminished [14]. Conversely, there is also genetic, clinical, and experimental evidence that a pre-existing tendency toward allergic inflammation is associated with more severe disease [15,16].

2. Pathology

RSV infects ciliated epithelium in the upper and lower respiratory tract. Bronchiolar epithelium is especially susceptible to infection, and type I pneumocytes in the alveoli are also commonly

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infected resulting in high frequency (~20%) of children with hypoxemia, even in those without other significant symptoms. In children with severe RSV disease, it is thought that a major feature of pathology is airway obstruction. The few autopsy studies of fatal RSV infection show that small airways can be obstructed by sloughed epithelium and inflammatory cells combined with mucus and fibrin [17]. The airways can also become hyper-reactive contributing to the signs of wheezing and retractions characteristic of infants with severe disease. RSV is one of the first pathogens encountered by young infants and in premature infants who are especially susceptible to severe disease, the impact of RSV on the developing lung and airways is not well understood. One of the important consequences of having a successful vaccine for RSV would be the opportunity to ask whether diminishing the severity of RSV disease in early childhood would reduce the frequency of childhood asthma and airway hypersensitivity.

3. Goals of vaccination

The primary clinical goal for an RSV vaccine is to prevent severe lower respiratory tract disease in young infants. Endpoints would include the prevention of hospitalization or medically attended lower respiratory tract infection (MALRI) in industrialized countries, prevention of mortality and hospitalization or MALRI in developing countries, and if possible, development of a clinical severity index as a continuous variable for disease severity. Secondary goals are to: (1) prevent medically attended lower respiratory tract infection in young children, (2) prevent hospitalization and mortality in the elderly, and (3) reduce childhood wheezing, otitis media, and overall morbidity associated with RSV infection in children and adults. To achieve these goals RSV vaccines have been considered for use in five main populations including (1) pregnant women, (2) infants <6 months of age, (3) infants and children >6 months to 2 years, (4) young (2–5 years old) and school-age children, and (5) individuals >60 years of age (Fig. 1). The critical distinction between target populations is whether the subject is RSV antigen naïve and vaccination will be the first inductive priming event or the subject has already experienced natural infection and vaccination will be boosting pre-existing immunity. This will influence which vaccine approach is selected for a given population.

While protecting infants prior to the peak of hospitalization at 2 months of age by direct vaccination would be ideal, there are several factors that make this challenging including presence of maternal antibody, lack of significant capacity for somatic mutation and affinity maturation of antibody, Th2-biased immune response patterns. In addition, there are more idiosyncratic events like apnea in neonates, which complicates the interpretation of adverse events temporally related to vaccination. Immunization of pregnant women is proposed as a way of protecting neonates by boosting maternal antibody that is acquired by the infant transplacentally. The main objective is to delay the time of first RSV infection until the child is at least 6 months old when airways are more fully developed and have larger diameters to reduce the risk of obstruction from mucus, inflammatory debris, and airway hypersensitivity. Children between 6 and 24 months still have significant morbidity from RSV and would directly benefit from a preventive vaccine. It would also allow the vaccination event to be the first exposure to RSV antigen in many cases, providing the opportunity to induce more effective priming than natural infection. Immunization of young and school-age children would be done in the presence of pre-existing immunity from prior natural infection. Therefore, the likelihood of adverse events would be lower, but the direct benefit to the individual would also be lower, since by age 5 most people have achieved a level of immunity that prevents serious lower airway disease unless immunity is compromised by disease or aging. Immunization of this population would be primarily to reduce transmission to neonates and the elderly, based on RSV transmission dynamics studies [18,19] showing that most neonatal infections come from older siblings, and the precedent in influenza showing that immunization of school-age children is more cost-effective than immunizing the elderly [20]. Boosting pre-existing immunity in the elderly may reduce RSV-related disease, but immunity and pathogenesis in this population is complex, making the definition of clinical endpoints short of hospitalization difficult. Typically viral shedding is limited in this population making pathogen-specific diagnosis more challenging, and disease is often manifest as multi-organ failure rather than confined to the respiratory tract. Deficiencies in both T cell- and antibody-mediated immunity may contribute to the higher susceptibility to disease, and may require alternative antigen designs, formulations, and delivery approaches than younger populations. Better definitions of severe lower respiratory tract disease in young infants and the elderly would facilitate the use of more discriminating clinical endpoints in future vaccine trials [21].

4. Virology

RSV is a pneumovirus in the Paramyxoviridae family. It has a single-stranded, negative-sense RNA genome of about 15 kilobases with 10 genes separated by stop/start sequences that encode 11 known proteins. There are two major subtypes of RSV that are distinguished largely by variation in the G glycoprotein [22]. The subtypes tend to alternate in dominance from year to year, but co-circulate and are not exclusive in any given season. While there is genetic variation between strains characteristic of any RNA virus, it is not extreme and does not seem to explain the susceptibility to reinfection. The first two genes at the 5′ end of the genome are NS1

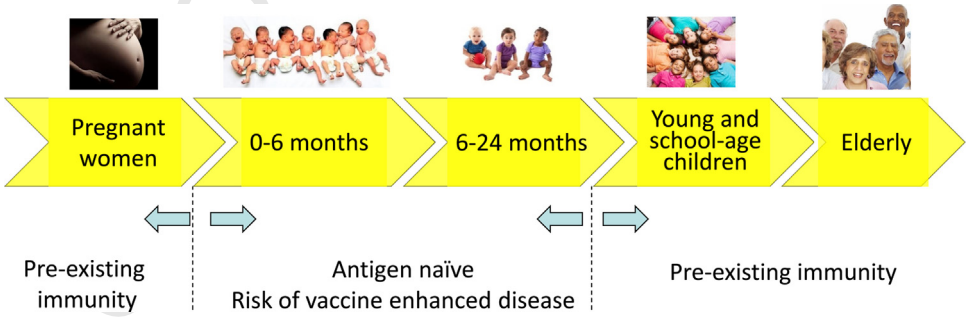

Fig. 1. Potential target populations for RSV vaccines include (1) pregnant women, (2) infants <6 months of age, (3) infants and children >6 months to 2 years, (4) young (2–5 years old) and school-age children, and (5) individuals >60 years of age. Children less than 2 years of age and the elderly would derive the most direct benefit from an effective vaccine. Since all children are infected early in life, anyone over 2 years of age is likely to have experienced natural infection, so vaccination of older children and adults is designed to boost pre-existing immunity. Vaccination in children under 2 years of age could be the primary immunization event.

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