Prospects for a Respiratory Syncytial Virus Vaccine

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From the time that respiratory syncytial virus (RSV) was discovered as the agent causing colds in chimps, control of the virus has lured but eluded investigators. RSV is the major respiratory pathogen of infants and young children worldwide and causes an estimated 91,000 hospitalizations and 4500 deaths annually in the United States alone (*1*). The virus produces a sizable outbreak of respiratory infections each year (figure) and is so highly contagious that essentially all children become infected within the first 2 years of life (*2*). RSV spreads with equal alacrity among older children, families, and through hospital wards (*3*). Previous infection does not prevent illness in subsequent outbreaks, even in the next year.

The RSV genome is a linear single-stranded RNA that encodes ten proteins, three associated with the nucleocapsid and four with the glycoprotein envelope (*1*, *4*, *5*). Two of the envelope glycoproteins, the F and G proteins, are of particular interest because they appear integral to viral pathogenicity and infectivity (*4*, *5*). The F protein promotes fusion of the viral and host cell membranes, and the G protein mediates viral attachment to host cells. The two major RSV strain subgroups, A and B, are distinguished primarily by the G protein, which shows about 50% sequence divergence between subgroups. Thus infection with one subgroup does not confer complete protection against the other.

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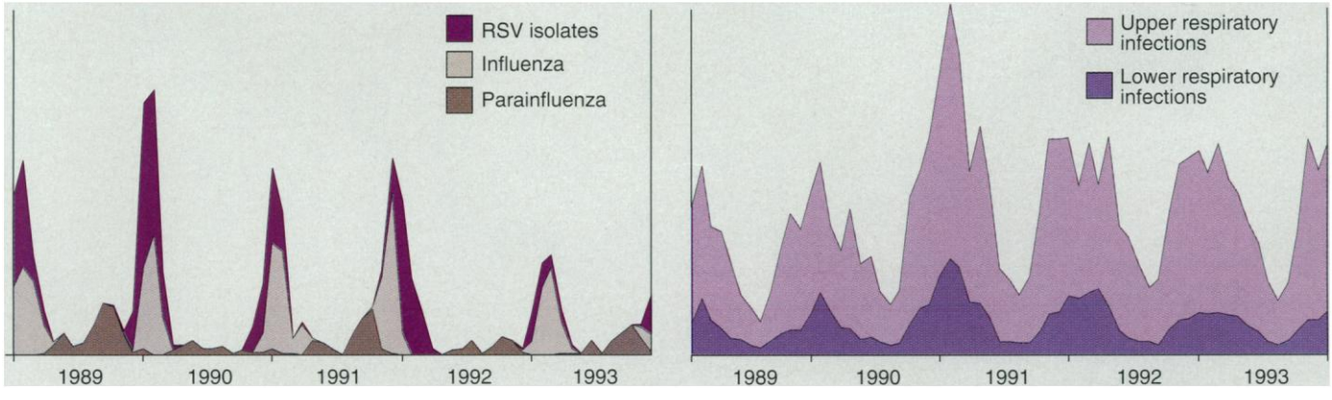
RSV elicits an imperfect immune response in humans that permits repeated infections. Severe lower respiratory tract disease generally occurs only in the first 2 years of life (and in the elderly), but this experience does not protect against less severe forms of RSV infection, such as upper respiratory tract and ear infections (*2*, *3*). Furthermore, the most severe and fatal disease often occurs in young infants who have high titers of maternally derived antibodies against RSV.

On the basis of these and other observations, it has been hypothesized that the immune response induced by RSV may be not only inadequate but potentially contributory to the development of disease (*4*, *6*). The initial evidence leading to this hypothesis came from field trials of the first vaccine developed for RSV, a formalin-inactivated whole-virus vaccine given parenterally to young children in the late 1960s (*7–9*). Most of the vaccinees produced both complement-fixing and neutralizing antibodies to RSV. On subsequent natural exposure to RSV, however, the vaccinated children were not only susceptible to RSV infection, but many of those under 2 years of age developed severe lower respiratory tract disease that necessitated hospitalization and, in some cases, was fatal.

Recent studies have attempted to delineate the immunologic basis of the vaccine-associated illness. Reexamination of stored sera from the vaccinees has suggested that these children may have had a defective antibody response with diminished viral neutralizing activity (*4*, *6*). Much additional information has been derived from studies with rodents (*4*, *5*, *10–12*). A similar enhanced pulmonary pathology can be induced by RSV infection after previous immunization with the formalin-inactivated vaccine, but not after immunization with live RSV. These studies have suggested that the inactivated vaccine elicited an altered T cell response to the virus (*1*, *10–12*). The formalin-inactivated vaccine induces an abundance of RSV-specific memory T cells, probably in the $CD4^+$ subset, and on subsequent challenge with live RSV, $CD4^+$ cells dominate in the inflamed lung (*11*). Mice that are depleted of their $CD4^+$ cells do not develop the exaggerated lung pathology. The subtype of T helper (T_H) cell involved also appears to be important (*10–12*). In mice previously immunized with killed RSV or with the F protein, subsequent challenge with live RSV leads to a cytokine response, primarily interleukin-4 (IL-4), that is characteristic of the T_H2 subset, whereas previous immunization with live RSV produces primarily interferon-γ, a cytokine characteristic of the T_H1 subset.

These elegant studies thus offer an exciting hypothesis for the etiology of enhanced disease in children vaccinated with the formalin-inactivated RSV and perhaps a new vista into the pathogenesis of infectious diseases in general (*11*, *12*). It is possible that the inactivated vaccine altered or prevented the secretory and neutralizing antibody response to RSV, so that upon re-infection the virus could replicate freely and spread to the lung. This may have induced amplification of the $CD4^+$ memory T cells and generated an inappropriate T_H cell response. The shifted pattern of released cytokines could have enhanced inflammation and altered B cell maturation, thereby producing the severe disease. Interestingly, the IL-4–associated T_H2 response has also been observed in progressive dis-



Viruses and respiratory disease. The occurrence of upper and lower respiratory tract infections in young children is shown in relation to community outbreaks of the major respiratory viruses, RSV, parainfluenza virus, and influenza virus. (Data are from an ongoing community surveillance program in Rochester, NY.)

ease caused by other infectious agents, such as *Leishmania major* and *Toxoplasma gondii*.

With the knell of the inactivated vaccine trials in the background, attention was redirected to the development of live attenuated RSV vaccines. Temperature-sensitive RSV mutants were tested as vaccine candidates in young children, but were abandoned because they produced unacceptable degrees of illness, were overly attenuated, or were genetically unstable (*4, 5*). New mutant strains with properties more suitable for an attenuated vaccine in infants currently are being investigated. In principle, today's technology offers the possibility of designing the ideal vaccine through the production of genetically engineered RSV mutants with all the attributes of attenuation, stability, and immunogenicity (*4, 5*).

Only recently has the idea of inactivated vaccines, especially subunit vaccines, been reexplored. Vaccines consisting of the F protein alone, or the F plus G proteins, have generally been immunogenic and protective in rodent models, but concerns have been raised about whether even such subunit vaccines could elicit the augmented disease seen with the formalin-inactivated vaccine (*13*). The F, G, and other RSV proteins also have been expressed in a variety of vaccine vectors and tested in animals, but thus far the results have been variable (*4, 5*).

What then are the prospects for the development of a successful RSV vaccine? Important hurdles remain. Perhaps most important is the uncertainty about which components would constitute the ideal vaccine—live virus, attenuated virus, or purified viral proteins? The F and G glycoproteins appear pivotal in initiating immunity. However, young infants respond poorly to heavily glycosylated proteins (*4*). Infants also have a diminished ability to produce protective neutralizing antibody to RSV in serum and respiratory secretions (*4, 6*). In addition, maternal antibody, which is uniformly present at the early age when vaccine would have to be administered, can have a dampening effect on the infant's immune response to RSV (*4*).

Currently there is no accurate way to predict the response of infants to a candidate vaccine before actual administration. Are there measurable parameters that correlate with an immune response that is protective, durable, or detrimental? We do not even know what type of immune response would be safe and protective in young infants. Evidence has accumulated that certain serum antibodies are beneficial and protective, but they are only one part of the collage of RSV immunity, as indicated by the virus's ability to infect some infants with high titers of maternal antibody (*3*). Cellular immunity is clearly important, perhaps both in protection and in pathogenesis (*3, 4, 10, 11*). Local defense mechanisms may also be critical, as RSV spreads from cell to cell on the respiratory mucosa, cloistered from circulating serum antibodies.

RSV immunization would most likely need to be initiated during the neonatal period, a time of variable and developing immunity and for which experience with immunizations is limited. Relatedly, we do not know whether the disease we see in infants is due to the replicating virus itself or to a cascade of inflammatory mediators it provokes.

Thus, control of RSV infections will require a creative approach. New techniques have generated a variety of potential peptide vaccines representing desirable epitopes that may ultimately allow more precise targeting of specific B and T cell responses. Novel routes, carriers, and adjuvants may be needed to augment the immune response of neonates. RSV proteins may be more immunogenic and activating to the faineant T cells of neonates when their presentation is altered [for example, when they are set in ISCOMs (vesicles of immunostimulating complexes)] (*14*). Alternatively, RSV components may be targeted to specific antigen-presenting cells by a genetically engineered glue of monoclonal antibody directed against the Fc receptors on the surface of these important cells (*15*).

The eventual goal is to combine all childhood vaccines into a single oral vaccine to be administered to newborns worldwide. Until this soothsayer's vision of the universal vaccine is realized, however, we may have to redefine and limit our goals for control of RSV. Temporary protection from or amelioration of disease in the first 1 to 2 years of life, as well as in the elderly, would markedly decrease the morbidity and the human and financial costs incurred by RSV. Such protection of the newborn may require a mix-and-meld approach involving subunit vaccines, prophylactically administered antibodies or antibody-binding fragments (Fabs) aerosolized into the respiratory tract (*16*), and live attenuated vaccines.

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