Respiratory syncytial virus vaccination: likely and less likely outcomes

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Purpose of review
Respiratory syncytial virus (RSV) remains a leading cause of lower respiratory tract infections in infants, older adults, and high-risk populations. The recent approval of new RSV vaccines and monoclonal antibodies marks a turning point in RSV prevention. This review explores these advancements, their immediate and potential long-term effects, and the remaining challenges.

Recent findings
Several novel RSV prevention strategies have been approved, including maternal RSVPreF vaccines, infant-targeted monoclonal antibodies like Nirsevimab, and vaccines for older adults. These interventions significantly reduce RSV-related hospitalizations, ICU admissions, and mortality, particularly in high-risk groups. Early evidence also suggests benefits in reducing wheezing during infancy; however, long-term impacts on asthma development remain uncertain. Challenges such as vaccine hesitancy and limited access in low-resource settings remain pressing issues that require sustained focus.

Summary
RSV vaccines and monoclonal antibodies are expected to alter clinical management and public health by reducing severe disease burden and RSV transmission. Further research is needed to evaluate their long-term effects, including implications for asthma prevention and pediatric obstructive sleep apnea. Addressing access disparities and public acceptance will be critical for maximizing their global impact.

Keywords
asthma prevention, respiratory syncytial virus vaccines, wheezing

INTRODUCTION

Respiratory syncytial virus (RSV) is a single-stranded RNA virus that primarily targets the respiratory epithelial cells, causing inflammation and excessive mucus production [1]. It is the leading cause of lower respiratory tract infections (LRTIs) in children under 2 years of age, with nearly all children experiencing at least one infection by this age [2–4]. Although most infections are mild, certain infants – both healthy and particularly those in high-risk groups such as premature infants or children with underlying heart or lung conditions – are more susceptible to severe illness [5].

Beyond its acute manifestations, RSV infection during infancy has been linked to long-term pulmonary morbidities, particularly an increased risk of developing asthma later in childhood [6–9,10▪▪]. Although the exact causal relationship between RSV and asthma is not fully understood, studies consistently show an association between RSV infection in the first year of life and subsequent respiratory issues [11]. Some researchers suggest that RSV may trigger a predisposition to asthma in genetically susceptible individuals, while others propose that the virus itself causes lasting damage to the developing lungs [11,12▪▪,13–14]. Despite these uncertainties, early-life RSV infection is considered a significant risk factor for ongoing respiratory problems, highlighting the need for preventive strategies [15▪].

Until recently, preventive measures for RSV were limited to Palivizumab, a monoclonal antibody administered monthly throughout the RSV season to protect high-risk infants. Its accessibility was significantly constrained, particularly in low-income and middle-income countries (LMICs) due

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KEY POINTS

- RSV overview and impact: respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract infections in children under 2 years, with potential long-term consequences like asthma and recurrent wheezing.
- Recent advances in prevention: new RSV vaccines and monoclonal antibodies, offer improved prevention strategies for infants, older adults, and pregnant individuals, addressing previous limitations of accessibility and efficacy.
- Public health implications: RSV vaccination is expected to reduce hospitalizations, ICU admissions, and mortality rates, particularly in high-risk populations, while also potentially decreasing community transmission and recurrent wheezing in infancy.
- Limitations and challenges: despite promising results, RSV vaccination faces challenges like inconsistent efficacy across populations, vaccine hesitancy, and limited long-term impact on asthma prevention.
- Future directions: ongoing research is needed to assess the long-term effects of RSV prevention, address vaccine equity access, and explore novel outcomes, including impacts on pediatric obstructive sleep apnea.

to financial and availability challenges [16,17]. However, recent advancements have introduced several vaccines and monoclonal antibodies (mAbs) aimed at preventing RSV infection, targeting both infants and older adults [18]. In 2022 and 2023, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved Nirsevimab, a human monoclonal antibody that binds the F1 and F2 subunits of the RSV fusion protein F, which provides passive immunity with a single injection [19–21]. In 2023, two vaccines were approved for adults aged 60 and over – Arexvy (containing RSVPreF3 protein) and Abrysvo (containing RSVPreF protein) – both providing active immunity to reduce the RSV burden in older populations [22,23]. Abrysvo was also approved by the FDA in 2023 for administration to pregnant individuals, typically between 32 and 36 weeks of gestation, to help protect newborns from severe RSV infection during their first 6 months of life [24,25▪▪]. By vaccinating the mother, antibodies are passed to the fetus, offering passive immunity during a critical period of vulnerability. The FDA also approved mRNA-Based RSV PreF Vaccine in older adults – mRESVIA [26].

These recent developments through various vaccination strategies mark a significant leap forward in global RSV prevention, with clinical guidelines rapidly evolving to incorporate these new interventions. Therefore, it is critical to assess their broader public health impact. This review explores likely and less likely outcomes associated with RSV vaccination, focusing on its clinical and public health implications.

LIKELY OUTCOMES

Reduced respiratory syncytial virus-related hospitalizations and medical visits

A randomized controlled trial (RCT) found that a single dose of Niservimab reduced medically attended RSV-associated LRTIs but showed a borderline significant 62% reduction in hospitalizations (95% CI = -8.6 to 86.8, $P = 0.07$) [27]. In a cohort of premature infants (29–35 weeks gestational age), the incidence of hospitalization for RSV-associated LRTI was 78.4% lower (95% CI 51.9–90.3) with Niservimab compared to placebo [0.8% (eight infants) vs. 4.1% (20 infants); $P < 0.001$], with these effects sustained over a 150-day follow-up period [19].

Clinical trials of the latest vaccines described above, including maternal immunization strategies and vaccines aimed at older adults, have shown substantial reductions in RSV-related hospitalizations. In comparison to the current mAb agent Palivizumab, RCTs involving 14 167 participants reported that Niservimab reduced RSV-related hospitalizations by 75% (OR = 0.25, 95% CI = 0.13–0.47), while Palivizumab reduced them by 55% (OR = 0.45, 95% CI = 0.34–0.60) [19,27–30]. Importantly, Niservimab has demonstrated higher potency in RSV inhibition than Palivizumab in cell culture and animal models [31], although relatively lower efficacy was observed in infants under 3 months of age and weighing less than 5 kg [19]. No significant differences in hospitalization reduction were observed between infants with and without comorbidities [30].

For infants whose mothers received the RSVPreF vaccine, efficacy against RSV-associated hospitalization was 67.7% (99.17%, 95% CI = 15.9–89.5) within 90 days and 56.8% (99.17%, 95% CI = 10.1–80.7) within 180 days after birth. Medically attended severe LRTI occurred within 90 days in 6 infants of vaccinated mothers and 33 infants of placebo group mothers, translating to an efficacy of 81.8% (99.5%, 95% CI = 40.6–96.3); for 180 days, this efficacy was 69.4% (97.58%, 95% CI = 44.3–84.1) [25▪▪]. A recent review on RSV vaccination during pregnancy found that maternal vaccination reduced laboratory-confirmed RSV hospitalizations in infants [risk ratio (RR): 0.50, 95% CI = 0.31–0.82) [32▪].

Reduced ICU admissions

A prospective and dynamic population-based cohort study demonstrated the effectiveness of Nirsevimab in reducing ICU admissions. The adjusted effectiveness was 94.4% (95% CI = 87.3–97.5) at 30 days and 92.1% (95% CI = 64–98.3) at 90 days [33].

Lower respiratory syncytial virus-associated mortality

Globally, 33 million RSV-associated acute LRTIs occur annually in children under 5 years, with 20% in infants under 6 months. Over 95% of cases of RSV-attributable deaths occur in LMICs [34]. Vaccination is expected to significantly reduce RSV-associated deaths, particularly in LMICs, where LRTIs contribute to high infant mortality rates. A mathematical model predicts maternal RSV vaccination could extend immunity in full-term infants for 6–7 months against RSV-A and 5 months against RSV-B [35▪]. Maternal vaccination could prevent 55–63% of RSV-related in-hospital deaths in infants under 6 months. These findings highlight the critical role of maternal RSV vaccination in reducing infant mortality in resource-limited settings.

Decreased respiratory syncytial virus transmission

Widespread RSV vaccination is expected to reduce community transmission. It may decrease RSV circulation in households and healthcare settings, indirectly protecting unvaccinated individuals like newborns or those with contraindications through herd immunity.

A dynamic RSV transmission model for an LMIC, accounting for household and community spread, demographic shifts, and seasonality, estimated the impact of maternal and older adult vaccination [36]. Using historical RSV hospitalization data, the model projected up to a 50% reduction in hospitalizations if maternal vaccination extends infant protection by 75 days, with 75% coverage among household members (~7.5% of the population).

Reduction in recurrent wheezing in the first year of life

The relationship between RSV infection in infancy and the development of subsequent wheezing and asthma remains a topic of ongoing debate. While the association between RSV and asthma is well established, the causal link is still under discussion. Some argue that RSV infection may modulate airway inflammation, making it a potential causative agent for asthma. Others suggest that RSV bronchiolitis is merely a marker for lung maldevelopment rather than a direct cause of asthma [6,12▪▪,13]. Establishing whether prevention or delay of RSV disease during infancy, a sensitive period of lung and immune development may reduce the risk of childhood asthma may be crucial to our understanding of the mechanism of asthma. RSV vaccines offer an opportunity to explore this causality further, as they may reduce the clinical manifestations of RSV. If a reduction in asthma incidence is observed alongside reduced RSV infections or severity of illness, it could suggest that RSV is a causal factor in the development of asthma. Conversely, if no such reduction is seen, it would support the idea that RSV is merely a marker for underlying conditions such as lung maldevelopment or immunologic dysregulation, which predispose individuals to asthma.

A study aimed to assess whether RSV infection contributes to recurrent wheezing in preterm infants, specifically those born at 33–35 weeks gestational age, by evaluating the impact of Palivizumab, an RSV monoclonal antibody, on wheezing days and related outcomes [37]. The results showed that Palivizumab treatment led to a 61% reduction in parent-reported wheezing days during the first year of life compared to a placebo (930 vs. 2,309 days, respectively). This effect persisted even after the treatment ended, demonstrating a 73% relative reduction in wheezing during the postprophylaxis period. Additionally, fewer infants in the Palivizumab group developed recurrent wheezing (11 vs. 21% in the placebo group, $P = 0.01$), and fewer used bronchodilators (13 vs. 23%, $P < 0.001$). The study concluded that Palivizumab treatment significantly reduced the incidence of wheezing days and the development of recurrent wheezing in preterm infants, even after the treatment period. This supports the hypothesis that RSV infection plays a critical role in the pathogenesis of wheezing during the first year of life in these infants. However, this finding also lends support to the theory that RSV may be linked to a specific type of asthma – one related to lung maldevelopment and appeared early in life. It is also possible that preventing RSV reduced triggers for wheezing in the first year of life but had little to no effect on long-term airway inflammation (see "Less Likely Outcomes" section below).

LESS LIKELY OUTCOMES

The impact on asthma

The impact of RSV prophylaxis on long-term inflammatory consequences following RSV infection in infancy has generally been disappointing, especially regarding asthma outcomes. Most research has centered on Palivizumab, given the limited follow-up

time with newer RSV prevention modalities. Furthermore, clinical trials on the different RSV preventive vaccines have primarily focused on laboratory-confirmed, moderate–severe acute RSV respiratory illness and therefore limit our ability to assess the long-term impact for those with mild–moderate illness, which is more common during infancy. A 10-year follow-up of preterm infants who received Palivizumab prophylaxis during their first year revealed no significant impact on rates of asthma [38,39]. Notably, maternal smoking and aeroallergen sensitization emerged as significant factors associated with asthma development in these children, emphasizing these as likely contributors to asthma independent of RSV exposure.

Studies have consistently found no association between Palivizumab, and asthma outcomes [39]. Although Palivizumab has been shown to reduce recurrent wheezing between ages 1 and 3, it did not prevent the onset of atopic asthma by age 6 [40]. This may reflect distinct phenotypes between RSV-induced viral wheezing and true atopic asthma, suggesting that RSV is more of a marker rather than a causative factor for asthma, with factors like prematurity and developmental issues playing a larger role in early-life wheezing without influencing asthma onset later in childhood.

A RCT following preterm infants for 6 years found that RSV prevention had no significant impact on asthma rates or lung function at age 6 years [41]. There was, however, a reduction in wheezing episodes at age 1 and fewer parent-reported asthma symptoms at age 6, though physician-diagnosed asthma, medication use, or lung function were unaffected. Additionally, a large-scale nationwide study on Palivizumab's impact on preschool asthma found no association with Palivizumab administration after adjusting for mode of delivery, prematurity, and maternal asthma [12▪▪]. These findings reinforce that while RSV prophylaxis may reduce short-term RSV-associated wheezing, it does not prevent long-term asthma development, adding nuance to understanding RSV's role in asthma development. The assumption that RSV interventions will not impact potential long-term consequences of RSV is accepted in some cost-effectiveness models [42▪]. However, further research specifically on the impact of maternal vaccination during pregnancy will continue to elucidate the long-term impact of RSV prevention.

Complete eradication of respiratory syncytial virus

Although vaccination is expected to significantly reduce the burden of RSV, complete eradication is unlikely. RSV has a complex virology, with multiple subtypes and high variability in seasonal circulation. Unlike smallpox, which was eradicated through mass vaccination, RSV's ability to cause mild or asymptomatic infections and its seasonality means it may continue to circulate, even in vaccinated populations.

Universal vaccine efficacy

Although RSV vaccines have shown promising results, their efficacy may vary across different population groups. The elderly and those with compromised immune systems may experience less robust immune responses, as seen with other vaccines like influenza. Similarly, premature infants, despite being a primary target for RSV prophylaxis, may not mount as strong a response as full-term infants. As a result, the level of protection may not be consistent across all age and risk groups, potentially limiting the overall impact of vaccination programs. The effectiveness of RSV vaccination may vary based on individual factors, such as underlying health conditions, and exposure to environmental risk factors like maternal smoking [32▪,39,43]. As the costs of these pharmaceuticals are high, RSV will continue to disproportionately impact those populations, with higher rates of morbidity and mortality due to health and socioeconomic disparities [44].

IMPORTANT CONSIDERATIONS

Long-term protection

Although some studies have shown positive short-term outcomes, more research is needed to fully understand the long-term effects of RSV vaccination on infant and adult health. Although Nirsevimab effectiveness was shown to decrease over time, it remained high for preventing hospital admissions at 150 days [33]. Further studies are needed to investigate the potential presence of waning immunity in this context.

Side effects

Concerns were raised about a 1% increase in preterm deliveries observed during RSVpreF clinical trials [45]. In response, the FDA recommended narrowing the gestational age window for vaccination from 24–36 weeks to 32–36 weeks. A postmarketing retrospective study found no significant increase in preterm deliveries but highlighted a potential concern regarding gestational hypertension [46▪▪]. A review on RSV vaccines during pregnancy found no increased risk of intrauterine growth restriction or

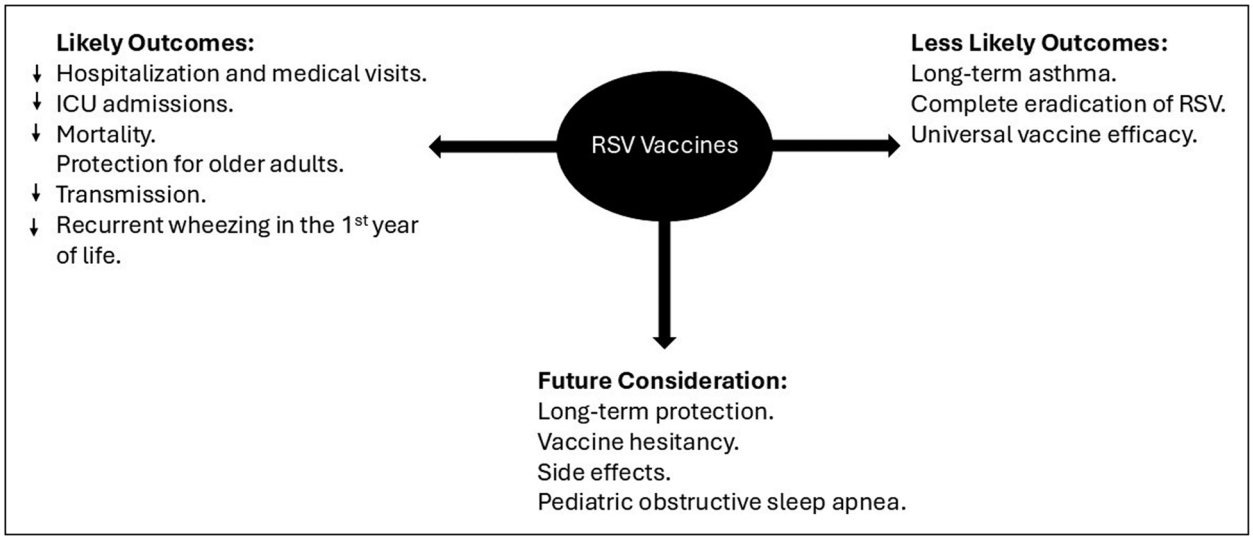

FIGURE 1. Potential outcomes and future considerations for respiratory syncytial virus preventive interventions.

congenital abnormalities [32▪]. However, it identified a potential signal warranting further investigation related to preterm birth (PTB), though the confidence interval was wide and uncertain (RR = 1.16, 95% CI = 0.99–1.36).

Vaccine hesitancy

As with other vaccines, public acceptance of RSV vaccination may be hindered by vaccine hesitancy. Concerns over safety, efficacy, and the relatively new nature of these vaccines may limit uptake. Public health campaigns that emphasize the safety and benefits of RSV vaccination, particularly for infants and the elderly, will be essential in achieving high coverage rates and maximizing the impact of these vaccines. This concern is further enhanced for maternal vaccination due to concerns related to vaccine safety during pregnancy and the potential impact on preterm delivery as described above. Furthermore, in contrast to high-risk populations where the understanding of the impact of severe infection on these vulnerable populations is clear, vaccination of healthy women during pregnancy might meet higher hesitancy and concern.

Pediatric obstructive sleep apnea

The pathogenesis of obstructive sleep apnea (OSA) in children is primarily linked to tonsillar hypertrophy, making adenotonsillectomy the standard treatment for most pediatric cases [47]. However, the mechanisms driving this hypertrophy remain poorly understood. Studies using quantitative PCR (qPCR) have detected nucleic acids from common respiratory viruses, including RSV, in hypertrophic tonsils of children with OSA, compared to those resected for recurrent throat infections in patients without OSA [48]. This finding suggests a potential role for viral infections in triggering the inflammatory cascade leading to tonsillar hypertrophy [48,49]. Investigating the impact of RSV prevention on the incidence of pediatric OSA, particularly following the introduction of RSV vaccines, could provide important insights.

CONCLUSION

RSV vaccination represents a significant advancement in the prevention of severe LRTIs, with the potential to reduce hospitalizations, and mortality rates in high-risk populations. However, challenges remain, including ensuring equitable access, addressing vaccine hesitancy, and managing expectations about the vaccine's ability to prevent all respiratory illnesses. While vaccination is unlikely to eradicate RSV or prevent long-term asthma development in all cases, it holds great promise in reducing the immediate and long-term burden of RSV infections. As new vaccines become available, ongoing research and surveillance will be critical to fully understand their impact on public health (Fig. 1).

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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