

More than Baby Steps: Preventing Respiratory Syncytial Virus in Infants

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Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis and pneumonia in infants. According to the Centers for Disease Control, RSV results in more than 500 deaths and 50,000 hospitalizations per year in the USA in children under 5 years of age. Infants born prematurely, or infants with certain lung or heart conditions are at an increased risk of morbidity and mortality. Prevention via immunization or other modalities can greatly reduce such risks. Recent RSV vaccine approvals for prevention of RSV infection in the elderly and studies of these vaccines in pregnant mothers are paving the way for protection of newborns and infants from RSV. The objective of this review is to provide an update on the current modalities used in RSV prevention (in particular monoclonal antibodies) with a focus on vaccine options for pregnant women.

Keywords

Infants, lower respiratory tract infection, monoclonal antibodies, respiratory syncytial virus, RSV, vaccine

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Respiratory syncytial virus (RSV) is often of increased concern in the autumn and winter months, especially for women who are pregnant, or those with newborns.¹ Worldwide, RSV is the second leading cause of death (second to malaria) in children during their first year of life.² Elderly people (>60 years of age) are also at an increased risk of hospitalization and death due to RSV.³ Transmission rates typically peak in December and January in the USA.⁴ However, the COVID-19 pandemic is believed to have disrupted RSV infections, reducing the circulation of RSV and altering typical peaks in infection. Clinicians should therefore monitor for ‘off-season’ increases in RSV activity.⁵

RSV symptoms typically mimic a mild cold: runny nose, coughing, fever and wheezing.⁶ Those at increased risk are more likely to experience severe respiratory symptoms (e.g. rapid breathing, retractions) and may need to be hospitalized.⁷ Important preventive measures include: cleaning touched surfaces, frequent hand washing, not kissing the face of an infant, covering a cough or sneeze, avoiding those who are sick and remaining at home when sick. Currently, two monoclonal antibodies, nirsevimab and palivizumab, are available to help prevent severe RSV infection. Prevention may now include the opportunity for a pregnant mother to receive a vaccination against the virus as an alternative form of protection, similar to vaccines for influenza and pertussis.⁸

Vaccine development for RSV prevention is focused on six different methods: chimeric, live-attenuated, nucleic acid, particle-based, recombinant vector and subunit vaccines.⁹ Of these, subunit vaccines are being developed for use in pregnant women, though use is not limited to this population. In 1967 a formalin-inactivated vaccine increased the severity of RSV infection following exposure, requiring hospitalization of 80% of recipients and the deaths of two children.¹⁰ The early failure of the vaccine probably led to a more cautious approach in future development. Over 50 years later, two subunit vaccines to prevent RSV were approved by the US Food and Drug Administration (FDA) in rapid succession: GSK’s RSV prefusion F3 vaccine (RSVPreF3) on 3 May 2023 and Pfizer’s RSV prefusion F subunit vaccine (RSVPreF) on 31 May 2023.^{11,12} Both vaccines, however, were approved for adults 60 years old and above. Of these two, research for GSK’s use as a maternal candidate vaccine has been suspended due to safety concerns, while Pfizer’s RSVPreF vaccine has been approved for use in pregnant mothers.

RSV-M-301 (Novavax)

In addition to vaccines for the elderly, manufacturers are developing products for protection of newborns and infants. To protect newborns and infants, vaccinating the pregnant mother is considered to be the most effective route. The PREPARE study (A Study to Determine the Safety and Efficacy of the RSV F Vaccine to Protect Infants Via Maternal Immunization; ClinicalTrials.gov identifier: NCT02624947) was the first phase III clinical study to test an RSV maternal vaccine, using a fusion protein nanoparticle-based vaccine as opposed to vaccines containing recombinant pre-F-proteins.¹³ In a 2:1 ratio pregnant women expected to give birth near the peak RSV season

received a single intramuscular dose of RSV F-protein vaccine or placebo. Of 4,636 women enrolled in the study, 4,579 live births were reported. The primary endpoint, which examined RSV-associated medically significant lower respiratory tract infection (LRTI) during the first 90 days of life, was not met between women receiving the vaccine compared with placebo (1.5% versus 2.4%, respectively).¹³ Despite not reaching statistical significance, a post hoc analysis showed that infants of mothers receiving the vaccine were less likely to have pneumonia in the first 6 months and first year of life.

The phase III RESOLVE study (A Study to Evaluate the Efficacy of an RSV F Vaccine in Older Adults; ClinicalTrials.gov identifier: NCT02608502), which previously examined this RSV F-protein vaccine in older adults, also did not achieve its primary endpoint. While the study showed the vaccine was well tolerated it did not show vaccine efficacy.¹⁴ It has been suggested that the design of the vaccine itself has led to its ineffectiveness. It is possible that the vaccine, since given to pregnant mothers, is only protecting the infant for a short period of time, or may not have sufficient immunogenicity due to its pre-fusogenic F-proteins as opposed to recombinant pre-F-proteins.¹⁵ With the data from these two phase III studies, it does not appear that this vaccine will move forward.

Respiratory syncytial virus prefusion F subunit vaccine in adults (Pfizer)

The phase IIb study of RSVPreF included a single dose of 120 or 240 µg administered to pregnant women between 24 and 36 weeks of gestation.¹⁶ Participants were randomized 1:1:1:1 to 120 or 240 µg, with or without aluminium hydroxide, or to placebo. A prespecified interim analysis was conducted and all 406 pregnant participants were included related to the safety analyses. Mild to moderate pain at the injection site was the most commonly reported adverse event and was more frequent in the group who received the vaccine with aluminium hydroxide. Serious adverse events reported were considered unrelated to the vaccination with most also unrelated to pregnancy.¹⁶ Furthermore, the investigators determined that none of the serious adverse events reported in the observation phase were related to maternal vaccination. Overall, 3 of the 405 infants in the RSVPreF groups and 5 of the 103 infants in the placebo group were reported to have medically attended RSV-associated LRTI. The observed efficacies against medically attended RSV-associated LRTI and severe RSV-associated LRTI were 84.7% and 91.5%, respectively.¹⁴ These results led to the FDA designation of Breakthrough Therapy for infants up to 6 months of age in preventing RSV-associated LRTI.¹⁷

A phase III randomized, double-blind study, MATISSE (MATernal Immunization Study for Efficacy and Safety; ClinicalTrials.gov identifier: NCT04424316), evaluated the safety and efficacy of a single 120 µg intramuscular injection of RSVPreF compared with placebo.¹⁸ Healthy women between 24 and 36 weeks of gestation were assigned to RSVPreF or placebo in a 1:1 ratio. Ultimately, infants born to healthy women vaccinated during pregnancy were assessed based on the percentage reduction in the incidence of medically attended respiratory infections due to RSV up to 180 days of life. Participants were also evaluated for safety and immunogenicity outcomes.¹⁹ A total of 3,682 women were evaluated with severe RSV-associated LRTI (at 180 days after birth), which occurred 19 times in those in the vaccine group compared with 62 times in the placebo group, contributing to a vaccine efficacy of 69.4% and 97.58%, respectively. Statistical significance was not met for medically attended RSV-associated LRTI, but at 90 days after birth LRTI occurred in 24 infants in the vaccine group compared with 56 infants in the placebo group, and in 57 infants and 117 infants at 180 days, respectively. The most common adverse event reported was injection-site pain, which

was higher in the vaccine group (41%) compared with the placebo group (10%).¹⁸ Overall, RSVPreF was successful in reducing the number of medically attended severe RSV-associated LRTIs in infants when the mother was vaccinated during pregnancy while also showing a favourable safety profile. However, concerns arose regarding an increased rate of premature births in the vaccinated group versus the unvaccinated group: 5.7% (202/3568) and 4.7% (169/3558), respectively.¹⁹ The difference was not statistically different, but it is unknown if this was due to the study being underpowered to detect a difference. Similarly, pre-eclampsia was observed in pregnant women at a higher rate in the study group compared with the placebo group: 1.8% (68/3682) versus 1.4% (53/3675). In August 2023, the RSVPreF vaccine was recommended to prevent RSV infection in infants up to 6 months of age via maternal immunization in the third trimester by the FDA Vaccines and Related Biological Products Advisory Committee.²⁰ Due to the potential risk of preterm birth, it was approved for 32 weeks of gestation, and up to 37 weeks. Finally, a possible interaction with the Tdap vaccine needs to be monitored. Considered to be statistically non-inferior, when RSVPreF was administered concurrently with Tdap, a reduced potency of the Tdap vaccine against pertussis was seen (as measured by lower geometric means of acellular pertussis antigens) compared with when Tdap was administered without RSVPreF.²⁰

In addition to RSVPreF, several other therapies are being developed, including additional vaccines and non-vaccine modalities, such as monoclonal antibodies (mAbs) and antivirals (See *Table 1*).

Other vaccines mRNA-1345 (Moderna)

Moderna's vaccine, mRNA-1345, is currently undergoing evaluation for RSV prevention. In its phase II/III study (A Study to Evaluate the Safety and Efficacy of mRNA-1345 Vaccine Targeting Respiratory Syncytial Virus [RSV] in Adults ≥60 Years of Age; ClinicalTrials.gov identifier: NCT05127434), participants at least 60 years of age were randomized to receive mRNA-1345 or placebo in a 1:1 ratio. The study is evaluating prevention of RSV-associated LRTI over a period of 12 months.²³ The interim analysis reported on the primary efficacy endpoints of RSV associated LRTI with either "at least two symptoms" or "at least three symptoms". For cases of RSV-associated LRTI with at least two symptoms, there were 9 cases in the mRNA-1345 group and 55 in the placebo group, for a total of 64 cases. For the endpoint evaluating RSV-associated LRTI with at least three symptoms, three cases were reported in the mRNA-1345 group compared with 17 cases in the placebo group, and thus the study met both primary endpoints with efficacy (83.7% for two or more symptoms and 82.4% for three or more symptoms).²⁴ The mRNA-1345 vaccine will be studied in the phase III study, ConquerRSV (ClinicalTrials.gov identifier: NCT05127434), including approximately 37,000 adults at least 60 years of age and will also be evaluated in paediatric patients in a phase I study (Dose Escalation Study to Evaluate Safety, Reactogenicity, and Immunogenicity of mRNA-1345 in Healthy Adults and in Children Who Are Respiratory Syncytial Virus [RSV]-Seropositive; ClinicalTrials.gov identifier: NCT04528719).²⁴ The phase I study is currently recruiting and aims to evaluate mRNA-1345 and mRNA-1365, the latter a vaccine targeting both RSV and human metapneumovirus in infants aged 5–24 months. The study expects to include 210 participants and conclude in July 2026.²⁵

Respiratory syncytial virus prefusion F3 subunit maternal vaccine (GSK)

A phase II study (Study of Safety, Reactogenicity and Immunogenicity of GlaxoSmithKline's (GSK) Respiratory Syncytial Virus [RSV] Maternal

Table 1: Summary of modalities to prevent RSV infection

Modality	Name	Effectiveness	Notes
Vaccine	RSV-M-301	Did not reach statistical analysis	A post hoc analysis showed that infants of mothers receiving the vaccine were less likely to have pneumonia in the first 6 months and 1 year of life
	RSVPreF	MATISSE study showed decreased LRTI occurring at 90 days and 180 days for maternal vaccination ¹⁹	Increased rate of premature births in the vaccinated group. Possible interaction with Tdap
	RSVPreF3	IgG titres were increased in infants studied and highest at birth with subsequent declines up to day 181 compared with placebo ²¹	Enrolment and vaccination stopped due to possible increased risk of premature births in pregnant mothers. Approved for individuals 60 years of age and older to prevent LRTD caused by RSV
mAb	Palivizumab	IMPACT-RSV study showed an absolute reduction (5.8%) in RSV hospitalizations among infants who received prophylaxis compared with placebo	A relative risk reduction of 45.3% in RSV hospitalizations was recorded in a study including children with congenital heart disease
	Niresvimab	The Melody study showed an approximately 75% relative risk reduction in RSV LRTI in infants compared with placebo ²²	
Antiviral	Ribavirin	Some clinical benefits if given early in infection	Limited due to potential toxicity and cost

LRTD = lower respiratory tract disease; LRTI = lower respiratory tract infection; mAb = monoclonal antibody; RSV = respiratory syncytial virus; RSVPreF = RSV prefusion F subunit vaccine; RSVPreF3 = RSV prefusion F3 vaccine.

Unadjuvanted Vaccine in Healthy Pregnant Women [Aged 18 to 40 Years] and Their Infants; ClinicalTrials.gov identifier: NCT04126213) randomized 534 healthy pregnant women to receive RSVPreF3 maternal vaccine (RSV MAT) 60 µg, RSV MAT 120 µg or placebo. The one intramuscular dose was administered in the deltoid and both vaccinated mothers and their infants were evaluated.²⁶ The primary safety outcome was percentage of maternal participants with any solicited administration site events including any pain, erythema and/or swelling. The most common event was any pain, with 57.1% of the 60 µg vaccine group experiencing the event compared with 52% in the 120 µg vaccine group and 15.2% in the placebo group.²⁶ Neutralizing antibody (nAb) geometric mean titres (GMT) at post-vaccination day 31 were compared with pre-vaccination values in all mothers. At pre-vaccination nAb titres for RSV-A and RSV-B in mothers were 672–736 and 970–1145, respectively. When compared with post-vaccination values, titres increased in the 60 and 120 µg groups 12.7–14.9-fold against RSV-A and 10.6–13.2-fold against RSV-B.²¹ Titres against RSV-A, RSV-B and anti-RSVPreF3 IgG geometric mean concentrations were recorded from infants and were highest at birth with subsequent declines up to day 181. The nAb titres in infants born from the 60 and 120 µg groups were higher at all time points compared with the placebo group.²¹

The GRACE (A Phase III Double-blind Study to Assess Safety and Efficacy of an RSV Maternal Unadjuvanted Vaccine, in Pregnant Women and Infants Born to Vaccinated Mothers; ClinicalTrials.gov identifier: NCT04605159) study, a phase III double-blind study evaluating a single intramuscular dose of the vaccine administered to pregnant women, has stopped enrolment and vaccination as a result of a safety signal detected by the independent data monitoring committee due to an increased risk of premature birth and neonatal deaths. The primary outcome of the study was the number of infants with medically assessed RSV-associated LRTIs up to 6 months of age.²⁷

Another phase III study (A Study on the Safety and Immune Response to an Unadjuvanted RSV Maternal Vaccine, in High Risk Pregnant Women Aged 15 to 49 Years and Infants Born to the Vaccinated Mothers; ClinicalTrials.gov identifier: NCT04980391) randomized 367 high-risk pregnant women to receive a single intramuscular injection of RSV MAT or placebo. The open-label study aimed to examine the safety, reactogenicity and immune response of RSV MAT in pregnant women between 24 and 36 weeks of gestation and in the infants born to the vaccinated mothers. Following

the recommendation of the independent data monitoring committee of the GRACE study, enrolment and vaccination was stopped.²⁸

Monoclonal antibodies

Palivizumab

In 1998 palivizumab was the first mAb to be approved for prophylaxis of LRTI caused by RSV in children, specifically those at risk of severe disease.²⁹ Palivizumab targets RSV's surface fusion glycoprotein and is indicated in infants less than 1 year of age who were born very pre-term (less than 29 weeks' gestation) before the start of the peak RSV season.³⁰ Infants with bronchopulmonary dysplasia who are 24 months of age or younger at the beginning of the peak RSV season and had required medical treatment within the previous 6 months and infants 24 months of age or younger with haemodynamically significant congenital heart disease at the beginning of the peak RSV season may benefit from palivizumab.³¹ Infants with certain conditions (e.g. chronic lung disease, congenital heart disease) may benefit from palivizumab; however, palivizumab is considered to be of little benefit in cases without these conditions.³² The Infectious Diseases and Bronchiolitis Guidelines Committee states that "palivizumab prophylaxis has limited effect on RSV hospitalizations on a population basis, no measurable effect on mortality, and a minimal effect on subsequent wheezing."³³ Further review of palivizumab is beyond the scope of this article, but additional discussion and recommendations can be found in the aforementioned American Academy of Pediatrics guidelines.³³

Niresvimab

A second mAb developed by Sanofi and AstraZeneca was approved on 16 July 2023 for children up to 2 years of age for the prevention of RSV infection.³⁴ Approval was based on data from A Study to Evaluate the Safety and Efficacy of MEDI8897 for the Prevention of Medically Attended Lower Respiratory Tract Infection Due to Respiratory Syncytial Virus in Healthy Late Preterm and Term Infants (MELODY; ClinicalTrials.gov identifier: NCT03979313).²² The injection may be administered prior to or during the infant's first seasonal exposure to RSV. Less than 1 month later, in autumn 2023, the Centers for Disease Control (CDC) recommended niresvimab to be used.³⁵ Those in particular who may benefit are: children who were born prematurely and have chronic lung disease, children who are severely immunocompromized, children with cystic fibrosis who have severe disease, and American Indian and Alaska Native children.

In the Melody study, 1,490 infants born at a gestational age of at least 35 weeks were randomized in a 2:1 ratio to receive either nirsevimab or placebo.²² The primary endpoint was “medically attended RSV-associated LRTI through 150 days” following injection. A secondary endpoint examined hospitalization for RSV-associated LRTI up to 150 days following injection. Nirsevimab was shown to be 74.5% effective in preventing infection, but showed no difference in preventing hospitalization. In regard to serious adverse events, percentages were similar between nirsevimab and placebo (6.8% and 7.3%, respectively). Additionally, the phase II/III MEDLEY (ClinicalTrials.gov identifier: NCT03959488) study examined the safety of nirsevimab in infants eligible to receive palivizumab.³⁶ In total, 900 preterm infants (less than 35 weeks’ gestational age), as well as infants with congenital heart disease or chronic lung disease requiring therapy within 6 months, were enrolled. Adverse events were similar between the two mAbs, regardless of disease severity.

Antivirals

Ribavirin

Currently, ribavirin is the only antiviral used for treatment of RSV infection, primarily the aerosolized formulation, though the oral formulation has

been used.³⁷ Ribavirin is rarely utilized due to few clinical benefits in studies: no decrease in mechanical ventilation, length of hospital stay or mortality. Additionally, adverse events such as nausea, headaches, the potential to worsen bronchospasm and the risk of teratogenicity have been reported.³⁸

Summary

Maternal vaccinations for preventing RSV infection in infants provides a much-needed addition to reducing serious RSV morbidity and mortality, LRTIs, and allows infants to gain protection well before any potential RSV exposure. Of note, passive immunity is dependent on gestational age with very little transfer of antibodies to RSV occurring prior to 28–32 weeks’ gestation; therefore, many pre-term infants, who are especially vulnerable to RSV, may not fully benefit from vaccines and may be candidates for treatment with mAbs.^{39,40} For mothers unable or unwilling to receive the vaccine, mAbs may be the only option. In conclusion, prevention is imperative at this time, as developing effective, well-tolerated treatment options has proved challenging.^{39,40}



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