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Respiratory Syncytial Virus Prevention within Reach: The Vaccine and Monoclonal Antibody Landscape

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Contributions

LB and NIM were involved in the design and plan for this Review. NIM, JT, and YL were involved in the data collection, data extraction, and quality assessment and contributed to the writing of the manuscript, in collaboration with all co-authors. JT created the figures for the manuscript with Biorender.com. The manuscript was written in collaboration with the ReSViNET Foundation.

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Summary

Respiratory syncytial virus (RSV) is the second most common cause of infant mortality and an important cause of morbidity and mortality in older adults. Efforts to develop an RSV vaccine or immunoprophylaxis remain highly active. Thirty-three RSV prevention candidates are in clinical development using six different approaches: recombinant vector, subunit, particle-based, live-attenuated, chimeric, and nucleic acid in addition to monoclonal antibodies (mAbs). Eight candidates are in phase III clinical trials. Understanding the epitopes targeted by highly neutralizing antibodies has resulted in a shift from empirical to rational and structure-based vaccine and mAb design. An extended half-life mAb for all infants is likely within one year of regulatory approval for high income countries. Live-attenuated vaccines are in development for older infants. Subunit vaccines are in late-stage trials for pregnant women to protect infants, while vector, subunit and nucleic acid approaches are being developed for older adults. Urgent next steps include ensuring access and affordability of an RSV vaccine globally. This review gives an overview of RSV vaccines and mAbs in clinical development highlighting different target populations, antigens, and latest trial results.

Keywords

respiratory syncytial virus; vaccines

Introduction

In the past decade, the substantial burden of RSV disease has received increasing recognition globally. RSV is the second leading cause of infant mortality after the neonatal period[1] with more than 99% of childhood deaths occurring in low and middle income countries (LMICs)[2]. Nevertheless, the RSV burden in children is likely underestimated, and

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major gaps in knowledge regarding RSV disease burden have only been recently addressed. More than 50% of pediatric RSV mortality occurs in the community in LMICs[3] with poverty as an important risk factor [Figure 1]. Infants at highest risk of RSV disease in HICs include the very young infants born prematurely and those with underlying congenital heart or chronic lung disease[4], Down's Syndrome[5] and neuromuscular disorders[6]. Maternal vaccination is insufficient to protect infants with extreme prematurity as transplacental antibody transfer only reaches mature levels towards the end of the third trimester[7].

In older adults (>60 years of age), the burden of morbidity and mortality due to RSV was also under recognized until recently. Modelling studies now estimate that the RSV burden is similar to the burden of seasonal influenza in adults >65 years of age[8–10]. Preliminary economic evaluations have highlighted the potential value of a vaccine for older adults, especially in high income countries (HICs). Key economic drivers of cost-effectiveness include RSV incidence, risk of death, and level and duration of protection[11,12].

Natural immunity to RSV is incomplete, and reinfection occurs throughout life[13]. A concern in the development of RSV vaccines is the potential for enhanced respiratory disease (ERD) in which more severe illness occurs upon natural infection after vaccination of RSV-naïve infants as was observed with formalin-inactivated RSV (FI-RSV) in the 1960s[14]. ERD was associated with induction of poorly neutralizing antibodies in vaccine recipients[15] and animal models of ERD suggest a Th-2 biased T cell response[16]. For this reason, an RSV vaccine for RSV-naïve recipients ideally elicits potent neutralizing antibodies without a Th2 bias. While a definitive correlate of protection against RSV infection remains elusive, cell-mediated immunity[17], mucosal IgA[18], and neutralizing antibodies[19–22] have been associated with protection from RSV infection.

Stabilization of the prefusion (pre-F) conformation of the RSV fusion (F) protein has led to the determination of viral epitopes that elicit highly neutralizing antibodies. Antibodies that recognize pre-F provide the majority of the neutralizing activity in human RSV-immune sera[23] supporting development of vaccine candidates and mAbs based on stabilized pre-F antigens. There are three different target populations for RSV prevention: (1) pediatric, (2) maternal, and (3) older adult population [Figure 3][24]. Leading strategies for the pediatric population include passive immunoprophylaxis with mAbs for young infants (<6 months) and live-attenuated vaccines for active immunization of older infants (> 6 months). Young infants may also be protected by passively transferred antibodies in immunized pregnant women. Stabilized pre-F subunit vaccines are in late-phase development for maternal vaccination. Finally, for older adults three vaccination approaches (nucleic acid, subunit and vector-based) that employ pre-F antigen are in late phase trials.

In 2018, we conducted a comprehensive review of the RSV vaccine landscape in which we distilled lessons learned from late-phase vaccine failures and identified 19 vaccine candidates and monoclonal antibodies in clinical trials[25]. The review may have provided vaccine developers with guidance for future vaccine development by endorsing pre-F as a new target for RSV preventive interventions. The pre-F antigen is now the basis of six vaccine candidates and two mAbs in phase III trials[26–29]. Furthermore, we endorsed controlled human infection models (CHIM) as a unique tool to generate rapid proof of

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concept of protection and extensive immunological characterization. This approach has been adopted into clinical development for six current RSV vaccine candidates (MV-012–968. RSVPreF, MVA-BN-RSV, palivizumab biosimilar, clesrovimab, Ad26.RSV.PreF). This updated review shows that the majority, 58% (11/19), of candidates from 2018 (and 30%, 3/10 candidates from our 2015 review) have continued development, with simultaneous expansion of the field with 19 additional candidates having entered clinical trials [Figure 2]. Finally, following the success of mRNA SAR-CoV-2 vaccine development, vaccines delivered as mRNA is a novel preventative approach that has rapidly accelerated to late-phase trials.

Methods

Vaccine and mAb candidates in clinical phases of development were identified using the PATH RSV Vaccine and mAb snapshot (last updated September 28, 2021[24]). The data collection template from previous reviews[25] was updated[Supplementary Table 1] and filled out by searching PubMed, clinical trial registries, WHO, European Medicines Agency (EMA) and pharmaceutical websites for each vaccine candidate, with no date or language restrictions (NM, JT, YL, TB, MW, FV). We did not intend to conduct a systematic review of the peer-reviewed literature but instead provide an update on the current development by capturing all recent publicly available information. No inclusion or exclusion criteria were used. Instead, for each vaccine candidate or mAb in clinical development information was selected by date (with preference for more recent literature) and by relevance (with preference for trial data). When available, peer-reviewed publications were preferred to information from trial registries or pharmaceutical websites. To supplement the data collected and the identified gaps in knowledge, data for this review were systematically collected using the data collection template [Supplemental Table 1] at the virtual RSV Vaccines for the World conference organized by the Respiratory Syncytial Virus Network (ReSViNET) from November 10–12, 2021. The goal of this meeting was to share scientific data and expertise on RSV vaccine development, and to connect stakeholders involved in RSV research. During the meeting, information was collected (NM, JT, YL, TB, MW, FV) from scientific presentations, posters, and discussions. Any publicly available data from this meeting has been included in this manuscript. Vaccines were divided into six major groups: recombinant vector, subunit, particle-based, live-attenuated, chimeric, and nucleic acid. Immunoprophylaxis with monoclonal antibodies included as a seventh category. Vaccine characteristics such as mechanism of action, adjuvants, route of administration and summary of trial results have been compiled in Table 1.

Lessons Learned

We examine lessons learned from three late phase clinical trial failures since our last review. The PREPARE trial was a milestone, the first phase III trial of an RSV maternal vaccine[30]. More than 4000 pregnant women received an RSV F nanoparticle vaccine or placebo (2:1 ratio) during the third trimester. RSV maternal vaccination was determined to be safe. Although the vaccine did not meet the primary endpoint, the candidate showed the first proof-of-concept for efficacy of RSV maternal immunization against severe RSV infection in infants. Efficacy was shown through day 90 in South Africa, where more than 50% of

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participants were enrolled: 56% (95% CI 33–71%) against medically significant RSV LRTI and 74% (95% CI 50–86%) against RSV LRTI with severe hypoxemia. Moreover, there was 49% efficacy against all-cause infant pneumonia through one year after vaccination[30]. The difference in efficacy may be explained by hospitalization for less severe disease and lower background rates of severe RSV infection in HICs compared to LMICs. Lessons learned include geographical heterogeneity of RSV disease burden and potential efficacy between different countries, the importance of timing of vaccination in relation to RSV season and gestational age[30]. Furthermore, it was shown that RSV-neutralizing antibodies and F surface glycoprotein binding antibodies were correlated with protection against RSV LRTI with severe hypoxemia, e.g. a vaccine-induced maternal anti-F IgG fold-rise of around 16-fold from the maternal enrollment to day 14 was associated with a baseline covariate-adjusted vaccine efficacy (VE) of 75%[31]. Proven efficacy poses an ethical dilemma that a potentially life-saving vaccine may not become available in these countries as drug development was discontinued because prespecified criteria for efficacy were not met[32]. A roll-over trial may be considered to confirm efficacy and develop this vaccine for LMICs.

At the time of our last review in 2018[25], analysis of the late-stage clinical trial failure of REGN2222 (suptavumab), an antigenic site V monoclonal antibody which did not meet its primary endpoint, had not yet been made public. In a phase III study in 18 countries, it was demonstrated that suptavumab did not reduce RSV hospitalization or outpatient RSV LRTI due to a natural mutation in the predominant circulation strain of RSV subgroup B that resulted in loss of antibody binding and neutralization. There were no changes in circulating RSV A strains and negligible anti-suptavumab antibody responses. Post-hoc analysis suggested the antibody was relatively efficacious against the subgroup A strains but not the new circulating B strain; the relative risk for RSV subgroup A hospitalization or outpatient LRTI versus placebo was 0.38 (95%CI 0.17–0.86)[33]. These findings highlight the importance of characterization of the viral fitness of monoclonal antibody resistant viral mutants (MARMs) in clinical development and the risk associated with targeting a single viral epitope as well as more potential variability of certain targeted antigenic sites.

Finally, ChAd155.RSV, a recombinant chimpanzee adenovirus vector vaccine expressing RSV F, N and M2–1 proteins, was in development for the pediatric population. Development was halted after preliminary analyses of a phase II trial in infants aged 3–7 months showed that the target efficacy profile was unlikely to be met[34]. The published first-in-human trial in healthy adults showed adequate safety as well as increased specific humoral and cellular immune responses[35]. The results of the phase II study have not yet been published so further lessons learned and analysis of this failure are pending. Potentially the choice of vaccine antigens was not optimal for an effective immune response.

Live-attenuated

Live-attenuated vaccines (LAV) are designed to generate a potent immune response (including a local mucosal antibody and cellular response) by mimicking natural infection while being attenuated for reduced virulence. Genetic stability is important to limit the chance of reversion to wildtype virus. A better understanding of the RSV genome and reverse genetics has allowed the rational design of LAV candidates by deleting (or

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reducing the expression of) proteins known to be important in RNA synthesis regulation or interference with host immune responses (M2–2, NS2, SH and G) leading to restricted viral replication[36].

An analysis of the compiled results of seven phase I trials using intranasal LAV (n=239 children 6–24 months of age) provides information on vaccine safety, efficacy and duration of protection of RSV LAV candidates[36]. LAV are considered safe following first exposure, since vaccine-enhanced disease has not been detected following LAV immunization, although LAV have the potential to induce upper respiratory illness if attenuation is insufficient[36]. Estimated efficacy from compiled data of five vaccine candidates was 67% (95%CI 24–85) against medically-attended RSV acute-respiratory illness and 88% (95%CI −9–99) against medically-attended RSV LRTI. On an immunologic level, a 4-fold rise in RSV-plaque reduction neutralizing antibody titer (RSV-PRNT) was predictive of vaccine efficacy and responses was durable through one year post vaccination[36].

Currently there are six phase I trials and four candidates that have progressed to phase II trials The NIH/NIAID and others are developing LAV candidates with an NS2 deletion and temperature-sensitivity mutation: RSV ΔNS2/Δ1313/I1314L (phase II)[37]; and RSV 6120/ΔNS2/1030s (phase II).[38,39] MV-012–968 (altered NS1/NS2 and G proteins, SH deletion, and ablation of secreted G protein[40]) has been shown to be safe and to generate a mucosal IgA response in seropositive adults and children[41]. A safety trial in seronegative children and a human challenge trial in healthy adults to demonstrate efficacy are being conducted for this vaccine candidate[42–44]. IT-RSV-ΔG (lacking the G protein) was safe in seropositive healthy adults. However, the serum neutralizing antibody response was limited, and nasal IgA antibodies were below the level of detection; immunogenicity needs to be further studied in children and eventually in seronegative infants[45]. Other candidates include LIDΔ M2–2/1030s[46], 6120/ΔNS1, and 6120/F1/G2/ΔNS1 in phase I trials, and VAD00001 in phase II trial. RSV-MinL4.0 (altered polymerase gene) showed a humoral and cellular immune response comparable to wildtype infection in non-human primates and is currently in phase I trials[47,48]. Overall, LAV provide an important needle-free tool for active intranasal immunization older infants who will not be sufficiently protected by a mAb or maternal vaccine. Moreover, a relatively small sample size (n=540) is needed for a phase III trial in this population[36]. Further clinical development using this vaccination approach may impact pediatric health directly by reducing pediatric infections and infections in older adults indirectly through herd immunity.

Chimeric

Chimeric live virus vaccine candidates express RSV proteins in related attenuated viruses with favorable safety profiles. In contrast to vectored vaccine candidates, chimeric show favourable antigen presentation which activates an adaptive immune response[49,50]. There are two chimeric RSV vaccine candidates in phase I trials. One of these candidates uses a replication-deficient Sendai virus modified to express RSV F protein (SeV/RSV)[49] and the other uses a live-attenuated recombinant BCG vector expressing RSV N protein (rBCG-N-hRSV) administered via the intradermal route. The latter vaccine candidate was found to be safe in phase I trials[51].

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Subunit

Subunit vaccines are protein based; this approach has been avoided in RSV-naïve children due to the FI-RSV experience with ERD in which it became clear ERD is a concern for persons not primed with live virus infection[52]. In parallel to the phase III failure of a post-F subunit vaccine candidate, five vaccine candidates have adopted pre-F as vaccine antigen. Currently, eight subunit candidates are in development for two different target populations: pregnant women and older adults. We discuss vaccine candidates using F antigens first, followed by candidates employing non-F antigens.

The phase I results of DS-Cav1, a subunit vaccine using stabilized pre-F developed by the NIAID/NIH, provide proof-of-concept of structure-based vaccine design. Vaccination resulted in >10-fold increase in serum neutralizing activity[53] and is sustainable for an entire RSV season[54]. Two other candidates use a stabilized pre-F protein as vaccine antigen. RSVpreF (PF-06928316) is a bivalent (subtype A and B) stabilized pre-F without adjuvants. A phase II trial was conducted in nonpregnant women with RSVpreF co-administered with Tdap which showed safety and noninferiority relative to RSVpreF alone[55]. The anti-pertussis response was inferior (GMC between 0.59 – 0.8 for pertussis antigens compared to Tdap alone) yet the clinical significance of these findings is still unclear and did not differ when adjusted for age[56]. The phase III MATISSE trial in pregnant women was started in 2020 and is expected to be unblinded Q4 of 2023[57]. A human challenge trial[58] showed 75% efficacy of RSVpreF against RSV infection and informed dose and formulation selection for the maternal vaccine candidate[59]. The phase III RENOIR trial using the same vaccine candidate has started in the fall of 2021 in 30,000 older healthy and high-risk adults[60]. Another pre-F subunit vaccine, RSVPreF3, is in phase III clinical trials without adjuvant (GSK3888550A) for RSV maternal immunization to protect infants “GRACE” trial[61] and with AS01 adjuvant (GSK3844766A)[62] to protect the older adult population. Development has been paused for the maternal vaccine candidate in February 2022 due to a safety signal. The older adult candidate was safe and induced approximately a tenfold increase in pre-F IgG and IgA antibodies (n=48 18–40 year old adults; n=1005 60–80 year old adults) in phase I/II clinical trials[63–65]. For the maternal candidate, phase I/II studies showed a 14-fold increase in RSV A and B neutralizing antibody titers one week after vaccination and maintaining a >6 fold increase after 91 days in healthy non-pregnant women (n=502)[65]. In the phase III study of the maternal vaccine candidate, the immune response was durable as antibody levels for vaccinees remained elevated against RSV A and RSV B for 6 months after birth[66]. Registration of RSVpreF maternal vaccine is expected in 2024 and RSVPreF older adult and both RSVPreF3 vaccine candidates in 2025 assuming registration is obtained within one year after phase III completion date according to the clinical trial registry. There are three protein-based vaccines in clinical development that use non-F viral antigens. First, BARS13 uses RSV G protein as an antigen and cyclosporine A (CSA) immunosuppressant to induce Treg cells. ADV110 was safe and immunogenic in phase I[67] and is now in phase II[68] trials. Second, DPX-RSV, uses the ectodomain of RSV A SH protein (SHe) as a vaccine antigen formulated in depot-based lipid-in-oil delivery platform to allow for prolonged antigen and adjuvant exposure. The proposed mechanism of action against this antigen is generation of SHe-specific antibodies which promote clearance of RSV-infected cells by alveolar macrophage phagocytosis. DPX-RSV showed safety and immunogenicity

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in a phase I first-in-human trial in older adults[69,70]. Finally, VN-0200, uses VAGA-9001a as antigen and an MABH-9002b adjuvant (phase I)[71]. We were not able to define the biological background of VAGA-9001a.

Particle-based

Particle-based vaccines harness the immunogenic potential of displaying multiple antigens via particle assembly. IVX-121 uses a self-assembling synthetic virus-like particle (SVLP) platform technology to deliver 20 copies of stabilized trimeric pre-F proteins (DsCav-1). The computationally designed nanoparticle allows for stabilization of the pre-F protein and in vitro adjustment of antigen density. IVX-121 showed 10 times higher neutralizing antibody responses than DSCav1 alone in preclinical studies[72]. A phase I trial[73] started in 2021 with first results expected in 2022. Following completion of the monovalent RSV candidate trial, the company plans to shift to development of a bivalent VLP vaccine with both RSV and human metapneumovirus (hMPV) antigens.

A second particle-based vaccine candidate, V306-VLP, uses a synthetic VLP to display a site II F protein epitope. The vaccine platform uses conformationally constrained synthetic peptides conjugated to a synthetic nanoparticle made from self-assembling lipopeptides containing a T-helper epitope and toll-like receptor (TLR) ligand[74]. The vaccine candidate aims to boost preexisting immunity in pregnant women or older adults[75]. A phase I trial is being conducted in healthy women[76]. The needle-free intradermal delivery route via an epicutaneous patch is being explored for boosters and has shown similar antibody titers for pertussis as a commercial vaccine in a phase I trial[75] but may require a delivery enhancement procedure to optimize vaccine delivery. Overall, particle-based vaccines are still in early development but have the potential to elicit a powerful immune response for pregnant women and the elderly.

Nucleic acid

mRNA vaccines have shown safety and high efficacy against SARS-CoV-2 infection and were developed based on previous work for RSV. Both mRNA COVID-19 vaccines express stabilized versions of SARS-CoV-2 prefusion spike protein patterned after the success of RSV pre-F as a vaccine antigen. The extensive work on RSV vaccine-associated enhanced respiratory disease was also important for the rapid development of COVID-19 vaccines and provided regulatory guidelines for vaccine safety. Because of the successful scale-up and establishment of a robust supply chain, mRNA will be a new vaccine modality available for other purposes including RSV vaccines. An mRNA vaccine (mRNA-1345) encodes stabilized RSV pre-F and uses the same lipid nanoparticle formulation as for the SARS-CoV-2 vaccine SpikeVax that is known to induce and boost antibody and T cell responses including CD8, Th1, and Tfh. The interim results of the phase I trial in younger and older adults showed favorable safety and potent boosting of neutralizing activity[77]. A phase II/III trial (ConquerRSV) started in November 2021 with 34,000 older adults >60 years of age[78]. The company intends to combine mRNA-1345 with mRNA-1653 (an mRNA vaccine against two other pediatric viruses, hMPV and parainfluenza virus type 3 (PIV-3)) intended for use in the pediatric population. A phase 1 trial is ongoing in women of childbearing age and seropositive children.

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Recombinant vectors

Recombinant vector vaccines use a modified replication-defective virus to induce humoral and cellular immunity by delivering genes for RSV antigens; 3 such candidates are currently in clinical development for the pediatric and elderly population.

Firstly, MVA-BN-RSV uses a poxvirus vector, modified vaccinia Ankara virus (MVA), to express RSV surface antigens F, and G (A&B) and intracellular proteins M2 and N[79]. In a phase I trial cellular and humoral immune responses were similar in younger and older adults[79]. Results of a phase IIa human challenge study (n=61) showed 79% reduction in symptomatic RSV infection and a significant reduction in viral load[80]. The phase II trial in older adults showed elevated antibody responses for 6 months which can be safely boosted at 12 months[81]. Following dose selection from the phase II trial, preparations for a phase III trial are ongoing[82]. Ad26.RSV.preF is being developed for two different target populations: (1) pediatric (phase II) and (2) elderly (phase III). Ad26.RSV.preF vaccine candidate uses an adenoviral vector to express the RSV F protein in the pre-F conformation[83]. The vaccine candidate showed improved immunogenicity in comparison to the previous vaccine candidate with post-F RSV protein (Ad26.RSV.FA2). In neonatal mice, the vaccine candidate showed a Th1-biased response[84]. A durable humoral and cellular immune response was shown for at least 2 years postimmunization in the first-in-human study in older adults[85]. Proof-of-concept was obtained in the first RSV vaccine human challenge study[86]. In the primary efficacy results from the proof-of-concept CYPRESS study, Ad26.RSV.preF showed 80% (95%CI: 52–93) efficacy against RSV LRTI through the first RSV season in the older adult population[87]. Ad26.RSV.preF was found to be safe and well-tolerated[88] and showed efficacy in adults ≥65 years with (68%, 95%CI: −27–95) or without risk factors (85%, 95%CI: 50–97)[89]. Furthermore, there was no interference when an RSV vaccine was co-administered with seasonal influenza vaccine in older adults in a phase II trial, and the vaccine candidate was determined to have an acceptable safety profile though showing increased reactogenicity compared to influenza vaccination[90]. In 2019, this candidate was granted FDA breakthrough therapy designation. Subsequently, the phase III EVERGREEN trial was started in Q3 2021 and will examine efficacy in across two RSV seasons in 23 000 adults aged 60 years and above[91]. For the pediatric vaccine candidate a phase I/II trial in seropositive infants aged 12–24 months showed Ad26.RSV.PreF was well-tolerated and elicited both humoral and cellular immune responses[92]. Of note, a Sars-CoV-2 adenovirus vector vaccine candidate uncovered new safety concerns with adenoviral vector vaccines including vaccine-induced immune thrombotic thrombocytopenia (VITT) which was observed for at least two of the COVID-19 adenoviral vector vaccines.[93]

mAbs

Monoclonal antibodies have been labelled as the “magic bullet” against infection given their high pathogen specificity[94]. For RSV, increased knowledge of the structure and immunogenicity of the RSV F protein has resulted in next generation antibodies targeting highly neutralization-sensitive epitopes located on the RSV pre-F protein. Furthermore, next generation RSV antibodies have been engineered with Fc mutations to extended half-life and enable protection of all infants against lower respiratory tract disease for an entire RSV season. The leading candidate is nirsevimab (formerly MEDI-8897), a human mAb targeting

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site Ø of the F protein with a YTE mutation in the Fc portion to allow for an extended half-life. In phase II trial results (n=1453) nirsevimab showed 70% (95%CI 52–81) efficacy against medically-attended RSV LRTI and 78% (95%CI 52–90) against RSV hospitalization in preterm infants[95], which is similar to the phase III trial interim results: 75% (95%CI 50–87) against RSV LRTI and 62% (95%CI −9–87) against RSV hospitalization among healthy late preterm and full-term infants (n=1490)[96]. The safety profile of nirsevimab is similar to that of the current standard-of-care, monthly palivizumab, administered to infants with congenital heart or lung disease (n=310) and preterm infants 29 to <35 weeks gestational age (n=615)[96]. RSV MARMs were generated and were shown not to have an impact on viral replication and had a low natural frequency amongst circulating strains[97]. The major advantages of nirsevimab in contrast to the currently approved palivizumab are: (1) a single intramuscular injection protects infants for an entire season compared to monthly doses, and (2) reduced costs (vaccine-like pricing expected) allowing for administration to all infants compared to only high-risk children.

Clesrovimab (MK-1654), an extended half-life mAb with the same YTE mutation as nirsevimab, targets site IV (though preferentially binding pre-F due to partial targeting of site V) of the RSV F protein. This mAb is currently in phase IIb/III clinical trials in infants. This mAb has shown high potency against RSV clinical isolates in vitro and is equipotent against RSV subgroup A and B strains[98]. A human challenge trial (n=70) showed reduced viral load after viral challenge and reduced RSV symptomatic infection rates[99]. A meta-analysis was performed to assess the relationship between serum neutralizing antibodies and clinical endpoints; the study estimated a single 75 mg dose would have more than 75% efficacy lasting 5 months in term infants[100]. The company developing this candidate has committed to helping navigate uncertainty and improving issues of access through ongoing research and innovation to help address the burden of potentially preventable childhood diseases (personal communications, Andrew W Lee).

Affordability remains a key consideration for mAb development as it is a potential barrier to global access. There are three different clinical development efforts underway to circumvent this problem: (1) an affordable extended half-life site Ø mAb (2) local administration, and (3) a biosimilar. First, A phase I trial of RSM01[101], a site Ø mAb, targeting the LMICs with a target price of less than $5 per dose[102]. Second, local needle-free administration of palivizumab, a market-approved site II mAb, via nose drops may significantly reduce costs by reducing the drug dose needed[103]. Results of a phase I and IIb trial will soon be published for intranasal palivizumab administration to prevent RSV infection. Finally, a biosimilar for palivizumab is being developed in a public-private partnership between the Utrecht Center for Affordable Biotherapeutics and MabXience for which a human challenge trial was performed in 2020 (n=56), but the results of this trial have not yet been made publicly available[104].

Important considerations for the development of next-generation mAbs: (1) affordability by investing in higher efficiency production or developing biosimilars and potentially through local administration, and (2) viral resistance which needs to be monitored and may be prevented through administration of a cocktail of monoclonals targeting multiple epitopes. Monthly administration of intranasal mAbs or a palivizumab biosimilar may

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pose a programmatic limitation in most LMICs. Potentially, a combination of monoclonal antibodies targeted to different epitopes may provide a solution to loss of efficacy due to viral resistance. However practical barriers exist to this solution as the combination would have to consist of separately registered antibodies. Thus far, the epitopes for mAbs currently in development are highly conserved with minimal naturally occurring antibody-resistant strains which have shown similar/lower viral fitness compared to non-resistant viral strains in vitro.

Discussion

In the past decade, the RSV vaccine landscape has undergone a major transition from empirical to rational vaccine design. In two previous reviews[25,105] we characterized the dynamics of the RSV vaccine landscape which included multiple late-phase failures. These failures have laid the foundation for future success by guiding development of vaccines: supporting pre-F as a vaccine antigen, highlighting the importance of conducting vaccine trials over more than one RSV season, providing knowledge of a protective immune response, emphasizing the importance of monitoring viral resistance to mAbs, and highlighting the value of CHIM to derisk RSV vaccine development. The number of candidates in late-phase development is expanding: only one mAb and one maternal vaccine candidate were in phase III development as of 2015 and 2018 respectively. Development was halted for both after failure to meet the primary endpoints of the trials, but important lessons learned have been incorporated into current trials. A better understanding of RSV neutralizing epitopes has resulted in rapid expansion to the current eight vaccine candidates in phase III trials. From 2015 to 2018, 60% of vaccine candidates did not continue development. Since 2018, 37% of vaccine candidates did not continue development. However, 30% (3/10) of vaccines are still in development from 2015.

RSV prevention appears to be on the horizon with market access expected for nirsevimab within the next 12 to 24 months. This approval may be followed shortly by approval of a maternal vaccine and a vaccine for older adults (subunit, vector-based and nucleic vaccines in late phase trials). In this case a situation will emerge in which multiple RSV vaccine candidates are approved. If all current phase III trials generate positive results, relative efficacy and safety trial data, delivery strategies, and costs may determine vaccine uptake for different maternal and older adult candidates. Despite the approval of next-generation antibodies, palivizumab may remain on the market to fill the gap in time to global market access of extended-half-life antibodies and because mAb supply may fail to meet global demand. RSV has shown negligible viral resistance against palivizumab after twenty years on the market[106]. For this reason, despite multidose schedule and costs, palivizumab may act as a back-up prophylaxis strategy while waiting for global real-time viral resistance data upon mAb implementation in HICs.

With both infant immunoprophylaxis and maternal vaccines on the market, it is important to consider how these two prevention strategies aiming to protect young infants will coexist. Maternal vaccines and infant immunoprophylaxis may play a complementary role in the prevention of severe RSV infection during infancy. There is a clear use-case for mAbs even if a maternal vaccine is approved. mAbs are expected to protect premature and full term

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infants, may have a longer duration of protection than maternal vaccines[107,108], may be applied flexibly where RSV seasonality is variable, and may be implemented in cases where maternal immunization did not occur. There is also a use-case for a maternal vaccine in co-existence with an approved mAb. Active maternal vaccination provides broad protection; it is still unclear whether maternal vaccination persists until a subsequent pregnancy and whether booster vaccination provides even stronger protection. Maternal vaccination may also provide an alternative for parents preferring not to vaccinate their babies. Finally, maternal vaccines serve as a back-up in the case of viral resistance to mAbs or prohibitively high costs related to the production of biologicals that limit administration only to select patient populations.

In LMICs, there is a use-case for mAbs to protect young infants: (1) if there is a substantial time gap until a vaccine becomes available, (2) if their mothers are not immunized, and (3) if there is insufficient time for an immune response after vaccination (i.e., premature infants)[102]. LMICs may even prefer mAbs over maternal immunization due to potential higher coverage and ease of implementation into EPI programs. However, there are several challenges to LMIC implementation, including (1) a year-round RSV circulation (mAb administration at birth may be more cost-effective than seasonal), (2) scalability dependent upon use of multi-dose vials and stability at ambient temperature, (3) limited burden and RSV healthcare utilization data in LMICs to build a case for implementation, (4) trial design in the case nirsevimab reaches the market (requiring a large sample size), and (5) potential limitations of surveillance of viral resistance in LMICs (though potentially enhanced post-COVID). Thus, mAbs could have a high impact in LMICs, but implementation challenges remain.

Passively acquired antibodies from maternal immunization or mAb immunoprophylaxis will wane over time, at which point pediatric vaccines for active immunization may serve an important role. Live-attenuated or replicating vector vaccines do not prime for ERD; delivered via the intranasal route, they are immunogenic in presence of maternal antibodies. Thus, these active immunization approaches may be safe and effective for the older pediatric age group and will be complementary to infant immunoprophylaxis and maternal vaccines.

Although the approval of multiple RSV vaccines is within reach, several obstacles to worldwide access remain. Not only are globally representative trials needed, but vaccine trials need to be performed in countries with the highest disease burden as efficacy can differ between LMIC and HICs as observed for vaccines against both RSV[30] and other pathogens[109]. Access in LMICs may be delayed due to (1) lack of trial data in populations with a high incidence of HIV and malaria as well as (2) regulatory drug lag between time of regulatory submission and approval in Sub-Saharan Africa[110]. The Vaccine Alliance (GAVI) vaccine investment strategy (VIS) includes RSV and will be important in making RSV prevention available in GAVI-eligible countries. Differential pricing may be an important consideration for non-GAVI eligible countries. Other challenges to global access include measuring protection in the case maternal vaccine boosters are indicated. A correlate of protection for RSV is lacking as well as a simple tool to measure protection following RSV vaccination. It will be important to assess the sustainability of RSV prevention via ongoing genetic surveillance. The development of viral resistance is most relevant for

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infant immunoprophylaxis with mAbs. A cocktail of mAbs targeting different epitopes may help prevent the emergence of viral resistance. However, there are currently no ongoing clinical trials with multiple mAbs which may hamper approval of a drug cocktail by regulatory bodies such as the approved mAb cocktail to prevent SARS-CoV-2. Finally, awareness of RSV is limited amongst patients, policymakers and healthcare providers and further cost-effectiveness studies of products are needed[111]. These knowledge gaps related to global vaccine implementation are important future research priorities [Box 1]. Overall, we have reached an exciting phase in which RSV prevention is within reach. It is likely that multiple immunization strategies with complementary value, unique advantages and use-case scenarios will share the RSV prevention landscape. To guarantee worldwide access, urgent steps are required to surmount challenges of measuring protection, monitoring viral resistance, and prioritizing LMIC access and affordability.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1.

Future RSV Vaccine and mAb Landscape Research Priorities

- Generating knowledge of RSV awareness
- Understanding cost-effectiveness of RSV prevention in different parts of the world
- Defining a correlate of protection for RSV
- Defining efficacy of RSV prevention in LMICs
- RSV genetic surveillance

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Key Points

- Knowledge of neutralization-sensitive viral epitopes informed a shift from empirical to structure-based vaccine and monoclonal antibody (mAb) design
- Market access for an extended half-life RSV mAb for prophylaxis in all infants is within reach in 2023 and may be followed by approval of a maternal vaccine to protect all infants
- No vaccine or mAb is within reach for resource poor areas with the highest pediatric mortality burden
- Subunit, vector-based, and nucleic acid vaccine approaches are in late-phase trials for older adults

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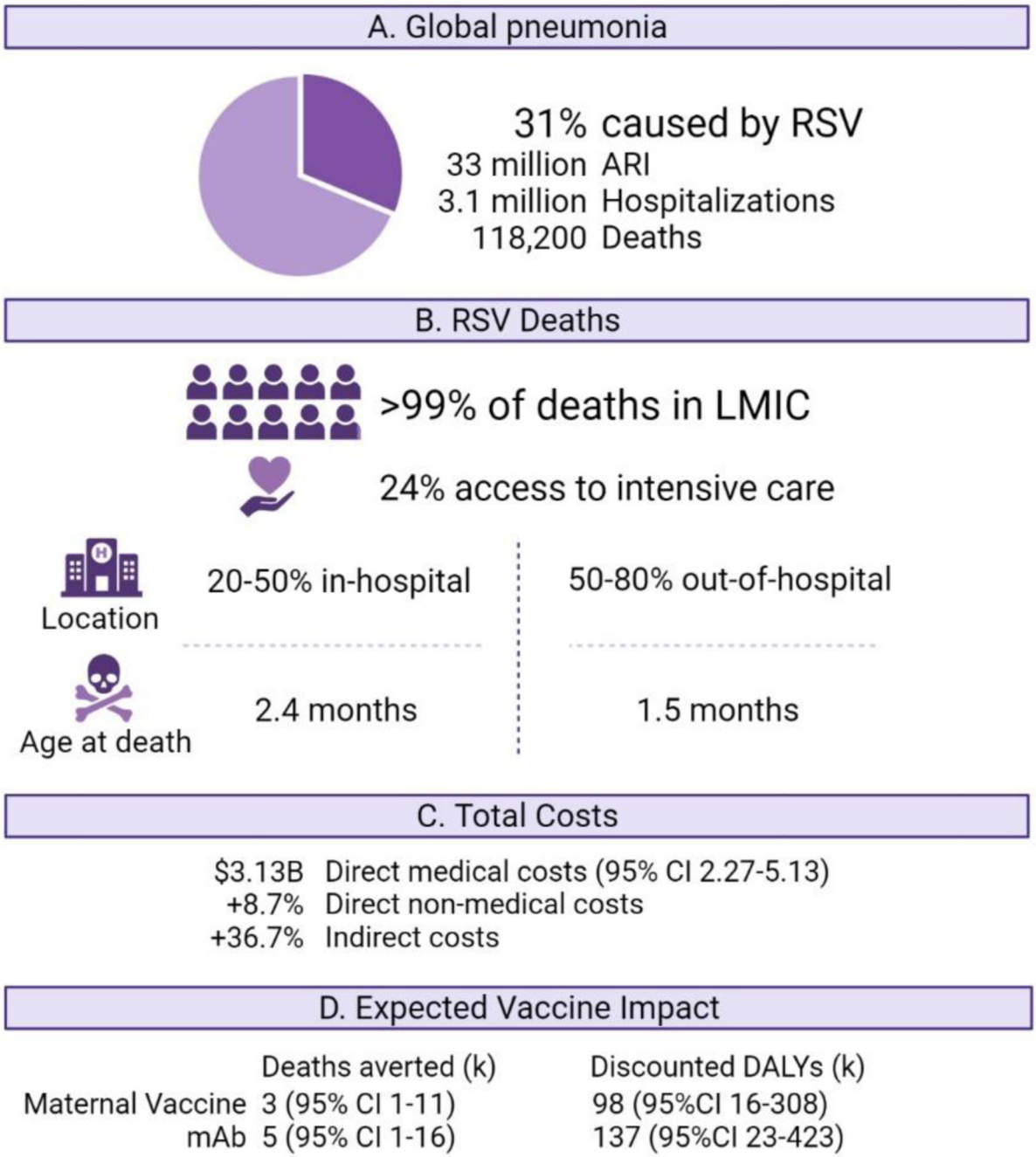


Figure 1: Pediatric RSV Disease Burden: Key facts and figures

A. Contribution to RSV for worldwide pneumonia: Approximately one-third of worldwide pneumonia is caused by RSV. B. RSV-related deaths: More than 99% of the RSV pediatric global mortality burden occurs in LMICs.[1] Access to care seems a key driver of the inequitable distribution of the mortality burden as less than one fourth of these children have access to an intensive care[112]. At least half of this burden was previously hidden, as it occurs out-of-hospital[3]. Recently the out-of-hospital burden has been characterized and is distinct from the in-hospital mortality burden which has implications for global

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vaccine development: out-of-hospital children die at a younger age and risk factors are linked to poverty instead of underlying conditions[113]. C. Total Costs: Estimated direct associated with RSV exceed 3 billion USD in LMICs, with additional direct non-medical and indirect costs[114]. D. Expected vaccine impact: The cost-effectiveness and potential impact of maternal immunization (MI) vs mAb (monoclonal antibody) has been estimated in deaths averted and discounted DALYs (disability adjusted life-years).[111]

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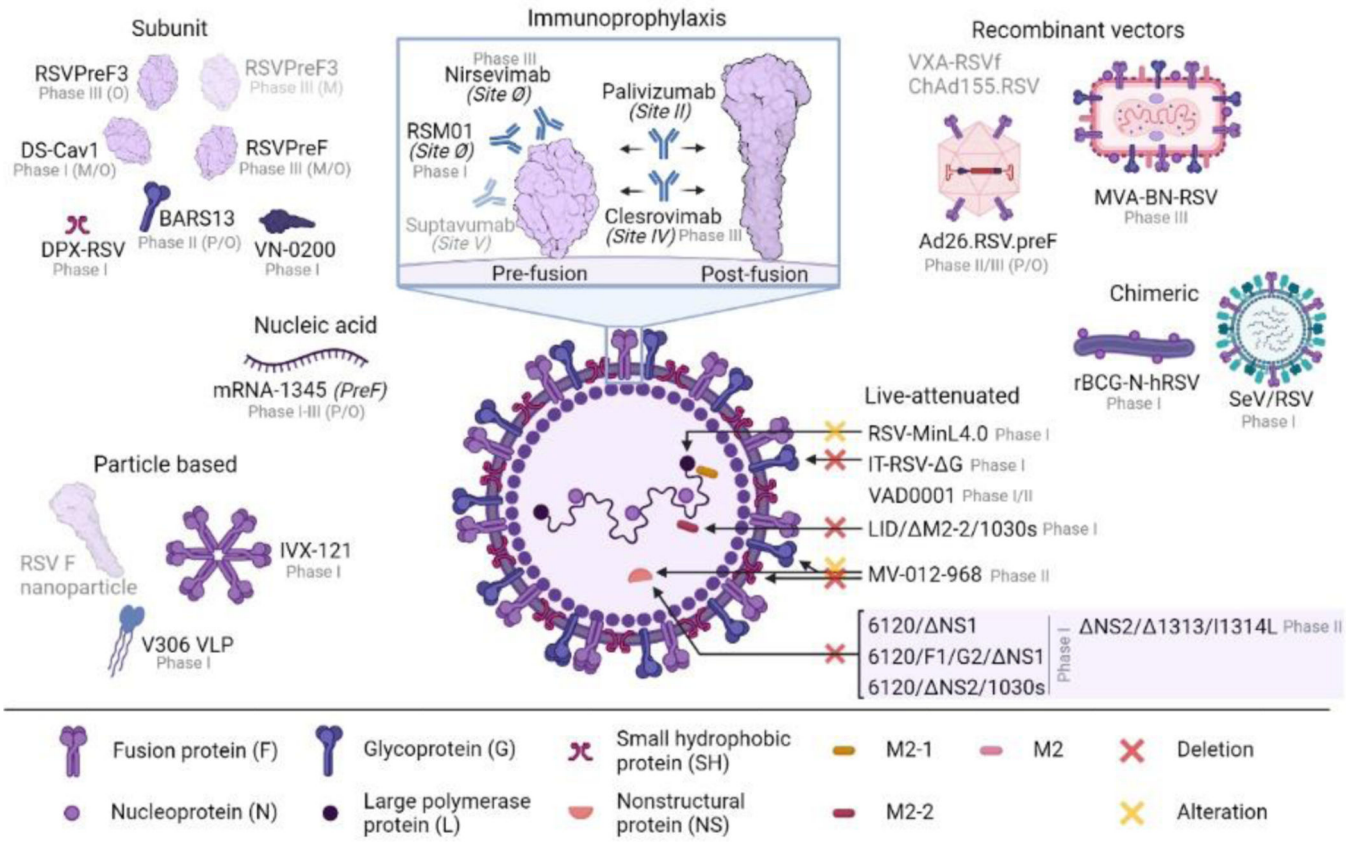


Figure 2: Overview of vaccine candidates by preventive approach

Pre- and post-fusion proteins were created with RCSB PDB 5C6B[115,116] and 3RRT[117,118], respectively.

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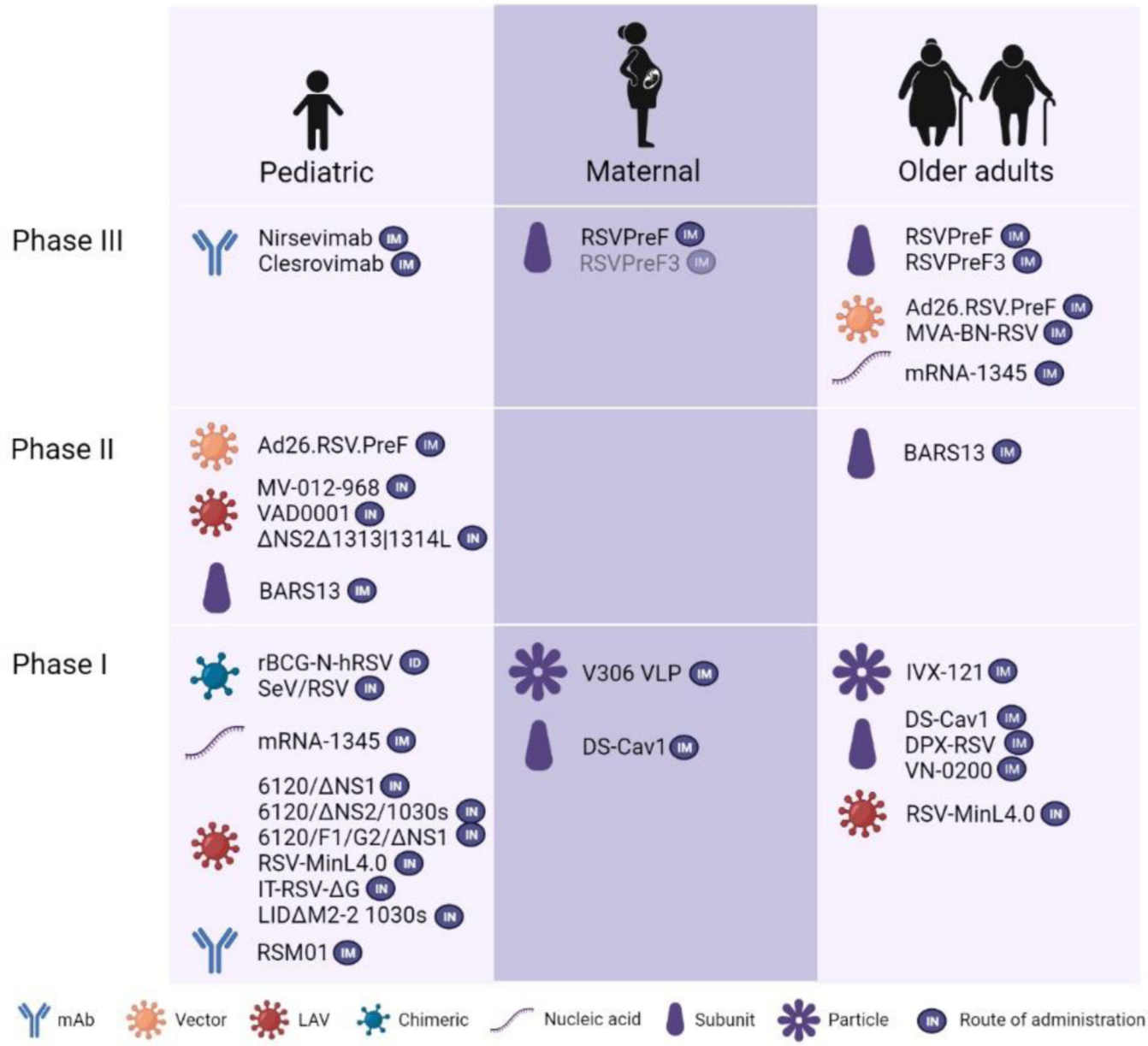


Figure 3: RSV vaccine and mAb candidates by target population.

Vaccine candidates and mAbs are categorized into three different target populations: (1) pediatric, (2) maternal, and (3) older adults and clinical phase of development: Phase I, II, or III. Different immunization approaches are indicated by the legend at the bottom. The route of administration is indicated in the small purple circles at the right: (1) intramuscular (IM), (2) intranasal (IN), (3) intradermal.

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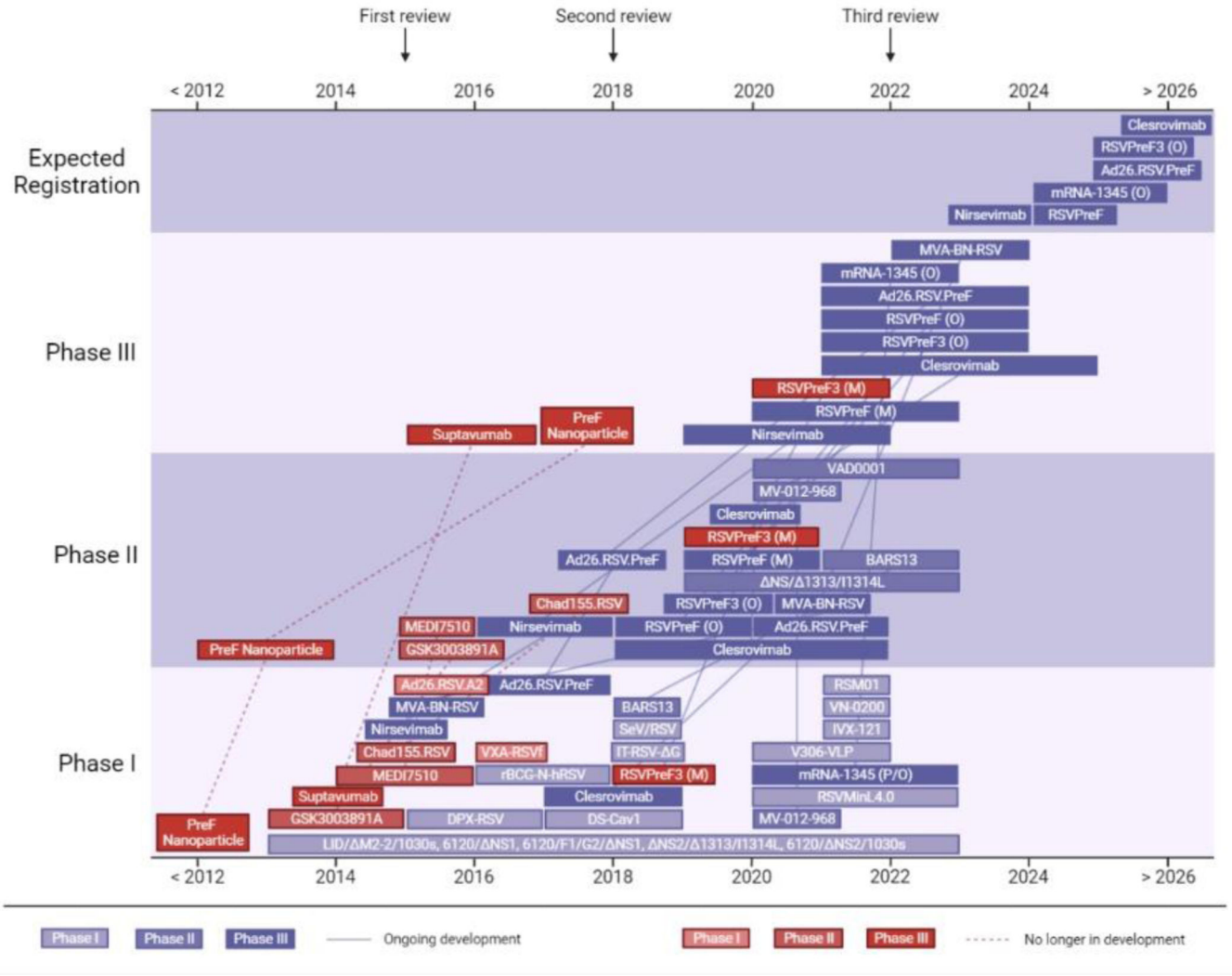


Figure 4. Historical perspective of RSV vaccine and immunoprophylaxis development over the last ten years and expected market access

Candidates that are in ongoing development (purple) or no longer in development (red) are presented at the timing of the clinical trials rounded off to full years. The darkness of the color represents the furthest development (Phase I – III) of the candidate. Candidates with multiple clinical trials are connected with full or dotted lines to show the speed of development. Live attenuated viruses by the same manufacturer are summarized in one box as development of these candidates largely overlaps. The timing of current and previous reviews are shown at the top.

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Table 1:

V vaccines and mAbs in clinical development

Company/ sponsor	Manufacturing process	Antigen	Adjuvant	Mechanism of action	Target population	Route of administration	Clinical Phase	Animal models	Phase I	Phase II	Phase III	Result summary
Daiichi Sankyo	N/A	VAGA-9001a	MABH-9002b	N/A	O	IM	I	N/A	Jun 2021-Jan 2022; NCT04914520 (n=48)	N/A	N/A	N/A
NIH/NIAID	Structure-based vaccine design	Stabilized PreF DS-Cav1	Non-adjuvanted / alum	RSV pre-F	M&O	IM	I	Cotton rats, Calves, Mice, Macaques	Feb 2017-Oct 2019; NCT03049488 (n=95)	N/A	N/A	PhI: safe & well-tolerated; vaccination elicited robust neutralizing Ab response sustained at 44 weeks
Immunovaccine	DepovaxTM, a lipid-in-oil delivery system	SHe	DepoVax (DPX-RSV[A]), DPX, or aluminum hydroxide	Exposure to SHe antigen to generate a nonneutralizing Ab & CD4+ T-cell response	O	IM	I	Cotton rats, Mice	May 2015-Jun 2017; NCT02472548 (n=40)	N/A	N/A	PhI: Safe & well-tolerated, no SAEs, antigen-specific Ab response durable >6 months
Advaccine	N/A	G	Non-adjuvanted/CSA	RSV G; immunosuppressant	P/O	IM	II	N/A	Oct 2018 – Aug 2019; NCT04851977/ ACTRN12618000948291 (n=60)	May 2021-Jun 2023; NCT04681833 (n=120)	N/A	PhI: Safe & well tolerated, significant Ab response (90% in low dose groups, 100% in high dose groups)
GlaxoSmithKline	N/A	PreF3	Non-adjuvanted	Induce immune response with stabilized pre-F	O	IM	III	N/A	Jan 2019-Nov 2020; NCT04090658/ NCT03814590/ NCT04657198 (n=1055)	Jan 2019-Nov 2020; NCT04090658/ NCT04657198 (n=1055)	Feb 2021May 2024; NCT04886596/ NCT04732871/ NCT05059301 (n=25000; n=1720; n=750)	PhI/II: humoral and cellular immune responses in all vaccines. Older adults: Higher humoral response (mostly neutralizing)

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Company/ sponsor	Manufacturing process	Antigen	Adjuvant	Mechanism of action	Target population	Route of administration	Clinical Phase	Animal models	Phase I	Phase II	Phase III	Result summary
												with higher dosage & higher cellular response with adjuvant
GlaxoSmithKline	NR	PreF3	Non-adjuvanted	Induce immune response with stabilized pre-F	M	IM	III	N/A	Oct 2018-Sep 2019; NCT03674177 (n=502)	Jul 2020-May 2021; NCT04126213 (n=534)	Nov 2020 – Feb 2024 NCT04605159 (GRACE, n=20,000) Sep 2021May 2022; NCT05045144 (n=1541)	PhI/II: robust increase in maternal RSV-specific Ab responses and RSVA/ RSV-B nAb titres. Successful Ab transfer to fetus until 6 months after birth
Pfizer	Bivalent stabilized prefusion F, sequence based on contemporary RSV A and B strains	pre-F	Non-adjuvante d or Al(OH)3 or alum-adjuvanted	Induce immune response with stabilized pre-F	M	IM	III	Animal studies, specifics unknown		Aug 2020-Sep 2021 & Nov 2020-Aug 2021; NCT03529773/ CHIM: NCT04785612/ NCT04071158/ NCT04032093 (n=1253; n=62; n=713;n=1154)	Jun 2020Nov 2023; NCT04424316 (n=10000)	PhI/II: 18 – 49-yearolds: Safe & well tolerated. Immunization elicited 10- to 20-fold increases in neutralizing Ab titers
Pfizer	Bivalent stabilized prefusion F, sequence based on contemporary RSV A and B strains	pre-F	Non-adjuvanted	Induce immune response with stabilized pre-F	O	IM	III	Animal studies, specifics unknown		Aug 2019-Sep 2021 & Nov 2020-Aug 2021; NCT03529773/ HCT NCT04785612/ NCT04071158/ NCT04032093 (n=1253; n=62; n=713;n=1154)	Aug 2021 – Jun 2024; NCT05035212 (n=30000)	PhI/II: 18–49-year-olds: Safe & well tolerated. Immunization elicited 10- to 20-fold increases in neutralizing Ab titers
)												
Virometix	The platform uses synthetic peptides conjugated to a synthetic nanoparticle made from	V-306	Pam2Cys	Synthetic VLP displays a ‘universal’ T-helper epitope, lipid component (Pam2C) and mimetic of	M	IM with epicutaneous skin patch boosters	I	Mice, Rabbits	Sep 2020-Mar 2022; NCT04519073 (n=60)	N/A	N/A	N/A

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Company/ sponsor	Manufacturing process	Antigen	Adjuvant	Mechanism of action	Target population	Route of administration	Clinical Phase	Animal models	Phase I	Phase II	Phase III	Result summary
	Self-assembling lipopeptides			the Palivizumab epitope (FSIIm)								
Icosavax	Self-assembling VLP platform technology to deliver stabilized trimeric pre-F proteins	Stabilized PreF DS-Cav1	Non-adjuvanted/ alum	presentation of DS-Cav1 on computationally designed VLP generates a neutralizing Ab response against pre-F protein	O	IM	I	Mice	July 2021 – 2022; 2020–003633-38 (n=90)	N/A	N/A	N/A
Moderna	Lipid nanoparticle containing optimized protein and codon sequences	pre-F	Non-adjuvanted	mRNA encodes for a stabilized pre-F glycoprotein eliciting neutralizing antibodies	O	IM	II/III	N/A	Sep 2020-Sep 2023; NCT04528719 (n=100 healthy adults, 300 older adults, 180 women, 40 children)	PhII/III Nov 2021-Nov 2024 (n=34000)	PhII/III Nov 2021-Nov 2024 (n=34000)	PhI: well tolerated at doses up to 200 μg. GMC-fold rise in nAbs at 1 month ≥9.8 for RSV-A and ≥5.3 for RSV-B; 3 doses helped maintain peak titers through month 5 in younger adults
Moderna	Lipid nanoparticle containing optimized protein and codon sequences	pre-F	Non-adjuvanted	mRNA encodes for a stabilized pre-F glycoprotein eliciting neutralizing antibodies	P	IM	I	N/A	Sept 2020 - Sept 2023 NCT04528719 (n=40 children 12-59 months)	N/A	N/A	N/A
VECTORS												
Bavarian Nordic	MVA-BN platform technology	F, G (A & B subtype), N and M2	Non-adjuvanted	Simulate robust T cell response against 5 RSV antigens nand moderate humoral response against both RSV subtypes	O	IM	III	BALB/c mice, cotton rats	Aug 2015-May 2016; NCT02419391 (n=63)	Sep 2016-Dec 2018 & Feb 2021-Jun 2021; NCT02873286/ NCT04752644 (n=420; n=73)	To be announced end 2021	PhII: Broad and durable Ab & T cell response, significant booster response after 1 year PhII: HCT: Significant

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Company/ sponsor	Manufacturing process	Antigen	Adjuvant	Mechanism of action	Target population	Route of administration	Clinical Phase	Animal models	Phase I	Phase II	Phase III	Result summary
												reduction in viral load & no vaccine-related SAE
Johnson & Johnson	human cell line, PERC6 (AD26) encoding RSV F from RSV-A2 strain	pre-F	Non-adjuvanted	Replicationin-competent Adenovirus 26 containing DNA for RSV F protein from A2 strain stabilized in pre-fusion conformation	O	IM	III	Neonatal & adult mice	Multiple trials between Nov 2016Jan 2021; NCT02926430/ NCT03795441/ NCT04354480 (n=73; n=24; n=36)	Multiple trials between Oct 2017-Jun 2022; NCT04453202/ NCT03502707/ NCT03303625/ NCT03334695/ NCT03339713/ NCT03982199 (n=459; n=669; n=48; n=64; n=180; n=5815)	Jul 2021-Jan 2024; NCT04908683 (n=23000)	PhI: Safe in older adults and sustaine immune responses after 2 years PhII: 80% vaccine efficacy and robust cellular and humoral immune response. PhII CHIM: Lower viral load and lower infection rate and disease severity in intervention group.
Johnson & Johnson	human cell line, PERC6 (AD26) encoding RSV F from RSV-A2 strain	Pre-F	Non-adjuvanted	Replication-incompetent Adenovirus 26 containing DNA for RSV F protein from A2 strain stabilized in pre-fusion conformation	P	IM	I/II	Neonatal & adult mice	Nov 2017-Apr 2020 & Jan 2019-Nov 2021; NCT03303625/ NCT03606512 (n=48; n=38)	Nov 2017-Apr 2020 & Jan 2019-Nov 2021; NCT03303625/ NCT03606512 (n=48; n=38)	N/A	PhI/II: Well-tolerated and elicited both humoral and cellular immune responses
LAXIS												
UMC Utrecht	Intranasal formulation of humanized mouse mAb	N.A	Non-adjuvanted	mAb targeting site II of the F-protein of RSV; neutralization	P	IN	II	Balb/c mice	Oct 2018-Nov 2018; NTR7378 (n=19)	Nov 2018 – Apr 2020 NTR7403 (n=408)	N/A	PhI: Safe in healthy adults
Merck	In vitro optimized human mAb with 3 YTE mutations in Fc-domain	N/A	Non-adjuvanted	mAb targeting site IV of the F-protein of RSV with extended half-life; neutralization	P	IM/IV	I/II/III	Cotton rats	Jun 2017-Feb 2019 (n=152 adults); Sep 2018-Sep 2022; NCT03524118 (n=180 infants)	Sep 2018-Sep 2022 NCT03524118 (n=180 intants) Mar 2020-Aug 2020 NCT04086472 (CHIM, n=80)	Nov 2021-Aug 2025 NCT0493883 0 (n=1000 high-risk infants) Apr 2021-Sep 2024 NCT04767373	PhI: Safe in adults CHIM: efficacy 0.62 (95%CI −0.05–0.86) for prevention of RSV-A LRTI

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Company/ sponsor	Manufacturing process	Antigen	Adjuvant	Mechanism of action	Target population	Route of administration	Clinical Phase	Animal models	Phase I	Phase II	Phase III	Result summary
											(n=3300 healthy infants)	
Astra Zeneca, MedImmune LLC	In vitro optimized human mAb with YTE mutation in Fc	N/A	Non-adjuvanted	mAb targeting site 0 of the F-protein of RSV with an extended half-life; neutralization	P	IM	III	Cotton rats, cynomolgus, monkeys	Apr 2015-June 2015 & Jan 2015-Sep 2016; NCT02114268/ NCT02290340 (n=342; n=151)	Nov 2016-Jul 2018; NCT02878330 (n=1453) Aug 2020 – Jan 2023 NTC04484935 (n=100 immunocompromised children)	Jul 2019-May 2022; NCT0395948 8 (MEDLEY n=925 high-risk children) Jul 2019 – Mar 2023; NCT0397931 3 (MELODY; n=3000 healthy children)	PhIIb: safety and tolerability similar to palivizumab in 25 countries worldwide Ph III interim: 75% efficacy against medically attended RSV LRTI
Gates MRI	In vitro optimized human mAb with YTE mutation in Fc	N/A	Non-adjuvanted	mAb targeting site 0 of the F-protein of RSV with an extended half-life; neutralization	P	IM/IV	I	N/A	Nov 2021 – Feb 2022 NCT05118386 (n=56)	N/A	N/A	N/A
NIAID	modified mouse parainfluenza virus type 1	F-Protein	Non-adjuvanted	RSV F-expressing SeV carrier	P	IN	I	AGM	May 2018-Feb 2019; NCT03473002 (n=21)	N/A	N/A	N/A
Pontificia Universidad Católica de Chile	Live-attenuated recombinant *Mycobacterium bovis* BCG (rBCG) based on Danish strain 1331 that expresses N	N-Protein	Non-adjuvanted	rBCG used as a vector to deliver RSV N	P	ID	I	Mice; Holstein calves	Jun 2016-Jun 2018; NCT03213405 (n=24)	N/A	N/A	PhI: Safe & well-tolerated. No SAEs. Humoral and cellular response against N and PPD.
ED												
Codagenix	Vero Master Cell Bank derived from Vero WHO-Seed Lot 1087	All viral proteins	Non-adjuvanted	Codon-pair deoptimization (CPD) of the L gene	O	IN	I	Non-human primates	Jul 2020-May 2021; NCT04295070 (n=36)	N/A	N/A	N/A
Codagenix	Vero Master Cell Bank derived from	All viral proteins	Non-adjuvanted	Codon-pair deoptimization (CPD) of the L gene	P	IN	I	Non-human primates	Mar 2022-Feb 2023; NCT04919109 n=36)	N/A	N/A	N/A

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Company/ sponsor	Manufacturing process	Antigen	Adjuvant	Mechanism of action	Target population	Route of administration	Clinical Phase	Animal models	Phase I	Phase II	Phase III	Result summary
	Vero WHO-Seed Lot 1087											
Intravacc	Reverse genetics used to construct LAV from which G protein deleted from RSV genome (RSVΔG)	All viral proteins	Non-adjuvanted	severely impaired binding to host cells due to lacking G-protein and therefore reducing infectivity	P	IN	I	Cotton rats	May 2018-Mar 2019; NTR7173 (n=48)	N/A	N/A	PhI: Safe & well-tolerated. neutralizing antibody response limited in seropositive adults.
Meissa	AttenuBlock synthetic biology platform used to construct LAV with codon deoptimization of NS1/NS2/G, SH deletion, and ablation of secreted form of G	All viral proteins	Non-adjuvanted	Reduced NS1 and NS2 expression for enhanced immunogenicity, SH deletion and G deoptimization for attenuation	P	IN	I/II	Balb/c mice; Cotton rats	Jan 2020-Aug 2020 & Jun 2020-May 2021&Jun 2021-Oct 2022; NCT04227210/ NCT04444284/ NCT04909021 (n=20; n=34; n=45)	Dec 2020-May 2021; NCT04690335 (n=60)	N/A	PhI: well-tolerated, heavily attenuated, and induces an RSV-specific mucosal IgA response in healthy seropositive adults and pediatric participants
NIAID (Sanofi)	NS2 gene deletion and deletion of L codon 1313; I1314L stabilizing mutation; via reverse genetics	All viral proteins	Non-adjuvanted	NS2 deletion bolsters innate response. Deletion at position 1313 of L protein, and I1314L stabilization confers moderate temperature sensitivity	P	IN	I/II	Mice and chimpanzees	Multiple trials between Jun 2013Apr 2023; NCT03227029/ NCT03422237/ NCT03916185/ NCT01893554 (n=65; n=80; n=160; n= 105)	May 2019-Apr 2023; NCT03916185 (n=160)	N/A	Genetically stable. Attenuated yet immunogenic in RSV-seronegative children, warranting further evaluation
NIAID (Sanofi)	M2–2 deletion via reverse genetics and temperature sensitivity mutation 1030s in the L polymerase protein	All viral proteins	Non-adjuvanted	Deletion of regulator factor M2–2causes inefficient replication but high immunogenicity; temperature sensitive mutation at position 1030 of L gene	P	IN	I	Mice, African green monkeys	Sep 2020-Apr 2022; NCT04520659 (n=81)	N/A	N/A	85% of vaccinees shed LID/ ΔM2-2/1030s vaccine & ≥4-fold rise in serum-neutralizing Abs

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Company/ sponsor	Manufacturing process	Antigen	Adjuvant	Mechanism of action	Target population	Route of administration	Clinical Phase	Animal models	Phase I	Phase II	Phase III	Result summary
NIAID (Sanofi)	NS2 gene deletion and temperature sensitivity mutation (1030s) in the L polymerase protein	All viral proteins	Non-adjuvanted	NS2 deletion bolsters innate response, 1030s mutation confers moderate temperature sensitivity	P	IN	I/II	N/A	May 2019-Apr 2023 & Oct 2017-May 2021; NCT03916185/ NCT03387137 (n=160; n=45)	May 2019-Apr 2023; NCT03916185 (n=160)	N/A	N/A
NIAID (Sanofi)	An optimized NS1 gene-deleted live attenuated vaccine	All viral proteins	Non-adjuvanted	NS1 gene-deletion; increased F and G expression by moving to first and second genome positions	P	IN	I	N/A	Jun 2018-dec 2023; NCT03596801 (n=75)	N/A	N/A	N/A
NIAID (Sanofi)	An optimized NS1 gene-deleted live attenuated vaccine	All viral proteins	Non-adjuvanted	NS1 genedeletion	P	IN	I	N/A	Jun 2018-dec 2023; NCT03596801 (n=75)	N/A	N/A	N/A
Sanofi (NIAID)	live, attenuated virus	N/A	Non-adjuvanted	N/A	P	IN	I/II	Mice	Sep 2020-apr 2023; NCT04491877 (n=300)	Sep 2020-apr 2023; NCT04491877 (n=300)	N/A	N/A

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P = Pediatric

pre-F = Pre-fusion protein

RSV = Respiratory Syncytial Virus

SAE = Serious adverse events

URT = Upper respiratory tract

VLP = Virus-like Particle