Advances and Challenges in RSV Vaccine Development: Pathways toward Global Protection

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Abstract: Respiratory syncytial virus (RSV) is the leading cause of acute lower respiratory tract infection in infants and young children worldwide. Recent breakthroughs in molecular biology and vaccine technology have shifted prevention efforts from antivirals to targeted immunization, including protein and nucleic acid–based platforms. Currently approved recombinant protein vaccines—Abrysvo (for pregnant women) and Arexvy (for older adults)—demonstrate strong safety and efficacy profiles. However, developing vaccines for neonates remains challenging due to their immature immune systems and variable responses. This review summarizes the evolution of RSV vaccine design, underlying immunological mechanisms, and results from pivotal clinical trials. We highlight ongoing strategies to overcome neonatal immunogenicity hurdles and outline future directions for creating safe, broad-spectrum RSV vaccines suitable for all age groups.

1 INTRODUCTION

RSV is a single-negative-strand RNA virus that causes respiratory infections and is mainly transmitted through droplets. The infection rate is higher in the elderly, infants and young children, and people with weakened immunity. RSV can easily cause infectious bronchiolitis in infants and young children, and in severe cases, it can lead to death (Esther Redondo et al., 2024). In older adults, RSV infection can lead to heart failure, stroke, and even acute kidney disease (Schmoele-Thoma et al., 2022). Viruses enter the human body mainly through glycoproteins on their membranes (especially G proteins) to recognize receptors on the host cell membrane (Schmoele-Thoma et al., 2022) and bind to F proteins to promote the fusion of viruses and cell membranes. Recently, it has been found that the integrin on the cell surface (integrin αvβ1) may also be an important medium for RSV to enter host cells (Zheng et al., 2022). RSV infection triggers elevated levels of cytokines such as IL-6 and IL-8, leading to neutrophil and eosinophil infiltration, which can lead to bronchiolitis. At the same time, the Th2 immune response induced by RSV infection may lead to asthma symptoms in infants and young children (Makrinioti et al., 2022; Van Royen et al., 2022). At present, the treatment of RSV infection mainly relies on monoclonal antibody (such as palivizumab) to target the viral F protein for prophylaxis, especially in neonates (Hammitt et al., 2022), but this therapy has limited effect on specific populations (such as neonates and immunocompromised patients), and the protection period is short (half-life about 20 days), which cannot provide lifelong immunity (Drysdale et al., 2023). In addition, there is a lack of effective monoclonal antibody therapy for older adults, especially in the setting of immune failure and the presence of chronic inflammatory underlying diseases such as COPD, chronic bronchitis, and cardiovascular disease (Falsey et al., 2022). There may also be some potential adverse effects, such as mild allergic reactions to the vaccine in infants (Terstappen et al., 2024). The immune escape mechanism of RSV virus itself, such as the non-structural protein NS2 inhibits the interferon pathway by blocking STAT2 phosphorylation (Jo et al., 2021), and the secretory G protein of RSV hinders the recognition of neutralizing antibodies, which brings difficulties to clinical treatment (Bukreyev et al., 2008).

Vaccines against RSV are mainly divided into inactivated vaccines, attenuated vaccines, recombinant protein vaccines, and mRNA vaccines. Live attenuated vaccines attenuate RSV strains through genetic engineering (e.g., reduce the expression of their antigens) to mimic the natural infection process, thereby inducing mucosal

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immunity; Viral vector vaccines use vectors such as adenoviruses that are not pathogenic and self-encoding to express antigens on RSV by presenting RSV antigen genes, thereby inducing T cells to produce immune responses. Recombinant vaccines (also known as recombinant protein vaccines) are vaccines based on pre-F, a pre-stabilized conformation of the RSV fusion protein (F protein), which can induce the production of neutralizing antibodies. The mRNA vaccine is the delivery of the mRNA encoding the RSV F protein through lipid nanoparticles to induce collective expression of antigens and elicit an immune response (Topalidou et al., 2023). However, compared with live attenuated vaccines, protein subunit vaccines usually require adjuvants to enhance immunogenicity (e.g., Pfizer/GSK), and at the same time, the storage requirements for mRNA vaccines are high, and long-term storage data have yet to be accumulated. For example, Moderna's vaccine not only did not protect infants and young children in the III clinical trial, but worsened respiratory symptoms (Mahase, 2024). In addition, the effectiveness of different vaccines in different age groups varies significantly, for example, the elderly and children are more suitable for live attenuated vaccines, less virulent vaccines such as mRNA vaccines, and for high-risk infants (preterm birth, heart and lung disease, etc.), monoclonal antibodies are required for passive immunization strategies to directly provide specific antibodies. In 2019, global RSV-associated hospitalizations occurred mainly in low- and middle-income countries, while vaccine coverage remained concentrated in high-income areas. This highlights the disparate challenges faced by RSV vaccination globally (Li et al., 2022). Despite this, the research and development of RSV vaccines and monoclonal antibodies is still very promising. This review discusses the current status of RSV vaccine development, analyze the main challenges, and look forward to future vaccine technologies, so as to provide new ideas for the prevention and control of RSV.

2 RSV INACTIVATED VACCINES

2.1 FI-RSV Vaccines

The formalin-inactivated RSV (FI-RSV) vaccine employs a traditional inactivation approach, wherein formalin treatment renders the virus noninfectious while preserving its fusion (F) protein to elicit immune responses and serve as the principal target of neutralizing antibodies. Although the FI-RSV vaccine has shown some immunogenicity in animal experiments, it has not only failed to respond to the expected immune response in clinical trials, but has instead led to serious side effects, mainly manifested as enhanced respiratory disease (ERD), which mainly occurs in the middle and lower respiratory tract, accompanied by clinical symptoms such as fever, bronchial and lung inflammation, and even leads to death in children. The failure mechanism of this method is mainly due to the recognition of the neutralizing antibody epitope of RSV only on the pre-F conformation and not on the post-F (Magro et al., 2012; Ngwuta et al., 2015), and the post-F conformation may induce non-neutralizing antibodies and Th2 immunotype responses.

2.2 RI-RSV Vaccine

The γ-irradiated RSV (RI-RSV) vaccine inactivates the virus via gamma irradiation, employing a development strategy analogous to that of the formalin-inactivated FI-RSV vaccine. In animal trials, RI-RSV vaccines have induced similar levels of neutralizing antibodies to FI-RSV vaccines. RI-RSV vaccine has shown certain advantages in enhancing immunogenicity and focusing on vaccine heterogeneity protection, but it also produces side effects, such as weight loss and lung inflammation, which may be related to RI-RSV vaccine-induced conversion from pre-F to post-F (Chen et al., 2023). Therefore, the design of inactivated vaccines should focus more on antigen design specificity and take into ac-count population differences. As structural insights into the RSV F protein deepen—particularly evidence demonstrating that the pre-F conformation presents superior neutralizing epitopes—vaccine development has increasingly focused on optimizing the balance between immunogenic potency and targeted immunoreactivity.

3 LIVE ATTENUATED RSV VACCINE

Live attenuated vaccines mainly weaken the virulence of the virus through gene editing or physical and chemical methods, simulating the natural infection process, so that its replication in the host is limited and does not cause host disease, while retaining its immunogenicity. The immune

mechanism is mainly through mucosal immunity to produce secretory IgA and local T cell responses. For example, CodaVax-RSVTM reduces viral virulence through codon optimization, while activating secreted IgA antibodies in the mucosa to form a local immune barrier and block early viral colonization. Deletion of NS1/NS2 virulence-related genes can reduce pathogenicity by reducing the ability of the virus to inhibit the production of interferon by the host, effectively detect immunogenicity during clinical treatment, and elicit a massive memory-immune response to RSV (Karron et al., 2024). Similarly, partial deletion of the G protein domain has been shown in animal models to reduce viral toxicity while preserving immunogenicity (Roe et al., 2022). The targeted design of the F antigen is to generate disulfide bonds through the DS-Cav1 mutation, which stabilizes the pre-F conformation that can produce highly effective neutralizing antibodies. CodaVx-RSVTM vaccine demonstrated a favorable safety profile in healthy adults during Phase I clinical trials, eliciting both mucosal IgA and systemic neutralizing antibodies; however, its safety and immunogenicity in neonates remain to be established.

4 RECOMBINANT RSV VACCINES

The RSV recombinant vaccine is a non-replicating formulations that express target antigens and require adjuvants to elicit robust immune responses. The sources of immune response elicited by using the virus's own information are mainly divided into recombinant protein vaccines, recombinant vector vaccines and DNA vaccines (Giese, 2015). In the development of RSV proteins, G membrane proteins are prone to mutations, so the breakthrough is mainly aimed at the relatively conserved F protein on the RSV membrane, which is responsible for helping the virus enter and fuse cells, and its conformational pre-F has more neutralizing antibody epitopes (such as site Ø, site V) than another conformational post-F, but because its pre-F is naturally unstable and easily spontaneously transformed into post-F, stabilizing the pre-F protein conformation is the core challenge of vaccine development(McLellan et al., 2013). Genetic engineering plays an important role here, as GSK's Arexvy (pre-F) vaccine has demonstrated its effectiveness in clinical trials – up to 80% in older adults by stabilizing pre-F by stabilizing the pre-F mutation with a DS-CAV1 mutation and increasing the disulfide bond to improve protection. The adenovirus vector AdC68 was used to express three different gene mutations (DS-CAV1, SC-TM, DS2), and then the neutralizing antibody titer and immunogenicity size were determined, and the results showed that DS2 showed better immunogenicity (Yang et al., 2024). Pregnant women receiving the pre-F vaccine during pregnancy are effective in preventing neonatal RSV-related respiratory illness, but in people aged ≥ 60 years, the immune efficacy (vaccine efficacy) of the two doses before and after vaccination within one year at the RSVAPREF3 time of vaccination is about the same (Ison et al., 2024). In 2024, Clover Biosciences Inc. developed an unadjuvanted bivalent RSV Pre-F-trimer vaccine, SCB-1019, induced two neutralizing antibodies (RSV-A and RSV-B) in animal trials, with antibody titers comparable to Arexvy within one month, yielding approximately 1.5-fold more specific antibodies than SCB-10191, and local adverse events (16.7%) significantly lower than Arexty (76.7%).

5 mRNA RSV VACCINES

mRNA vaccines do not require cell culture or risk integration into the host genome, with lower risk and higher antigenicity because they do not integrate nucleic acids into the host genome. LVRNA007 is a lipid nanoparticle mRNA vaccine encoding a DS-Cav1–stabilized prefusion (pre-F) RSV F protein. In animal experiments, LVRNA007 showed a long-lasting cellular and humoral immune response, effectively fighting RSV while avoiding vaccine-enhanced disease (VED) (Li et al., 2025). The production of mRNA-1345 is introduced to optimize structural biology, exposing pre-F neutralizing antibody epitope, using pseudouridine instead of natural uridine to reduce the immunogenicity of mRNA and prolong its half-life in the human body (Bansal, 2023). Packaging mRNA into nanoparticles prevents enzyme degradation and improves delivery efficiency. Finally, modification and purification are made, and the lipid components in the nanoparticles act as adjuvant ingredients to enhance the immune response. At the same time, in clinical trials, the vaccine has a protective effect of up to 80% on RSV-A and RSV-B subtypes, and its neutralizing antibody titers are significantly higher than those of traditional protein vaccines. No vaccine-enhanced diseases are seen. The possible side effects are local injection reactions and temporary fatigue (Wilson et al., 2023). A team from Xiamen University designed a new type of truncated pre-F protein to make a vaccine as an immunogen. By removing inefficient neutralizing

antibody epitopes and enhancing high-efficiency neutralizing antibody epitopes, the vaccine antibody response generated by the delivery of lipid nanoparticles can effectively target the two subtypes of RSV A and B. Moreover, no vaccine-enhanced disease (VED) was found (Lin et al., 2025).

6 CHALLENGES FOR RSV VACCINES

6.1 Immune Evasion

RSV infection is characterized by dysregulation of type I interferon (IFN) signaling. Nonstructural proteins on the RSV membrane (such as NS1 and NS2 proteins) will hinder the host's natural immune response. For example, the key molecule MAVS (mitochondrial antiviral signaling protein) on the outer mitochondrial membrane is a key molecular platform of the antiviral RLR pathway. The specific recognition effect of RSV's NS1 protein on the protein TUFM on the mitochondria will initiate the mitochondrial autophagy mechanism, thereby affecting the host's immune signaling (Cheng et al., 2023). At the same time, N protein can isolate the antiviral protein, the immune-stimulating protein, in the inclusion body, and then negatively regulate the innate immune-related proteins (Cheng et al., 2023). In addition, the Post-F conformation of RSV exposed inefficient binding antibody epitopes (siteI and site III), inducing nonprotective antibodies and at risk of inflammation, which is more common in clinical trials of advanced vaccines (inactivated and partially attenuated vaccines). When the human body is infected with RSV normally, due to the instability of pre-F, it will turn into a relatively stable post-F conformation, thereby escaping the pre-F-specific antibodies produced by the host, resulting in immune failure (Venkatesan, 2023). To overcome this challenge, the key to vaccine design is how to stabilize the pre-F conformation and prevent it from transitioning to post-F. According to the recombinant protein vaccines prepared by RSV viruses for proteins (F and G proteins) that are closely involved in the host response, although they can activate immune responses as antigenic components, they require adjuvants to enhance their immunogenicity in most cases. New research direction - RSV nano-lipid particle mRNA vaccine, which uses viral mRNA to generate antigen proteins in host cells and activate immune responses while lipid nanoparticles help stabilize antigens and enhance immunogenicity.

6.2 Vaccine Efficacy and Adverse Events across Age Groups

Infants and young children benefit most from recombinant protein vaccines due to their lower reactogenicity. For example, in the Abrysvo clinical trial, after pregnant women received the maternal vaccine, the antibodies were passed to the infant through the placenta, and the vaccine protective efficacy reached 81.8%. Although no serious adverse events were reported, potential effects of maternally derived antibodies on infant immune development warrant monitoring. Palivizumab, an RSV monoclonal antibody, prevents RSV infection by inducing passive immunity, but is ineffective for RSV treatment. In clinical experiments, severe respiratory-related infections were observed in the RSV mRNA-1345 vaccine produced by Moderna. This may be related to the infancy of the immune system of infants and young children, which leads to the inability to make timely immune responses. Elderly and high-risk populations (such as those with low immunity) performed well in the second-generation vaccine, Pfizer's Abrysvo RSV-preF bivalent recombinant protein vaccination trial (Alfano et al., 2024; Havers et al., 2023; Surie et al., 2024). The two vaccines Abrysvo and Arexvy can have similar side effects on the body after vaccination, including fatigue, muscle headaches, headaches, and pain at the vaccination site. But these effects are temporary and transitional (Andreoni et al., 2024). RSV infection prevention is mainly aimed at newborns, especially babies within one year of birth. The current strategy is composed of multiple steps: first, the maternal antibodies that deliver anti-RSV are delivered to the baby; then, within 3 months of the baby, monoclonal antibodies are injected to produce passive immunity, and then natural infection is simulated by vaccinating vector vaccines or attenuated vaccines to test whether an effective immune response is generated (Zheng et al., 2022). High-risk groups also have corresponding vaccine response strategies (E. Redondo et al., 2024).

7 CONCLUSION

After the failure of clinical trials of the first-generation RSV vaccine, the development of RSV vaccines has focused more on the role of vaccines in the human body, especially for special groups such as newborns, the elderly, and those with immunodeficiency.

With the maturity of modern biotechnology, the direction of vaccine research and development has gradually shifted to artificially manipulating viral antigens, such as enhancing the immunogenicity of vaccines through lipid nanoparticles as adjuvants while ensuring their safety. These innovations have successfully transitioned to recombinant vaccines, and have prompted mRNA vaccines and monoclonal antibody vaccines to show great potential in immunogenicity and safety. However, RSV vaccines still face some challenges, including the limited vaccine supply, price issues, public inadequate awareness of the RSV virus, and differences in the effects and side effects of different vaccines on different age groups. The effectiveness of vaccines, especially in neonatal and immunity-lowering populations, still needs further verification, and long-term tracking of the immune response and side effects of vaccinated people is the key to vaccine research. With the in-depth understanding of the RSV immune escape mechanism and the continuous innovation of vaccine technology, RSV vaccines are expected to be widely used worldwide in the future, thereby effectively controlling the spread and harm of RSV infection.

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