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So Where Is a Vaccine for Respiratory Syncytial Virus?

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Vaccines and antibiotics have made many infectious diseases a thing of the past; we have come to expect that public health and modern science can conquer all microbes. But nature is a formidable adversary.
—Tom Frieden (https://www.brainyquote.com/authors/tom-frieden-quotes)

RESPIRATORY SYNCYTIAL VIRUS IMPACT ON WORLD HEALTH

Respiratory syncytial virus (RSV) is a major cause of severe respiratory tract infection without a vaccine or clinically effective treatments.[1,2] Evidence suggests that RSV may be responsible for up to 5% of community-acquired pneumonia rather than influenza and may be more responsible for primary care visits, hospitalizations, and deaths in persons older than 65 years.[1] Respiratory syncytial virus is a frequent cause of lower respiratory tract disease throughout the life span with postinfection immunity that is neither complete nor long-lasting.[3] Respiratory epithelial cells are the primary target for RSV infection and cause immune dysregulation and disease pathogenesis.[2]

The burden of RSV on the US healthcare system is significant with greater than 2 million outpatient visits for children younger than 5 years with up to 80 000 hospital admissions. For those older than 65 years, hospitalization rates are higher with nearly 10 000 deaths compared with 100 to 300 deaths in children younger than 5 years.[4] Respiratory syncytial virus is a leading cause of respiratory disease in infants and the elderly with significant disease burden for premature infants, the immunocompromised, and elderly populations. Nearly all children are infected with RSV by age 2 years.[2]

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Respiratory syncytial virus has a substantial impact worldwide as well; particularly for children aged 0 to 60 months, especially during the first 6 months of life. One in every 50 deaths in children aged 0 to 60 months and 1 in every 28 deaths in children aged 28 days to 6 months are related to RSV infection. It is estimated that for every RSV-associated acute lower respiratory tract infection in-hospital death, approximately 3 more deaths are attributable to RSV in the community.[5]

Respiratory syncytial virus is the most common cause of bronchiolitis and pneumonia in children younger than 1 year in the United States. In infants and children, RSV most often presents as a cold-like illness but can present as bronchiolitis and pneumonia, with 1% to 2% of children younger than 6 months with RSV requiring hospitalization. Premature infants or those younger than 2 years with chronic lung or heart disease, depressed immunity, or neuromuscular disorders are at particular risk for severe disease.[6]

In older adults, RSV can present with mild symptoms similar to an upper respiratory tract infection or no symptoms at all. However, for some persons, especially those older than 65 years with chronic illness, RSV can present with pneumonia or exacerbation of asthma, chronic obstructive pulmonary disease, or congestive heart failure.[6]

WHY IS THERE NO VACCINE FOR RSV?

Discovered in 1956, RSV circulation begins in the fall and peaks in the winter for the United States, and the timing and severity of any RSV season in a given community can vary from year to year.[6] Gaps in understanding virus-host interaction have contributed to the absence of a vaccine because the viral load is not predictably correlated with disease expression in RSV.[3] In addition, the lack of a reliable, reproducible, and cost-effective animal model has complicated RSV research.[2]

In 1966, a formalin-inactivated RSV vaccine was provided to infants and children in US field trials. Instead of being protected against RSV infection, vaccinated children who were seronegative for RSV before vaccination experienced

vaccine-induced enhanced clinical reactions when naturally exposed to RSV, and 2 children died. As a result, there is hesitation providing seronegative infants with nonreplicating RSV vaccines, and the focus has shifted to use nonreplicating RSV vaccines for seropositive adults.[7,8]

Multiple vaccine and monoclonal antibody (mAb) candidates are in current development for children and adults in the race to the first licensed vaccine via 38 clinical trials targeting pregnant women, infants, and elderly.[1,3,8] Currently studied vaccine platforms include virus particle based, nucleic acid, live attenuated, subunit, and vector based.[2] Evidence suggests that patient age, previous exposure to RSV, and community location will drive the type of vaccine used in the future.[1,3]

Replicating vaccines are proposed to protect infants older than 3 months from severe diseases. This strategy and live-attenuated vaccine products have shown promising results by reducing severe RSV disease. Through passive and active immunization strategies, perhaps the probability of asthma development will be reduced. For seronegative children, live-attenuated vaccines are highly immunogenic and can be administered intranasally, which may increase acceptance by parents and children. Furthermore, because RSV first replicates in the upper airways, the immune response is theorized to be similar to natural infection, which may provide enhanced protection from severe RSV infection and reduce overall transmission. Only through continuing clinical trials can the right amount of viral attenuation be determined to develop a safe and effective vaccine.[3,7]

The wait for an RSV vaccine may be a bit longer despite progress in current clinical trials.[7] Although cardiac, respiratory, or immunological comorbidity increases the risks with RSV infection at any age, severe RSV disease is different for infants and adults. As a result, vaccine-induced immune responses to RSV will likely need to be tailored specifically for each age group. Vaccine timing will remain as a thorny issue because RSV transmission is limited to autumn and winter in temperate climates versus year-round transmission in the tropical climates. Because RSV infection does not provide immunity to reinfection, the future RSV vaccine probably will not provide immunity to RSV but rather prevention of severe disease.[1]

Each developing preventive and treatment strategy has individual merits and challenges yet to be overcome. The 3 major preventive strategies include RSV F-protein–based vaccines for pregnant women, extended half-life mAbs for neonates, and live-attenuated vaccines for infants. Because neonate immune responses are not fully operational, preventive strategies for RSV are focused on provision of passive immunity mAbs and administration of RSV F-protein–based vaccines to pregnant women to provide infants RSV antibodies through transplacental transfer.[1]

Perhaps the best approach to protect young infants and children from severe RSV infection may be a combined strategy using passive and active immunization. The ideal RSV vaccine should provide improved and long-lasting B- and T-cell memory responses than natural infection and reduce disease severity. Also, a vaccine should prevent post-RSV wheezing and asthma, prevent severe disease, and limit disease transmission.[3]

CURRENT CARE FOR RSV

Respiratory syncytial virus has the ability to evade and block the work of the immune system, which leads to bronchiolitis, pneumonia, and acute otitis media. Treatment for RSV infection is currently limited to supportive care and prophylactic antibody use, with the latter reserved only for preemies. Bronchodilators and corticosteroids relieve RSV symptoms; however, efficacy has been marginal at best in clinical trials. Systemic corticosteroids help elderly patients with wheezing and bronchospasm. However, for infants younger than 12 months, there are safety concerns regarding corticosteroid effect on lung growth.[8]

The only specific agent available for RSV is palivizumab (Synagis; Swedish Orphan Biovitrum AB, Stockholm, Sweden [synagis.com]), which was licensed more than 20 years ago. Palivizumab is a humanized mAb that targets the F protein and is restricted for use in high-risk infants.[2] Palivizumab is recommended by the American Academy of Pediatrics (AAP) to be administered to high-risk infants and young children likely to benefit from immunoprophylaxis based on gestational age and certain underlying medical conditions. This monthly intramuscular injection administered during the RSV season is not a preferable preventive strategy for general infant populations because protection lasts only a month, repeated doses are needed, and it is very expensive.[7]

For the latest palivizumab guidance, please consult the AAP policy statement. An accompanying AAP technical report provides additional context and rationale for the guidance. Interim guidance addressing the disruption in typical RSV seasonal patterns during the pandemic has also been provided: Updated Guidance: Use of Palivizumab Prophylaxis to Prevent Hospitalization From Severe Respiratory Syncytial Virus Infection During the 2022-2023 RSV Season (aap.org).[9,10]

Vaccines for RSV in adults will also be an arduous journey. With no clinical end points for RSV disease detection, a population with high prevalence of comorbidities, and variable rates of infection, very large and very expensive clinical trials are necessary to establish efficacy of an RSV vaccine for adults. Many believe this is the era when an RSV vaccine will become available.[1] In addition to vaccine options, mAbs and antiviral therapies to protect infants and young children, pregnant persons, and older adults from severe RSV infection will also become available.[6]

Current RSV-associated hospitalization rates are updated weekly on the RSV-NET Interactive Dashboard. This population-based surveillance platform tracks seasonal trends, risk factors, rates of disease, and patient data from those seeking care. This platform currently includes

58 counties in 12 states that participate in the Emerging Infections Program or the Influenza Hospitalization Surveillance Program. The 12 participating states are California, Colorado, Connecticut, Georgia, Maryland, Michigan, Minnesota, New Mexico, New York, Oregon, Tennessee, and Utah, which covers approximately 8% of the US population. Although this sample of states participating is generally similar to US demographics; however, trends may not represent all areas of the United States.[4]

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