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REVIEWS



# Maternal RSV vaccine development. Where to from here?

Ahinsa Gunatilaka and Michelle L. Giles

Department of Obstetrics and Gynaecology, Monash University, Melbourne, Australia

**ABSTRACT**

Respiratory syncytial virus (RSV) is a common cause of acute lower respiratory tract infection and is responsible for a large proportion of infant morbidity and mortality worldwide. Most RSV-related deaths occur in children under six months, and the majority of these occur in low-income settings. To date, there is no known efficacious treatment for RSV infection; hence, prevention remains an important strategy to reduce the global burden of disease. Monoclonal antibodies and vaccinations are currently the two main approaches for prevention of RSV disease. Maternal RSV vaccination is of particular interest as a strategy to protect infants during their most vulnerable period as this approach has proven highly efficacious in other vaccine-preventable conditions such as pertussis and influenza. As results from ongoing phase III clinical trials become available, important decisions will need to be made about the priority and potential implementation of RSV vaccines alongside other public health measures.

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## Introduction

Respiratory syncytial virus (RSV), of the *Pneumoviridae* family, is a common pathogen responsible for approximately 22% of severe acute lower respiratory tract infections in children worldwide.[1,2] Around 50–70% of infants are exposed to RSV by the age of two years,[3] and in most healthy adults and older children, RSV has a mild to moderate, self-limiting clinical presentation of upper respiratory tract infection.[4,5] Yet, in certain patient groups, such as infants and young children, the elderly, the immunocompromised, and those with existing comorbidities, the consequences of RSV infection can be severe.[1,6] In fact, lower respiratory tract infection (LRTI) is the leading cause of infant morbidity and mortality globally, ahead of malaria, responsible for 20% of post-neonatal infant death; RSV is estimated to be associated with at least 22% of LRTIs.[2,7] In 2015, RSV was responsible for approximately 3.2 million hospital admissions and over 59,000 in-hospital deaths in children under five years of age.[2,6,8] Approximately 46% of the in-hospital deaths occurred in infants under six months of age.[2] Infants less than one year of age are at the highest risk of severe RSV infection and hospitalization,[2,8] and infants born prematurely are particularly susceptible to serious illness resulting from RSV infection, with rates of hospitalization around three times that of term infants less than one year of age (63.8 per 1000 children per year amongst preterm infants compared with 19.2 per 1000 children amongst term infants <1 year).[8]

Most pediatric RSV episodes occur in low- and middle-income countries, with an incidence of around 117.2 per 1000 children aged 0–5 months in low-income settings as compared with 66.1 per 1000 children aged 0–5 months in high-income settings.[2] RSV is a leading cause of mortality in low-income settings, although the exact burden of disease in developing countries is unclear as not all countries collect RSV surveillance data.[9] Given the absence of effective treatment, it is vital that we continue to explore diverse preventative strategies and treatment options ensuring a multifaceted approach to controlling this disease. An important aspect to the advancement of these preventative strategies is robust data on the burden of disease from this pathogen, particularly in low- and middle-income countries.[2,9] The overwhelming proportion of RSV-associated deaths in childhood (approximately 99%) occur in low-income settings, usually in children under six months of age.[2] The median age for RSV-related deaths in low- or lower middle-income countries is slightly younger, reported as five months as compared with seven months in high-income countries.[10]

## RSV disease in pregnant women

RSV infection in pregnant women can have a variable clinical course, ranging from mild disease comparable to that of a non-pregnant immunocompetent adult to more severe illness with potential for complications. Two case series from health services in the United States described several pregnancies in which RSV was diagnosed.[11,12] The outcomes for the mothers described in these studies ranged from a relatively mild clinical presentation for which outpatient management alone was adequate, to cases of RSV disease requiring admission to the intensive care unit and mechanical ventilation.[11,12] In some reported cases, RSV infection also resulted in adverse pregnancy outcomes, requiring early delivery by cesarean section.[11,12] Similarly, a cohort study conducted across four high-income countries identified that among hospitalized pregnant women, there was a significantly higher rate of pneumonia diagnosed in RSV-positive women compared to RSV-negative women, affecting 38% and 19% of

**CONTACT** Michelle L. Giles Michelle.giles@monash.edu Infectious Diseases Physician, Department of Obstetrics and Gynaecology, Monash University, 246 Clayton Road, Clayton, Victoria, 3168

women, respectively.[13] Overall, significant differences in rates of adverse pregnancy outcomes, such as preterm birth, small-for-gestational age, or low birthweight, have not been recognized;[13,14] however, Regan's cohort study did note that following hospitalizations for acute respiratory illness where delivery did not occur, there was a higher rate of subsequent preterm birth amongst RSV-positive women which was statistically significant (RSV-positive women, 29%, and RSV-negative women, 15%).[13] In general, the incidence of symptomatic RSV illness in pregnancy is low, but the potential for serious illness and pregnancy complications should be considered.[13,15] Existing studies in this area are limited by their small sample sizes which may be underpowered to detect differences in adverse maternal and pregnancy outcomes.[13,15,16]

In addition to protection resulting from transplacental passage of antibodies during pregnancy, a further potential benefit of maternal RSV vaccines may be obtained from the effect of herd immunity. High rates of vaccine coverage in maternal populations may provide protection for newborn infants whose mothers are unvaccinated by reducing the prevalence of RSV disease amongst the vaccinated maternal and infant population.[17] While there are currently minimal data demonstrating this potential protective effect, further studies including mathematical modeling of disease may be warranted to understand the full impact of RSV vaccination programs beyond just protection of newborns at birth.

## RSV disease in children

The effect of RSV infection in infants tends to be more severe than that seen in healthy adults and remains one of the leading causes of infant morbidity and mortality, estimated to be responsible for 118,200 deaths in children under 5 years in 2015.[2,8] The mortality rate of RSV infection is highest in the first year of life, estimated to be around 6.19 per 100,000 children, and subsequently decreases with increasing age, dropping to 0.79 per 100,000 children in the second year of life and reaching 0.18 per 100,000 children by the fifth year of life.[18] The range of clinical presentations caused by RSV infection in infants is wide, with bronchiolitis the most common. RSV has been reported to be responsible for approximately 50–90% of infant hospitalizations for bronchiolitis and 5–40% of infant hospitalizations for pneumonia.[19] But RSV infection can also lead to complications such as acute otitis media and conjunctivitis, with rates of 48% and 11%, respectively, among children hospitalized due to RSV infection.[20] Usually, RSV has an incubation period of around 4–6 days, which is then followed by symptoms such as nasal congestion, mucus discharge, fever, and cough, and can progress to more significant respiratory distress presenting with chest retractions and wheezing, while preterm infants (<37 weeks) may also present with apnea.[3,4,21] The clinical course of RSV infection depends on a complex interplay of host, virus, and environmental factors, and predicting disease progression and outcomes for individual infants is challenging.[22] The severity of illness is often associated with underlying factors, including prematurity, chronic lung disease, and immunodeficiency, but children who are previously well can also experience severe, life-threatening RSV-related illness.[23] In fact, a large-scale prospective population-based surveillance study of acute respiratory infections in children conducted in 2009 found that amongst children hospitalized for RSV infections, only 34% had an existing high-risk comorbidity.[4] Prematurity and young age are the key independent risk factors associated with illness severity,[4] although other factors have been associated with severity, including altered gut microbiota and vitamin D deficiency.[23–25] In the CASTOR study, compared to full-term infants, preterm infants had a fourfold higher risk of being hospitalized for bronchiolitis, RSV-confirmed, and all types.[26] Given the significant impact of RSV infection in young infants, this age group remains a priority population for preventative strategies.

## Preventative strategies

In the absence of efficacious treatment modalities for RSV disease in infants, prevention remains the most important strategy to impact on the burden of disease caused by RSV. There are two modalities currently being considered for prevention or studied in clinical trials: passive immunity conferred by monoclonal antibodies to the RSV fusion (F) protein and maternal immunization.

Palivizumab and Motavizumab are two such monoclonal antibodies.[27–29] Palivizumab is a monoclonal antibody to the RSV F glycoprotein that has been demonstrated in randomized controlled trials to reduce hospitalization for RSV-associated lower respiratory tract infection in infants born prematurely, infants with chronic lung disease and infants with congenital cardiac disease.[27] The rates of reduction for palivizumab alone were not presented in this study, however, relative risks presented for all antibodies in these three patient groups showed relative risk of hospitalization of 0.29, 0.55, and 0.56, respectively.[27] However, palivizumab has not been demonstrated to be effective in all studies, including one randomized trial which found no significant improvement in outcomes of patients with RSV bronchiolitis treated with palivizumab compared with those who received placebo.[30,31] Moreover, palivizumab is expensive, and existing studies of cost-analysis justify use of palivizumab in high-risk population groups only, such as infants with active chronic lung disease, rather than widespread use for prophylaxis.[32,33] Given these limitations of palivizumab, it is prudent to explore alternative monoclonal antibodies for RSV prophylaxis. Motavizumab is a version of palivizumab with greater affinity for the F glycoprotein.[29] Existing guidelines recommend prophylaxis with palivizumab for high-risk infants to significantly reduce the rate of RSV-related hospitalization.[34] Motavizumab's greater potency could further improve this outcome; preliminary results from a comparative phase III study reported that motavizumab reduced the incidence of RSV-related hospitalizations in high-risk infants by 26% compared with palivizumab.[29]

Another more potent monoclonal antibody, nirsevimab, that targets the prefusion conformation of the RSV F glycoprotein is under development. Nirsevimab is a modified antibody with a longer half-life and potent neutralizing activity. It has been trialed in preterm infants born between 29 and 34 weeks' gestation and has reduced the absolute incidence of medically attended lower respiratory tract

infection attributable to RSV from 9.5% to 2.6%.[35] The main limitation to this preventative strategy is the high cost associated with this treatment, which precludes its use in many of the low- and middle-income settings where the greatest burden of RSV disease remains.

To date, no licensed RSV vaccine exists for children, nor for people of any other age group. Furthermore, there are inherent challenges in immunizing children in a timely manner that can afford sufficient protection in the first three to six months of life. These challenges include immature immunity, potential suppression of the immune response by maternal antibody and the risk of enhanced disease in infants who are subsequently infected with wild-type virus.

Vaccines currently in development for prevention of RSV infection are based on four distinct approaches: particle-based, vector-based, subunit, and live-attenuated or chimeric vaccines.[36] Particle-based vaccines are being explored as potential candidates for maternal immunization to protect infants through placental transmission of antibodies, and as vaccines in children between six months and five years, and older adults aged 60 years and older. One trial is investigating the RSV F nanoparticle; this is a randomized clinical trial (RCT) which has completed phase III trials.[36,37] Two other phase III trials are currently recruiting (Table 1). Vector-based vaccines use modified versions of vector viruses to generate a protective immune response against RSV. There are five vector-based vaccines in development: one vaccine candidate uses a modified vaccinia Ankara (MVA) smallpox viral vector while the others are derived from adenovirus vectors. These vaccines are being developed and trialed for administration in pediatric and older adult populations. There are five subunit vaccines under development using various antigens (Table 1), including versions of the RSV F protein, the RSV pre-F protein, and parts of the RSV SH protein. Finally, live-attenuated and chimeric vaccines are being developed for RSV-naïve infant populations: five live-attenuated vaccines are in phase 1 trials and a single chimeric vaccine derived from BCG are being investigated for potential use in newborns and infants under two years of age.[36]

## Maternal immunization

The use of maternal immunization to prevent disease in infants is not new. Maternal influenza and pertussis vaccination are routinely recommended in many countries to reduce burden of neonatal influenza and pertussis infection through vertical transmission of antibodies.[38–40] Based on the principle of passive antibody transfer harnessed by maternal influenza and pertussis vaccination, to protect the infant against disease during their most vulnerable period either before vaccination can occur (in the example of influenza) or before active immunization can produce sufficient autologous antibodies (in the setting of pertussis), maternal RSV immunization is an attractive preventative strategy. Further immunity may also be provided via transfer of antibodies in breast milk.[40] Maternal IgG is the only antibody subtype which is transferred to the fetus through the placenta.[41] This passive transfer commences as early as 6 weeks' gestation and shows a continuous rise during pregnancy, with maximum levels of antibody transfer occurring in the third trimester.[41] In contrast, IgA is the main antibody transferred through breast milk, although IgG has also been detected in breast milk for certain respiratory infections, including COVID-19.[41] Maternal pertussis vaccination serves as an example of protection provided through transplacental IgG transfer, whereby maternal vaccination between 27- and 36-weeks' gestation significantly reduces the risk of neonatal pertussis disease in the first six months of life prior to active infant immunization,[41] and demonstrates a vaccine effectiveness of around 95% for preventing infant deaths.[42] It is unclear, however, whether the presence of IgA antibodies transferred through breast milk correlates with a reduction in clinically significant respiratory illness. One study investigated this correlation and found no difference in IgA antibody levels for RSV between cases and controls,[43] but further research is required to confirm the level of protection provided by breast milk IgA antibodies against respiratory infections. One Australian study demonstrated the potential effect of a maternal RSV vaccine through a mathematical model, reporting a likely reduction in rates of hospitalization for RSV by 6–37% for infants under three months of age, and 30–46% for children between three and five months of age, depending on the level of vaccine efficacy.[44] The effect was most pronounced in the first three months of life due to maternally acquired passive immunity, but declined over time so that by six months of age, the reduction in hospitalizations was minimal.[44] This model is not generalizable to all settings as it was conducted in a high-income setting with different RSV-related hospitalization and mortality rates compared with low-income settings; however, the overall effect demonstrated by this model is consistent with

**Table 1.** Randomized clinical trials for maternal RSV vaccine formulations as listed on clinicaltrials.gov website.

| Vaccine | Setting | No. of participants | Trial identifier | Phase of trials (recruitment status) |
|---|---|---|---|---|
| Intramuscular adjuvanted RSV F maternal vaccine | 88 study locations, mostly high-income, several low- and middle-income sites | 4,636 | NCT02624947 | Phase 3 (Completed) |
| RSVpreF maternal vaccine | 421 study locations, mostly high-income, one low-income site | 10,000 (projected) | NCT04424316 | Phase 3 (Recruiting) |
| RSV maternal unadjuvanted vaccine containing recombinant subunit pre-fusion RSV antigen | 119 study locations, mostly high-income, several low- and middle-income sites | 20,000 (projected) | NCT04605159 | Phase 3 (Recruiting) |
| Investigational RSV vaccine (GSK3003891A) | N/A | N/A | NCT03191383 | Phase 2 (Withdrawn) |
| Investigation RSV maternal vaccine (RSVPreF3)(GSK3888550A) | 34 study locations, upper middle-income to high income settings only | 420 | NCT04126213 | Phase 2 (Active, not recruiting) |
| RSV stabilized pre-fusion F subunit vaccine | 153 study locations, upper middle-income to high income settings only | 650 | NCT04032093 | Phase 2 (Active, not recruiting) |

the expected benefits of an RSV vaccination based on principles of maternal-fetal antibody transfer.

## RSV vaccines in pregnancy: clinical trials

There are currently five clinical trials investigating the safety, efficacy, and tolerability of various maternal RSV vaccine candidates (Table 1). One phase III vaccine trial has published its results,[37] while two others are currently ongoing (clinicaltrials.gov identifiers NCT04424316, NCT04605159).

A randomized placebo controlled clinical trial investigating an intramuscular adjuvanted RSV fusion (F) nanoparticle vaccine completed phase III clinical trials in 2020 and was found not to meet the pre-specified primary endpoint for efficacy against RSV illness (clinicaltrials.gov identifier NCT02624947).[37] To date, this trial is the only maternal RSV vaccine candidate which has completed phase III trials and published findings. This randomized trial was conducted across 87 countries and randomized 4,636 women to receive either active vaccine or placebo between 28 and 36 weeks' gestation. The trial included women from high-, middle-, and low-income settings. RSV antibody levels were higher in infants whose mother received RSV F vaccination compared to infants of women who received placebo; however, this did not translate to reach statistical significance for reduction in RSV-specific medically significant lower respiratory tract infection (presence of RT-PCR-confirmed RSV genome in respiratory secretions; and at least one pre-specified manifestation of lower respiratory tract infection; and evidence of medical significance defined by presence of hypoxemia or tachypnea) for infants 0–90 days of age.[37] The percentage of infants with medically significant RSV lower respiratory infection was 1.5% in the group who received the vaccine compared to 2.4% in the group who received placebo (vaccine efficacy 39.4%, 95% CI 5.3 to 61.2, 97.52% CI −1.0 to 63.7). One possible explanation for why the findings did not reach statistical significance include the possibility that the study was underpowered. The calculated number of participants needed to enroll was based on a primary event end point rate of 4% and a vaccine efficacy of 60% (in the absence of antecedent data). The actual event rate in the study was lower than this. Furthermore, although not powered to evaluate differences between countries of different income levels, the reported vaccine efficacy was higher in low- and middle-income countries compared to high-income countries, which may have been due to the substantially lower number of cases reported in high-income settings.

The percentage of infants with RSV attributable lower respiratory tract infection and severe hypoxemia (defined as peripheral oxygen saturation [SpO2] <92% at sea level or <87% at altitudes >1800 meters) was 0.5% compared to 1.0% (vaccine efficacy 44.4%, 95% CI 19.6 to 61.5). The reported vaccine efficacy against hospitalization due to RSV disease was 44.4%, with a 95% CI of 19.6 to 61.5.[37] Overall, there was an acceptable safety profile reported with similar rates of adverse events and birth outcomes reported between the two groups except for local injection site reactions which were more commonly reported in the RSV vaccine group.

Pfizer's vaccine candidate in phase III trials commenced its double-blind placebo-controlled randomized trial in June 2020 and is currently recruiting (clinicaltrials.gov identifier NCT04424316). This study is trialing an RSV prefusion F (RSVpreF) subunit vaccine. The study population is estimated to include 10,000 pregnant women and their fetuses who will be randomized 1:1 into either active or placebo arms. Primary outcomes of this trial include RSV-related medically attended lower respiratory tract illness in infants up to 180 days after delivery, birth outcomes, rates of adverse events and chronic medical conditions diagnosed in infants in first year of life, and local and systemic adverse events in mothers. This trial is expected to be completed by September 2023.

The other RSV vaccine currently in phase III clinical trials, developed by GlaxoSmithKline, commenced recruiting in October 2020 (clinicaltrials.gov identifier NCT04605159). This vaccine is an unadjuvanted maternal RSV formulation which contains a recombinant subunit pre-fusion RSV antigen administered through intramuscular injection.[45] The study population is estimated to include around 20,000 pregnant women and their fetuses, who will be randomized to either the active or placebo groups. The primary outcome of interest is medically assessed, RSV-related lower respiratory tract illness in infants up to six months of age. Rates of infant hospitalizations, maternal adverse effects, and measurements of humoral immune response comprising maternal and infant RSV IgG antibody and RSV neutralizing antibody levels are included as part of secondary outcome analysis. This trial is expected to be completed in February 2024.

Based on the published results from phase III trials, there remain a number of unanswered questions. As results become available for the ongoing studies, it is hoped that further evidence will provide clarification in relation to the role (if any) of maternal RSV vaccines in the future.

There are a further two vaccine formulations currently in phase II clinical trials. These are an RSV stabilized prefusion F subunit vaccine by Pfizer (NCT04032093) and an RSVPreF3 vaccine by GlaxoSmithKline (NCT04126213). Another formulation previously developed by GlaxoSmithKline was withdrawn due to instability of the PreF antigen during manufacturing (NCT03191383).

### *Where to from here?*

In 2019, global health organization PATH in collaboration with the World Health Organization (WHO) published a roadmap for advancing RSV maternal immunization.[46] Prevention of RSV disease is viewed as a global priority due to the number of attributable hospitalizations and deaths per year in children under five years of age and nearly half of these under six months of age. This road map was based on a gap analysis report which highlighted gaps essential and specific to maternal immunization such as RSV burden of disease data, evidence of maternal RSV vaccine effect and health economics and financing of this preventative strategy; and gaps essential to all immunizations such as collection of standardized data, funding support for low- and middle-income countries (LMICs), and the availability of a WHO

prequalified maternal RSV vaccine.[47] The roadmap outlines the activities needed to make the introduction and wide-scale implementation in LMICs possible. In summary, this includes: ensuring the availability of safe, effective and affordable RSV vaccines; supporting evidence-based global and country decision-making; and enabling systems to equitably deliver maternal RSV vaccines. This was published in May 2019, prior to the publication of the phase III maternal RSV clinical trial data.

One of the challenges now facing policymakers and healthcare providers is how to apply the findings from the published clinical trials to date, namely the large phase III Novavax study which did not meet the primary endpoint of interest but did demonstrate other important clinical benefits such as reduced hospitalization due to RSV attributable lower respiratory tract disease with severe hypoxemia and all-cause pneumonia in the first 12 months of life.[37] As the authors of the study point out however, these are of an exploratory nature, and based on expanded-data, rather than pre-specified criterion for success, so should be viewed as hypothesis-generating.[37] Examples of these unanswered questions include why infants of vaccinated mothers were less likely to have all cause pneumonia in the first year of life, what was the mechanism of protection against lower respiratory tract infection from any cause with severe hypoxemia, why were there differences between high-income and low-income countries, and what may be contributing factors to the lower efficacy reported in high-income settings?

Other maternal vaccine studies are underway which will be essential to help clarify vaccine efficacy across a range of clinical endpoints and across different income settings, noting the differences reported between low- and high-income countries in the study published by Madhi SA, et al.[37] Initial safety data in relation to maternal RSV vaccine is reassuring. However, with the suggestive, but not definitive clinical benefits reported to date, women and babies remain vulnerable to the effects of RSV infection with no viable prevention strategies in LMICs. Unfortunately, many babies will continue to be hospitalized and die whilst we await more clinical trial data. What can be done whilst we await results from these ongoing studies?

In many settings there is ongoing research and operational work which can be started or continued to ensure successful implementation if a safe, effective maternal RSV vaccine becomes available in the future.[48] This includes raising stakeholder awareness of RSV disease and maternal immunization, improving coordination and collaboration between Expanded Programs on Immunization (EPI) and Maternal, Neonatal and Child Health (MNCH) programs who may be responsible in many settings for the implementation of maternal immunization,[49] ensuring operations and logistics are in place to procure, deliver and monitor new vaccine implementation,[50] and ensuring systems are implemented to track local epidemiology of disease and subsequently vaccine safety and impact.[50]

It is crucial that we do not lose sight of the profound positive health benefits maternal immunization can have on pregnant women and their children. We must continue to advance the maternal immunization agenda, fill the knowledge gaps, and strive to obtain an RSV vaccine that is safe and effective with a robust evidence base ensuring its consideration by health policymakers for implementation in countries most affected by RSV disease.

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## ORCID

Michelle L. Giles http://orcid.org/0000-0003-3007-1822

## References

1. Nam HH, Ison MG. Respiratory syncytial virus infection in adults. Br Med J. 2019;366:5021. doi:10.1136/bmj.l5021.
2. Shi T, McAllister DA, O'Brien KL, EAF S, Madhi SA, Gessner BD, Polack FP, Balsells E, Acacio S, Aguayo C, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Lancet. 2017;390 (10098):946–58. doi:10.1016/s0140-6736(17)30938-8.
3. Walsh EE. Respiratory syncytial virus infection: an illness for all ages. Clin Chest Med. 2017;38(1):29–36. doi:10.1016/j.ccm.2016.11.010.
4. Hall CB, Weinberg GA, Iwane MK, Blumkin AK, Edwards KM, Staat MA, Auinger P, Griffin MR, Poehling KA, Erdman D, et al. The burden of respiratory syncytial virus infection in young children. N Engl J Med. 2009;360(6):588–98. doi:10.1056/NEJMoa0804877.
5. Reeves RM, Hardelid P, Gilbert R, Warburton F, Ellis J, Pebody RG. Estimating the burden of respiratory syncytial virus (RSV) on respiratory hospital admissions in children less than five years of age in England, 2007-2012. Influenza Other Respir Viruses. 2017;11(2):122–29. doi:10.1111/irv.12443.
6. Pierangeli A, Scagnolari C, Antonelli G. Respiratory syncytial virus. Minerva Pediatr. 2018;70(6):553–65. doi:10.23736/s0026-4946.18.05312-4.
7. Wegzyn C, Toh LK, Notario G, Biguenet S, Unnebrink K, Park C, Makari D, Norton M. Safety and effectiveness of palivizumab in children at high risk of serious disease due to respiratory syncytial virus infection: a systematic review. Infect Dis Ther. 2014;3 (2):133–58. doi:10.1007/s40121-014-0046-6.
8. Stein RT, Bont LJ, Zar H, Polack FP, Park C, Claxton A, Borok G, Butylkova Y, Wegzyn C. Respiratory syncytial virus hospitalization and mortality: systematic review and meta-analysis. Pediatr Pulmonol. 2017;52(4):556–69. doi:10.1002/ppul.23570.
9. Geoghegan S, Erviti A, Caballero MT, Vallone F, Zanone SM, Losada JV, Bianchi A, Acosta PL, Talarico LB, Ferretti A, et al. Mortality due to respiratory syncytial virus. Burden and risk factors. Am J Respir Crit Care Med. 2017;195(1):96–103. doi:10.1164/rccm.201603-0658OC.
10. Scheltema NM, Gentile A, Lucion F, Nokes DJ, Munywoki PK, Madhi SA, Groome MJ, Cohen C, Moyes J, Thorburn K, et al. Global respiratory syncytial virus-associated mortality in young children (RSV GOLD): a retrospective case series. Lancet Glob Health. 2017;5(10):e984–e991. doi:10.1016/s2214-109x(17)30344-3.
11. Wheeler SM, Dotters-Katz S, Heine RP, Grotegut CA, Swamy GK. Maternal effects of respiratory syncytial virus infection during pregnancy. Emerg Infect Dis. 2015;21(11):1951–55. doi:10.3201/eid2111.150497.
12. Hause AM, Panagiotakopoulos L, Weintraub ES, Sy LS, Glenn SC, Tseng HF, McNeil MM. Adverse outcomes in pregnant women hospitalized with respiratory syncytial virus infection: a case series. Clin Infect Dis. 2021;72(1):138–40. doi:10.1093/cid/ciaa668.

13. Regan AK, Klein NP, Langley G, Drews SJ, Buchan S, Ball S, Kwong JC, Naleway A, Thompson M, Wyant BE, et al. Respiratory syncytial virus hospitalization during pregnancy in 4 high-income countries, 2010-2016. Clin Infect Dis. 2018;67 (12):1915–18. doi:10.1093/cid/ciy439.
14. Madhi SA, Cutland CL, Downs S, Jones S, van Niekerk N, EAF S, Nunes MC. Burden of respiratory syncytial virus infection in South African Human Immunodeficiency Virus (HIV)-infected and HIV-uninfected pregnant and postpartum women: a longitudinal cohort study. Clin Infect Dis. 2018;66(11):1658–65. doi:10.1093/cid/cix1088.
15. Chu HY, Katz J, Tielsch J, Khatry SK, Shrestha L, LeClerq SC, Magaret A, Kuypers J, Steinhoff MC, Englund JA. Clinical presentation and birth outcomes associated with respiratory syncytial virus infection in pregnancy. PLOS ONE. 2016;11(3):e0152015. doi:10.1371/journal.pone.0152015.
16. Hause AM, Avadhanula V, Maccato ML, Pinell PM, Bond N, Santarcangelo P, Ferlic-Stark L, Ye X, Iwuchukwu O, Maurer L, et al. Clinical characteristics and outcomes of respiratory syncytial virus infection in pregnant women. Vaccine. 2019;37(26):3464–71. doi:10.1016/j.vaccine.2019.04.098.
17. Smith DR. Herd immunity. Vet Clin North Am Food Anim Pract. 2019;35(3):593–604. doi:10.1016/j.cvfa.2019.07.001.
18. Gil-Prieto R, Gonzalez-Escalada A, Marín-García P, Gallardo-Pino C, Gil-de-miguel A. Respiratory syncytial virus bronchiolitis in children up to 5 years of age in Spain: epidemiology and comorbidities: an observational study. Medicine. 2015;94(21): e831. doi:10.1097/MD0000000000000831.
19. Hall CB. Respiratory syncytial virus and parainfluenza virus. N Engl J Med. 2001;344(25):1917–28. doi:10.1056/nejm200106213442507.
20. Wrotek A, Kobiałka M, Grochowski B, Kamińska I, Pędziwiatr K, Skoczek-Wojciechowska A, Godek M, Jackowska T. Respiratory complications in children hospitalized with respiratory syncytial virus infection. Adv Exp Med Biol. 2020;1279:113–20. doi:10.1007/5584_2020_530.
21. Carbonell-Estrany X, Rodgers-Gray BS, Paes B. Challenges in the prevention or treatment of RSV with emerging new agents in children from low- and middle-income countries. Expert Rev Anti Infect Ther. 2020:1–23. doi:10.1080/14787210.2021.1828866.
22. Tahamtan A, Askari FS, Bont L, Salimi V. Disease severity in respiratory syncytial virus infection: role of host genetic variation. Rev Med Virol. 2019;29(2):e2026. doi:10.1002/rmv.2026.
23. Tahamtan A, Samadizadeh S, Rastegar M, Nakstad B, Salimi V. Respiratory syncytial virus infection: why does disease severity vary among individuals? Expert Rev Respir Med. 2020;14(4):415–23. doi:10.1080/17476348.2020.1724095.
24. Harding JN, Siefker D, Vu L, You D, DeVincenzo J, Pierre JF, Cormier SA. Altered gut microbiota in infants is associated with respiratory syncytial virus disease severity. BMC Microbiol. 2020;20(1):140. doi:10.1186/s12866-020-01816-5.
25. Belderbos ME, Houben ML, Wilbrink B, Lentjes E, Bloemen EM, Kimpen JL, Rovers M, Bont L. Cord blood vitamin D deficiency is associated with respiratory syncytial virus bronchiolitis. Pediatrics. 2011;127(6):e1513–1520. doi:10.1542/peds.2010-3054.
26. Gouyon JB, Rozé JC, Guillermet-Fromentin C, Glorieux I, Adamon L, Di Maio M, Miloradovich T, Anghelescu D, Pinquier D, Escande B, et al. Hospitalizations for respiratory syncytial virus bronchiolitis in preterm infants at <33 weeks gestation without bronchopulmonary dysplasia: the CASTOR study. Epidemiol Infect. 2013;141(4):816–26. doi:10.1017/s0950268812001069.
27. Morris SK, Dzolganovski B, Beyene J, Sung L. A meta-analysis of the effect of antibody therapy for the prevention of severe respiratory syncytial virus infection. BMC Infect Dis. 2009;9:106. doi:10.1186/1471-2334-9-106.
28. O'Brien KL, Chandran A, Weatherholtz R, Jafri HS, Griffin MP, Bellamy T, Millar EV, Jensen KM, Harris BS, Reid R, et al. Efficacy of motavizumab for the prevention of respiratory syncytial virus disease in healthy Native American infants: a phase 3 randomised double-blind placebo-controlled trial. Lancet Infect Dis. 2015;15 (12):1398–408. doi:10.1016/s1473-3099(15)00247-9.
29. Wu H, Pfarr DS, Johnson S, Brewah YA, Woods RM, Patel NK, White WI, Young JF, Kiener PA. Development of motavizumab, an ultra-potent antibody for the prevention of respiratory syncytial virus infection in the upper and lower respiratory tract. J Mol Biol. 2007;368(3):652–65. doi:10.1016/j.jmb.2007.02.024.
30. Alansari K, Toaimah FH, Almatar DH, El Tatawy LA, Davidson BL, Qusad MIM. Monoclonal antibody treatment of RSV bronchiolitis in young infants: a randomized trial. Pediatrics. 2019;143:3. doi:10.1542/peds.2018-2308:.
31. Linnane B, Kiernan MG, O'Connell NH, Kearse L, Dunne CP. Anti-RSV prophylaxis efficacy for infants and young children with cystic fibrosis in Ireland. Multidiscip Respir Med. 2015;10:32. doi:10.1186/s40248-015-0029-9.
32. Harkensee C, Brodlie M, Embleton ND, McKean M. Passive immunisation of preterm infants with palivizumab against RSV infection. J Infect. 2006;52(1):2–8. doi:10.1016/j.jinf.2005.08.003.
33. Prescott WA Jr., Doloresco F, Brown J, Paladino JA. Cost effectiveness of respiratory syncytial virus prophylaxis: a critical and systematic review. Pharmacoeconomics. 2010;28(4):279–93. doi:10.2165/11531860-000000000-00000.
34. 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. Pediatrics. 2014;134:e620. doi:10.1542/peds.2014-1666.
35. Griffin MP, Yuan Y, Takas T, Domachowske JB, Madhi SA, Manzoni P, EAF S, Esser MT, Khan AA, Dubovsky F, et al. Single-dose nirsevimab for prevention of RSV in preterm infants. N Engl J Med. 2020;383(5):415–25. doi:10.1056/NEJMoa1913556.
36. Mazur NI, Higgins D, Nunes MC, Melero JA, Langedijk AC, Horsley N, Buchholz UJ, Openshaw PJ, McLellan JS, Englund JA, et al. The respiratory syncytial virus vaccine landscape: lessons from the graveyard and promising candidates. Lancet Infect Dis. 2018;18(10):e295–e311. doi:10.1016/s1473-3099(18)30292-5.
37. Madhi SA, Polack FP, Piedra PA, Munoz FM, Trenholme AA, EAF S, Swamy GK, Agrawal S, Ahmed K, August A, et al. Respiratory syncytial virus vaccination during pregnancy and effects in infants. N Engl J Med. 2020;383(5):426–39. doi:10.1056/NEJMoa1908380.
38. Nunes MC, Madhi SA. Influenza vaccination during pregnancy for prevention of influenza confirmed illness in the infants: a systematic review and meta-analysis. Hum Vaccin Immunother. 2018;14 (3):758–66. doi:10.1080/21645515.2017.1345385.
39. Romanin V, Acosta AM, Juarez MDV, Briere E, Sanchez SM, Cordoba BL, Sevilla ME, Lucion MF, Urrutia A, Sagradini S, et al. Maternal vaccination in Argentina: tetanus, diphtheria, and acellular pertussis vaccine effectiveness during pregnancy in preventing pertussis in infants <2 months of age. Clin Infect Dis. 2020;70(3):380–87. doi:10.1093/cid/ciz217.
40. Murray A, Chu HY. RSV, antibodies and the developing world. Pediatr Infect Dis. 2019;38:6S. doi:10.1097/INF.0000000000002333.
41. Ciobanu AM, Dumitru AE, Gica N, Botezatu R, Peltecu G, Panaitescu AM. Benefits and risks of IgG transplacental transfer. Diagnostics (Basel). 2020;10:8. doi:10.3390/diagnostics10080583.
42. Amirthalingam G, Campbell H, Ribeiro S, Fry NK, Ramsay M, Miller E, Andrews N. Sustained effectiveness of the maternal pertussis immunization program in England 3 years following introduction. Clin Infect Dis. 2016;63(suppl 4):s236–s243. doi:10.1093/cid/ciw559.
43. Mazur NI, Horsley NM, Englund JA, Nederend M, Magaret A, Kumar A, Jacobino SR, Cam DH, Khatry SK, LeClerq SC, et al. Breast milk prefusion F immunoglobulin G as a correlate of protection against respiratory syncytial virus acute respiratory illness. J Infect Dis. 2019;219(1):59–67. doi:10.1093/infdis/jiy477.
44. Hogan AB, Campbell PT, Blyth CC, Lim FJ, Fathima P, Davis S, Moore HC, Glass K. Potential impact of a maternal vaccine for RSV: a mathematical modelling study. Vaccine. 2017;35 (45):6172–79. doi:10.1016/j.vaccine.2017.09.043.

45. GSK starts phase 3 study of RSV maternal candidate vaccine [press release]. GlaxoSmithKline. 2020 Nov 23.
46. PATH. A Roadmap for advancing RSV maternal immunization. Seattle (WA): PATH; 2018.
47. PATH. Advancing RSV maternal immunization: a gap analysis report. Seattle (WA): PATH; 2018.
48. Krishnaswamy S, Lambach P, Giles ML. Key considerations for successful implementation of maternal immunization programs in low and middle income countries. Hum Vaccin Immunother. 2019;15(4):942–50. doi:10.1080/21645515.2018.1564433.
49. Giles ML, Mason E, Muñoz FM, Moran AC, Lambach P, Merten S, Diaz T, Baye M, Mathai M, Pathirana J, et al. Antenatal care service delivery and factors affecting effective tetanus vaccine coverage in low- and middle-income countries: results of the Maternal Immunisation and Antenatal Care Situational Analysis (MIACSA) project. Vaccine. 2020;38(33):5278–85. doi:10.1016/j.vaccine.2020.05.025.
50. Giles ML, Mantel C, Muñoz FM, Moran A, Roos N, Yusuf N, Diaz T, Ahun M, Nic Lochlainn LM, Wootton E, et al. Vaccine implementation factors affecting maternal tetanus immunization in low- and middle-income countries: results of the Maternal Immunization and Antenatal Care Situational Analysis (MIACSA) project. Vaccine. 2020;38(33):5268–77. doi:10.1016/j.vaccine.2020.05.084.