INFECTIOUS DISEASE

# Preventing respiratory syncytial virus (RSV) disease in children

## After many decades, promising strategies for RSV immunization are on the horizon

By **Ruth A. Karron**

In 1957, a virus recovered from infants with lower respiratory tract illness (LRTI) was named respiratory syncytial virus (RSV) for its ability to form multinucleated cells (syncytia) in cell culture (*1*). Early epidemiologic studies in high-income countries described the spectrum of RSV disease, including pneumonia, bronchiolitis (a characteristic wheezing LRTI), otitis media (middle ear infection), and apnea (pauses in breathing) in very young infants. Later studies demonstrated that RSV infection causes substantial disease in young children globally and that the burden of RSV in high-income countries is only a small fraction of the global burden. There is an urgent and universal need to develop products to reduce child mortality and morbidity through prevention of RSV disease. Fortunately, substantial progress has been made in the development of several promising RSV vaccines and monoclonal antibodies (mAbs) to achieve this goal.

RSV is the leading cause of hospitalization for pneumonia and other LRTI in young children (*2*). Annual RSV epidemics typically occur seasonally during cooler months in temperate climates but may be nearly year-round in tropical equatorial climates. Approximately 33 million cases of LRTI and up to 59,600 deaths worldwide annually are attributed to RSV, with more than 90% occurring in low- and middle-income countries (*3*). Although very young infants are at increased risk of RSV morbidity and mortality, >80% of RSV-associated LRTI and more than half of RSV deaths occur in children aged 6 months and older (*3*). In addition, RSV infection in infancy may predispose to recurrent wheezing and impaired lung function in early life (*4*).

RSV only became a priority for vaccine development in the 21st century, likely for at least two reasons. Although pneumonia has long been recognized as a major cause of early childhood disease and death, it was only after the widespread deployment of highly effective vaccines for the leading bacterial causes of pneumonia, *Haemophilus influenzae* type B and *Streptococcus pneumoniae*, that RSV was recognized as a leading contributor to the residual childhood pneumonia burden. An even more important obstacle was the legacy of RSV vaccine–associated disease enhancement, which stymied RSV vaccine development for decades.

In the 1960s, Lot 100 formalin-inactivated (FI) RSV vaccine was administered to infants and children at several US trial sites. RSV-experienced children were unaffected, but RSV-naïve children experienced a marked increase in severe disease and hospitalization when they encountered RSV in the winter following vaccination. In one study, 80% of RSV-infected children who had received the FI-RSV vaccine were hospitalized, compared with 5% of RSV-infected children in the control group (*5*). Tragically, a 14-month-old and a 16-month-old died, children who were well outside the age range normally associated with RSV mortality. For the remainder of the 20th century, considerable effort was put into understanding the pathogenesis of this catastrophe, through development of animal models and evaluation of the limited human samples available (*6*). Enhanced RSV disease was associated with high titers of poorly functioning (non-neutralizing) antibodies, T helper 2 ($T_H2$)–biased $CD4^+$ T cell responses, and immune complex deposition, likely related to the nonfunctional conformation of the fusion (F) protein in the inactivated RSV vaccine (*6*).

From a vaccine development standpoint, the practical consequence of these findings has been to tailor the immunization platform to the target pediatric population, avoiding administration of subunit (nonreplicating protein) vaccines to RSV-naïve infants and children. For infants younger than 4 to 6 months, the goal has been to provide passive immunity, either through direct administration of extended half-life RSV F-specific mAbs or through administration of an RSV F subunit vaccine to pregnant women to promote transplacental transfer of RSV-neutralizing antibodies. For RSV-naïve infants over 6 months and young children, the goal has been to provide active immunity through administration of replicating vectored or live-attenuated vaccines (*7*) (see the figure).

The strategy of protecting young infants against RSV LRTI through delivery of RSV-neutralizing antibodies is rooted in epidemiologic data demonstrating an association between neutralizing antibody titers and protection against RSV LRTI (*8*), and in the development of two products that have protected preterm infants against RSV LRTI: intravenous immunoglobulin containing high titers of RSV-neutralizing antibodies (RSV-IGIV), and an RSV F mAb (palivizumab) with potent neutralizing activity (*9*). Although palivizumab is used in very premature infants in high-income countries, its high cost and the need for monthly dosing have precluded wider use. However, nirsevimab, MK-1654, and RSM-01 are mAbs with modifications to the Fc region to prolong antibody half-life. These extended half-life mAbs have been termed "vaccine-like" because they could be given as a single dose and provide protection for several months. The development of these highly potent next-generation RSV F-specific mAbs, as well as new RSV maternal vaccines, was made possible by a critical advance: determining the crystal structure of the RSV F glycoprotein in its key conformations before and after it mediates viral membrane fusion with host cells (*10*).

RSV F exists in a metastable prefusion (pre-F) conformation and stable postfusion (post-F) state. Triggering of RSV pre-F induces a conformational transition to a stable post-F state; this rearrangement is required to drive viral entry into a target cell (*10*). RSV pre-F contains the six major antigenic sites (∅ through V) that have been mapped to the fusion protein, and most neutralizing activity in human sera is directed toward RSV pre-F (*6*). Nirsevimab, which binds to site ∅, has more than 50-fold greater neutralizing activity than palivizumab. A phase 2B study of nirsevimab in preterm infants demonstrated 70.1% efficacy against all RSV-LRTI and 78.4% efficacy against hospitalization for RSV-LRTI (*11*). These promising results also set expectations for the efficacy of passive immunization against RSV in young infants, whether through mAb administration or maternal immunization. It was recently announced that the phase 3 MELODY trial of nirsevimab in late preterm and full-term infants (NCT03979313) reached its primary endpoint, with significant reduction in LRTI. RSM-01, which is also a site ∅–specific mAb, is expected to enter clinical trials later this year, and MK-1654, a site IV–specific mAb, is currently being evaluated in a phase 1/2 trial in healthy preterm and full-term infants (NCT03524118).

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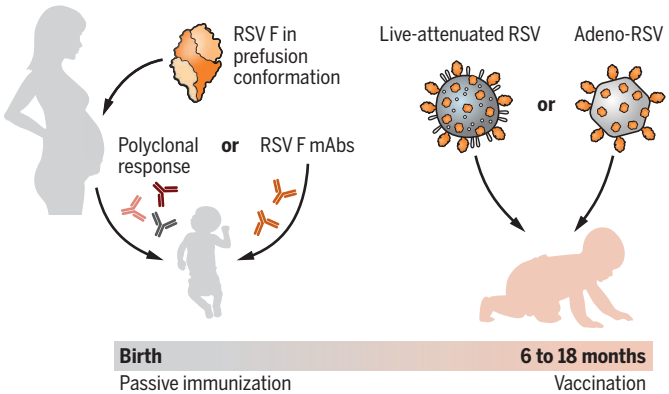
Maternal immunization to boost RSV-neutralizing antibodies is an alternative strategy for passive immunization of young infants (see the figure). The largest maternal immunization trial completed to date evaluated the baculovirus-expressed RSV F nanoparticle vaccine in 4636 pregnant women (*12*). The RSV F nanoparticle vaccine does not contain engineered mutations to stabilize the pre-F state and most closely resembles post-F (*7*). The overall efficacy of this vaccine against medically significant RSV LRTI and against RSV hospitalization was 39.4% and 44.4%, respectively (*12*). Although this landmark study failed to meet its primary efficacy endpoint for prevention of RSV LRTI in the first 90 days of life, it provided important lessons to guide subsequent maternal immunization studies with other candidate vaccines. Two RSV maternal vaccines containing engineered stabilized RSV pre-F are in phase 3 clinical development; both induce substantial neutralizing antibodies against RSV. The MATISSE trial of RSVpreF (NCT04424316) began in 2020 and is expected to enroll 6900 pregnant women over several RSV seasons. The GRACE trial of RSVpreF3 (NCT04605159) also began in 2020 and will enroll up to 10,000 pregnant women. In both of these multicountry trials, medically attended or assessed RSV LRTI and severe RSV LRTI in infants up to 6 months of age are primary endpoints.

Based on the outcomes of these trials, countries and funders may ultimately be able to choose between mAb administration and maternal immunization to protect young infants against RSV disease. In addition to the efficacy of individual products, each strategy has potential biologic advantages and disadvantages. mAbs are given directly to infants and would be unaffected by conditions that could influence transplacental antibody transfer (prematurity, HIV infection, hypergammaglobulinemia, administration late in pregnancy). However, mAbs are epitope-specific, and the emergence of escape mutants could threaten efficacy over time. Successful maternal immunization would induce high titers of polyclonal RSV-neutralizing antibodies, which should prevent immune escape, but transfer from mother to infant could be affected by the aforementioned conditions. Duration of protection, cost, and country-specific concerns such as the strength of maternal and neonatal health systems and of the Expanded Program on Immunization platform will also be important considerations.

## Passive and active immunization

Passive immunization against respiratory syncytial virus (RSV) is based on the fusion (F) protein. Young infants can be protected with F-specific antibodies, either administered directly to the infant as monoclonal antibodies (mAbs) or acquired through transplacental transfer from mother to infant following maternal immunization. Older infants and young children will be protected against RSV disease through vaccination with live-attenuated virus or adenoviruses expressing F.




Replicating vaccines for young children should generate immunity in a manner that avoids the aberrant immune response seen with the FI-RSV vaccine. Vectored and live-attenuated vaccines are being evaluated in phase 1/2 clinical trials. These studies typically require sequential evaluation in adults, RSV-experienced (seropositive) young children, and RSV-naïve (seronegative) infants, who are the target population. Vectored vaccines include Sendai virus expressing RSV F, evaluated in adults (NCT03473002), and adenovirus vectors expressing either RSV pre-F (Ad26.RSV.preF), evaluated in RSV-seropositive toddlers (NCT03303625) and now in RSV-seronegative toddlers (NCT03606512), or RSV F, nucleocapsid (N), and the transcription antitermination protein M2-1 (ChAd155-RSV), previously evaluated in toddlers (NCT02927873) and currently in 6- to 7-month-old infants (NCT03636906). Intranasal human parainfluenza virus type 3 (HPIV3) expressing RSV preF could offer protection against both RSV and HPIV3 (*13*) but awaits clinical evaluation.

Live-attenuated intranasal RSV vaccines are likely to induce durable local and systemic immune responses, including B and T cell responses, because they contain internal and surface viral proteins. Codon deoptimization (use of suboptimal codons to decrease gene expression) is one approach to attenuation, and a vaccine candidate with deoptimized expression of the viral interferon antagonists nonstructural protein 1 (NS1) and NS2, RSV G, and deletion of the small hydrophobic (*SH*) gene (MV-012-968 vaccine) was evaluated in adults and will be evaluated in RSV-seropositive children (NCT04444284). An alternative approach has been deletion of *NS1*, *NS2*, or of *M2-2*, which regulates viral RNA synthesis. Several of these vaccines have been evaluated in phase 1 trials in RSV-seronegative infants; the most promising induce durable immunity and prime for potent immune memory responses with substantial increases in neutralizing antibodies after natural exposure to RSV. In a preliminary post hoc pooled analysis, these vaccines protected against any medically attended RSV-associated respiratory illness, as well as RSV-LRTI (*14*). Further development of these vaccines is under way. Other approaches, including messenger RNA (mRNA) vaccines, are in early-stage clinical development.

Advances in structural biology and understanding of gene function have led to substantial progress in RSV vaccine and mAb development. Within the next decade, it is likely that more than one product will be available to protect the youngest infants. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic created particular challenges for progress during 2020, not least because RSV seasons were nearly absent in some settings (*15*) and markedly shifted in others. However, the high efficacy of SARS-CoV-2 vaccines, combined with the promising preliminary data from RSV products in development (*11, 14*), allows us to imagine similar results for RSV vaccines and mAbs in young children. Ultimately, global and equitable deployment of safe and effective vaccines and mAbs will allow us to fully appreciate and mitigate the burden of RSV disease in children. ■

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