In Search of a Vaccine for Respiratory Syncytial Virus: The Saga Continues

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(See the article by Karron et al., on pages 1093–104.)

More than 150 years ago, Eberle described bronchiolitis in infancy: the disease "commences with cough and breathing [and] soon becomes laborious and wheezing.... The cough is at first dry, attended with a wheezing sound in the chest; but towards the termination of the complaint it frequently becomes humid and rattling" (p. 222) [1]. This descriptive portrayal of respiratory syncytial virus (RSV) bronchiolitis remains accurate today. RSV epidemics continue to be characterized by lower respiratory tract disease in young infants, sleepless anxiety in parents, and increased workloads for medical personnel. It is now recognized that RSV is the major cause of respiratory tract disease in infants worldwide [2] and that infection with this virus consistently results in the increased use of health-care resources, including visits to physicians and the occupancy of hospital beds [3]. The importance of RSV in causing disease and morbidity in adults—particularly in the debilitated and elderly—is also now appreciated [4]. It is known that, to prevent severe disease in infants, high levels of RSV-specific antibody can be administered as a monthly injection [5], but the costs of this antibody prophylaxis force health-care providers to make difficult choices when confronted by both expanding populations of high-risk infants and limited budgets.

The seriousness and ubiquity of RSV disease was recognized and characterized by astute clinicians and researchers beginning in the late 1950s [6], although histologically confirmed disease from a 1937 outbreak was described as early as 1941 by Adams (figure 1) [7]. Propagation of the viral agent, obtained from infants with bronchiolitis, was reported from Chanock’s laboratory at the National Institutes of Health (NIH) in 1957 [8], and RSV vaccine development began shortly after this time. This laboratory confirmed that this virus was the causal agent of “chimpanzee coryza,” described a year earlier by Morris et al. [9]. By 1969, it was stated with confidence that “RS virus has been shown to be the most important viral respiratory tract pathogen of infants and children” (p. 405) [10]. The medical need for an RSV vaccine was recognized then and remains a priority today.

The 1950s and 1960s were remarkable for the successful development of other inactivated vaccines, such as the Salk polio vaccine, and such success induced both public and scientific appreciation of and support for vaccines in general. The development of formalin-inactivated RSV vaccine candidates began during the mid-1960s at both the Merck Institute for Therapeutic Research and Chanock’s laboratory at the NIH [11]. Unfortunately, the formalin-inactivated, alum-precipitated RSV vaccine candidate developed at the NIH not only failed to protect young seronegative infants against RSV disease during the following RSV season, but the vaccine recipients actually experienced enhanced disease after wild-type RSV infection and had increased rates of pneumonia [12]. These findings, and the death in 1967 of 2 vaccine recipients who were naturally infected with RSV after receiving the inactivated vaccine, effectively slowed RSV vaccine development for decades. There has not been universal agreement with respect to the disease processes that led to enhanced disease in...
Figure 1. Thin section of lung from an 11-week-old infant dying of “primary virus pneumonitis,” reported by Adams in 1941 [7]. This photomicrograph demonstrates cytoplasmic inclusion bodies and lymphocytic infiltrate, characteristic of respiratory syncytial virus infection, with hemorrhage and atelectasis. Photomicrograph courtesy of C. B. Hall, who was bequeathed the original slide by Adams.

these vaccine recipients, further hampering RSV vaccine development.

The history of these early RSV vaccine trials has haunted researchers. At present, no RSV vaccine candidate is ready for wide-scale clinical testing. Vaccine development has been further hindered by difficulties associated with the development of animal models, the immunologic immaturity of the neonatal target population, the potential confounding of immunogenicity in the presence of maternal antibodies, and the existence of 2 antigenic subgroups of RSV [13]. Nonetheless, new approaches to the creation of an RSV vaccine have been developed in the laboratory, and several candidates have undergone clinical trials in humans. During the past decade, RSV protein vaccine candidates, recombinant RSV subunit vaccine candidates, fusion protein vaccine candidates for maternal immunization, and live attenuated vaccine candidates have all been evaluated in humans. To date, only live attenuated vaccine candidates have been tested in young infants—the group at highest risk for severe RSV disease—and the trial reported by Karron et al. [14] in this issue of The Journal of Infectious Diseases demonstrates, for the first time, that a recombinant RSV vaccine with multiple mutations can be well tolerated and can likely be protective in this age group. Despite this important step forward, ongoing clinical development of RSV vaccine candidates remains extremely limited.

The importance of the recombinant vaccine candidates described in Karron et al.’s article lies in the creation of a live attenuated RSV vaccine that is well tolerated in infants and demonstrates protection by challenge studies. The careful stepwise and sequential clinical testing of the vaccine candidates was conducted by a consortium of investigators as part of a cooperative agreement between industry (Wyeth Vaccines Research) and government laboratories (at the National Institute of Allergy and Infectious Diseases [NIAID], NIH). The study serves as a model for the continued testing and evaluation of new RSV candidate vaccines, and Karron et al. are to be congratulated for their rigorous approach to clinical testing. Earlier clinical-trial results [15] had demonstrated that RSV strains that are attenuated in adults and RSV-seropositive children are not necessarily attenuated to the same degree in younger children. In Karron et al.’s most recent trial [14], the candidate vaccine rA2cp248/404/1030ΔSH appeared to be relatively well tolerated and was responsible mainly for mild illnesses; the lower respiratory tract illness that was observed was associated with other viral infections.

The administration of a second dose of rA2cp248/404/1030ΔSH demonstrated restriction of viral replication, providing excellent proof that this vaccine could induce protective immunity. Furthermore, it was demonstrated that the antibody responses to the vaccine were not the sole or even the major mediators of protection induced by this live attenuated vaccine.
New approaches to the genetic manipulation of vaccine candidates can now be considered, including the use of gene re-arrangement or genetic recombination of several candidate viral genes. Further careful stepwise evaluation of this potential RSV vaccine in humans should be highly encouraged.

The true tragedy that resulted from the failure of the formalin-inactivated vaccine was not only the death of the 2 infants but also the decreased support for the development and study of respiratory vaccines—and of a vaccine for RSV, in particular. Academic researchers themselves have been hesitant to pursue RSV vaccine development and testing, and RSV vaccine development by manufacturers has been adversely affected by the financial risk involved, the high level of investment required, and the low return the investment provides. In fiscal year 2003, total support for RSV research by NIAID was only 0.36% of its nearly $3.5 billion budget (personal communication, NIAID budget office). An absolute decrease in RSV research and development by both pharmaceutical and biotech companies since the mid-1990s has also been well documented, with a decrease from 25 pharmaceutical and biotech companies pursuing treatment and prevention strategies for RSV to “less than a handful” currently [16]. Meanwhile, RSV continues to be a major cause of hospitalization in young infants worldwide, an economic burden, and an important cause of morbidity and mortality [2, 17, 18].

The study by Karron et al. is one of the few that has evaluated RSV vaccine candidates in young children in the 21st century—a time during which our understanding of molecular science continues to grow exponentially. At the same time, it has been documented that lower respiratory tract illness heads the list of diseases that adversely affect disability-adjusted life-year outcome measures, which were developed by the Global Burden of Disease study [19]. Respiratory diseases have received some of the lowest overall levels of funding in terms of health-related research [19], and, despite the fact that vaccines continue to be promoted domestically and internationally as beneficial and cost-effective, only limited resources are currently allocated for RSV vaccine development. Ongoing issues with liability continue to plague RSV vaccine development, in particular because the tainted history of inactivated vaccine candidates inhibits novel approaches. These liability issues effectively prohibit vaccine manufacturers from pursuing studies involving maternal immunization, a promising modality of prevention [20]. Furthermore, the financial profits that can be gained from vaccines are low, compared with those that can be gained from drugs that require chronic administration—or even from new versions of old drugs. The causes of decreased involvement in the development of new respiratory vaccines by the pharmaceutical industry are certainly multifactorial and can be attributed to consolidation within the pharmaceutical industry, recent adverse experiences with the live attenuated rotavirus vaccines, and the huge costs involved in vaccine development, clinical trials, and manufacturing facilities. RSV vaccine development received high priority in the first edition of the Jordan Report, which describes NIAID research priorities and activities, and still remains an important priority in the 20th anniversary report that was published in 2002 [21], but progress in this field has been frustratingly slow.

As hospitals continue to overflow with admissions during the RSV season, residents of nursing homes bear the weight of RSV disease, and children in developing countries go on suffering, RSV vaccine development remains a low national and global priority. Perhaps the work by Karron et al. will motivate us to move forward on this important public-health problem.

References