More than Baby Steps: Preventing Respiratory Syncytial Virus in Infants

Jessica Huston[1] and Eric F Egelund[1,2]

1. Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida, Jacksonville, FL, USA; 2. Infectious Disease Pharmacokinetics Laboratory, Gainesville, FL, USA

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

Disclosures: Jessica Huston and Eric Egelund have no financial or non-financial relationships or activities to declare in relation to this article.

Review process: Double-blind peer review.

Compliance with ethics: This article involves a review of the literature and did not involve any studies with human or animal subjects performed by any of the authors.

Data availability: Data sharing is not applicable to this article as no datasets were generated or analysed during the current study/during the writing of this article.

Authorship: The named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Received: 16 August 2023

Accepted: 8 November 2023

Citation: *touchREVIEWS in Infectious Diseases.* 2024;3(1):Online ahead of journal publication

Corresponding author: Dr. Eric F Egelund, Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida, 580 W. 8th Street, Jacksonville, FL 32209, USA. E: eegelund@ufl.edu

Support: No funding was received in the publication of this article.

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 1:1:1:1:1 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 Unadjuvanted Vaccine in Healthy Pregnant Women [Aged 18 to 40 Years] and Their Infants; ClinicalTrials.gov identifier: NCT04126213) randomized

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 tites 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.

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 conditons.[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 niresvimab and placebo (6.8% and 7.3%, respectively). Additionally, the phase II/III MEDLEY (ClinicalTrials.gov identifier: NCT03959488) study examined the safety of niresvimab 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] ❑

1. McLaughlin JM, Khan F, Schmitt H-J, et al. Respiratory syncytial virus-associated hospitalization rates among US infants: A systematic review and meta-analysis. *J Infect Dis*. 2022;225:1100–11. DOI: 10.1093/infdis/jiaa752.
2. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the global burden of disease study 2010 [Erratum in Lancet. 2013;381(9867):628. Almazroa, Mohammad A [added]; Memish, Ziad A [added]]. *Lancet*. 2012;380:2095–128. DOI: 10.1016/S0140-6736(12)61728-0.
3. McLaughlin JM, Khan F, Begier E, et al. Rates of medically attended RSV among US adults: a systematic review and meta-analysis. *Open Forum Infect Dis*. 2022;9:ofac300. DOI: 10.1093/ofid/ofac300.
4. Hamid S, Winn A, Parikh R, et al. Seasonality of respiratory syncytial virus — United States, 2017-2023. *MMWR Morb Mortal Wkly Rep*. 2023;72:355–61. DOI: 10.15585/mmwr.mm7214a1.
5. Olsen SJ, Winn AK, Budd AP, et al. Changes in influenza and other respiratory virus activity during the COVID-19 pandemic — United States, 2020–2021. *MMWR Morb Mortal Wkly Rep*. 2021;70:1013–9. DOI: 10.15585/mmwr.mm7029a1.
6. Centers for disease control. Respiratory syncytial virus infection (RSV). symptoms and care. 2023. Available at: www.cdc.gov/rsv/about/symptoms.html (Date last accessed: 4 April 2024).
7. Updyke EA, Welsh E. Episode 111 RSV: What's syncytial anyway? This podcast will kill you. 2023. Available at: https://thispodcastwillkillyou.com/2023/01/31/episode-111-rsv-whats-syncytial-anyway/ (Date last accessed: 28 June 2023).
8. Centers for Disease Control and Prevention. Respiratory syncytial virus infection (RSV). RSV prevention: how to protect yourself and others. 2024. Available at: www.cdc.gov/rsv/about/prevention.html (Date last accessed: 4 April 2024).
9. Mazur NI, Terstappen J, Baral R, et al. Respiratory syncytial virus prevention within reach: The vaccine and monoclonal antibody landscape. *Lancet Infect Dis*. 2023;23:e2–21. DOI: 10.1016/S1473-3099(22)00291-2.
10. Acosta PL, Caballero MT, Polack FP. Brief history and characterization of enhanced respiratory syncytial virus disease. *Clin Vaccine Immunol*. 2015;23:189–95. DOI: 10.1128/CVI.00609-15.
11. GSK. US FDA APPROVES GSK's Arexvy, the world's first respiratory syncytial virus (RSV) vaccine for older adults. [press release]. 2023. Available at: www.gsk.com/en-gb/media/press-releases/us-fda-approves-gsk-s-arexvy-the-world-s-first-respiratory-syncytial-virus-rsv-vaccine-for-older-adults/ (Date last accessed: 4 April 2024).
12. Pfizer. US FDA Approves ABRYSVO™, Pfizer's Vaccine for the Prevention of Respiratory Syncytial Virus (RSV) in Older Adults. 2023. Available at: www.pfizer.com/news/press-release/press-release-detail/us-fda-approves-abrysvotm-pfizers-vaccine-prevention#:~:text=(NYSE%3A%20PFE)%20announced%20today,individuals%2060%20years%20and%20olde (Date last accessed: 4 April 2024).
13. Madhi SA, Polack FP, Piedra PA, et al. Respiratory syncytial virus vaccination during pregnancy and effects in infants. *N Engl J Med*. 2020;383:426–39. DOI: 10.1056/NEJMoa1908380.
14. Novavax. Novavax Annnounces Topline RSV F vaccine data from two clinical trials in older adults [press release]. 2016. Available at: https://ir.novavax.com/press-releases/2016-09-25-Novavax-Announces-Topline-RSV-F-Vaccine-Data-from-Two-Clinical-Trials-in-Older-Adults (Date last accessed: 4 April 2024).
15. Pharmaceutical Technology. After second phase III failure, is Novavax's RSV vaccine finished? 2019. Available at: www.pharmaceutical-technology.com/analyst-comment/novavax-rsv-vaccine-failure/ (Date last accessed: 4 April 2024).
16. Simões EAF, Center KJ, Tita ATN, et al. Prefusion F protein-based respiratory syncytial virus immunization in pregnancy. *N Engl J Med*. 2022;386:1615–26. DOI: 10.1056/NEJMoa2106062.
17. Pfizer. Pfizer announces positive top-line data from phase 3 trial of older adults for its Bivalent respiratory syncytial virus (RSV) vaccine candidate. 2022. Available at: www.pfizer.com/news/press-release/press-release-detail/pfizer-announces-positive-top-line-data-phase-3-trial-older (Date last accessed: 4 April 2024).
18. Kampmann B, Radley D, Munjal I. Bivalent prefusion F vaccine in pregnancy to prevent RSV illness in infants. *N Engl J Med*. 2023;389:1053–5. DOI: 10.1056/NEJMc2307729.
19. AbrysvoTM [Package Insert]. New York, NY. Pfizer Inc. 2023. Available at: www.fda.gov/media/168889/download (Date last accessed: 27 March 2024).
20. Pfizer. FDA advisory committee votes in support of approval for Pfizer's vaccine candidate to help prevent RSV in infants through maternal immunization [press release]. 2023. Available at: www.pfizer.com/news/press-release/press-release-detail/fda-advisory-committee-votes-support-approval-pfizers (Date last accessed: 4 April 2024).
21. Bebia Z, Reyes O, Jeanfreau R, et al. Safety and Immunogenicity of an investigational respiratory syncytial virus vaccine (Rsvpref3) in mothers and their infants: A phase 2 randomized trial. *J Infect Dis*. 2023;228:299–310. DOI: 10.1093/infdis/jiad024.
22. Hammitt LL, Dagan R, Yuan Y, et al. Nirsevimab for prevention of RSV in healthy late-preterm and term infants. *N Engl J Med*. 2022;386:837–46. DOI: 10.1056/NEJMoa2110275.
23. ClinicalTrials.gov. A study to evaluate the safety and efficacy of mRNA-1345 vaccine targeting respiratory syncytial virus (RSV) in adults ≥60 years of age. 2024. Available at: https://clinicaltrials.gov/study/NCT05127434 (Date last accessed: 4 April 2024).
24. Contagion Live. New regulatory filings advance Moderna's mRNA-1345 RSV vaccine. 2023. Available at: www.contagionlive.com/view/new-regulatory-filings-advance-moderna-s-mrna-1345-rsv-vaccine (Date last accessed: 4 April 2024).
25. ClinicalTrials.gov. A Safety, Tolerability, and Immunogenicity Study of mRNA-1345 and mRNA-1365 in Participants Aged 5 Months to <24 Months. 2024. Available at: https://classic.clinicaltrials.gov/ct2/show/NCT05743881 (Date last accessed: 4 April 2024).
26. Clinicaltrials.Gov. Study of Safety, Reactogenicity and Immunogenicity of GlaxoSmithKline's (GSK)Respiratory Syncytial Virus (RSV)Maternal Unadjuvanted Vaccine in Healthy Pregnant Women (Aged 18 to 40 Years) and Their Infants. 2021. Available at: www.clinicaltrials.gov/study/NCT04126213 (Date last accessed: 4 April 2024).
27. ClinicalTrials.gov. 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 (GRACE). 2024. Available at: https://classic.clinicaltrials.gov/ct2/show/NCT04605159 (Date last accessed: 4 April 2024).
28. ClinicalTrials.gov. 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. 2024. Available at: https://classic.clinicaltrials.gov/ct2/show/NCT04980391 (Date last accessed: 4 April 2024).
29. Goldstein M, Harding B, Fayard E. Guidance for palivizumab prophylaxis and implications for compliance. *Pediatr Pulmonol*. 2021;56:3575–6. DOI: 10.1002/ppul.25634.
30. Huang K, Incognito L, Cheng X, et al. Respiratory syncytial virus-neutralizing monoclonal antibodies motavizumab and palivizumab inhibit fusion. *J Virol*. 2010;84:8132–40. DOI: 10.1128/JVI.02699-09.
31. Chatterjee A, Mavunda K, Krilov LR. Current state of respiratory syncytial virus disease and management. *Infect Dis Ther*. 2021;10:5–16. DOI: 10.1007/s40121-020-00387-2.
32. Palivizumab, a Humanized respiratory syncytial virus Monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. The impact-RSV study group. *Pediatrics*. 1998;102:531–7.
33. American Academy of Pediatrics Committee on Infectious Diseases; American Academy of Pediatrics Bronchiolitis Guidelines Committee. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection [Erratum in: *Pediatrics*. 2014 Dec;134(6):1221. PMID: 25070315.]. *Pediatrics*. 2014;134:415–20. DOI: 10.1542/peds.2014-1665.
34. Astrazeneca. Beyfortus approved in the US for the prevention of RSV lower respiratory tract disease in infants. 2023. Available at: www.astrazeneca.com/media-centre/press-releases/2023/beyfortus-approved-in-the-us-for-the-prevention-of-rsv-lower-respiratory-tract-disease-in-infants.html#:~:text=AstraZeneca%20and%20Sanofi's%20Beyfortus%20(nirsevimab,remain%20vulnerable%20to%20severe%20RSV (Date last accessed: 4 April 2024).
35. Centers for disease control and prevention. CDC recommends a powerful new tool to protect infants from the leading cause of hospitalization [press release]. 2023. Available at: www.cdc.gov/media/releases/2023/p-0803-new-tool-prevent-infant-hospitalization-.html (Date last accessed: 4 April 2024).
36. Domachowske J, Madhi SA, Simões EAF, et al. Safety of nirsevimab for RSV in infants with heart or lung disease or prematurity. *N Engl J Med*. 2022;386:892–4. DOI: 10.1056/NEJMc2112186.
37. Mir WAY, Shrestha DB, Rana W, et al. Successful treatment of respiratory syncytial virus infection in an immunocompromised patient with ribavirin. *Cureus*. 2021;13. DOI: 10.7759/cureus.16930.
38. Eiland LS. Respiratory syncytial virus: Diagnosis, treatment and prevention. *J Pediatr Pharmacol Ther*. 2009;14:75–85. DOI: 10.5863/1551-6776-14.2.75.
39. Langedijk AC, Bont LJ. Respiratory syncytial virus infection and novel interventions. *Nat Rev Microbiol*. 2023;21:734–49. DOI: 10.1038/s41579-023-00919-w.
40. Hayden FG, Whitley RJ. Respiratory syncytial virus antivirals: Problems and progress. *J Infect Dis*. 2020;222:1417–21. DOI: 10.1093/infdis/jiaa029.