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Prevention of respiratory syncytial virus infections: A promising future

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Respiratory syncytial virus (RSV) is the leading causative agent of acute lower respiratory tract infections (ALRTIs) and associated death in infants and toddlers worldwide. In countries with temperate climates, such as Argentina, RSV activity is higher during periods of moderate humidity and cold temperature, with seasonal outbreaks lasting 4–5 months during the autumn and winter months.

Globally, RSV is estimated to be responsible for 30 million episodes of ALRTIs and more than 50 000 deaths annually in children younger than 5 years. A multicenter study of RSV mortality in countries in different regions estimated that RSV is responsible of one third of deaths in the first year of life.[1]

The ideal RSV vaccine would provide protection from bronchiolitis in the first 6 months of life when infants are more vulnerable, would offer sustained immunity, and should be affordable and acceptable for its use in infants.

Knowing the structure and configuration of the F protein in its prefusion state, which is the form in which it is found before RSV infects the cell, and the development of stable antigens based on the F protein has been a critical recent breakthrough that has enabled progress to be made in the development of vaccine candidates. The best immunizing epitopes are found in the prefusion F protein, but this form is highly unstable and rapidly changes its configuration to postfusion F protein, and such change in the configuration leads to the loss of the best immunizing epitopes. Only antibodies against the prefusion F protein, but not antibodies against the postfusion form, have a neutralizing capacity against the virus and protect against infection and its severity.

There are currently more than 30 ongoing clinical trials of RSV vaccines in different phases and with different platforms.[2]

At present, 3 main strategies have been proposed to achieve protection in this vulnerable group: passive immunization through monoclonal antibodies administered directly to infants, maternal vaccination during pregnancy, and direct vaccination of infants.

Recently, 2 important milestones have been achieved that constitute a significant progress in the prevention of RSV:

The first one is the announcement by Pfizer, on 11/1/2022, that reported the results of the MATISSE study, a phase 3 study of their RSV vaccine in pregnant women.[3] This is a randomized, double-blind, placebo-controlled phase 3 study designed to evaluate the efficacy, safety, and immunogenicity of the RSVpreF

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vaccine, which contains the prefusion F subunit of type A or B RSV. A total of 7400 healthy pregnant women aged ≤ 49 years were recruited and randomized in a 1:1 ratio to receive a single 120 µg dose of the vaccine or a placebo during the second or third trimester of their pregnancy. In a preliminary analysis, the vaccine has been shown to meet the first primary endpoint, with an observed efficacy against *severe lower respiratory tract illness* of 81.8% (95% confidence interval [CI]: 40.6–96.3%) in infants during the first 90 days of life and of 69.4% (95% CI: 44.3–84.1%) during the 6-month follow-up period. Although the expected objective was not met, the vaccine also showed an acceptable efficacy in the prevention of *medically attended* lower respiratory tract illness in infants of 57.1% (95% CI: 14.7–79.8 %) during the first 90 days of life and 51.3% (95% CI: 29.4–66.8 %) during the 6-month follow-up period.

Regarding safety, side effects were consistent with the results of previous phase 1–2 clinical studies and were mostly mild to moderate. However, a signal was recorded due to an imbalance –although not statistically significant– in the number of preterm births, with a higher incidence in the vaccine group (5.6%) than in the control group (4.7%). This situation warrants a close epidemiological surveillance and has led experts to request further evaluation of this potential adverse event.

The second milestone has been the announcement by the European Commission on 11/4/2022 regarding the approval of nirsevimab, a monoclonal antibody for the prevention of lower respiratory tract infection caused by RSV in newborns and infants.[4] Nirsevimab is a monoclonal antibody directed against the site Ø epitope on the prefusion configuration of the F protein, which is 50 times more potent than palivizumab and which, with a single injection, maintains protective levels for at least 150 days. This means that, if administered in a timely manner, it would provide protection throughout the RSV season.[5]

The next challenge will be to define strategies for the use of these new prevention approaches to have the greatest impact on infants´ health, prioritizing affordability and timing of administration according to the RSV epidemic seasonality.[6] ■

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