Respiratory syncytial virus: not just for kids

LONDON, UK----1 July 2008----ExpertREACT. Recent research continues to highlight the economic and medical burden of RSV infection in the elderly population and those with underlying pulmonary deficiencies. Indeed it is estimated that 14.5 million US elderly adults are at risk from hospitalization due to the pathogen. Bearing in mind the challenges in designing a vaccine to protect infants and increasing influenza/pneumo vaccination, manufacturers should include the elderly in their RSV strategy.

Respiratory syncytial virus (RSV) is a highly variable and contagious human pathogen of the *Paramyxoviridae* family causing respiratory tract infections in patients of all ages. Although it is the number one of cause of lower respiratory tract infection (LRTI) among infants and young children worldwide it can also cause serious complications in the elderly or those with compromised pulmonary or immune systems. Each year it is estimated that RSV accounts for 9,000 deaths (1) and 177,000 hospital admissions (2) in US adults aged 65 years of age or older. In 2003, the WHO estimated 64 million cases and 160,000 deaths from RSV worldwide each year (3).

In healthy adults, RSV infection causes a symptomatic mild to moderate upper respiratory tract illness resembling a common cold, with symptoms often difficult to distinguish from those of influenza. However, in the elderly, patients with chronic lung disease, and patients with a high degree of immunosuppression e.g. bone marrow transplant (BMT) recipients, RSV infection may progress into lower respiratory tract illness including acute bronchitis, exacerbations of chronic obstructive pulmonary disease (COPD), and secondary viral or bacterial bronchopneumonia.

Present treatment options for RSV infection are limited. On occasions, the inhalable broad-spectrum antiviral ribavirin (virazole, approved in 1985) is used to treat infection in selected patients but on the whole has not met expectations in terms of efficacy and convenience. In pre-term babies (<36 weeks gestation) and those with congenital heart and/or lung disease (CHD), the monoclonal antibody, Synagis (palivizumab) has been shown in two pivotal trials to reduce the risk of hospitalization due to RSV infection. Palivizumab, licensed by the US FDA in 1998 is directed at the F-glycoprotein of the virus known to be important in cell-to-cell migration. The product is administered during the RSV season (colder months) for 5-6 months and is expensive, around $900 per month generating greater than $1 billion in annual sales for its manufacturer, AZ/Medimmune.

Studies have shown that neonates tend to be more protected by higher levels of maternal antibody levels in RSV-specific cord blood Ab and later breast feeding (4). This relationship and need for early prevention has continuously spurned the search for an active RSV vaccine. However, this quest has proved to be challenging because immunity to RSV infection is complex and poorly understood. Virus directed antibodies (humoral response) and cell-based mechanisms are stimulated upon RSV infection and play a role in host defense but their protective capacity is not long-lasting especially in immune naïve children. Individuals remain susceptible to repeated RSV reinfection throughout life and some are more severely affected than others suggesting a role of genetically variable host components.

The development of an RSV vaccine for infants has also been hindered by studies in the 1960s with a formalin-inactivated (FI) alum adsorbed RSV vaccine developed at the National Institutes of Health (NIH). The FI-RSV vaccine not only failed to protect infants from infection but also resulted in exacerbated RSV disease following subsequent natural exposure to RSV. Two vaccine recipients died with many more hospitalized (5). These observations suggest that RSV specific immunity, besides being protective might also be involved in immune pathologic mechanisms.

Despite the challenges, the area of RSV active vaccines remains a priority research area amongst the major vaccine pharmaceutical companies: AstraZeneca (MedImmune), GSK Biologicals, Novartis Vaccines, Sanofi Pasteur and Bavarian Nordic all have active programs or vaccine intellectual property according to recent **VacZine Analytics** research (6). The most advanced program is MedImmune's MEDI-534, a live, attenuated intranasal vaccine currently in Phase I/II clinical trials to help protect against RSV infection in children. The vaccine also

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contains antigens to parainfluenza virus type 3 (PIV- 3) another significant cause of mortality especially in BMT patients.

Interestingly, no present clinical trials for RSV vaccines appear to be ongoing in adult populations where an RSV vaccine may be beneficial for use in the elderly with underlying pulmonary disease or immunocompromisation. Unlike in children, for the elderly the priming for enhanced disease upon natural RSV infection is not expected to be a major problem because of pre-existing immunity.

VacZine Analytics believes that producing an RSV vaccine for the elderly/COPD populations will be economically cost effective. Although epidemiological data regarding incidence of RSV infections in adults is poor it is estimated that that 14.5 million US elderly adults are at risk of hospitalization due to RSV each year (7). While vaccination in these groups may not prevent infection, it may reduce progression of the virus to the lower respiratory tract and hence prevent more severe downstream outcomes that require hospitalization.

From a commercial perspective because immunological responses to RSV would likely wane after one year, annual immunization might be necessary giving potential synergies for co-administration with influenza and/or pneumococcal vaccines. With newer technologies e.g. 13-valent Prevnar and "improved/adjuvanted flu", coverage is predicted to increase in the coming years providing a valuable springboard for any new elderly vaccine. Lastly, the fact that an elderly RSV vaccine is likely to be a recombinant protein subunit vaccine might also facilitate its combination with other vaccine antigens making product development more straightforward.

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(2) Falsey AR *et al.* Respiratory syncytial virus infection in elderly and high-risk adults. N Engl J Med. 2005 Apr 28;352(17):1749-59.

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(5) Fulginiti VA *et al.* Respiratory virus immunization. A field trial of two inactivated respiratory virus vaccines; an aqueous trivalent parainfluenza virus vaccine and an alum-precipitated respiratory syncytial virus vaccine. Am J Epidemiol. 1969 Apr;89(4):435–448.

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(7) **VacZine Analytics**. DiseaseINFOPACK: Respiratory Syncytial Virus (CAT No: VADIP007), June 2008.

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About VacZine Analytics:
VacZine Analytics is a new strategic research agency based in the United Kingdom. Its aim is to provide disease and commercial analysis for the vaccine industry and help build the case for developing new vaccines.