[1] Princess Alexandra Hospital, Harlow, UK

[2] UCL Great Ormond Street Institute of Child Health, London, UK

Correspondence to: R L Smyth
rosalind.smyth@ucl.ac.uk

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Preventing respiratory syncytial virus bronchiolitis in infants

Early vaccine trials are under way, but other strategies look more promising at present

Elisabeth Robinson, [1] Rosalind L Smyth[2]

Bronchiolitis caused by respiratory syncytial virus (RSV) is the most common lower respiratory tract infection in young children. Around 2% of affected children require hospital admission, many of whom require intensive care. In 2019, an estimated 3.6% of all deaths worldwide in children aged 28 days to 6 months were attributable to RSV, with 97% of these deaths occurring in low and middle income countries.[1]

The covid-19 pandemic saw much of the world go into some form of lockdown from March 2020, lasting on and off until 2022, which meant children had much less exposure to all respiratory viruses. In the second half of 2022 the seasonal epidemic of RSV in Europe and the US happened early, caused many more children to be admitted to hospital, and, unusually, affected children over the age of 2 years, who had not yet been exposed.[2] A surge in the incidence of many different respiratory viral infections in the second half of 2022 may have caused novel interactions between different viruses, with uncertain consequences.[3]

Why is it that several vaccines against SARS-CoV-2 (a virus whose lethal effects accelerate with age) were developed and deployed in under a year, whereas a vaccine against RSV (which causes death at the other extreme of life) has not materialised after several decades of endeavour? Challenges for RSV vaccine development include the young age of peak incidence of bronchiolitis (2-3 months) and the difficulty, outside known high risk groups, in identifying infants susceptible to severe disease.

An ideal RSV vaccine would provide protection from bronchiolitis in the first six months of life when babies are most vulnerable, offer sustained immunity, and be both affordable and acceptable for administration to infants. Three main approaches to protection are currently being pursued: giving passive monoclonal antibodies directly to infants, maternal vaccination during pregnancy, and direct vaccination of infants. The F (fusion) glycoprotein on the surface of the virus is a recognised target for vaccine development, and the stabilisation of this protein before it fuses with the host cell membrane (prefusion) has been a recent critical advance.[4]

Passive monoclonal antibodies

Until recently, the anti-F monoclonal antibody palivizumab was the only licensed RSV prophylaxis for infants. Palivizumab reduces hospital admissions in infants at risk but requires monthly intramuscular administration at relatively high cost.[5 6] New anti-F antibodies with extended half lives are now becoming available, with one (clesrovimab) in phase 3 trials[7] and another (nirsevimab) approved by the European Medicines Agency and the UK Medicines and Healthcare Products Regulatory Agency in 2022. The Melody trial of nirsevimab in healthy term infants recently reported 76.4% (95% confidence interval 62.3% to 85.2%) efficacy against RSV lower respiratory tract infection 150 days after a single intramuscular dose.[8 9]

Maternal vaccination

Maternal vaccination strategies have recently shown great progress in phase 3 trials. Pfizer recently reported a preplanned, interim analysis showing that maternal vaccination with its prefusion protein vaccine was 81.8% effective (95% CI 40.6% to 96.3%) at preventing severe RSV infection through the first 90 days of the infant's life.[10] However, GSK's trial of another prefusion protein maternal vaccine halted recruitment early because of concerns about an increased incidence of preterm delivery among vaccinated participants.[11 12] The Pfizer trial did not report a significant increase in preterm births associated with its vaccine, but a non-significant imbalance between the vaccine and placebo groups has prompted experts to call for further evaluation of this potential adverse effect.[12] Of note, the GSK trial was conducted in low and middle income countries, where baseline rates of preterm birth are greater than in higher income settings.

Vaccines for infants

Two classes of infant vaccines are currently in phase 2 trials. A recombinant adenovirus vaccine encoding RSV prefusion F is being evaluated in children aged 12-24 months[13 14] and live attenuated vaccines for nasal administration are being tested in babies over the age of 6 months.[15-17] Nasal drop vaccines are an attractive option for young babies, and phase 1 studies showed that these live attenuated vaccines are immunogenic in seronegative children.[18 19] However, no trials have yet been done in babies younger than 6 months (the most vulnerable age group); the results of phase 2 trials in children are not published; and there's no sign of progression to phase 3.

Equitable access

While the burden of illness caused by RSV is substantial worldwide, it is particularly important that new vaccines and monoclonal antibodies are available to infants in low and middle income countries, where the greatest morbidity and mortality occurs.[20] Cost effectiveness models comparing maternal vaccination with monoclonal antibodies given to infants suggest that seasonal administration of monoclonal antibodies to neonates is currently the most cost effective strategy against RSV in high income countries.[21 22] Further research is urgently

needed to identify the best prevention strategies for low and middle income countries, where affordability is paramount and timing of administration is complicated by the lack of predictable seasonal RSV epidemics.[23]

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