Chapter

RSV: Available Prophylactic Options and Vaccines in Clinical Trials

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Abstract

Respiratory syncytial virus (RSV) is the leading cause of serious lower respiratory infection (ALRI)-related hospitalization in children worldwide, and a source of morbidity and mortality in high-risk adults. There are strong associations between RSV, persistent wheezing and childhood asthma. Despite extensive research, no effective treatment is available aside from supportive care. The trial of a formalin-inactivated RSV vaccine in the 1960s resulted in priming the severe illness upon natural infection. Palivizumab, a monoclonal antibody approved for RSV prophylaxis in high-risk infants, has only moderately decreased hospital admissions due to RSV infection. Live-attenuated, vector, and protein-based vaccine candidates are being investigated in many clinical trials. Developing a vaccine remains challenging due to finding the right balance between adequate immunogenicity and attenuation of vaccine. Here we review the clinical significance of RSV in infants, young children, high-risk adults, elderly population, pregnant women; clinical manifestations and consequences of RSV infection; the pharmacologic strategies currently available, the current stages of RSV vaccine clinical trials, different strategies, and major hurdles in the development of an effective RSV vaccine.

Keywords: respiratory syncytial virus (RSV), pediatric, respiratory infection, palivizumab, antiviral therapy, immuno-prophylaxis, RSV vaccine, clinical trials

1. Introduction

RSV, a member of the Paramyxoviridae family, is an enveloped, negative-sense, single-stranded RNA virus [1]. Especially within the winter months, it is an important cause of morbidity and mortality among young children, the elderly, and immunocompromised individuals [2]. Infection is transmitted by either direct or indirect contact with respiratory droplets, and prior infection does not result in persistent immunity.

RSV accounts for approximately 2.1 million outpatient visits among children younger than 5 years old [3]. Additionally, there are 177,000 hospitalizations and 14,000 deaths among adults older than 65 years due to RSV infection [4, 5] each year in the United States. Human studies have shown strong associations between RSV, persistent wheezing, and childhood asthma [6–8].

Symptoms usually begin 4–6 days after transmission and present with nasal congestion, rhinorrhea, fever, or cough. RSV is one of the leading causes of lower respiratory tract infection (LRTI), and can cause tachypnea, wheeze, hypoxemia, or respiratory distress, resulting in an emergency department visit or hospital admission [9]. Males are more severely affected than females, and for reasons that are not fully elucidated, Native Americans and Alaskan Native children are more likely than children of other ethnicities to have severe infection requiring hospitalization.

To date, supportive care is the main treatment option for RSV admission [9, 10]. There is no vaccine approved for RSV prophylaxis in the general population. In 1966, the first vaccine for RSV, a formalin-inactivated (FI-RSV) type, was developed. However, it resulted in vaccine-enhanced disease (VED). Among vaccinated infant, 80% developed severe bronchiolitis or pneumonia and two died, compared to only 5% for the placebo group [11]. There was increased eosinophilic and neutrophilic infiltration and mononuclear cells in the lung parenchyma found in the autopsies of two infants that died, which suggests a Th2-biased immune response, however the mechanism of the VED remains unclear [12].

RSV is composed of 10 genes encoding 11 proteins: small hydrophobic (SH) protein, nucleocapsid associated proteins N, P, L, M2–1, and M2–2, the matrix (M) protein, nonstructural proteins NS1 and NS2, glycoprotein (G), and fusion (F) protein. The SH, N, M2–2, NS2, G, and F proteins are the most commonly manipulated proteins in vaccine production (**Figure 1**). The SH protein inhibits cell apoptosis through inhibition of the TNF-α pathway [13]. The N protein initiates encapsidation of the genome, the M2–2 protein mediates the balance between transcription and RNA replication, and the NS2 protein inhibits host interferon (IFN) response [14, 15]. G protein mediates viral attachment to the host cell, while F protein enables fusion of the virus [16, 17]. RSV A and RSV B, the two antigenic subtypes, differ in their amino acid sequence of the G protein and reactivity to antibodies, resulting in differences in disease severity [18]. Targeting the F protein is of particular interest, as it is highly conserved between the two antigenic subgroups.

In this chapter, we will discuss the current and candidate antiviral drugs and prophylactic agents against RSV infection and some of the ongoing clinical trials of RSV vaccines. Evaluation of drugs typically proceeds in a methodical order, from studies in healthy adults, to hospitalized adults, to older seropositive children, to

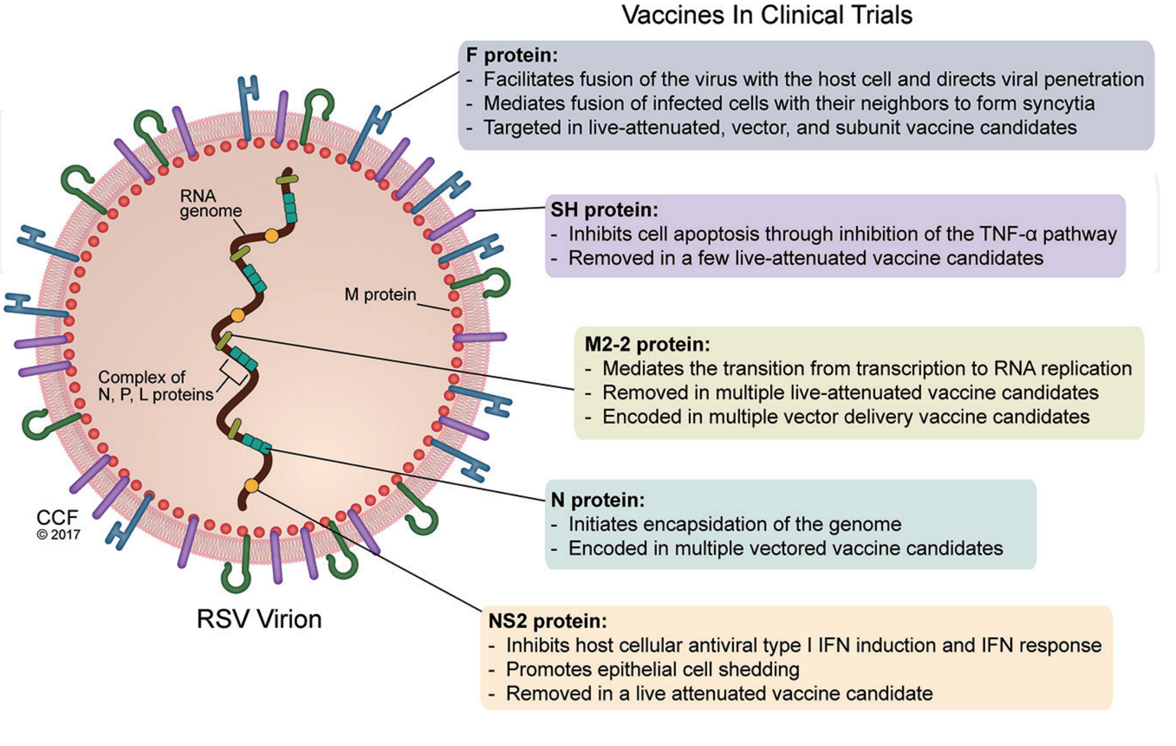

Figure 1.
Current and future options for RSV treatment or prophylaxis. No RSV vaccine is currently on the market, but diverse vaccine candidates, targeting different proteins within the RSV virion, are undergoing clinical trials.

seronegative infants/toddlers. For purposes of this chapter, we will highlight the most recent trials where research is ongoing. We will also elucidate many of the complex hurdles that have impeded progress in the development of an effective vaccine.

2. Available pharmacologic strategies

2.1 Ribavirin

Ribavirin, a synthetic guanosine analogue antiviral agent, was first synthesized in the 1970s. It is believed that ribavirin is phosphorylated intracellularly and can then disrupt purine metabolism by inhibiting inosine monophosphate dehydrogenase, thereby inhibiting nucleic acid synthesis. Furthermore, it promotes antiviral cytokine production and Type 1 T-cell mediated immune responses. Starting in 1993, the American Academy of Pediatrics (AAP) Committee on Infectious Diseases supported the use of Ribavirin for severe RSV infections. However, in 1996, the recommendation changed to "may be considered" [19]. Currently, the use of aerosolized Ribavirin is limited to immunocompromised patients with RSV due to the inconvenient route of delivery, which requires prolonged aerosol administration; risks for potential toxicity, such as teratogenic effects during pregnancy; cost of therapy; and need for hospital admission. The safety of oral ribavirin in moderately to severely immunocompromised adults with PCR-proven RSV infection was examined in a retrospective cohort study. The main outcome of this study was the rate of adverse events, and authors conclude that ribavirin is well tolerated in immunocompromised adults [20]. However, the rate of progression of disease from URTI to the LRTI was not measured. In another retrospective study, immunosuppressed patients were given either oral, intravenous, aerosol or a combination of these treatments and showed that ribavirin therapy reduces progression from RSV URTI to LRTI [21]. In a similar study, Khanna et al. reported that 32% of patients who were treated with ribavirin progressed to LRTI compared to 68% of the untreated group [22]. Their study showed that oral ribavirin therapy was likely as effective as aerosolized therapy. However, because of the sample size and retrospective nature, neither of these studies could determine the precise role of ribavirin therapy in this patient population. In addition, ribavirin is being used for Hepatitis C infection, in conjunction with an interferon agent [23]. Furthermore, a recent study showed that ribavirin inhibited Zika virus replication and Zika virus-induced cell death in mammalian cells [24].

2.2 ALS-008176

ALS-008176, a prodrug of a cytidine nucleoside analogue, decreased viral load and more readily cleared RSV than placebo in a randomized, double-blind clinical trial in healthy adults [25]. However, participants' preexisting immune memory, which may promote RSV clearance, was not assessed [26]. A randomized, double-blind Phase I study assessing both a single and multiple ascending dosing in hospitalized infants (Clinicaltrials.gov identifier #NCT02202356) was completed in February 2018, but results have not been published yet.

2.3 Presatovir

During viral entry, the F protein undergoes conformational changes to fuse with the host cell membrane [17]. Presatovir (GS-5806) is an orally bioavailable agent that inhibits these conformational changes, thereby blocking viral fusion [27]. It was found in a Phase 2a trial with healthy adults (Clinicaltrials.gov identifier

#NCT01756482) to reduce viral load and severity of disease. However, it also caused low neutrophil counts and increased levels of alanine aminotransferase [27]. Despite these adverse events and because of its promise as an efficacious antiviral agent, a Phase 2b, randomized, double-blind trial in RSV-infected hospitalized adults was completed in April 2017 (Clinicaltrials.gov identifier #NCT02135614). The primary outcome was the time-weighted average change in RSV load from baseline to Day 5. There appeared to be no significant differences between Presatovir and placebo (−0.77 vs. −0.89, respectively, p value = 0.46).

3. Currently available and under development immuno-prophylaxis

3.1 RSV-IVIG

RSV Immunoglobulin (RSV-IVIG, RespiGam) is a pooled hyperimmune polyclonal immunoglobulin preparation made from donors with high titers of anti-RSV antibodies. RSV-IVIG significantly reduced morbidity and mortality in high-risk infants [28]. It was initially licensed in 1996, but taken off the market in 2004, due to the need for long intravenous infusion sessions and supervision in a hospital setting, high volume doses resulting in fluid overload in already at-risk infants, and potential risk for blood-borne pathogens [29]. Furthermore, immunizations with live-attenuated viruses, such as the measles/mumps/rubella (MMR) vaccine, need to be postponed until 9 months after RSV-IVIG infusion.

ALX-0171 is an inhaled trivalent nanobody that targets the RSV F protein [30]. A Phase I/IIa in RSV-infected infants and toddlers was recently completed in February 2016 (Clinicaltrials.gov identifier #NCT02309320). A Phase II dose ranging study RSV-infected hospitalized infants was recently completed in May 2018. Results from both studies have not been published yet.

3.2 Palivizumab and motavizumab

Palivizumab (Synagis), developed by MedImmune (Gaithersburg, MD, USA) in 1998, is the only currently approved prophylaxis agent against RSV infection [31]. It has been shown to reduce severe RSV infections by 55% and reduce RSV hospitalizations by 50%. Palivizumab is a humanized monoclonal IgG1 antibody that recognizes the RSV F protein and is administered intramuscularly monthly, for a maximum of 5 months, during the RSV season. It has no significant adverse side effects and other required live-attenuated vaccines can still be administered. However, because of the high cost, it is selectively given to high-risk infants: preterm infants born at <29 weeks of gestation; infants with chronic lung disease (CLD) of prematurity defined as gestational age <32 weeks of gestation and requirement of supplemental oxygen for the first 28 days of life; hemodynamically significant congenital heart disease; and might be considered for neuromuscular disorders that impair the airway clearance [32, 33].

Motavizumab (MEDI-524, Numax), an affinity-matured derivative of palivizumab, was shown to be more efficient than palivizumab with higher virus neutralizing effects [34]. However, it failed to receive FDA approval due to lack of greater clinical efficacy compared to palivizumab and cutaneous hypersensitivity reactions in some treated infants [35].

3.3 Suptavumab

Suptavumab (REGN2222) completed a Phase III trial in July 2017 (Clinicaltrials.gov identifier #NCT02325791). It is a human monoclonal IgG1 antibody against

RSV-F [36]. 1177 preterm infants for whom palivizumab was not recommended were randomly assigned to one of three groups: Group 1 received one dose of intramuscular suptavumab and one dose of placebo, Group 2 received two doses of suptavumab, and Group 3 received two doses of placebo. There were no significant differences between the three groups in terms of the primary outcome of preventing medically attended RSV infection up to Day 150 [36]. All further development of Suptavumab has been stopped.

3.4 MEDI8897

MEDI8897 is another recombinant human monoclonal antibody with a modified Fc region that extends its half-life. MEDI8897 is being developed as RSV prophylaxis for all infants. The phase I (Clinicaltrials.gov identifier #NCT02114268) of study recruited 136 healthy adults, who received either MEDI8897 or placebo intravenously or intramuscularly, a single dose of 300–3000 mg. The half-life of the antibody was 85–117 days across the groups [37]. The phase Ib/IIa of the study, recruited healthy preterm infants with a gestational age of 32–35 weeks. The antibody group received as single intramuscular dose of 10–50 mg MEDI8897. The half-life of the antibody was 62.5–72.9 days. The authors concluded that the antibody has a favorable safety profile and can be administered as single dose during RSV season [38]. A Phase IIb trial in preterm infants' ineligible for Synagis was completed in 2018 and there is a plan for the Phase III trial in healthy full-term and late pre-term infants in 2019.

4. RSV vaccines under development

To date, there is no vaccine against RSV. Developing a vaccine against RSV remains a challenge, as the proper balance is required in eliciting an immune response, while avoiding vaccine-enhanced disease. While many of the proteins within RSV are being manipulated in different vaccine strategies, RSV F comprises a highly conserved amino acid sequence called antigenic site II, between RSV-A and RSV-B antigenic subgroups, and has been considered an important antigen for an RSV vaccine.

Designing a vaccine against RSV requires careful considerations. Infants, the elderly, and pregnant women are the three targeted populations for RSV vaccine development [39]. Each of the three types of vaccines, live-attenuated, vector delivery, and protein based, have benefits and drawbacks that have to be considered when developing vaccine technology (**Table 1**). Live-attenuated vaccines contain extracted components of viral proteins and present antigens most similarly to the naturally occurring infection [40]. They stimulate both humoral and cell-mediated immune responses. Live-attenuated vaccines are employed against many viral diseases, like measles, rubella, polio, rotavirus, varicella, and yellow fever.

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One major drawback of live attenuated vaccines is that they cannot be given to patients with compromised immunity including pregnant woman. Vector-delivery system vaccines utilize a non-pathogenic virus genome with inserted portions of RSV proteins. Similar to live-attenuated vaccines, these vaccines increase mucosal IgA and cellular immune responses, yet without the risk of insufficient attenuation [40]. Protein-based vaccines include whole-inactivated viruses, subunit antigens, and particle-based vaccines. Live-attenuated or vector vaccines hold the greatest promise for infants due to the risk of vaccine-enhanced RSV disease. Pregnant women and the elderly are not susceptible to vaccine-enhanced RSV disease, and therefore protein-based RSV vaccines are likely the most effective candidates [40].

	Advantages	Disadvantages
Live-attenuated (For young infants and children <24 months of age)	• Induces immunity • Does not exacerbate future RSV exposure • Administered intranasally	• Need to obtain delicate balance between immunogenicity and adequate attenuation
Vector delivery system (For young infants and children <24 months of age)	• Induced potent cellular and humoral responses in a primate model and preclinical studies • Safer option than live attenuated vaccines in children with no risk of insufficient attenuation	• Prior exposure to the vector and immunological memory against common serotypes may reduce the immune response and limit their use • The potential oncogenicity and pathogenicity of some Adenovirus serotypes
Protein-based (For pregnant women and elderly)	• Maternal immunization could increase transplacental antibody transfer and provide immunity for infants	• High risk of exacerbation for RSV-naïve infants

Table 1.
Advantages and disadvantages of the main strategy categories for RSV vaccine development.

Vaccine type	Current strategies
Live-attenuated	M2–2 gene deletion LID ΔM2–21030s LID cp ΔM2–2 RSV D46/NS2/N/ΔM2–2-HindIII NS2 gene deletion ΔNS2/Δ1313/1314 L RSV 6120/ΔNS2/1030s SH gene deletion MEDI–559 RSV cps2
Vector delivery system	Adenovirus vector GSK3389245A GSK3003891A VXA-RSV-f Ad26.RSV.preF PanAd3-RSV Modified Vaccinia Ankara vector MVA-RSV MVA-BN
Protein-based	Particle based vaccine F-protein nanoparticle Subunit vaccine MEDI-7510

Table 2.
Current vaccine candidates undergoing clinical trials.

Live-attenuated, vector, and protein-based vaccines each possess advantages and disadvantages. Because non-replicating vaccines may elicit enhanced disease in RSV-naïve infants during subsequent infection, replicating or vectored vaccines might be a better choice in this group [41, 42]. Additionally, active immunization for infants is challenging due to passive immunity received from the mother [43]. Because of these factors, different vaccines may be required for different target populations. Understanding these complexities is crucial in RSV vaccine advancement. We will now discuss in depth the different vaccine strategies and current clinical trials in each category. A list of the vaccine candidates is summarized in **Table 2**.

4.1 Live-attenuated vaccines

The tragic results of the formalin-inactivated RSV vaccine in the 1960s spurred research in the development of live-attenuated vaccine candidates. The live virus has parts of the genome deleted and is passaged at gradually lower temperatures. Live-attenuated vaccines require a delicate balance: maintain sufficient viral genome RNA replication to illicit enough antibody response in RSV-naïve infants, yet with a low risk of deattenuation and no harmful effects [44]. Live-attenuated vaccines are, in theory, safe for RSV-naïve infants because it does not exacerbate future exposure to RSV. Furthermore, it may be administered intranasally, which can mimic a milder form of a natural infection, and lead to viral replication in the upper respiratory tract [40]. This will induce mucosal and humoral immunogenicity, despite the potential presence of maternal antibodies acquired transplacentally.

Several live-attenuated RSV vaccine candidates have deletions of a large segment of the M2–2 gene. The M2–2 gene mediates the transition from transcription to RNA replication [14]. *In vitro* studies have shown that M2–2 gene deletion leads to decreased viral RNA replication, but increased F and G protein expression through transcription. This means that the virus is adequately attenuated, yet potentially could lead to augmentation of the neutralizing antibody response [14]. A Phase I study explored the safety of a LID ΔM2–2 vaccine, delivered intranasally to RSV-seronegative infants (aged 6 to 24 months). This vaccine infected the subjects successfully, but the peak shedding titers were higher than wanted, and therefore the study was terminated [45, 46]. Further attenuation to the LID ΔM2–2 vaccine, to counter the high shedding titers, is currently under investigation. The LID ΔM2–21030s vaccine has a mutation conferring temperature sensitivity. A Phase I placebo-controlled study in RSV-seronegative infants aged 6 to 24 months (Clinicaltrials.gov identifier #NCT02794870) completed in July 2017, showed that roughly 60% of vaccine recipients and 27% of placebo recipients had solicited adverse events. Conclusions regarding the LID ΔM2–21030s vaccine have not yet been made. A Phase I LID cp ΔM2–2 vaccine, which in comparison to the LID ΔM2–2 contains 5 amino acid substitutions, was terminated early in seronegative infants 6 to 24 months of age due to indication that the vaccine "did not meet the protocol criteria for a good vaccine candidate" (ClinicalTrials.gov identifier #NCT02890381). We believe that this is because only 6/11 patients in the vaccine arm of the trial were infected with the vaccine virus from Study Day 0–28, thereby suggesting that there was not a strong enough immune response against the vaccine. Another vaccine candidate is RSV D46/NS2/N/ΔM2–2-HindIII that contains one point mutation in the NS2 and N proteins and a modified version of the M2–2 deletion [47]. A Phase I study in RSV-seronegative infants and children 6–24 months of age was completed in May 2018.

Aside from deleting the M2–2 gene, the NS2 gene is another potential "knock-out" gene for a live-attenuated vaccine. The RSV NS2 gene is known to promote epithelial cell shedding and inhibit host IFN response [15]. ΔNS2/Δ1313/1314 L, a vaccine candidate with a deleted NS2 gene, is genetically stable and moderately temperature-sensitive [48]. Another candidate, RSV 6120/ΔNS2/1030s, also has a deleted NS2 gene, in combination with the "1030s" missense mutation, which provides further restriction of replication. Both of these candidates are currently being assessed in both seropositive and seronegative children and infants (Clinicaltrials.gov identifiers #NCT03422237 and #NCT03387137).

Strategies have also targeted the SH gene. The RSV SH gene has multiple functions, including inhibiting cell apoptosis, inhibiting signals from TNF-α, and modifying membrane permeability [49]. One vaccine that has a complete deletion of the SH gene, rA2cp248/404/1030ΔSH, demonstrated restricted antibody response in the subjects, as well as viral genotypic and phenotypic instability primarily due to reversion of the 1030 mutation [42, 48]. MEDI-559 differs from rA2cp248/404/1030ΔSH by silent nucleotide substitutions throughout the viral genome [42, 50]. A Phase I/IIa trial studying the safety and efficacy of MEDI-559, showed a higher incidence of medically attended LRTI in RSV seronegative infants 5 to <24 months of age and in infants 1 to <3 months of age regardless of baseline serostatus within 28 days, as compared to placebo [50]. RSV neutralizing antibodies were detected in 59% of MEDI-559 recipients, in comparison to 9% of placebo subjects. Interestingly, this microneutralization response was lower than the rA2*cp*248/404/1030ΔSH vaccine's response. Adverse events, most notably URTI, occurred in 67% MEDI-559 and 57% placebo recipients, which was not clinically significantly different. Further safety trials are warranted to determine the safety profile of MEDI-559 as there was increased incidence of medically attended LRTI.

In comparison to MEDI-559, RSVcps2 contains 5 nucleotide changes and 1 amino acid substitution. The level of attenuation of RSVcps2 and MEDI-559 was shown to be similar in a study in seronegative chimpanzees [48]. This study also showed that it was temperature-sensitive and phenotypically and genetically stable. A Phase I trial in RSV-seronegative, healthy 6–24 month old children demonstrated that RSVcps2 is safe and effective [51]. Furthermore, unlike MEDI-559, medically attended LRTI was not observed. There were no significant differences in the number of adverse events between the experimental and control groups. However, in comparison to rA2cp248/404/1030ΔSH, RSVcps2 had decreased levels of replication and immunogenicity. The study investigators believe that this is due to the 37 silent nucleotide differences between the two vaccine candidates [51]. An ideal candidate would therefore combine the genetic stability of RSVcps2 and the greater replication and immunogenicity of rA2cp248/404/1030ΔSH. Other ΔSH vaccine candidates include OE4 (RSV-A2-dNS1-dNS2-ΔSH-dGm-Gsnull-line19F) and DB1 (RSV-A2-dNS-ΔSH-BAF), which have both been found to be immunogenic in cotton rats [52, 53].

4.2 Vector delivery systems

Vaccine technology is currently utilizing adenovirus and non-pathogenic viral genomes that can act as immune potentiators of delivery systems. These vaccines contain inserted portions of RSV F, N, and M2–1 proteins [54]. Vector vaccines increase mucosal IgA and cellular immune responses similar to live-attenuated vaccine candidates, yet without the risk of insufficient attenuation [55]. Furthermore, adjuvants used with these vector vaccines could potentially enhance the immune response to the vaccine [56].

GlaxoSmithKline's ChAd155-RSV (GSK3389245A) and GSK3003891A are RSV vaccine candidates encoded by a chimpanzee-derived adenovector. A Phase II trial (Clinicaltrials.gov identifier #NCT02360475) evaluating GSK3003891A in healthy, non-pregnant women aged 18–45 years was recently completed. The study showed that GSK3003891A is both safe and immunogenic. However, a Phase II trial in healthy pregnant women and infants born to vaccinated mothers was canceled due to instability of the PreF antigen during manufacturing. A Phase I study investigating ChAd155-RSV in healthy adults aged 18 to 45 years was recently completed (Clinicaltrials.gov identifier #NCT02491463), and a Phase II study in RSV-seropositive infants aged 12–23 months is underway (Clinicaltrials.gov identifier #NCT02927873). Another adenoviral-vector based RSV vaccine candidate, VXA-RSV-f, expressing the F-protein and a dsRNA adjuvant, is recently completed a Phase I, placebo-controlled, dose-ranging study, using subjects aged 18–49 years. Results have not been released yet.

Adenoviruses of serotype 26 (Ad26) are engineered to comprise a nucleotide sequence encoding RSV F protein, which showed efficacy against RSV in mice and cotton rats [57]. Two Phase I, placebo-controlled studies assessed the administration of Ad26.RSV.FA2, given either once or twice, followed by Ad35.RSV.FA2, and vice versa, to adults aged 18–50 years. Ad26.RSV.FA2 was shown to be safe and well tolerated. There was also increased humoral and cellular immunity for 6 months. Ad26.RSV.preF differs by 5 amino acids and contains the pre-fusion conformation stabilized F protein, and showed increased immunogenicity in comparison to Ad26.RSV.FA2 in pre-clinical studies [58]. It is currently undergoing a Phase II clinical trials in adults aged 18–50 years and RSV-seropositive toddlers aged 12–24 months (Clinicaltrials.gov identifier #NCT03303625) and in healthy adults greater than age 60 (Clinicaltrials.gov identifier #NCT03339713). PanAd3-RSV, a vaccine based on the RSV viral proteins F, N and M2–1 encoded by Simian Adenovirus, completed a Phase I trial in subjects 18–75 years of age (ClinicalTrials.gov identifier #NCT01805921) in 2015, alongside a Modified Vaccinia Virus Ankara (MVA) non-replicating vector vaccine candidate. Both of these vector vaccines contain RSV viral proteins F, N and M2–1.

PanAd3-RSV and MVA-RSV were both safe and effective in cotton rats, mice, and calves [59] and immunogenic in a primate model [54]. Most adverse effects were mild to moderate, self-limiting at the site of injection and the study concluded that the vaccine was safe and immunogenic [60]. Despite the promising results, no current clinical trial is investigating these vaccine candidates. MVA-BN (modified Vaccinia Ankara—Bavarian Nordic) is another MVA-based vaccine undergoing investigation. In August 2018, Bavarian Nordic announced that in a Phase II trial in older adults the MVA-BN vaccine elicited broad antibody and T cell responses to both RSV subtypes that lasted 6 months. Furthermore, a booster shot 1 year later again initiated a robust cellular immune response [61].

4.3 Protein-based vaccines

Pregnant women and the elderly are not susceptible to vaccine-enhanced RSV disease like infants, and therefore RSV protein-based vaccines are most likely the most effective candidates. Protein-based vaccine candidates include whole-inactivated viruses, subunit antigens, and particle-based vaccines. Vaccinating a pregnant woman can provide passive immunity to the fetus, as RSV-neutralizing antibodies have been shown to pass from mother to fetus *in utero* [43]. The higher RSV neutralizing antibody in cord blood was associated with reduced risk of hospitalization and disease severity in RSV infection has been shown by several studies [62, 63]. A recent comprehensive study measured multiple serum neutralizing RSV of the infants presented with primary RSV infection and did not find a direct relationship between the disease severity and level of most of anti–respiratory syncytial virus (RSV) antibody titers. However, they found a significant inverse relationship between antibody titer to RSV F protein and disease severity [64]. This is particularly important as the post-fusion form of RSV F protein has been used in clinical trial [65]. Additionally, experimental studies have shown that RSV infection during pregnancy can alter the offspring's postnatal immunity and airway hyperresponsiveness [66]. Therefore, a protein-based vaccine not only provides immunization for the pregnant woman, but also for the fetus in utero and the offspring once baby is born.

MEDI-7510 is a subunit RSV vaccine candidate that contains the post-fusion F glycoprotein, with or without a glucopyranosyl lipid A (a synthetic TLR-4 agonist) adjuvant [67]. A Phase IIb trial in adults aged 60 and older showed that the vaccine candidate was immunogenic but did not protect the study population from RSV illness [68].

Novavax's RSV F-protein nanoparticle vaccine has been trialed in a few Phase I and II studies in healthy human adults and one study of subjects 24 to <72 months of age, and was found to be well-tolerated and immunogenic in all studies [69, 70].

This vaccine consists of nearly the full-length F glycoprotein. This nanoparticle vaccine prompted transplacental antibody transfer within a guinea pig model [71]. Furthermore, in a Phase II study in healthy women of child-bearing age, the vaccine was well tolerated. The peak of Anti-F IgG antibody was day 14 and persisted for 3 months, optimal for administration during the third trimester [72]. Recently, the immunogenicity, with an aluminum adjuvant, was evaluated in a Phase II trial (Clinicaltrials.gov identifier #NCT02247726) in healthy third-trimester pregnant women. In this study in pregnant women, the primary outcome measures were safety and immunogenicity of the vaccine, as well as its impact on the number of infants with medically-attended RSV LRTI and age of onset of the infection. No results have been posted for this study. However, a Phase III study investigation in the same study population is set to be completed in 2019, thereby suggesting that the Phase II trial met its goals.

5. Conclusions

RSV is one of the most common causes of lower respiratory disease in infants, young children, and the elderly. Treatment is currently limited to supportive care, such as supplemental oxygen, bronchodilators, or corticosteroids. Palivizumab prophylaxis is currently restricted to high-risk infants. There is currently no vaccine to prevent RSV infection. There are many challenges associated with developing an RSV vaccine candidate. When developing a live attenuated vaccine, an equilibrium must be struck between adequate immunogenicity and attenuation of the virus. Non-replicating vaccines, like in some vector-delivery systems and protein-based vaccines, can enhance RSV infection in RSV-naïve infants. Therefore, it may be necessary to develop separate vaccines for each at-risk population: neonates and young children, pregnant women, and the elderly. One highly promising strategy appears to be maternal immunization with a nonreplicating vaccine, as this may provide protection during the first few months of life in the neonate.

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Conflict of interest

The authors report no conflicts of interest.

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