The Respiratory Syncytial Virus Vaccine Landscape

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Abstract: The global burden of disease caused by respiratory syncytial virus (RSV) is increasingly recognized, not only in infants, but also in older adults. Advances in knowledge of the structural biology of the RSV surface fusion (F) glycoprotein have revolutionized RSV vaccine development by providing a new target for preventive interventions. The RSV vaccine landscape has rapidly expanded to include 19 vaccine candidates and monoclonal antibodies (mAbs) in clinical trials, reflecting the urgency of reducing this global health problem and hence the prioritization of RSV vaccine development. The candidates include mAbs and vaccines using four approaches: (1) particle-based, (2) live-attenuated/chimeric, (3) subunit, (4) vector-based. Late phase RSV vaccine trial failures highlight gaps in knowledge regarding immunologic protection and provide lessons for future development. In this review we highlight promising new approaches to RSV vaccine design and provide a comprehensive overview of RSV vaccine candidates and mAbs currently in clinical development to prevent one of the most common and severe infectious diseases in young children and older adults worldwide.
The Respiratory Syncytial Virus Vaccine Landscape

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The global burden of disease caused by respiratory syncytial virus (RSV) is increasingly recognized, not only in infants, but also in older adults. Advances in knowledge of the structural biology of the RSV surface fusion (F) glycoprotein have revolutionized RSV vaccine development by providing a new target for preventive interventions. The RSV vaccine landscape has rapidly expanded to include 19 vaccine candidates and monoclonal antibodies (mAbs) in clinical trials, reflecting the urgency of reducing this global health problem and hence the prioritization of RSV vaccine development. The candidates include mAbs and vaccines using four approaches: (1) particle-based, (2) live-attenuated/chimeric, (3) subunit, (4) vector-based. Late phase RSV vaccine trial failures highlight gaps in knowledge regarding immunologic protection and provide lessons for future development. In this review we highlight promising new approaches to RSV vaccine design and provide a comprehensive overview of RSV vaccine candidates and mAbs currently in clinical development to prevent one of the most common and severe infectious diseases in young children and older adults worldwide.
Search strategy and selection criteria

References for this review were identified through a search of PubMed for clinical trials with “syncytial” in the title published after January 1, 2013 with no language restrictions, through April 3, 2018. We did not intend to do a systematic review of the literature. No inclusion or exclusion criteria were used. Instead, we selected articles that were most relevant to the subheadings used in this review. The PATH RSV vaccine and mAb Snapshot was used as a reference to identify all vaccine and mAb candidates in clinical trials. ClinicalTrials.gov as well as the WHO vaccine pipeline tracker for RSV were used to identify all relevant trials for these vaccine candidates and mAbs. Additional data was collected during the RSV Vaccines for the World Conference on November 29-December 1, 2017 and through pharmaceutical websites for the respective vaccine and mAb candidates.
Introduction

Respiratory syncytial virus (RSV) acute lower respiratory infection (ALRI) has gained recognition as a global health problem with a high burden of disease and no vaccine licensed for prevention. In children under 5 years, it is estimated that 33.1 million episodes of ALRI, 3.2 million hospital admissions and as many as 118,200 deaths were attributable to RSV worldwide in 2015[1] [Figure 1]. Although often characterized as a pediatric disease, RSV in adults represents a significant health burden. Mortality attributable to RSV in adults ≥65 years of age is estimated to be 7.2 per 100,000 person years[2] and 8% of RSV ARLI among older hospitalized adults was reported to result in death[3] in the United States(US). The. RSV vaccine candidates aim to protect at least three target populations that are at risk for severe RSV disease: (1) young infants through passive immunization, (2) older infants and young children through active immunization, and (3) older adults.

Development of effective RSV vaccines and monoclonal antibodies (mAbs) presents both opportunities and challenges. First, concerns of enhanced respiratory disease (ERD) following vaccination with the formalin-inactivated RSV (FI-RSV) vaccine in the 1960s have complicated the design and testing of RSV vaccines[4]. Current vaccine candidates, especially those designed for RSV naïve infants and children, must demonstrate safety by avoiding these immunologic hallmarks of ERD. Second, an absolute correlate of protection against a clinically relevant RSV infection remains elusive, although cell-mediated immunity[5], mucosal IgA[6] and potent neutralizing antibodies[7] have been associated with decreased disease severity.

Recently, three phase IIb/III trials (two vaccine trials in older adults[8,9] and one mAb trial in infants[10]) failed to meet clinical endpoints. In addition to possible inadequacies in trial design and implementation, the failure of these candidates demonstrates the continued gaps in knowledge regarding immunologic mechanisms of protection in the different target populations. Another challenge to RSV vaccine design is the lack of consensus regarding clinical endpoints though attempts have been made to define these for RSV prevention trials[11–13]. Furthermore, these endpoints may differ according to the target population. Finally, a consideration in RSV vaccine development is the limited protection conferred by immune responses elicited by natural RSV infection. Natural immunity provides only transient protection against subsequent infection and re-infection occurs frequently[14] though the most severe RSV disease is usually observed during the primary infection. Disease in older children and healthy younger adults is typically mild. Monoclonal antibodies circumvent the problem of transient immunity to RSV and an immature immune response to vaccination in young infants at risk of severe disease. An ideal RSV vaccine candidate should prevent severe disease in at risk populations. Certain vaccines might also lessen person-to-person transmission and thereby provide secondary benefits in those who cannot benefit directly from vaccination[15].

Despite these obstacles, there are several opportunities for RSV vaccine and mAb development. First, RSV disease burden has received increasing attention from international stakeholders such as the World Health Organization (WHO)[16] and the Bill & Melinda Gates Foundation based on better estimates of RSV-associated mortality worldwide[17]. Second, the discovery and stabilization of the prefusion
(pre-F) conformation of the RSV F protein provided a new target for vaccines and mAbs (18,19) as pre-F specific antibodies may be more potent than postfusion (post-F) antibodies in protecting against RSV ALRI. Third, pharmaceutical companies have recognized the urgent unmet need of RSV prevention and prioritized the development of RSV vaccines and mAbs.

In 2015, a review of RSV prevention and therapeutic strategies was conducted which demonstrated that 10 vaccines were in clinical development (20). An update of that review is necessary in light of the recent failures and new candidates in the last few years. In this review, we show that only 50% (5/10) of candidates from 2015 are currently continuing in clinical trials and 14 additional new candidates have entered clinical trials [Figure 2]. In the context of RSV as an increasingly recognized global health problem, these rapid changes and expansion show the prioritization of RSV vaccine and mAb development.
Methods

A data collection template was designed for all vaccines in clinical development according to the PATH RSV vaccine and mAb Snapshot (updated November 2017 (21)) [Supplementary Table 1]. Gaps in knowledge were identified by searching PubMed, clinical trial registries, WHO, European Medicines Agency (EMA) and pharmaceutical websites for each vaccine candidate, with no language restrictions, through April 3, 2018 (NM, ACL, NH, IR, EP, JS). We did not intend to do a systematic review of the literature. No inclusion or exclusion criteria were used. Instead, articles were selected based on relevance to the subheadings used in this review as well as each vaccine candidate or mAb in clinical development. Furthermore, data for this review were systematically collected using a data collection template [Supplemental Table 1] at the RSV Vaccines for the World conference organized by the Respiratory Syncytial Virus Network (ReSViNET) from November 29 - December 1, 2017 in Malaga, Spain. 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, ACL, NH, IR, EP, JS) from scientific presentations, posters and personal communications.

We included all vaccine candidates and mAbs in clinical development according to the PATH RSV vaccine and mAb Snapshot. Vaccines were divided into four major groups: particle-based, vector-based, live-attenuated/chimeric and subunit vaccines. Immunoprophylaxis with mAbs was included as a fifth category.

RSV Vaccine History

RSV vaccine development started shortly after the first identification of the virus in humans in 1957(22). However, ERD upon natural RSV infection after vaccination with a formalin-inactivated RSV (FI-RSV) candidate in a series of trials in the 1960s severely hindered inactivated virus and subunit vaccine development for many years. In the youngest age group, 20 of 31 of RSV naïve infants were infected with community-acquired wild-type RSV during the next RSV season and 16 (80%) required hospitalization including two deaths(4) in whom ERD was documented. Decades of research have revealed that priming with FI-RSV vaccine triggered a strong but non-neutralizing antibody response(23), followed by a T-helper 2 (Th2) skewed immunologic response(24) which led to ERD upon natural RSV infection. Other aspects of the immune response implicated in ERD include distinct subsets of CD4 T-cells(25) and memory CD8 T-cells(26). The failure to mount a protective cytotoxic T-lymphocyte (CTL) response was coupled with excess lung eosinophilia and neutrophilia, monocytic infiltration, and immune complex deposition in the lungs(27).

Nevertheless, work continued on development and human testing of live-attenuated RSV vaccine candidates. In the following 60 years, only two products were licensed for prevention of RSV. The first product was RSV intravenous immunoglobulin (RSV-IVIG), a polyclonal immunoglobulin preparation with high titers of anti-RSV neutralizing activity that was approved in the US and Canada and discontinued after 2003. RSV-IVIG was replaced by the second approved product palivizumab, a humanized mAb directed against the RSV F glycoprotein(28,29). Since its initial approval in 1998, palivizumab remains the only licensed preventive
intervention against RSV after demonstrating a reduction of 39% to almost 80% reduction of RSV hospitalizations in preterm infants < 35 weeks gestational age with and without chronic lung disease respectively(29). Palivizumab has an excellent safety profile and is indicated for the prevention of severe RSV ALRI in children born prematurely, with congenital heart disease, for with chronic lung disease(30).

Motavizumab, a higher affinity variant of palivizumab, was developed in early 2000 but was discontinued in 2010(31). In a non-inferiority head-to-head comparative trial motavizumab recipients had a slightly higher frequency of mild skin reactions following administration when compared to palivizumab(32). However, in a placebo-controlled trial, motavizumab was highly efficacious against inpatient and outpatient RSV LRI in healthy term American Indian infants (33). Nevertheless, without evidence of superiority compared to palivizumab, for protection from RSV-related hospitalization, evidence of slightly higher side effects, and no plan for dose reduction or cost-saving, the product did not attain regulatory approval(34,35).

With respect to vaccines for active immunization, many approaches targeted for RSV naïve children were evaluated preclinically over the years. Live-attenuated vaccine candidates were considered safe for clinical evaluation in these children because these vaccines are not expected to cause ERD(36). Over the past 40 years, several biologically derived live-attenuated vaccine candidates with attenuating temperature sensitivity or cold-passage mutations were evaluated clinically, including in the pediatric population, but the appropriate balance of attenuation and immunogenicity, suitable for RSV-naive children and infants, remained elusive. After reverse genetics techniques became available in the 1990s, it became possible to design vaccines with the appropriate level of attenuation, but with increased immunogenicity(37). While pediatric live-attenuated RSV vaccine candidates were under continued evaluation since the 1970s there were relatively few trials of RSV subunit vaccines conducted before 2000, with the exception of the purified F protein (PFP) vaccines(38,39), and an RSV fusion (F) attachment (G), and matrix (M) subunit vaccine(40).

Over the past 10 years development of preventive interventions for RSV has rapidly expanded. Currently, 19 vaccine candidates and mAbs for different target populations are in clinical trials, and many more are in preclinical development(21).

Lessons from the vaccine and mAb graveyard
While vaccine development has accelerated, there have been three recent late-phase vaccine and mAb trial failures. It is important to distil lessons learned from these results to inform future vaccine development.

1. A phase III double-blind, placebo-controlled trial (NURSERY) evaluating REGN2222 (suptavumab), a mAb against antigenic site V on the RSV pre-F protein(41) was conducted at 250 sites in 19 countries. REGN2222 was administered once or twice during the respiratory season to 1,149 healthy preterm infants < 6 months of age with a gestational age ≤35 weeks who were not eligible to receive palivizumab prophylaxis. The trial did not meet its primary efficacy endpoint to prevent medically-attended RSV infections through day 150 of life(42). REGN2222 was accelerated from phase I to phase
III due to promising results and the US Food and Drug Administration (FDA) granted Fast Track designation in October 2015. A speculation for this failure may be inadequate dosing schedule in regard to the antibody half-life. Ultimately, the basis for failing to meet the primary clinical endpoint is not known, as analyses of this late-stage failure have not yet been made public.

2. The second candidate that failed to meet the predefined study endpoint in phase III clinical trials was the RSV F nanoparticle vaccine candidate for older adults, a candidate based on aggregates of full-length post-F. The results of the preceding phase II showed modest efficacy(43) and promising immunogenicity measures, as determined by rise in geometric mean titer for IgG antibodies against the F protein and palivizumab competing antibodies (PCA), in the phase II trial(44). In the phase III trial, 11,850 subjects ≥60 years of age were enrolled in 60 US sites in a double-blind placebo-controlled trial (RESOLVE) over a single season starting November 2015 with 182 days follow-up for the efficacy outcome. The trial was granted fast track designation by the FDA in 2016. (45). However, the vaccine candidate failed to show efficacy against RSV moderate–severe lower respiratory tract disease (ms-LRTD) in phase III results(9). Compared to the previous season, RSV acute respiratory disease (RSV-ARD) and ms-LRTD attack rates were lower than expected in the 2015 – 2016 season (RSV-ARD: 2.0% versus 4.9% and RSV-msLRTD 0.4% versus 1.8% during the vaccine and previous season respectively). The vaccine manufacturer speculates that the difference in vaccine efficacy observed may in part be due to this lower attack rate as well as high pre-existing immunity in the study population(43). Another proposed explanation for failure of this vaccine candidate is that the quantity of the immune response to vaccination may not represent effective immunity. For example, PCA titers may not correspond to effective immunity as non-neutralizing antibodies can also bind the palivizumab binding site and can interfere with the binding of neutralizing antibodies(46). In a post-hoc subgroup analysis, the vaccine candidate showed efficacy against hospitalizations for all-cause chronic obstructive pulmonary disease (COPD) exacerbations(43). Upon further analysis of the phase III results, there was a non-statistically significant trend towards higher RSV microneutralization titers in adults without RSV-ARD when compared to adults with RSV-ARD, but this difference was not statistically significant. One conclusion that can be drawn from this trial is that late-phase clinical research for RSV vaccine candidates should include evaluation across more than one RSV season.

3. Development of the MEDI-7510 vaccine candidate, a subunit vaccine candidate for older adults, was discontinued after a phase IIb trial in North America, Europe, South Africa, and Chile. The vaccine candidate was evaluated in 1900 adults ≥60 years and the study failed to meet its primary objective, efficacy against RSV-associated respiratory illness between 14 days post vaccination throughout the end of the surveillance period, approximately 7 months. MEDI-7510 was a subunit vaccine using soluble (unaggregated) postfusion (post-F) conformation of the F protein with a TLR4 agonist adjuvant. The vaccine candidate showed safety and immunogenicity with increased B and T cell
responses in the vaccine compared to the placebo group in a phase I clinical trial(47) after safety and improved immunogenicity with an adjuvant was demonstrated in a first-in-human trial(48). The incidence of RSV-associated respiratory illness as diagnosed by PCR was 1.7% and 1.6% in the vaccine and placebo groups respectively, for a vaccine efficacy (VE) of -7.1(47). No efficacy was found in secondary subset analyses. On day 29, 93% of vaccinees had an anti-F IgG antibody seroresponse and there was a 4.6 geometric mean fold rise in anti-F IgG titer at the end of the RSV season in vaccine recipients compared to the placebo group(47). One proposed explanation for the negative results may be that the choice of a post-F antigen induced antibodies without appropriate epitope specificity(49). Upon further analysis, other proposed explanations include a low incidence of laboratory-confirmed RSV in the study population, or selection of the study population, which included high-risk and low-risk older adults. Considerations for the future include selection of an older study population at higher risk of RSV infection.

Vaccine antigens
Vaccine antigens included in RSV vaccine candidates are diverse. The majority of vaccines in clinical trials (11/18) use the F protein, a class I viral fusion protein, as an antigenic target. The RSV F protein is highly conserved and facilitates viral fusion with host cells. Understanding the structural differences between pre-F and post-F conformations, as well as stabilization of the pre-F soluble forms, has resulted in advances in vaccine antigen design(19,50). Current vaccine candidates use pre-F and post-F as vaccine antigens [Table 1]. Of note, the predominant conformation displayed on the FI-RSV vaccine candidate was the post-F conformation(51). It remains unclear as to whether there is a trigger for the pre-F to post-F conformational change, but it does occur spontaneously, making it difficult to ensure that a wild-type F vaccine antigen maintains a pre-F conformation. However, stabilizing mutations have been identified that can preserve the pre-F-specific epitopes(50,52). The antigenicity of some stabilized pre-F constructs has not been rigorously investigated, and it remains an open question as to whether certain stabilizing mutations affect the conformation of antibody binding sites Assays to assess antigen conformation are needed. Likewise there is no consensus on cellular receptors that determine viral tropism(53).

Other less frequent vaccine antigens, used alone or in combination with other antigens, include the RSV envelope associated glycoproteins G (1/18) and small hydrophobic (SH) protein (1/18) as well as internal proteins: nucleocapsid (N) (3/18), M (1/18), and M2-1 (1/18). Besides the F protein, the G protein is the only other target for neutralizing antibodies on the viral surface. The G protein is most important for viral attachment and is less frequently utilized as a vaccine antigen due to high variability across RSV strains(54), and limited knowledge of its surface structure(55). The G protein exists as an oligomer on the surface of RSV particles and as a monomer when secreted from infected cells in soluble form(56). There is evidence that the soluble form of the G protein can act as a decoy that helps the virus evade the antibody response(57). Another possible vaccine target, the SH protein, is not well understood, but data suggest that it plays a role in viral
replication in vivo(53) and inflammasome activation(58). The SH protein contains a transmembrane and extracellular domains(59); the latter has been used as a vaccine antigen(60). Internal proteins are particularly relevant to induce T cell-mediated immunity(55). As such, three non-membrane RSV proteins have been included in RSV vaccine design. The N protein is the major nucleocapsid protein that encapsidates the RNA genome of the virus(61). The M2-1 and M2-2 proteins are specific to RSV and other Pneumoviridae. M2-1 is essential for viral transcription (62), and M2-2 deletion is utilized in live vaccine candidates for viral attenuation. Finally, the M protein is a membrane-associated protein that gives virions their filamentous shape(63,64). In summary, different viral proteins are being employed as antigens in RSV vaccine design. Viral surface glycoproteins such as F and G are known to induce antibodies with differing neutralization capacity. The SH protein may be important for induction of antibody dependent cell-mediated cytotoxicity (ADCC), whereas non-membrane proteins are especially important to induce a robust T-cell response(55).

**Target populations**

RSV prophylactic interventions are designed to protect at least two populations most vulnerable to severe RSV disease: RSV-naive young infants and children, and older adults, although other high-risk populations are important to consider. It is estimated that 45% of hospital admissions and in-hospital deaths due to RSV-ALRI occur in infants younger than 6 months of age(1), an age at which vaccines are generally less immunogenic. Older adults and adults with chronic cardiopulmonary conditions have emerged as an important target for RSV prevention due to an increased understanding of RSV burden in this population. An overview of all RSV vaccine candidates per target population is shown in Table 2.

Maternal vaccination is utilized to provide passive immunity to young infants by boosting maternal vaccine-specific antibody titers that are actively transferred through the placenta, thereby extending the period of protection conferred by maternal antibodies. Historically, epidemiologic studies have demonstrated an association between higher maternal RSV antibody concentrations and protection from ALRI in infants(65). Passive transfer of antibodies to infants has been shown to be protective against severe RSV infection through the administration of high-titer polyclonal and monoclonal antibodies (RSV-IVIG and palivizumab) (28,29). The duration of protection of maternal vaccination is defined by the antibody half-life. Administration of mAbs is an alternative form of passive vaccination that can circumvent this hurdle due to extended antibody half-life through Fc alterations(66). The proof-of-principle of maternal vaccination as a tool to prevent infant disease has been demonstrated by the effective near-elimination of maternal and neonatal tetanus worldwide through tetanus toxoid vaccination in pregnancy(67). Maternal vaccination may also play a role in preventing RSV infection in pregnant women and adverse birth outcomes, however data on the burden of RSV disease in pregnant women and the effect of RSV infection during pregnancy on the fetus is limited(68–71).

Premature infants, a population at high risk for severe RSV disease, may be insufficiently protected by maternal vaccination given that the majority of IgG
transport occurs after 32 weeks gestational age(72). Globally 10% of children are born preterm(73). The burden is especially relevant in low and middle-income countries (LMICs) as more than 60% of preterm birth occurs in Sub-Saharan Africa and South Asia(74). Thus, a maternal vaccination strategy may not be sufficient to protect the high-risk preterm population if administered during the third trimester of pregnancy. Tetanus-diphtheria-acellular pertussis (Tdap) immunization in the second trimester is associated with higher cord-blood antibody titers as compared to third trimester immunization(75). A strategy of earlier vaccination could be considered for maternal RSV immunization to maximize protection for preterm infants. Other populations in which impaired transplacental antibody transfer may limit protection by maternal vaccination include infants of mothers with chronic infection, hypergammaglobulinaemia, malaria, and HIV infection(76). The ratio of transplacental antibody transfer and antibody decay kinetics are currently considered the main parameters to assess protection conferred via maternal vaccination. However, protection may also be mediated by breast milk antibodies transferred postnatally.

A combined strategy that utilizes passive immunization to protect young infants, via maternal vaccination or mAbs, followed by pediatric active immunization may be effective to prevent severe RSV infection in young children(77). The combined strategy is estimated to avert at least twice as many admissions per 100 births and four times as many in-hospital deaths per 1000 births than maternal vaccination alone(77). This strategy will be particularly relevant to prevent morbidity and mortality in children with comorbidities who are at risk of severe RSV disease at older ages(78,79). A similar maternal and pediatric combined passive and active immunization strategy is currently employed for pertussis and influenza vaccination(76).

Although RSV is frequently considered a pediatric pathogen, it is important to consider the older adult population with regard to prevention of severe RSV disease. RSV has been identified as an important disease in older and high-risk adults, with a disease burden similar to that of influenza(3). It is estimated that RSV accounts for 10,000 – 14,000 deaths annually in adults over the age of 65 years in the US(2,3). In addition, older adults with comorbidities such as underlying heart or lung disease are at elevated risk of severe RSV disease; 4-10% of high-risk adults will develop acute RSV infection annually(3).

**Immunologic endpoints**

Antibodies are thought to be the key players in limiting RSV ALRI as evidenced by proven protection in immunophylaxis trials in children (28,29,33). Recent evidence from experimental human infection in adults shows a protective role for nasal RSV-specific IgA against RSV infection(6), underscoring the importance of mucosal immunity. A limited ability to generate memory IgA responses after RSV infection may be in part responsible for incomplete immunity and subsequent RSV re-infection. Antibodies directed against different antigenic sites of the F protein display different neutralization capacities with the most neutralization-sensitive epitopes exclusive to the pre-F conformation. Antibodies with specificity for antigenic sites Ø and V show high neutralizing activity and are exclusive to the pre-F
conformation (41, 80). Antigenic site Ø is located at the apex of the pre-F conformation, the most variable region of the highly conserved F protein (19). Antibodies against antigenic site III prefer the pre-F conformation and exhibit high neutralizing activity (81). Antibodies directed against site II and IV, present on both pre-F and post-F, exhibit medium to high neutralization potency (80, 82). Finally, antibodies against antigenic site I, present primarily on post-F, show weak or no neutralization. Escape mutants of these antigenic sites have been identified, but global RSV genetic data are needed to assess the molecular heterogeneity of RSV and the subsequent susceptibility or resistance to mAbs targeting RSV among circulating viruses.

The mechanisms of protection may differ according to vaccine type, and therefore, many different immunologic assays are employed in clinical trials. Neutralizing activity of serum is a frequent immunologic endpoint of vaccine trials. A measure of functional antibody response can be elucidated by the ratio of fold-increase in RSV-binding antibodies to fold-increase in RSV-neutralizing antibodies (ELISA-to-neutralization response ratio). A ratio of <1 may be an important correlate of protection (83). Furthermore, rather than a definitive protective threshold for antibodies, fold-rise in antibody titer may be a relevant correlate of protection for live-attenuated vaccines, since that may be the best indicator of B-cell priming. Recent efforts by PATH, the WHO, and the National Institute for Biological Standards and Control (NIBSC) examined the variability of RSV neutralization assays across laboratories and recommended steps for improved standardization globally (84), resulting in the development of a new WHO International Standard for Antiserum to RSV with 1000 International Units of RSV subtype A neutralizing activity per vial now available through the NIBSC (85). Standardization of other frequently used immunologic assays such as PCA, ELISA and T-cell assays has not yet taken place.

Once infection of the lower airways is established, CD8 T-cells play an important role in viral clearance (86). Th2-biased responses have been associated with animal models of RSV ERD and measurement of Th1 and Th2 responses are considered important to predict safety of vaccine candidates other than live-attenuated vaccines in clinical trials in young children.

Animal models are important for preclinical development of vaccine candidates and assessing the possibility of enhanced disease. Alveolitis in the cotton rat and priming of a Th2 response in mice are considered markers to assess possible ERD; there is no consensus on the ability to reproduce ERD in calves (87).

Although we discuss several potential immunological correlates of protection for vaccine trials, we considered cell-mediated immunity beyond the scope of the manuscript. However, we highlight the different aspects of the expected immune response for all 19 vaccine candidates and mAbs in clinical development in Table 3. A definitive threshold for protection against RSV disease remains elusive. So far no vaccine candidates have been tested in the experimental human infection model, but the model provides a unique opportunity to test vaccine candidates in the natural host despite practical and ethical challenges (88). Ultimately, the outcome of large-scale vaccine trials will inform which immunologic measures correspond to protection from clinical RSV disease.
Vaccine strategies

We have divided vaccines in clinical development into four categories in accordance with the PATH RSV vaccine and mAb snapshot: particle-based, vector-based, subunit and live-attenuated/chimeric vaccines(21). We have also included mAbs in clinical development for the prevention of RSV ALRI. In the snapshot there are 43 vaccines and 4 mAbs in development of which 19 are in clinical stage development. An important consideration for all vaccines is not only to prevent severe RSV disease, but also to avoid the risk of priming for RSV ERD. Based on our current understanding of the underlying mechanisms leading to RSV ERD, caution should be taken in the use of protein-based vaccines in RSV naïve individuals. Replication deficient vectors, engineered to induce CD8 T cell responses expressing RSV antigens intracellularly, are considered more similar to live-attenuated virus vaccines which have been shown not to cause ERD in this population. In Table 1 we provide a comprehensive overview and more detailed comparison of all characteristics of the 19 vaccine candidates and mAbs in clinical development.

Particle-based vaccines

The RSV F nanoparticle-based vaccine platform is currently being evaluated for protection of three target populations: (1) infants through maternal vaccination, (2) children between 6 months and 5 years, and (3) older adults. These vaccine candidates utilize aggregates of a modified stabilized F protein which exhibits the post-F morphology(89). The maternal RSV F nanoparticle vaccine candidate is farthest along in clinical development and the PREPARE trial has entered the third year of a phase III trial to enroll up to 8,618 pregnant women at 80 sites in 11 countries(43). In January 2018 an informational analysis of the phase III trial was announced in which the vaccine candidate successfully targeted an efficacy threshold against the primary endpoint in infants at day 90 of >40%(90). Second in clinical development is the RSV F nanoparticle vaccine for older adults. Despite lack of efficacy in a phase III trial (RESOLVE) with a non-adjuvanted vaccine candidate, development was continued in a phase II roll-over study initiated in January 2017 in Australia in 300 adults. The aim of this rollover trial is to determine whether 2 dose regimens with an adjuvant (Matrix-M, a saponin-based adjuvant, or aluminum-phosphate) may increase the magnitude and quality of the immune response in this population. The results from the RESOLVE trial in older adults suggested vaccine efficacy in adults with COPD, leading to considerations to initiate a future trial in this older adult population at high risk for severe RSV infection(43). Finally, the phase I trial was completed in young children 24-72 months of age in 2016, but no data have been published yet(91).

SynGEM is a particle-based needle-free vaccine candidate containing the RSV F protein attached to empty bacterial particles made from Lactococcus lactis. In this vaccine platform an antigen is presented by a bacterial particle. An influenza vaccine candidate in clinical trials which uses the same vaccine platform, has shown both local and systemic antibody responses(92) but needs further optimization for RSV vaccination. The preliminary results of immunogenicity testing have been reported. The immunogenicity of this vaccine was evaluated after delivery as a nasal spray to
healthy adult volunteers. Two intranasal doses of SynGEM were administered 28
days apart at low or high dose in 24 subjects per group (6 subjects in each group
receiving placebo, double blinded). Assays of serum RSV F-specific antibodies, PCA,
and F-specific IgA indicated some immunogenicity, but the results did not reach the
threshold set for continuation to viral challenge and the studies were suspended in
2017 (Openshaw and Chiu, personal communication).

Vector-based vaccines
There are five vector-based vaccines in clinical development. The first uses a
modified vaccinia virus Ankara (MVA), a replication-defective smallpox viral vector,
and the remaining four vaccine candidates employ an adenovirus vector to display
viral antigens. The MVA vector has been safely used in vaccines for other infectious
diseases(93). This vaccine candidate, MVA-BN-RSV, induces both humoral and cell-
mediated responses by displaying four vaccine antigens: F, G, N and M2-1. Phase II
results in healthy older adults from this candidate will soon be announced.

The second vector-based vaccine candidate, VXA-RSV-f, uses an innovative
platform with an adenovirus 5 based oral tablet that is stable at room temperature.
Using the same oral adenovirus vaccine delivery platform, a phase I trial for
influenza has been conducted, which showed neutralizing antibody responses
against influenza and no interference of pre-existing vector immunity(94).
Preclinical studies for the RSV vaccine candidate in the cotton rat model showed an
increase in anti-F antibodies and protection against RSV challenge(95). In the older
adult population immunosenescence may be characterized by impaired T-cell
responses to RSV(96,97). This vaccine candidate which induces a humoral response
may be a promising intervention in this population..

Third and fourth, Ad26.RSV.preF, is a vaccine candidate being developed for
two populations: the older adult and the pediatric population. In this candidate pre-
F antigen is expressed in the human adenovirus strain 26, a vector with a favorable
safety profile when used for other infectious diseases(98,99). Previously, the
vaccine candidate vector expressed post-F as antigen (FA2) but has now been
changed to stabilized pre-F conformation. The stabilized pre-F protein has 5 amino
acid changes from wild-type, and is stable at 4C and heat-stable(50). With the
expectation that this vaccine candidate will induce highly neutralizing antibodies
against pre-F, phase II trials will be conducted in RSV-seropositive children. In
December 2017 a phase II trial was initiated comparing concomitant administration
of RSV vaccine and seasonal influenza vaccine versus seasonal influenza vaccine
alone in healthy older adults(100).

Fifth, ChAd155-RSV, a replication-incompetent chimpanzee adenovirus 155
has been used as a vector for the F, N and M2.1 proteins. The anticipated use for this
pediatric vaccine is to start immunization at two months of age, and to use two
doses alongside the normal pediatric vaccination schedule, instead of
seasonally(101). This vaccine candidate is currently being evaluated in 12-23 month
old RSV seropositive children. In the future, there are plans to conduct clinical trials
in seronegative children sequentially from older to younger ages (12-24 months
followed by 6-12 months and subsequently 2-6 months of age) to ensure safety in
RSV-naïve populations. Results of phase II trials are expected to be announced in 2020.

In summary, vector-based vaccines are used to display various RSV viral proteins and three of these vaccine candidates are in phase II trials.

**Subunit vaccines**

Due to concerns of ERD associated with protein-based vaccines, subunit vaccines are only in development for pregnant women and older adult populations. One subunit vaccine in development is the GSK RSV F vaccine candidate, which uses a version of soluble secreted F protein empirically engineered to maintain the Pre-F conformation. Phase I results demonstrated safety and immunogenicity as evidenced by RSV neutralizing antibody response in healthy men(102). However, a phase II trial scheduled for 2017 was halted due to instability of the pre-F antigen during manufacturing.

Structure-guided stabilization of the pre-F conformation has yielded a subunit vaccine candidate, DS-Cav1. The stabilization includes a foldon trimerization domain, the introduction of cysteine residues to form a disulfide bond, and cavity-filling hydrophobic residues(52). The vaccine is able to preserve neutralization-sensitive epitopes on a functional pre-F form of the viral surface protein. In preclinical studies the subunit vaccine induced high levels of RSV-neutralizing antibodies in mice and non-human primates(52). Preliminary results from the phase I trial, VRC 317, are promising and are expected to be published soon.

DPX-RSV is a vaccine candidate with a unique choice of vaccine antigen; the extracellular domain of the SH protein of RSV(60). The DepoVax technology allows for a prolonged exposure of antigen and adjuvant, and aims to induce ADCC using a liposome and oil-based depot(103). The antigen and adjuvant are encapsulated in a liposome, lyophilized and suspended in oil and the process is expected to produce vaccines with long shelf-life stability(104). Phase I results on safety and immunogenicity in the older adult population have been released and are expected to be published from this investigator-initiated study.

**Live-attenuated and chimeric vaccines**

In the context of historical concerns for enhanced RSV disease, live-attenuated vaccines can be considered safe for RSV naïve infants, based on consistent clinical study results showing that these candidates do not prime for ERD following subsequent exposure to wild-type RSV after vaccination(105). Another benefit of live-attenuated vaccines against RSV in young infants is their ability to replicate in the respiratory tract despite the presence of maternally-acquired antibodies, and to elicit a broad humoral and cellular response(106). Live-attenuated vaccines are likely limited to the pediatric population under two years of age, as pre-existing immunity in older populations might not permit sufficient replication to generate protective immune responses. Safety could be a concern for intranasal live-attenuated vaccines, in particular if attenuation is insufficient. However, evaluation of current vaccines has not shown evidence of increased rates of vaccine-associated
ALRI or fever, though there may be increased rates of rhinorrhea, similar to what has been observed with the live-attenuated influenza vaccines.

Five live-attenuated vaccine candidates in phase I clinical trials are being developed in partnership with the National Institutes of Health. Live-attenuated vaccines face the challenge of achieving sufficient attenuation to be safe while remaining immunogenic enough to induce a protective immune response. An improved understanding of the RSV viral genome has informed the development of new vaccine candidates that may overcome this challenge. Two main modifications to the RSV genome have been engineered through reverse genetics: the ΔM2-2 deletion which attenuates viral replication and upregulates antigen expression(37) as well as the ΔNS2 deletion which reduces viral suppression of host interferon thereby boosting the innate immune response. RSV MEDI ΔM2-2 reduced viral replication while inducing a strong primary serum neutralizing antibody as well as potent anamnestic response in RSV-seronegative infants and children(37). Further results from phase I clinical trials with the other live-attenuated vaccine candidates are expected.

The only chimeric vaccine candidate, rBCG-N-hRSV, currently in clinical development is delivered via a BCG strain. BCG has a safe profile in newborns and infants, induces a Th1 response(107,108), and allows for combined vaccination against two major respiratory pathogens: Mycobacterium tuberculosis and RSV. Not only is the Th1 cellular response important in protecting against lung pathology, inflammation and viral replication(109) but the candidate also induces a humoral response. The antigen presented by this vaccine candidate is the RSV N protein(110). Presently, this candidate is the only vaccine candidate intended for administration to newborn infants(110).

Monoclonal antibodies
A promising highly potent monoclonal antibody has emerged as a passive administration strategy to prevent severe RSV infection. MEDI8897, also known as nirsevimab, was optimized from the human antibody D25 that targets antigenic site Ø on the pre-F conformation, which is more neutralization sensitive than the palivizumab epitope, antigenic site II. Using the YTE technology which extends antibody half-life as well as modulates ADCC(111), the three-fold increase in half-life of MEDI8897(112) compared to palivizumab offers the possibility of passive protection for all infants for an entire season through a single intramuscular injection. The intended use is for both term and preterm infants entering their first RSV season. Passive vaccination with an extended half-life antibody offers an approach to protecting infants that is safe and may be reasonably priced. Representatives of the pharmaceutical company have indicated that they expect vaccine-like pricing for MEDI8897. Given the increased potency, the extended half-life, and the required dose, it is expected that the cost to protect an infant during the RSV season can be kept relatively low(66).

Other approaches not in clinical development
Other emerging approaches not yet in clinical development include nucleic acid-based vaccines(113). Importantly these vaccines induce a T-cell response mimicking
the response to live virus infection. Both DNA and messenger RNA (mRNA) vaccines against RSV have shown promising results in preclinical studies(113). Notably, through a collaboration with the Bill & Melinda Gates Foundation, an mRNA technology vaccine platform for HIV and rotavirus has also expanded to include RSV. Another vaccine approach in preclinical development is a whole-inactivated vaccine to be delivered intranasally via a nanoemulsion technology, for which development has been supported by the Bill & Melinda Gates Foundation(114). Furthermore, with the first of the palivizumab patents expiring in October 2015 and the last in 2022, there has been active development to produce a biosimilar in order to provide a low-cost RSV preventive intervention.

Considerations by regulatory agencies and the World Health Organization
The FDA has articulated that differences between high income countries (HICs) and LMICs are not particularly relevant to regulatory decisions, though a bridging study in the US must be performed if all clinical trials have been performed outside of the US(115). The EMA does not require that trials intended to support a regulatory decision are conducted in the European Union. Other considerations in population selection for vaccine trials mentioned by EMA include: first testing a vaccine candidate in a seropositive before testing in a seronegative population, testing a maternal vaccine in non-pregnant women of child-bearing age before testing in pregnant women, and including older adults with comorbidities in vaccine trials. No particular considerations were mentioned for population selection in studies for mAbs. In October 2017 the EMA released draft guidelines for the clinical evaluation of RSV prophylactic interventions which included guidance regarding trial design, assessment of efficacy, and safety(116). The draft guidelines will be revised after a period of public consultation based on comments and new publications.

The WHO has recognized the importance of RSV as a global health problem and has identified the development of RSV vaccines as a priority for the WHO Initiative for Vaccine Research and for Biological Standardization. WHO recently developed RSV vaccines preferred product characteristics and research and development technical roadmap documents(117,118). Further guidance for development will contribute to adequate policy-making. WHO standardization activities led to the development and establishment of the first international standard for antiserum to RSV. Development of guidelines for evaluation of quality, safety and efficacy of RSV vaccines has been initiated and will be part of consultation with regulators, manufacturers and academia in 2018 with the aim of finalizing it in 2019. Further discussion on guiding principles for mAbs is needed before proceeding with the development of the WHO Guidelines. These and other WHO standards serve as a basis for setting national regulatory requirements as well as WHO prequalification.

Finally, the WHO is now performing a surveillance pilot study in 14 countries to test the feasibility of using the Global Influenza Surveillance and Response System platform for RSV surveillance and it is expected that this pilot will contribute to our understanding of the RSV disease burden and seasonality in different geographical regions(119).
Discussion

Challenges in RSV vaccine design include concerns of ERD post-vaccination, lack of definitive immunologic correlates of protection, lack of consensus regarding clinical endpoints, and limited natural immunity following RSV infection. Despite these challenges, recent developments such as an understanding of the structural biology of the RSV fusion protein as well as lessons learned from late-phase vaccine trial failures have informed the field as it moves forward.

We attempted to collect data regarding expected plans for access to a preventive intervention in LMICs and expected pricing for all vaccine candidates, however this information is not publicly available. The only information obtained regarding expected pricing was for MEDI8897, though a more specific estimate than vaccine-like pricing was not available. Given that the most severe RSV infection occurs in LMICs(17), information regarding LMIC target countries and potential pricing for vaccine candidates will be essential to facilitate access to vaccines worldwide, especially in areas where the mortality burden is highest. In LMICs the most important target for vaccine candidates is young children(120). A mechanism should be introduced to ensure that information regarding expected pricing and access to interventions is transparent and available in the public domain. RSV vaccines and mAbs will be considered in the development of the Vaccine Investment Strategy by GAVI, the Vaccine Alliance in 2018(121).

A vaccine trial may be considered a probe study to determine whether a causal relationship exists between RSV infection and asthma, a longstanding question in the field. If long-term follow-up had been undertaken during the pivotal RSV prevention trials using palivizumab, these trials would now have provided 20 years of follow-up on respiratory morbidity after RSV prevention in high-risk infants. Lack of long-term surveillance for airway morbidity in vaccine trials are missed opportunities to provide novel scientific insights important not only to understand the pathogenesis but also the long-term vaccine efficacy against airway morbidity following RSV infection. In addition to wheeze, objective outcomes, such as lung function measurements including demonstration of bronchial hyperreactivity and IgE measurements will ideally be incorporated in vaccine trials to fully understand the impact of RSV prevention on asthma development.

Viral interference, in which RSV inhibits infection by other viruses, is becoming an increasingly important concept to understand in the context of an approved RSV vaccine. RSV vaccination may conceivably result in an increased prevalence of other respiratory viruses. There is evidence supporting viral interference for influenza vaccination(122,123), for RSV prevention(124,125), and during the RSV season in the absence of RSV(126). It is important for vaccine trials to examine this phenomenon by evaluating the incidence of all-cause ALRI, as well as RSV-specific ALRI, to better understand the implications of viral interference for an RSV vaccine.

This review provides an extensive overview of the 19 vaccine candidates and mAbs in clinical trials to prevent RSV infection. RSV vaccine development is moving rapidly and shows promise to address an unmet global health problem. Vaccines for various target populations are in clinical development. One vaccine candidate and one mAb are in late phase trials (IIb/III) and aim to prevent the disease burden in
young infants. Despite some recent failures, RSV vaccine candidates and mAbs in clinical development hold the promise that a preventive intervention for RSV is on the horizon.
Contributors: LJB and NIM were involved in the design and plan for this review. ACL and NH were involved in the data collection. All authors contributed to the final manuscript.

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## Table 1: Overview of RSV vaccines and mAbs in clinical development

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Company / Sponsor</th>
<th>Manufacturing Process</th>
<th>Antigen (antigens expressed in attenuated modified vaccinia Ankara)</th>
<th>Adjuvant</th>
<th>Mechanism of Action</th>
<th>Target Population</th>
<th>Route of Administration</th>
<th>Clinical Phase</th>
<th>Animal Models</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Result Summary</th>
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</thead>
<tbody>
<tr>
<td><strong>PARTICLE-BASED</strong></td>
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<tr>
<td>RSV F Nanoparticle</td>
<td>Novavax</td>
<td>SP9/BV recombinant technology</td>
<td>Stabilized F protein exhibiting post-F morphological change</td>
<td>Aluminum phosphate</td>
<td>F forms nanoparticle in multimeric micelle format</td>
<td>M</td>
<td>IM</td>
<td>III</td>
<td>Cotton rats (127,128) baboons (129) Guinea pig (130)</td>
<td>Dec 2010 – Dec 2011 NCT01290419 (n=150)</td>
<td>Oct 2012 – May 2013 NCT01704365 (n=330)</td>
<td>Oct 2015 – Jun 2020 NCT02624947 (n=8618)</td>
<td>Phil: all formulations well-tolerated and immunogenic; most robust Ab response with 120ug and 0.4mg aluminum formulation, peak d14 and persistence through d91; RSV infection measured by Western blot was reduced by 52% (p=0.009) in healthy women of childbearing age (n=720)(131,132) Vaccine safe, immunogenic and reduced RSV infection in healthy women of childbearing age (n=330)(133)</td>
</tr>
<tr>
<td>RSV F Nanoparticle</td>
<td>Novavax</td>
<td>SP9/BV recombinant technology</td>
<td>Stabilized F protein exhibiting post-F morphological change</td>
<td>Aluminum phosphate/Matrix M-1</td>
<td>F forms nanoparticle in multimeric micelle format</td>
<td>P</td>
<td>IM</td>
<td>I</td>
<td>Cotton rats (127,128) baboons (129)</td>
<td>Nov 2014 – Apr 2016 NCT02296463 (n=32)</td>
<td>N/A</td>
<td>N/A</td>
<td>Phil: well-tolerates; Anti-F IgG &amp; PCA increase d14, Peak d28, elevated to d56; 10-fold increase PCA &amp; anti-F IgG adjuvanted 6-fold increase in unadjuvanted(135) (n=32)</td>
</tr>
<tr>
<td>SynGeM</td>
<td>Mucois</td>
<td>Bacterium-like particle (BLP) mimopath technology carrying F antigens</td>
<td>F protein, unclear whether conformation</td>
<td>BLP</td>
<td>BLP allows presentation of F protein and elicits mucosal IgA</td>
<td>O &amp; P</td>
<td>IN</td>
<td>I</td>
<td>Mice</td>
<td>July 2016 – Dec 2017 NCT02958540 (n=48)</td>
<td>N/A</td>
<td>N/A</td>
<td>Phil: some immunogenicity in healthy adults but did not meet threshold; development suspended.</td>
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<td><strong>VECTOR-BASED</strong></td>
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<tr>
<td>MVA-BN RSV</td>
<td>Bavarian Nordic</td>
<td>MVA-BN technology (antigens expressed in attenuated modified vaccinia Ankara)</td>
<td>F, G (subtype A &amp; B), N, M2</td>
<td>None</td>
<td>Virus replication blocked at a late stage</td>
<td>O</td>
<td>IM/IN</td>
<td>II</td>
<td>Cotton rats BALB/c mice (137)</td>
<td>IM: Aug 2015-May 2016 NCT02419391 (n=63) IN: Sep 2018 – Aug 2019 NCT0282064628</td>
<td>Sep 2016 – Aug 2018 NCT02873286 (n=408)</td>
<td>N/A</td>
<td>Phil: safe, 2x increase IgG &amp; IgA; 3-5x increase in T cell responses (n=63)(137) Phil interim results: well-tolerated; broad Ab &amp; T cell response in older adults after single vaccination (n=421) (138)</td>
</tr>
<tr>
<td>Antigen and Adjuvant System</td>
<td>Phase(s)</td>
<td>Adjuvant</td>
<td>Initial Dose Deployed</td>
<td>Dose Schedule</td>
<td>Study Status</td>
<td>Clinical Trials</td>
<td>Notes</td>
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<td><strong>VXA-RSV oral</strong></td>
<td>Ph I</td>
<td>Mice, cotton</td>
<td>Neonatal</td>
<td>IM</td>
<td>May 2015 - June 2016</td>
<td>NCT02294773 (n=53)</td>
<td>Phase: Systemic protection against RSV infection in cotton rat model (95)</td>
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<tr>
<td><strong>Ad26.RSV.preF</strong></td>
<td>Ph II</td>
<td>Mice, cotton</td>
<td>Neonatal</td>
<td>IM</td>
<td>Nov 2016 - Dec 2017</td>
<td>NCT02026392 (n=73)</td>
<td>Phase: well-tolerated; durable humoral and cellular immune response for preF candidate; comparable or higher for preF candidate in older adults (140)</td>
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<tr>
<td><strong>Ad26.RSV.preF</strong></td>
<td>Ph II</td>
<td>Mice, cotton</td>
<td>Neonatal</td>
<td>IM</td>
<td>Nov 2017 - Mar 2019</td>
<td>NCT02033015 (n=60)</td>
<td>N/A</td>
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<tr>
<td><strong>ChAd155-RSV</strong></td>
<td>Ph II</td>
<td>Mouse, cotton</td>
<td>Neonatal</td>
<td>IM</td>
<td>Jul 2015 - Feb 2017</td>
<td>NCT02029783 (n=96)</td>
<td>Plan to start post 2020 with age de-escalation in seronegative infants</td>
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<tr>
<td><strong>GSK RSV F</strong></td>
<td>Ph II</td>
<td>Mice, cotton</td>
<td>Neonatal</td>
<td>IM</td>
<td>Mar 2015 - Jun 2016</td>
<td>NCT02360475 (n=508)</td>
<td>N/A PhII: Increased RSV-A neutralizing Ab 30 days post-vaccination in healthy non-pregnant women (142)</td>
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<td><strong>DPX-RSV</strong></td>
<td>Pre-F</td>
<td>Cotton, rats, pigs, cows</td>
<td>Neonatal</td>
<td>IM</td>
<td>May 2015 - June 2017</td>
<td>NCT02024725 (n=40)</td>
<td>N/A PhII: Well-tolerated, antigen-specific Ab response durable to day 421, low immunogenicity with alum adjuvant in healthy older adults (143)</td>
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<tr>
<td><strong>RSV F DS-Cav1</strong></td>
<td>Pre-F</td>
<td>Cotton, rats, mice, calves</td>
<td>Neonatal</td>
<td>IM</td>
<td>Feb 2017 - Jan 2020</td>
<td>NCT03011804 (n=96)</td>
<td>Preclinical: Induction of high neutralizing Abs and differential adjuvant-induced Ab responses (143)</td>
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<td>Recombinant</td>
<td>Origin</td>
<td>Ancestry</td>
<td>Mutation/Deletion</td>
<td>Candidate Name</td>
<td>Modality</td>
<td>Immune Response</td>
<td>Recipient</td>
<td>Immunization End</td>
<td>NCT Number</td>
<td>Enhancements</td>
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<tr>
<td>rBCG-N-hRSV</td>
<td>Pontificia Universidad Catolica de Chile</td>
<td>CHO cell line</td>
<td>antibodies against pre-F epitopes</td>
<td>4)</td>
<td>macaques (52)</td>
<td>n=100</td>
<td>Immunization of mice and macaques induces RSV-neutralizing Ab many times Protective threshold(52)</td>
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<tr>
<td>RSV D46 cpΔM2-2</td>
<td>Sanofi Pasteur/LID/N IAIID/NIH</td>
<td>M2-2 deletion via reverse genetics and 5 aa substitutions in 3 proteins called the 'cp' mutations, originally identified in a cold-passaged vaccine candidate cpRSV</td>
<td>native RSV</td>
<td>P</td>
<td>IN</td>
<td>I</td>
<td>African green monkeys</td>
<td>Oct 2015- May 2018 NCT0260 1612 (n=45)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSV LID ΔM2-2 1030s</td>
<td>Sanofi Pasteur/LID/N IAIID/NIH</td>
<td>M2-2 deletion via reverse genetics and temperature sensitivity mutation 1030s</td>
<td>native RSV</td>
<td>P</td>
<td>IN</td>
<td>I</td>
<td>Mice, African green monkeys</td>
<td>Jun 2016- Jul 2017 NCT0279 4870, NCT0295 2339 (n=33)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSV ΔNS2 Δ1313 I1314L</td>
<td>Sanofi Pasteur/LID/N IAIID/NIH</td>
<td>NS2 and 1313 deletion via reverse genetics L1314L substitution.</td>
<td>native RSV</td>
<td>P</td>
<td>IN</td>
<td>I</td>
<td>Mice and chimpanzees</td>
<td>Jun 2013- May 2017 NCT0189 3554 (n=75) Aug 2017- May 2019 NCT0322 7029 (n=80)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSV ΔM2-2 HindIII</td>
<td>Sanofi Pasteur/LID/N IAIID/NIH</td>
<td>LID backbone without deletions or substitutions in SH gene, point mutation in NS2 and N proteins, modified M2-2 deletion, based on RSV MEDI ΔM2-2,</td>
<td>native RSV</td>
<td>P</td>
<td>IN</td>
<td>I</td>
<td>African green monkeys</td>
<td>Mar 2017- Apr 2019 NCT0310 2034, NCT0309 9291 (n=53)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSV LID cp ΔM2-2</td>
<td>Sanofi Pasteur/LID/N IAIID/NIH</td>
<td>M2-2 deletion via reverse genetics, and cp mutation</td>
<td>native RSV</td>
<td>P</td>
<td>IN</td>
<td>I</td>
<td>African green monkeys</td>
<td>Sep 2016- Apr 2018 NCT0289 0381 (n=17)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MONOCLONAL ANTIBODY (mAb)</td>
<td>MedImmune</td>
<td>In vitro-optimized human mAb with YTE mutation in Fc</td>
<td>N/A</td>
<td>N/A</td>
<td>Antibody targeting site</td>
<td>Ø of the F protein of RSV with an extended half-life</td>
<td>P</td>
<td>IV/IM</td>
<td>II</td>
<td>Cotton rats, cynomolgus monkeys</td>
<td>Apr 2014–Jun 2015 NCT02114268 (n=342)</td>
<td>Nov 2016–Nov 2018 NCT02878330 (n=1454)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Target Population</th>
<th>Vaccine</th>
<th>Vaccine type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant mothers</td>
<td>RSV F nanoparticle (Novavax)</td>
<td>Nanoparticle</td>
</tr>
<tr>
<td>Third trimester</td>
<td>RSV F (GSK)</td>
<td>Subunit</td>
</tr>
<tr>
<td>Third trimester</td>
<td>RSV F protein (NIH/NIAID/VRC)</td>
<td>Subunit</td>
</tr>
<tr>
<td>Pediatric</td>
<td>RSV F nanoparticle (Novavax)</td>
<td>Nanoparticle</td>
</tr>
<tr>
<td>6m-5y</td>
<td>Adenovirus (GSK)</td>
<td>Vector</td>
</tr>
<tr>
<td>Start 2m</td>
<td>Adenovirus (Janssen)</td>
<td>Vector</td>
</tr>
<tr>
<td>Start 2-3m</td>
<td>BCG/RSV (Pontificia Universidad Catolica de Chile)</td>
<td>Chimeric</td>
</tr>
<tr>
<td></td>
<td>RSV D46 cp ΔM2-2 (Sanofi Pasteur/LID/NIAID/NIH)</td>
<td>Live-attenuated</td>
</tr>
<tr>
<td></td>
<td>RSV LID ΔM2-2 1030s (Sanofi Pasteur/LID/NIAID/NIH)</td>
<td>Live-attenuated</td>
</tr>
<tr>
<td></td>
<td>RSV ΔNS2 Δ1313 Δ1314L (Sanofi Pasteur/LID/NIAID/NIH)</td>
<td>Live-attenuated</td>
</tr>
<tr>
<td></td>
<td>RSV D46/N52/ΔNS2-ΔAM2-2-HindIII (Sanofi Pasteur/LID/NIAID/NIH)</td>
<td>Live-attenuated</td>
</tr>
<tr>
<td></td>
<td>RSV LID cp ΔM2-2 (Sanofi Pasteur/LID/NIAID/NIH)</td>
<td>Live-attenuated</td>
</tr>
<tr>
<td></td>
<td>MEDI8897 (MedImmune)</td>
<td>Monoclonal antibody</td>
</tr>
<tr>
<td>Older adults</td>
<td>RSV F nanoparticle (Novavax)</td>
<td>Nanoparticle</td>
</tr>
<tr>
<td></td>
<td>RSV BLP (Mucosis)</td>
<td>Nanoparticle</td>
</tr>
<tr>
<td></td>
<td>MVA (Bavarian Nordic)</td>
<td>Vector</td>
</tr>
<tr>
<td></td>
<td>Adenovirus (Vaxart)</td>
<td>Vector</td>
</tr>
<tr>
<td></td>
<td>Adenovirus (Janssen)</td>
<td>Vector</td>
</tr>
<tr>
<td></td>
<td>DPX-RSV-SH Protein (Immunovaccine)</td>
<td>Subunit</td>
</tr>
<tr>
<td></td>
<td>RSV F protein (NIH/NIAID/VRC)</td>
<td>Subunit</td>
</tr>
</tbody>
</table>

Legend: m: months; y: years
### Table 3: Expected immune response and previous successes for vaccine candidates and monoclonal antibodies

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Target Population</th>
<th>Pre-F Immunity* (86)</th>
<th>Immune response</th>
<th>Mucosal/Systemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nanoparticle</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSV F Nanoparticle (Novavax)</td>
<td>M</td>
<td>Pre-F &lt; post-F</td>
<td>Broadly neutralizing antibodies</td>
<td>Systemic</td>
</tr>
<tr>
<td>RSV F Nanoparticle (Novavax)</td>
<td>O</td>
<td>Pre-F &lt; post-F</td>
<td>Broadly neutralizing antibodies</td>
<td>Systemic</td>
</tr>
<tr>
<td>RSV F Nanoparticle (Novavax)</td>
<td>P</td>
<td>Pre-F &lt; post-F</td>
<td>Broadly neutralizing antibodies</td>
<td>Systemic</td>
</tr>
<tr>
<td>RSV BLP (Mucos)</td>
<td>O &amp; P</td>
<td>unclear F confirmation</td>
<td>Activation of B &amp; T cells; local secretion of neutralizing IgA in the nose; production of IgG neutralizing IgG in the blood</td>
<td>Mucosal &amp; Systemic</td>
</tr>
<tr>
<td>Vector</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVA (Bavarian Nordic)</td>
<td>O</td>
<td>Pre-F &lt; post-F</td>
<td>B &amp; T cell response; antibodies against 5 RSV antigens</td>
<td>Systemic</td>
</tr>
<tr>
<td>Adenovirus (GSK)</td>
<td>O</td>
<td>Pre-F &gt; post-F</td>
<td>B &amp; T cell response; neutralizing antibodies against F antigen; CD8 T cells against F, N and M2.1 antigens</td>
<td>Systemic</td>
</tr>
<tr>
<td>Adenovirus (Vaxart)</td>
<td>O</td>
<td>Pre-F &lt; post-F</td>
<td>B &amp; T cell immunity, protection at mucosal surface</td>
<td>Mucosal &gt; Systemic</td>
</tr>
<tr>
<td>Adenovirus (Janssen)</td>
<td>P</td>
<td>Pre-F</td>
<td>B &amp; T cells</td>
<td>Systemic</td>
</tr>
<tr>
<td>Adenovirus (Janssen)</td>
<td>O</td>
<td>Pre-F</td>
<td>B &amp; T cells</td>
<td>Systemic</td>
</tr>
<tr>
<td>Subunit</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSV F (GSK)</td>
<td>M</td>
<td>Pre-F</td>
<td>B &amp; T cell response</td>
<td>Systemic</td>
</tr>
<tr>
<td>RSV F protein (NIH/NIAID/VRC)</td>
<td>O &amp; M</td>
<td>Pre-F</td>
<td></td>
<td>Systemic</td>
</tr>
<tr>
<td>Live-attenuated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCG/RSV (Pontificia Universidad Catolica de Chile)</td>
<td>P</td>
<td>Pre-F &amp; post-F</td>
<td>B &amp; T cell response; Th1 polarized response; antibodies against N, F, G</td>
<td>Systemic</td>
</tr>
<tr>
<td>RSV D46 cp ΔM2-2</td>
<td>P</td>
<td>Pre-F &amp; post-F</td>
<td>B &amp; T cell response; enhanced antibody production due to increased antigen production from M2-2 deletion</td>
<td>Mucosal &amp; Systemic</td>
</tr>
<tr>
<td>RSV D46 ΔNS2 ΔM2-2 HindIII</td>
<td>P</td>
<td>Pre-F &amp; post-F</td>
<td>B &amp; T cell response; enhanced antibody production due to increased antigen production from M2-2 deletion</td>
<td>Mucosal &amp; Systemic</td>
</tr>
<tr>
<td>RSV ΔNS2 Δ1313/11314L</td>
<td>P</td>
<td>Pre-F &amp; post-F</td>
<td>B &amp; T cell response</td>
<td>Mucosal &amp; Systemic</td>
</tr>
<tr>
<td>RSV D46 ΔNS2 N ΔM2-2</td>
<td>P</td>
<td>Pre-F &amp; post-F</td>
<td>B &amp; T cell response</td>
<td>Mucosal &amp; Systemic</td>
</tr>
<tr>
<td>Monoclonal Antibody</td>
<td>P</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>---------------------</td>
<td>---</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>MEDI8897 (MedImmune)</td>
<td>P</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Legend:** Pre-F: prefusion conformation of the RSV F protein; Post-F: postfusion conformation of the RSV F protein; N: RSV nucleocapsid protein; F: RSV fusion protein; G: RSV attachment protein; O: older adults; M: maternal; P: pediatric.
Figure 1: RSV global burden of disease in children under 5 years of age: key facts and figures

Incidence is shown worldwide for children under 5 years of age unless otherwise stated. The hospital admission rate of 15.9 hospital admissions per 1000 neonates per year is in developing countries. The RSV ALRI hospitalization 63.9 among premature infants <1 year is reported per 1000 children per year globally. Legend: OR: odds ratio; LRTI: lower respiratory tract infection, RSV: respiratory syncytial virus, HIC: high income country, *: compared to children who survived RSV hospitalization and were mechanically ventilated. References: (a)(1) (b)(78) (c)(147) (d)(148) (e)(149) (f)(150)
Figure 2: Overview of Vaccine candidates and monoclonal antibodies in clinical trials per preventive approach including candidates for which development was recently halted.

Legend: For vaccine candidate names listed in gray development has been halted since the last RSV therapeutics review performed in 2015 (20). Abbreviations: PH I: phase I; PH II: phase II; PH III: phase III.
<table>
<thead>
<tr>
<th>Type of Vaccine</th>
<th>Nano particle</th>
<th>Vec tor</th>
<th>Sub unit</th>
<th>Live-attenuated/Chimeric</th>
<th>Mab-s/biosimilars</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAT H snapshot/ Candidate</td>
<td>RSV F nano particle (Novavax, M)</td>
<td>RSV F nano particle (Novavax, E)</td>
<td>RSV BLP (Mucos, E)</td>
<td>MV A (Bavarian Nordic, E)</td>
<td>Adenovirus (Janssen, P)</td>
</tr>
</tbody>
</table>

| Person responsible |
| RSVV W related program items/names |

| Manufacturing process |
| Adjuvant |

<p>| Animal models |
| Pre-F Immunity |</p>
<table>
<thead>
<tr>
<th>Immunity (general)</th>
<th>Antigens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td></td>
</tr>
<tr>
<td>Mode of administration</td>
<td></td>
</tr>
<tr>
<td>Target populations</td>
<td></td>
</tr>
<tr>
<td>Results of clinical studies so far</td>
<td></td>
</tr>
<tr>
<td>Efficacy</td>
<td></td>
</tr>
<tr>
<td>Endpoints</td>
<td></td>
</tr>
<tr>
<td>PMID results</td>
<td></td>
</tr>
<tr>
<td>Timing Ph1</td>
<td></td>
</tr>
<tr>
<td>Timing Ph2</td>
<td></td>
</tr>
<tr>
<td>Timing Ph3</td>
<td></td>
</tr>
<tr>
<td>Current development</td>
<td></td>
</tr>
<tr>
<td>pment status</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>---------</td>
</tr>
<tr>
<td>Trial names</td>
<td></td>
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<tr>
<td>Expected herd immunity</td>
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</tr>
<tr>
<td>Previous vaccine successes</td>
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<tr>
<td>Description current trial(s), register</td>
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<td>Summary corporate website</td>
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<td>LMIC target</td>
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<tr>
<td>Expected price</td>
<td></td>
</tr>
<tr>
<td>Important Links</td>
<td></td>
</tr>
<tr>
<td>Important Links</td>
<td></td>
</tr>
</tbody>
</table>
The Respiratory Syncytial Virus Vaccine Landscape

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*: indicates full professorship
¥: deceased

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Declaration of interest

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JAE: My institution receives research funding from Novavax, Medimmune, Alios, and GlaxoSmithKline

BSG has pending patent applications for candidate subunit RSV F vaccines. **JM is an inventor on patent No. 9,738,689, Prefusion RSV F Proteins and Their Use with royalties paid.**

AM and OR: Our institution received research funding from Janssen, Bill & Melinda Gates Foundation and NIH/NIAID

The authors alone are responsible for the views expressed in this publication, which do not necessarily represent the decisions or the stated policy of any organization, institution or agency.
The global burden of disease caused by respiratory syncytial virus (RSV) is increasingly recognized, not only in infants, but also in older adults. Advances in knowledge of the structural biology of the RSV surface fusion (F) glycoprotein have revolutionized RSV vaccine development by providing a new target for preventive interventions. The RSV vaccine landscape has rapidly expanded to include 19 vaccine candidates and monoclonal antibodies (mAbs) in clinical trials, reflecting the urgency of reducing this global health problem and hence the prioritization of RSV vaccine development. The candidates include mAbs and vaccines using four approaches: (1) particle-based, (2) live-attenuated/chimeric, (3) subunit, (4) vector-based. Late phase RSV vaccine trial failures highlight gaps in knowledge regarding immunologic protection and provide lessons for future development. In this review we highlight promising new approaches to RSV vaccine design and provide a comprehensive overview of RSV vaccine candidates and mAbs currently in clinical development to prevent one of the most common and severe infectious diseases in young children and older adults worldwide.
References for this review were identified through a search of PubMed for clinical trials with “syncytial” in the title published after January 1, 2013 with no language restrictions, through April 3, 2018. We did not intend to do a systematic review of the literature. No inclusion or exclusion criteria were used. Instead, we selected articles that were most relevant to the subheadings used in this review. The PATH RSV vaccine and mAb Snapshot was used as a reference to identify all vaccine and mAb candidates in clinical trials. ClinicalTrials.gov as well as the WHO vaccine pipeline tracker for RSV were used to identify all relevant trials for these vaccine candidates and mAbs. Additional data was collected during the RSV Vaccines for the World Conference on November 29-December 1, 2017 and through pharmaceutical websites for the respective vaccine and mAb candidates.
Introduction

Respiratory syncytial virus (RSV) acute lower respiratory infection (ALRI) has gained recognition as a global health problem with a high burden of disease and no vaccine licensed for prevention. In children under 5 years, it is estimated that 33.1 million episodes of ALRI, 3.2 million hospital admissions and as many as 118,200 deaths were attributable to RSV worldwide in 2015 [Figure 1]. Although often characterized as a pediatric disease, the burden of RSV in adults is also represents a significant health burden, with Mortality attributable to RSV in adults ≥65 years of age is estimated to be 7.2 per 100,000 person years [2] and a mortality rate of 7 to 8% of RSV ARLi among older hospitalized adults [3] in the United States (US). The mortality attributable to RSV in adults ≥65 years of age is estimated to be 7.2 per 100,000 person years (3). RSV vaccine candidates aim to protect at least three target populations that are at risk for severe RSV disease: (1) young infants through passive immunization, (2) older infants and young children through active immunization, and (3) older adults.

Development of effective RSV vaccines and monoclonal antibodies (mAbs) presents both opportunities and challenges. First, concerns of enhanced respiratory disease (ERD) following vaccination with the formalin-inactivated RSV (FI-RSV) vaccines in the 1960s have complicated the design and testing of RSV vaccines [4]. ERD occurred in RSV-naive infants who experienced infection with community-acquired wild-type RSV following receipt of FI-RSV. Decades of research have revealed that in these FI-RSV primed infants, natural RSV infection triggered a strong but non-neutralizing antibody response [5], followed by a T helper 2 (Th2) skewed immunologic response [6]. The failure to mount a protective cytotoxic T lymphocyte (CTL) response was coupled with excess lung eosinophilia and neutrophilia, monocytic infiltration, and immune complex deposition in the lungs [7]. Current vaccine candidates, especially those designed for RSV naïve infants and children, must demonstrate safety by avoiding these immunologic hallmarks of ERD. Second, an absolute correlate of protection against a clinically relevant RSV infection remains elusive, although cell-mediated immunity [5], mucosal IgA [6] and potent neutralizing antibodies [7] have been associated with decreased disease severity.

Recently, three phase IIb/III trials [two vaccine trials in older adults [8,9] and one mAb trial in infants [10]) failed to meet clinical endpoints. The in addition to possible inadequacies in trial design and implementation, the failure of these vaccine and mAb candidates demonstrates the continued gaps in knowledge regarding immunologic mechanisms of protection in the different target populations. Another challenge to RSV vaccine design is the lack of consensus regarding clinical endpoints of vaccine trials though attempts have been made to define these for RSV both—prevention trials [11–13]—and treatment trials [17]. Furthermore, these endpoints may differ based on according to the target population. Finally, a consideration in RSV vaccine development is the limited protection conferred by immune responses elicited by natural RSV infection. Natural immunity provides only transient protection against subsequent infection and re-infection occurs frequently [14] though the most severe RSV disease is usually observed during the primary infection. Disease in older children and healthy younger adults is typically
Monoclonal antibodies circumvent the problem of transient immunity to RSV and an immature immune response to vaccination in young infants at risk of severe disease. An ideal RSV vaccine candidate should prevent severe disease in at risk populations. Certain vaccines might also lessen person-to-person transmission and thereby provide secondary benefits in those who cannot benefit directly from vaccination\(^{(15)}\).

Despite these obstacles, there are several opportunities for RSV vaccine and mAb development. First, the RSV disease burden has received increasing attention from international stakeholders such as the World Health Organization (WHO)\(^{(16)}\) and the Bill & Melinda Gates Foundation based on better estimates of RSV-associated mortality worldwide\(^{(17)}\). Second, the discovery and stabilization of the prefusion (pre-F) conformation of the RSV F protein has advanced the field provided a new target for vaccines and mAbs\(^{(18,19)}\), as shown by providing that pre-F specific antibodies may be more potent in protecting against RSV LRTI than antibodies that also bind the postfusion (post-F) conformation antibodies in protecting against RSV ALRI and by thus providing a new target for vaccines and mAbs\(^{(21,22)}\). Third, pharmaceutical companies have recognized the urgent unmet need of RSV prevention and prioritized the development of RSV vaccines and mAbs.

In 2015, a review of RSV prevention and therapeutic strategies was conducted which demonstrated that 10 vaccines were in clinical development\(^{(20)}\). An update of that review is necessary in light of the recent failures and new vaccine candidates in the last several years. In this review, we show that only 50% (5/10) of candidates from 2015 are currently continuing in clinical trials and 14 additional new vaccine candidates have entered clinical trials [Figure 2]. In the context of RSV as an increasingly recognized global health problem, these rapid changes and expansion show the prioritization of RSV vaccine and mAb development.
Methods

A data collection template was designed for all vaccines in clinical development according to the PATH RSV vaccine snapshot (updated November 2017) [Supplementary Table 1]. Gaps in knowledge were identified by searching PubMed, clinical trial registries, WHO, European Medicines Agency (EMA) and pharmaceutical websites for each vaccine candidate, with no date or language restrictions, on January 31, 2018 through April 3, 2018 (NM, ACL, NH, IR, EP, JS). We did not intend to do a systematic review of the literature. No inclusion or exclusion criteria were used. Instead, we selected articles that were most relevant to the subheadings used in this review as well as each vaccine candidate or mAb in clinical development. To supplement the data collected and the identified gaps in knowledge, further data for this review were systematically collected using the data collection template [Supplementary Table 1] at the RSV Vaccines for the World conference organized by the Respiratory Syncytial Virus Network (ResViNET) from November 29 - December 1, 2017 in Malaga, Spain. 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, ACL, NH, IR, EP, JS) from scientific presentations, posters and personal communications.

We included all vaccine candidates and mAbs in clinical development according to the PATH RSV vaccine snapshot and mAb snapshot. Vaccines were divided into four major groups: particle-based, vector-based, live-attenuated/chimeric and subunit vaccines. Immunoprophylaxis with mAbs was included as a fifth category.

RSV Vaccine History

RSV vaccine development started shortly after the first identification of the virus in humans in 1957. However, ERD upon natural RSV infection after vaccination with a formalin-inactivated RSV (FI-RSV) candidate in a series of trials in the 1960s severely hindered inactivated virus and subunit vaccine development for many years. In the youngest age cohort of RSV naïve infants, 20 of 31 of RSV naïve infants were infected with community-acquired wild-type RSV during the next RSV season and 16 (80%) required hospitalization including two deaths, in whom ERD was documented. ERD occurred in RSV naïve infants who experienced infection with community-acquired wild-type RSV following receipt of FI-RSV. Decades of research have revealed that in these priming with FI-RSV vaccine primed infants, natural RSV infection triggered a strong but non-neutralizing antibody response, followed by a T-helper 2 (Th2) skewed immunologic response which led to ERD upon natural RSV infection. Other aspects of the immune response implicated in ERD include distinct subsets of CD4 T-cells and memory CD8 T-cells. The failure to mount a protective cytotoxic T-lymphocyte (CTL) response was coupled with excess lung eosinophilia and neutrophilia, monocytic infiltration, and immune complex deposition in the lungs.

Nevertheless, work continued on development and human testing of live-attenuated RSV vaccine candidates. In the following 60 years, only two products were licensed for prevention of RSV. The first product was RSV intravenous...
immunoglobulin (RSV-IVIG), a polyclonal immunoglobulin preparation with high titers of anti-RSV neutralizing activity—that was approved in the United States and Canada and discontinued after 2003, when RSV-IVIG was replaced by the second approved product palivizumab, a humanized mAb directed against the RSV F glycoprotein. Since its initial approval in 1998, palivizumab remains the only licensed preventive intervention against RSV after demonstrating a reduction of 39% to almost 80% reduction of RSV hospitalizations in preterm infants < 35 weeks gestational age with and without chronic lung disease respectively (29). Palivizumab has an excellent safety profile and is indicated for the prevention of severe RSV ALRI in children born prematurely, with congenital heart disease, or with chronic lung disease (30).

Motivazumab, a higher affinity variant of palivizumab, was developed in early 2000 but was withdrawn and discontinued in 2010 (31). In a non-inferiority head-to-head comparative trial designed to show non-inferiority to palivizumab, motivizumab recipients had a slightly higher frequency of mild skin reactions following administration when compared to palivizumab (32). However, in a placebo-controlled trial, motivizumab was highly efficacious against inpatient and outpatient RSV LRI in healthy term American Indian infants (33). Without Nevertheless, without evidence of superiority compared to palivizumab, for protection from RSV-related hospitalization, evidence of slightly higher side effects, and no plan for dose reduction or cost-saving, the product did not attain regulatory approval (34,35). However, in a placebo-controlled trial, motivizumab was highly efficacious against inpatient and outpatient RSV LRI in healthy term American Indian infants (35).

With respect to vaccines for active immunization, many approaches targeted for RSV naïve children were evaluated preclinically over the years. Only Live-attenuated vaccine candidates were considered safe for clinical evaluation in these children because these vaccines are not expected to cause ERD (36). Over the past 40 years, several biologically derived live-attenuated vaccine candidates with attenuating temperature sensitivity or cold-passage mutations were evaluated clinically, including in the pediatric population, but the appropriate balance of attenuation and immunogenicity, suitable for RSV-naïve children and infants, remained elusive. After reverse genetics techniques became available in the 1990s, it became possible to design vaccine candidates with the appropriate level of attenuation, but with increased immunogenicity (37). While pediatric live-attenuated RSV vaccine candidates were under continued evaluation since the 1970s there were relatively few trials of RSV subunit vaccines conducted before 2000, with the exception of the purified F protein (PFP) vaccines (38,39), and an RSV fusion (F) attachment (G), and matrix (M) subunit vaccine (40).

Over the past 10 years development of preventive interventions for RSV has rapidly expanded. Currently, 19 vaccine candidates and mAbs for different target populations are in clinical trials, and many more are in preclinical development (21).

Lessons from the vaccine and mAb graveyard
While vaccine development has accelerated, there have been three recent late-phase vaccine and mAb trial failures. It is important to distil lessons learned from these results to inform future vaccine development.

1. A phase III double-blind, placebo-controlled trial (NURSEY) evaluating REGN2222 (suptavumab), a mAb against antigenic site V on the RSV pre-F protein, a major target for high-potency mAbs (41) was conducted at 250 sites in 19 countries. REGN2222 was administered once or twice during the respiratory season into 1,149 healthy preterm infants < 6 months of age with a gestational age ≤ 35 weeks who were not eligible to receive palivizumab prophylaxis, and The trial did not meet its primary efficacy endpoint to prevent medically-attended RSV infections through day 150 of life (42). REGN2222 was accelerated from phase I to phase III due to promising results and the United States US Food and Drug Administration (FDA) granted Fast Track designation in October 2015. A speculation for this failure may be inadequate dosing schedule in regard to the antibody half-life. The ultimate, the basis for failing to meet the primary clinical endpoint is not known, as analyses of this late-stage failure have not yet been made public.

2. The second candidate that failed to meet the predefined study endpoint in phase III clinical trials was the RSV F nanoparticle vaccine candidate for older adults, a candidate based on aggregates of full-length post-F. The results of the preceding phase II RSV F nanoparticle trial suggested the candidate vaccine might have showed modest efficacy (43) and promising immunogenicity measures, as determined by rise in geometric mean titer for IgG antibodies against the F protein and palivizumab competing antibodies (PCA), in the phase II trial (44). In the phase III trial, 11,585 subjects ≥ 60 years of age were enrolled in 60 US sites in a double-blind placebo-controlled trial (RESOLVE) over a single season starting November 2015 with 330–182 days follow-up for the efficacy outcome. The trial was granted fast track designation by the FDA in 2016. (45). Although the vaccine showed promising results in phase II and comparable immunogenicity measures in the two phases as determined by neutralizing and palivizumab competing antibody induction, However, the vaccine candidate failed to show efficacy against RSV moderate–severe lower respiratory tract disease (msLRTD) in phase III results (9). Compared to the previous season, RSV acute respiratory disease (RSV-ARD) and ms-LRTD attack rates were lower than expected in the 2015–2016 season (RSV-ARD: 2.0% versus 4.9% and RSV-msLRTD 0.4% versus 1.8% during the vaccine and previous season respectively). The pharmaceutical company vaccine manufacturer speculates that the difference in vaccine efficacy observed may in part be due to this lower attack rate as well as high pre-existing immunity in the study population (43). Another proposed explanation for failure of this vaccine candidate is that the quantity of the immune response to vaccination may not represent effective immunity. For example, PCA titers may not correspond to effective immunity as non-neutralizing antibodies can also bind the palivizumab binding site and can interfere with the binding of neutralizing antibodies (46). In a post-hoc subgroup analysis, the vaccine candidate showed efficacy against
hospitalizations for all-cause chronic obstructive pulmonary disease (COPD) exacerbations from all causes (43). Upon further analysis of the phase III results, there was a non-statistically significant trend towards higher RSV microneutralization titers in adults without RSV-ARD when compared to adults with RSV-ARD, but this difference was not statistically significant. One conclusion that can be drawn from this trial is that late-phase clinical research for an RSV vaccine candidate should include evaluation across more than one RSV season.

3. Development of the MEDI-7510 vaccine candidate, a subunit vaccine candidate for older adults, was discontinued after a phase IIb trial in North America, Europe, South Africa, and Chile. The vaccine candidate was evaluated in 1900 adults ≥60 years after and the study failed to meet its primary objective, efficacy against RSV-associated respiratory illness between 14 days post vaccination throughout the end of the surveillance period, approximately 7 months. MEDI-7510 was a subunit vaccine using soluble (unaggregated) postfusion (post-F) conformation of the F protein with a TLR4 agonist adjuvant. The vaccine candidate showed safety and immunogenicity with elevated increased B and T cell responses in the vaccine group compared to the placebo group in a phase I clinical trial after safety and improved immunogenicity with adjuvant was demonstrated in a first-in-human trial. The incidence of RSV-associated ARI as diagnosed by PCR was 1.7% and 1.6% in the vaccine and placebo groups respectively, for a vaccine efficacy (VE) of -7.1 (47). No efficacy was found in secondary subset analyses. On day 29, 93% of vaccinees had an anti-F IgG antibody seroresponse and there was a 4.6 geometric mean fold rise in anti-F IgG titer at the end of the RSV season in vaccine recipients compared to the placebo group. One proposed explanation for the negative results may be that the choice of a post-F antigen induced antibodies without appropriate epitope specificity (49). Upon further analysis, other proposed explanations include a low incidence of laboratory-confirmed RSV in the study population, or a selection of the study population, which included high-risk and low-risk older adults. Considerations for the future include selection of an older study population at higher risk of RSV infection.

Vaccine antigens
Vaccine antigens included in RSV vaccine candidates are diverse. The majority of vaccines in clinical trials (11/18) utilize the F protein, a class I viral fusion protein, as an antigenic target. The RSV F protein is highly conserved and facilitates viral fusion with host cells. Understanding of the structural differences between pre-F and post-F conformations, as well as stabilization of the pre-F soluble forms, has resulted in advances in vaccine antigen design (19,50). Current vaccine candidates use pre-F and post-F as vaccine antigens [Table 1]. Of note, the predominant conformation displayed on the Fl-RSV vaccine candidate was the post-F conformation.

There is no consensus on the remaining unclear as to whether there is a trigger for the pre-F to post-F conformational change, but it does occur spontaneously, making it difficult to ensure that a wild-type F vaccine antigen
maintains a pre-F conformation. However, but stabilizing mutations have been identified that can preserve the pre-F-specific epitopes. The antigenicity of some stabilized pre-F constructs has not been rigorously investigated, and it remains an open question as to whether certain stabilizing mutations affect the conformation of antibody binding sites. Assays to assess antigen conformation are needed. Likewise there is no consensus on cellular receptors that determine viral tropism.

Other less frequently utilized vaccine antigens, used alone or in combination with other antigens in vaccine candidates, include the RSV envelope associated glycoproteins G (1/18) and small hydrophobic (SH) protein (SH) (1/18) as well as internal proteins: nucleocapsid (N) (3/18), M (1/18), and M2-1 (1/18). Other than the F protein, the G protein is the only other target for neutralizing antibodies on the viral surface. The G protein is most important for viral attachment of RSV and is less frequently utilized as a vaccine antigen due to high variability across RSV strains, and limited knowledge of its surface structure. The G protein exists as an oligomer on the surface of RSV particles and as a monomer when secreted from infected cells as a soluble form. There is evidence that the soluble form of the G protein can act as a decoy that helps the virus evade the antibody response.

Another possible vaccine target, the SH protein, is not well understood, but has been observed to play a role in viral replication in vivo and inflammasome activation. The SH protein contains a transmembrane and extracellular domain; the latter has been used as a vaccine antigen. Internal proteins are particularly relevant to induce T cell-mediated immunity. As such, three non-membrane RSV proteins have been included in RSV vaccine design. The N protein is the major nucleocapsid protein that encapsidates the RNA genome of the virus. The M2-1 and M2-2 proteins are specific to RSV and other Pneumoviridae. M2-1 is an essential protein for viral transcription, and deletion of M2-2 is utilized in live vaccine candidates for viral attenuation. Finally, the M protein is a membrane-associated protein which is important for formation of the viral envelope that gives virions their filamentous shape. In summary, different viral proteins are being employed as antigens in RSV vaccine design. Viral surface glycoproteins such as F and G are known to induce antibodies with differing neutralization capacity. The SH protein may be important for induction of antibody-dependent cell-mediated cytotoxicity (ADCC), whereas non-membrane proteins are especially important to induce a robust T-cell response.

Target populations

RSV prophylactic interventions are designed to protect at least two populations most vulnerable to severe RSV disease: RSV-naive young infants and children, and older adults, although other important high-risk populations are important to consider. It is estimated that 45% of hospital admissions and in-hospital deaths due to RSV-ALRI occur in infants younger than 6 months of age, an age at which vaccines are generally less immunogenic. Older adults and adults with chronic cardiopulmonary conditions have emerged as an important target for RSV
Maternal vaccination is utilized to provide passive immunity to young infants by boosting maternal vaccine-specific antibody titers that are actively transferred through the placenta to the infant, thereby extending the period of protection conferred by maternal antibodies. Historically, epidemiologic studies have demonstrated an association between higher maternal RSV antibody concentrations and protection from lower respiratory tract infection (ALRI) in infants. Passive transfer of antibodies to infants has been shown to be protective against severe RSV infection through the administration of high-titer polyclonal and monoclonal antibodies (RSV-IVIG and palivizumab) (28, 29). The duration of protection of maternal vaccination is defined by the antibody half-life. Administration of mAbs is an alternative form of passive vaccination that can circumvent this hurdle due to extended antibody half-life through Fc alterations (66). The proof-of-principle of maternal vaccination as a tool to prevent infant disease has been demonstrated by the effective near-elimination of maternal and neonatal tetanus worldwide through tetanus toxoid vaccination in pregnancy (67). Maternal vaccination may also play a role in prevention of RSV infection in pregnant women and prevention of adverse birth outcomes, however data on the burden of RSV disease in pregnant women and the effect of RSV infection during pregnancy on the fetus is limited (68–71).

Premature infants, a population at high risk for severe RSV disease, may be insufficiently protected by maternal vaccination given that the majority of IgG transport of IgG occurs after 32 weeks gestational age (72). Globally 10% of children are born preterm (73). The burden is especially relevant in low and middle-income countries (LMICs) as more than 60% of preterm birth occurs in Sub-Saharan Africa and South Asia (74). Thus, a maternal vaccination strategy may not be sufficient to protect the high-risk preterm population if administered during the third trimester of pregnancy. Tetanus–diphtheria–acellular pertussis (Tdap) immunization in the second trimester is associated with higher cord-blood antibody titers by time of birth as compared to third trimester immunization (75). A strategy of earlier vaccination could be considered for maternal RSV immunization to maximize protection in preterm infants. Other populations in which impaired transplacental antibody transfer may limit protection by maternal vaccination include infants of mothers with chronic infection, hypergammaglobulinaemia, malaria, and HIV infection (76). The ratio of transplacental antibody transfer and antibody decay kinetics are currently considered the main parameters to assess protection conferred via maternal vaccination. However, protection may also be mediated by breast milk antibodies transferred postnatally.

A combined strategy that utilizes maternal passive vaccination immunization to protect young infants, via maternal vaccination or mAbs, followed by pediatric active vaccination immunization may be effective to prevent severe RSV infection in young children (77). The combined strategy is estimated to avert at least twice as many admissions per 100 births and four times as many in-hospital deaths per 1000 births than maternal vaccination alone (77). This strategy will be particularly relevant to prevent morbidity and mortality in children with
comorbidities who are at risk of severe RSV disease at older ages (78,79). A similar maternal and pediatric combined passive and active immunization strategy is currently employed for pertussis and influenza vaccination (76).

Although RSV is frequently considered a pediatric pathogen, it is important to consider the older adult population with regard to prevention of severe RSV disease. RSV has been identified as an important disease in older and high-risk adults, with a disease burden similar to that of influenza (3). It is estimated that RSV accounts for 10,000 – 14,000 deaths annually in adults over the age of 65 years in the United States (2,3). In addition, older adults with comorbidities such as underlying heart or lung disease are at elevated risk of severe RSV disease; 4-10% of high-risk adults will develop acute RSV infection annually (3).

Immunologic endpoints

Antibodies are thought to be the key players in limiting RSV ALRI as evidenced by proven protection in immunoprophylaxis trials in children (28,29,33). Recent evidence from experimental human infection in adults shows a protective role for nasal RSV-specific IgA against RSV infection (6), underscoring the importance of mucosal immunity. A limited ability to generate memory IgA responses after RSV infection may be in part responsible for incomplete immunity and subsequent RSV re-infection. Antibodies directed against different antigenic sites of the F protein display different neutralization capacities with the most neutralization-sensitive epitopes exclusive to the pre-F conformation. Antibodies with specificity for antigenic sites Ø and V show high neutralizing activity and are exclusive to the pre-F conformation (41,80). Antigenic site Ø is located at the apex of the pre-F conformation, the most variable region of the highly conserved F protein (19). Antibodies against antigenic site III prefer the pre-F conformation and exhibit high neutralizing activity (81). Antibodies directed against site II and IV, present on both pre-F and post-F, exhibit medium to high neutralization potency (80,82). Finally, antibodies against antigenic site I, present primarily on post-F, show weak or no neutralization. Escape mutants of these antigenic sites have been identified, but global RSV genetic data are needed to assess the molecular heterogeneity of RSV and the subsequent susceptibility or resistance to mAbs targeting RSV among circulating viruses.

The mechanisms of protection may differ according to the type of vaccine, and therefore, many different immunologic assays are employed in clinical trials. Neutralizing activity of serum is a frequent immunologic endpoint of vaccine trials. A measure of functional antibody response can be elucidated by the ratio of fold-increase in RSV-binding antibodies to fold-increase in RSV-neutralizing antibodies (ELISA-to-neutralization response ratio). A ratio of <1 may be an important correlate of protection (83). Furthermore, rather than a definitive protective threshold for antibodies, fold-rise in antibody titer may be a relevant correlate of protection for live-attenuated vaccines, since that may be the best indicator of B-cell priming. Recent efforts by PATH, the WHO, and the National Institute for Biological Standards and Control (NIBSC) examined the variability of RSV neutralization assays across laboratories and recommended steps for improved standardization globally (84), resulting in the development of a new WHO
International Standard for Antiserum to RSV with 1000 International Units of RSV subtype A neutralizing activity per vial now available through the NIBSC(85). For other standardization of other frequently used immunologic assays such as palivizumab competing antibodies (PCA), ELISA and T-cell assays such standardization has not yet taken place.

Once infection of the lower airways is established, CD8 T-cells play an important role in viral clearance(86). Th2-biased responses have been associated with animal models of RSV ERD and measurement of Th1 and Th2 responses are considered important to predict safety of vaccine candidates other than live-attenuated vaccines in clinical trials in young children.

Animal models are important for preclinical development of vaccine candidates and assessing the possibility of enhanced disease. Alveolitis in the cotton rat and priming of a Th2 response in mice are considered markers to assess possible ERD; there is no consensus on the ability to reproduce ERD in calves(87).

Although we discuss several potential immunological correlates of protection for vaccine trials, we considered cell-mediated immunity beyond the scope of the manuscript. However, we highlight the different aspects of the expected immune response for all 19 vaccine candidates and mAbs in clinical development in Table 3.

A definitive threshold for protection against RSV disease remains elusive. So far no vaccine candidates have been tested in the experimental human infection model, but the model provides a unique opportunity to test vaccine candidates in the natural host despite practical and ethical challenges(88). Ultimately, the outcome of large-scale vaccine trials will inform which immunologic measures correspond to protection from clinical RSV disease.

Vaccine strategies
We have divided vaccines in clinical development into four categories in accordance with the PATH RSV vaccine and mAb snapshot: particle-based, vector-based, subunit and live-attenuated/chimeric vaccines(21). We have also included mAbs in clinical development for the prevention of RSV ALRI. In the snapshot there are 43 vaccines and 4 mAbs in development of which 19 are in clinical stage development. An important consideration for all vaccines is not only to prevent severe RSV disease, but also to avoid the risk of priming for RSV ERD. Based on our current understanding of the underlying mechanisms leading to RSV ERD, this would suggest caution should be taken in the use of protein-based vaccines in RSV naïve infants and children individuals. Replication deficient vectors, engineered to induce CD8 T cell responses expressing RSV antigens intracellularly, are considered more similar to live-attenuated virus vaccines which have been shown to be safest to cause ERD in this population. In Table 1 we provide a comprehensive overview and more detailed comparison of all characteristics of the 19 vaccine candidates and mAbs in clinical development.

Particle-based vaccines
The RSV F nanoparticle-based vaccine platform is currently being evaluated for protection of three target populations: (1) infants through maternal vaccination, (2) children between 6 months and 5 years, and (3) older adults. These vaccine
candidates utilize aggregates of a modified stabilized F protein which exhibits the post-F morphology(89). The maternal RSV F nanoparticle vaccine candidate is farthest along in clinical development and the PREPARE trial has entered the third year of a phase III trial to enroll up to 8,618 pregnant women at 80 sites in 11 countries(43). In January 2018 an informational analysis of the phase III trial was announced in which the vaccine candidate successfully targeted an efficacy threshold against the primary endpoint in infants at day 90 of >40%(90). Second in clinical development is the RSV F nanoparticle vaccine for older adults. Despite lack of efficacy in a phase III trial (RESOLVE) with a non-adjuvanted vaccine candidate, development was continued in a phase II roll-over study initiated in January 2017 in Australia in 300 adults. The aim of this rollover trial is to determine whether 2 dose regimens with an adjuvant (Matrix-M, a saponin-based adjuvant, or aluminum-phosphate) may increase the magnitude and quality of the immune response in this population. The results from the RESOLVE trial in older adults suggested vaccine efficacy in adults with COPD, leading to considerations to initiate a future trial in this older adult population at high risk for severe RSV infection(43). Finally, the phase I trial was completed in young children 24-72 months of age in 2016, but no data have been published yet(91).

SynGEM is a particle-based needle-free vaccine candidate containing the RSV F protein attached to empty bacterial particles made from *Lactococcus lactis*. The in this vaccine platform in which an antigen is presented by a bacterial particle. An influenza vaccine candidate in clinical trials which uses the same vaccine platform, has shown both local and systemic antibody responses for the influenza candidate in clinical trials using the same platform(92) but needs further optimization for RSV vaccination. The preliminary results of immunogenicity testing have been reported. The immunogenicity of this vaccine was evaluated after delivery as a nasal spray to healthy adult volunteers. Two intranasal doses of SynGEM were administered 28 days apart at low or high dose in 24 subjects per group (6 subjects in each group receiving placebo, double blinded). Assays of serum virus neutralization, RSV F-specific antibodies, palivizumab competing antibodiesPCA, and F-specific IgA indicated some immunogenicity, but the results did not reach the threshold set for continuation to viral challenge and the studies were suspended in 2017 (Openshaw and Chiu, personal communication).

Vector-based vaccines
There are five vector-based vaccines in clinical development. The first uses a modified vaccinia virus Ankara (MVA), a replication-defective smallpox viral vector, and the remaining four vaccine candidates employ an adenovirus vector to display viral antigens. The MVA vector has been safely used in vaccines for other infectious diseases(93). This vaccine candidate, MVA-BN-RSV, induces both humoral and cell-mediated responses by displaying four vaccine antigens: F, G, N and M2-1. Phase II results in healthy older adults from this candidate will soon be announced.

The second vector-based vaccine candidate, VXA-RSV-f, uses an innovative platform with an adenovirus 5 based oral tablet delivery platform that is stable at room temperature. Using the same oral adenovirus vaccine delivery platform, a phase I trial for influenza has been conducted, which showed neutralizing antibody...
responses against influenza and no interference of pre-existing vector immunity(94). The results from preclinical studies for the RSV vaccine candidate in the cotton rat model showed that mucosal immunization with the oral vaccine candidate enhanced mucosal IgA in the upper airways and protection against RSV challenge(95). Given that severe disease in the older adult population is thought to be mediated by immunosenescence, a subunit vaccine candidate, DS-Cav1, has been developed for pregnant women and older adult populations. 

In this population, the increase in anti-F antibodies and protection against RSV challenge(95). This vaccine candidate, which induces a humoral response characterized by impaired T-cell responses to RSV(96,97), is a promising intervention in this population for the older adult population(98).

Third and fourth, Ad26.RSV.preF, is a vaccine candidate being developed for two populations: the older adult and the pediatric population. In this candidate uses pre-F antigen is expressed in the human adenovirus strain 26, a vector with a favorable safety profile when used for other infectious diseases(98,99). Previously, the vaccine candidate vector expressed post-F as antigen (FA2) but has now been changed to the stabilized pre-F conformation as vaccine antigen. The stabilized pre-F protein has 5 amino acid changes from wild-type, and is stable at 4C and heat-stable(50). With the expectation that this vaccine candidate will induce highly neutralizing antibodies against pre-F, phase II trials will be initiated in RSV-seropositive children. In December 2017 a phase II trial has been initiated comparing concomitant administration of influenza vaccination with RSV vaccine and seasonal influenza vaccine versus seasonal influenza vaccine alone co-administration in healthy older adults(100).

Fifth, ChAd155-RSV, a replication-competent chimpanzee adenovirus 155 has been used as a vector for the F, N and M2.1 proteins. The anticipated use for this pediatric vaccine is to start immunization at two months of age, and to use two to three doses alongside the normal pediatric vaccination schedule, instead of seasonally(101). This vaccine candidate is currently being evaluated in 12-23 month old RSV seropositive children. In the future, there are plans to conduct clinical trials in seronegative children sequentially from older to younger ages (12-24 months followed by 6-12 months and subsequently 2-6 months of age) to ensure safety in RSV-naïve populations. Results of phase II trials are expected to be announced in 2020.

In summary, vector-based vaccines are used to display various RSV viral proteins and three of these vaccine candidates are in phase II trials.

Subunit vaccines

Due to concerns of ERD associated with protein-based vaccines, subunit vaccines are only in development for pregnant women and older adult populations. One subunit vaccine in development is the GSK RSV F vaccine candidate, which uses a version of soluble secreted F protein empirically engineered to maintain the Pre-F conformation. Phase I results demonstrated safety and immunogenicity as evidenced by RSV neutralizing antibody response in healthy men(102). However, a phase II trial scheduled for 2017 was halted due to instability of the pre-F antigen during manufacturing.

Structure-guided stabilization of the pre-F conformation has yielded a subunit vaccine candidate, DS-Cav1. The stabilization includes a foldon
trimerization domain, the introduction of cysteine residues to form a disulfide bond, and cavity-filling hydrophobic residues. The vaccine is able to preserve neutralization-sensitive epitopes on a functional pre-F form of the viral surface protein. In preclinical studies the subunit vaccine induced high levels of RSV-neutralizing antibodies in mice and non-human primates. Preliminary results from the phase I trial, VRC 317, are promising and will soon be published. DPX-RSV is a vaccine candidate with a unique choice of vaccine antigen, the extracellular domain of the SH protein of RSV. The DepoVax technology allows for a prolonged exposure of antigen and adjuvant, and aims to induce ADCC using a liposome and oil-based depot. The antigen and adjuvant are encapsulated in a liposome, lyophilized and suspended in oil and the process is expected to produce vaccines with long shelf-life stability. Phase I results on safety and immunogenicity in the older adult population will soon have been released and are expected to be published soon.

Live-attenuated and chimeric vaccines

In the context of historical concerns for enhanced RSV disease, live-attenuated vaccines can be considered safe for RSV naive infants, based on consistent clinical study results showing that these candidates do not prime for ERD following subsequent exposure to wild-type RSV after vaccination. Another benefit of live-attenuated vaccines against RSV in the pediatric population is their ability to generate an immune response in the respiratory tract, despite the presence of maternally-acquired antibodies, and to elicit a more-broad antibody response in infants and young children. Live-attenuated vaccines are likely limited to the pediatric population under two years of age, as pre-existing immunity in older populations might not permit sufficient replication to generate protective immune responses. Safety could be a concern for intranasal live-attenuated vaccines, in particular if attenuation is insufficient. However, evaluation of current vaccines has not shown evidence of increased rates of vaccine-associated ALRI or fever, though there may be increased rates of rhinorrhea, similar to what has been observed with the live-attenuated influenza vaccines.

Five live-attenuated vaccine candidates in phase I clinical trials are being developed in partnership with the National Institutes of Health (NIH). Live-attenuated vaccines face the challenge of achieving sufficient attenuation to be safe while remaining immunogenic enough to induce a protective immune response, but an improved understanding of the RSV viral genome has informed the development of new vaccine candidates that may overcome this challenge. Two main modifications to the RSV genome have been engineered through reverse genetics: the ΔM2-2 deletion which attenuates viral replication and upregulates antigen expression, as well as the ΔNS2 deletion which reduces viral suppression of host interferon thereby boosting the innate immune response. RSV MEDI ΔM2-2 strongly reduces viral replication while inducing a strong primary serum neutralizing antibody as well as potent anamnestic response in RSV-seronegative infants and children. Further results from phase I clinical trials with the other live-attenuated vaccine candidates are expected.
The only chimeric vaccine candidate, rBCG-N-hRSV, currently in clinical development is delivered via a BCG strain. BCG has a safe profile in newborns and infants, induces a Th1 response\(^\text{(107,108)}\), and allows for combined vaccination against two major respiratory pathogens: *Mycobacterium tuberculosis* and RSV. Not only is the Th1 cellular response important in protecting against lung pathology, inflammation and viral replication\(^\text{(109)}\) but the candidate also induces a humoral response. The antigen presented by this vaccine candidate is the RSV N protein\(^\text{(110)}\).

**Importantly** Presently, this candidate is the only vaccine candidate intended for administration to newborn infants\(^\text{(110)}\).

**Monoclonal antibodies**
A promising highly potent monoclonal antibody has emerged as a passive administration strategy to prevent severe RSV infection. MEDI8897, also known as nirsevimab, was optimized from the human antibody D25 that targets antigenic site Ø on the pre-F conformation, which is more neutralization sensitive than the palivizumab epitope, antigenic site II. Using the YTE technology\(^\text{for extending which extends antibody half-life as well as modulates ADCC}\(^\text{(111)}\), the three-fold increase in half-life of MEDI8897\(^\text{(112)}\) compared to palivizumab offers the possibility of passive protection for all infants for an entire season through a single intramuscular injection. The intended use is for both term and preterm infants entering their first RSV season. Passive vaccination with an extended half-life antibody offers an approach to protecting infants that is safe and may be reasonably priced.

Representatives of the pharmaceutical company have indicated that they expect vaccine-like pricing \textit{of for} MEDI8897. Given the increased potency, the extended half-life, and the required dose, it is expected that the cost to protect an infant during the RSV season can be kept relatively low\(^\text{(66)}\).

**Other approaches not in clinical development**
Other emerging approaches not yet in clinical development include nucleic acid-based vaccines\(^\text{(113)}\). Importantly these vaccines induce a T\(_\text{\text{c}}\)-cell response mimicking the response to live virus infection. Both DNA and messenger RNA (mRNA) vaccines against RSV have shown promising results in preclinical studies\(^\text{(113)}\). Notably, through a collaboration with the Bill & Melinda Gates Foundation, an mRNA technology vaccine platform for HIV and rotavirus has also expanded to include RSV. \textit{Another vaccine approach in preclinical development is a whole-inactivated vaccine to be delivered intranasally via a nanoemulsion technology, for which development has been supported by the Bill & Melinda Gates Foundation}\(^\text{(114)}\). Furthermore, with the first of the palivizumab patents expiring in October 2015 and the last in 2022, there has been active development to produce a biosimilar in order to provide a low-cost RSV preventive intervention.\(^2\)

**Considerations by regulatory agencies and the World Health Organization**
The FDA has articulated that differences between high income countries (HICs) and LMICs are not particularly relevant to regulatory decisions, though a bridging study in the US must be performed if all clinical trials have been performed outside of the US\(^\text{(115)}\). The EMA does not require that trials intended to support a regulatory
decision are conducted in the European Union. Other considerations in population selection for vaccine trials mentioned by EMA include: first testing a vaccine candidate in a seropositive before testing in a seronegative population, testing a maternal vaccine in non-pregnant women of child-bearing age before testing in pregnant women, and including older adults with comorbidities in vaccine trials. No particular considerations were mentioned for population selection in studies for mAbs. In October 2017 the EMA released draft guidelines for the clinical evaluation of RSV prophylactic interventions which included guidance regarding trial design, assessment of efficacy, and safety(116). The draft guidelines will be revised after a period of public consultation based on comments and new publications.

The WHO has recognized the importance of RSV as a global health problem and has identified the development of RSV vaccines as a priority for the WHO Initiative for Vaccine Research and for Biological Standardization. WHO recently developed RSV vaccines preferred product characteristics and research and development technical roadmap documents(117,118). Further guidance for development will contribute to adequate policy-making. WHO standardization activities led to the development and establishment of the first international standard for antiserum to RSV. Development of guidelines for evaluation of quality, safety and efficacy of RSV vaccines has been initiated and will be part of consultation with regulators, manufacturers and academia in 2018 with the aim of finalizing it in 2019. Further discussion on guiding principles for mAbs is needed before proceeding with the development of the WHO Guidelines. These and other WHO standards serve as a basis for setting national regulatory requirements as well as WHO prequalification.

Finally, the WHO is now performing a surveillance pilot study in 14 countries to test the feasibility of using the Global Influenza Surveillance and Response System platform for RSV surveillance and it is expected that this pilot will contribute to our understanding of the RSV disease burden and seasonality in different geographical regions(119).

Discussion
Challenges in RSV vaccine design include concerns of ERD post-vaccination, lack of definitive immunologic correlates of protection, lack of consensus regarding clinical endpoints, and limited natural immunity following RSV infection. Despite these challenges, recent developments such as an understanding of the structural biology of the RSV fusion protein as well as lessons learned from late-phase vaccine trial failures have informed the field as it moves forward.

We attempted to collect data regarding expected plans for access to a preventive intervention in LMICs and expected pricing for all vaccine candidates, however this information was not publicly available. The only information obtained regarding expected pricing was for MEDI8897, though a more specific estimate than vaccine-like pricing was not available. Given that the most severe RSV infection occurs in LMICs(17), information regarding LMIC target countries and potential pricing for vaccine candidates will be essential to facilitate access to vaccines worldwide, especially in areas where the mortality burden is highest. In LMICs the most important target for vaccine candidates is young children(120). A mechanism
should be introduced to ensure that information regarding expected pricing and access to interventions is transparent and available in the public domain. RSV vaccines and mAbs will be considered in the development of the Vaccine Investment Strategy (VIS) by GAVI, the Vaccine Alliance in 2018(121).

A vaccine trial may be considered a probe study to determine whether a causal relationship exists between RSV infection and asthma, a longstanding question in the field. If long-term follow-up had been undertaken during the pivotal RSV prevention trials using palivizumab, these trials would now have provided 20 years of follow-up on respiratory morbidity after RSV prevention in high-risk infants. Lack of long-term surveillance for airway morbidity in vaccine trials are missed opportunities to provide novel scientific insights important not only to understand the pathophysiology–pathogenesis but also the long-term vaccine efficacy against airway morbidity following RSV infection. In addition to wheeze, objective outcomes, such as lung function measurements including demonstration of bronchial hyperreactivity and IgE measurements will ideally be incorporated in vaccine trials to fully understand the impact of RSV prevention on asthma development.

Viral interference, in which RSV inhibits infection by other viruses, is becoming an increasingly important concept to understand in the context of an approved RSV vaccine. RSV vaccination may conceivably result in an increased or decreased prevalence of other respiratory viruses. There is evidence supporting viral interference for influenza vaccination(122,123), for RSV prevention(124,125), and during the RSV season in the absence of RSV-(126). It is important for vaccine trials to examine this phenomenon by evaluating the incidence of all-cause ALRI, as well as RSV-specific ALRI, to better understand the implications of viral interference for an RSV vaccine.

This review provides an extensive overview of the 19 vaccine candidates and mAbs in clinical trials to prevent RSV infection. RSV vaccine development is moving rapidly and shows promise to address an unmet global health problem. Vaccines for various target populations are in clinical development. One vaccine candidate and one mAb are in late phase trials (IIb/III) and aim to prevent the disease burden in young infants. Despite some recent failures, RSV vaccine candidates and mAbs in clinical development hold the promise that a preventive intervention for RSV is on the horizon.
Contributors: LJB and NIM were involved in the design and plan for this review. ACL and NH were involved in the data collection. All authors contributed to the final manuscript.

Acknowledgements

We would like to acknowledge Ichelle van Roessel, Emily Phijffer, and Juliette Simons for excellent assistance collecting data for the manuscript.

Sadly and unexpectedly, José Melero, a leader in the RSV field and friend to many, passed away March 3, 2018.
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# Tables/Figures

## Table 1: Overview of RSV vaccines and mAbs in clinical development

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Company/Sponsor</th>
<th>Manufacturing Process</th>
<th>Antigen</th>
<th>Adjuvant</th>
<th>Mechanism of Action</th>
<th>Target Population</th>
<th>Route of Administration</th>
<th>Clinical Phase</th>
<th>Animal Models</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Result Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PARTICLE-BASED</strong></td>
<td></td>
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<tr>
<td>RSV F Nanoparticle</td>
<td>Novavax</td>
<td>SP/BV recombinant technology</td>
<td>F protein expressed in post-F morphol...</td>
<td>Aluminum phosphate</td>
<td>F protein nanoparticle in multimeric micelle format</td>
<td>M IM II</td>
<td>Gattom rate (127,128) baboons (129)</td>
<td>Oct 2012 - May 2013</td>
<td>Dec 2015 - Oct 2020</td>
<td>NCT01299419 (n=150)</td>
<td>Oct 2013 - Apr 2014</td>
<td>NCT01966686 (n=720)</td>
<td>NCT02247726 (n=50)</td>
</tr>
<tr>
<td>RSV F Nanoparticle</td>
<td>Novavax</td>
<td>SP/BV recombinant technology</td>
<td>F protein expressed in post-F morphol...</td>
<td>Aluminum phosphate/Matrix M-1</td>
<td>F protein nanoparticle in multimeric micelle format</td>
<td>F IM I</td>
<td>Gattom rate, (127,128) baboons (129)</td>
<td>Nov 2014 - Apr 2015</td>
<td>Dec 2015 - Nov 2016</td>
<td>NCT02296463 (n=32)</td>
<td>N/A</td>
<td>N/A</td>
<td>PhII: well-tolerated; Anti-F IgG &amp; PCA increase d14, Peak d28, elevated to d56; 10-fold increase PCA &amp; anti-F IgG adjuvanted 6-fold increase in unadjuvanted(135) (n=21)</td>
</tr>
<tr>
<td>System</td>
<td>Mucovis</td>
<td>Bacterium-like-particle (BLP) mimopath technology expressing F protein</td>
<td>BLP</td>
<td>BLP allows presentation of F protein and elicits mucosal IgA</td>
<td>O &amp; P</td>
<td>IN I</td>
<td>Mice</td>
<td>July 2016</td>
<td>N/A</td>
<td>N/A</td>
<td>PhII: some immunogenicity in healthy adults but did not meet threshold; development suspended.</td>
<td></td>
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<tr>
<td><strong>VECTOR-BASED</strong></td>
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<tr>
<td>MYA-BN RSV</td>
<td>Bavarian Nordic</td>
<td>MYA-BN technology (antigens expressed in attenuated modified vaccine Ankara)</td>
<td>F, G (subtypes A &amp; B), N, M2</td>
<td>none</td>
<td>Virus replication blocked at a late stage</td>
<td>D IM/IN II</td>
<td>Gattom rate, BALR/c mice(137)</td>
<td>IM-Aug 2015 - May 2016</td>
<td>Dec 2015 - Nov 2016</td>
<td>NCT02419301 (n=63)</td>
<td>Oct 2016 - Aug 2019</td>
<td>NCT02873236 (n=409)</td>
<td>NCT02064628</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Details</td>
<td>Endpoint</td>
<td>Results</td>
<td></td>
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<tr>
<td>VXA-RSV oral</td>
<td>Vaxart antigen and adjuvant expressed in non-replicating adenovirus vector (Ad5)</td>
<td>F, dA DNA that activates TLR3 receptor</td>
<td>Oral</td>
<td>Cotton rat</td>
<td>2018</td>
<td>N/A</td>
<td>Preclinical: Systemic Anti-F Abs and protection against RSV infection in cotton rat model (95)</td>
<td></td>
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</tbody>
</table>

**Ad26.RSV.preF**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Details</th>
<th>Endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janssen Antigen expressed in human adenovirus type 26 produced in PER.C6 human cell line</td>
<td>Pro-F (previous ly FA2)</td>
<td>Ad26 vector is replication incompetent but expresses immunogenic F antigen</td>
<td>Mice, cotton rats (139)</td>
<td>Nov 2016 - Dec 2018 NCT02296430 (n=73)</td>
</tr>
<tr>
<td>Janssen Antigen expressed in human adenovirus type 26 produced in PER.C6 human cell line</td>
<td>Pro-F (previous ly FA2)</td>
<td>Ad26 vector is replication incompetent and expresses immunogenic F antigen</td>
<td>Mice, cotton rats (139)</td>
<td>Nov 2017 - Mar 2019 NCT03303625 (n=60)</td>
</tr>
</tbody>
</table>

**ChAd155-RSV**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Details</th>
<th>Endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK Chimeranase adenovirus ChAd155-RSV with F, N, M2.1 insert and E1 deletion</td>
<td>F, N, M2.1</td>
<td>Intracellular RSV antigen expression; replication incompetent vector</td>
<td>Mice, cotton rats, calves (101)</td>
<td>Jul 2015 - Feb 2017 NCT02491463 (n=73)</td>
</tr>
</tbody>
</table>

**SUBUNIT**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Details</th>
<th>Endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK RSV F</td>
<td>GSK</td>
<td>Pre-F produced in CHO cells</td>
<td>Pre-F</td>
<td>Mice, cotton rats, guinea pigs, cows</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Details</th>
<th>Endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPA-RSV Dalhousie University</td>
<td>DepovaxTM delivery in 100% oil-based platform preventing release at injection site</td>
<td>Site</td>
<td>Mice, cotton rats</td>
<td>May 2015 - June 2017 NCT02254825 (n=40)</td>
</tr>
</tbody>
</table>

**RSV F DS-Cav1**

<table>
<thead>
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<th>Study</th>
<th>Design</th>
<th>Details</th>
<th>Endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH/NIAID/NCI</td>
<td>PreF: stabilized trimers RSVF</td>
<td>Pre-F</td>
<td>Cotton rats, mice, calves (14)</td>
<td>Feb 2017 - Jan 2020 NCT03040155</td>
</tr>
<tr>
<td>nBCG-N-hRSV</td>
<td>Recombinant BCG expressing N antigen</td>
<td>CHO cell line</td>
<td>Antibodies against pre-F epitopes</td>
<td>4</td>
</tr>
<tr>
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<td>---</td>
</tr>
<tr>
<td>M2-2 deletion via reverse genetics and 5 aa substitutions in 3 proteins called the “cp” mutations, originally identified in a cold-passaged vaccine candidate cpRSV</td>
<td>native RSV</td>
<td>P</td>
<td>IN</td>
<td>I</td>
</tr>
</tbody>
</table>

| RSV D46 cpΔM2-2 | native RSV | P | IN | I | African green monkeys | Oct 2015–May 2018 NCT02601612 (n=45) |

| RSV LID ΔM2-2 | native RSV | P | IN | I | Mice, African green monkeys | Jan 2016–July 2017 NCT02794070, NCT02952339 (n=33) |
| 1030s | native RSV | P | IN | I | Mice and chimpanzees | Jun 2015–May 2017 NCT01893554 (n=75) Aug 2015–May 2019 NCT03227029 (n=80) |

| RSV ΔM2 | NS2 and 1313 deletion via reverse genetics and temperature sensitivity mutation 1313s | native RSV | P | IN | I | Mice and chimpanzees | Mar 2017–April 2019 NCT03102034, NCT03098291 (n=33) |

| RSV D46/NS2/NΔM2-2 HindIII | native RSV | P | IN | I | African green monkeys | Sep 2016–Apr 2018 NCT02890381 (n=17) |

| RSV LID cp ΔM2-2 | native RSV | P | IN | I | African green monkeys | Sep 2016–Apr 2018 NCT02890381 (n=17) |
### MONOCLONAL ANTIBODY (mAb)

<table>
<thead>
<tr>
<th>Name</th>
<th>Manufacturer</th>
<th>Human/mouse type</th>
<th>Human/mouse target site</th>
<th>Phase</th>
<th>Route</th>
<th>Duration</th>
<th>NCT Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDI8897</td>
<td>MedImmune</td>
<td>In vitro-optimized human mAb with YTE mutation in Fc</td>
<td>Antibody targeting site of the F protein of RSV with an extended half-life</td>
<td>IV/IM</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Legend:**
- N/A: not applicable or not available
- IM: intramuscular
- ID: intradermal
- IN: intranasal
- IV: intravenous
- ARD: acute respiratory disease
- PCA: palivizumab-competing antibodies
- P: pediatric
- M: maternal
- O: older adults
- SHe: small hydrophobic protein ectodomain
- RSV ARD: all symptomatic respiratory disease due to RSV
- msLRTD: moderate-severe RSV-associated lower respiratory tract disease
- NIAID: National Institutes of Allergy and Infectious Diseases
- VRC: Vaccine Research Center
- NIH: National Institute of Health
- Ab: antibody
- aa: amino acid

Mean half-life 85-117d; time to max concentration 5-9 days; bioavailability 77% in healthy adults (n=136) (146).
<table>
<thead>
<tr>
<th>Target Population</th>
<th>Vaccine</th>
<th>Vaccine type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant mothers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Third trimester</td>
<td>RSV F nanoparticle (Novavax)</td>
<td>Nanoparticle</td>
</tr>
<tr>
<td>Third trimester</td>
<td>RSV F (GSK)</td>
<td>Subunit</td>
</tr>
<tr>
<td></td>
<td>RSV F protein (NIH/NIAID/VRC)</td>
<td>Subunit</td>
</tr>
<tr>
<td>Pediatric</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6m-5y</td>
<td>RSV F nanoparticle (Novavax)</td>
<td>Nanoparticle</td>
</tr>
<tr>
<td>Start 2m</td>
<td>Adenovirus (GSK)</td>
<td>Vector</td>
</tr>
<tr>
<td>Start 2-3m</td>
<td>Adenovirus (Janssen)</td>
<td>Vector</td>
</tr>
<tr>
<td></td>
<td>BCG/RSV (Pontificia Universidad Catolica de Chile)</td>
<td>Chimeric</td>
</tr>
<tr>
<td></td>
<td>RSV D46 cp ΔM2-2 (Sanofi Pasteur/LID/NIAID/NIH)</td>
<td>Live-attenuated</td>
</tr>
<tr>
<td></td>
<td>RSV LID ΔM2-2 1030s (Sanofi Pasteur/LID/NIAID/NIH)</td>
<td>Live-attenuated</td>
</tr>
<tr>
<td></td>
<td>RSV ΔNS2 Δ1313 H1314L (Sanofi Pasteur/LID/NIAID/NIH)</td>
<td>Live-attenuated</td>
</tr>
<tr>
<td></td>
<td>RSV D46/NS2/ N/ΔM2-2-HindIII (Sanofi Pasteur/LID/NIAID/NIH)</td>
<td>Live-attenuated</td>
</tr>
<tr>
<td></td>
<td>RSV LID cp ΔM2-2 (Sanofi Pasteur/LID/NIAID/NIH)</td>
<td>Live-attenuated</td>
</tr>
<tr>
<td></td>
<td>MEDI8897 (MedImmune)</td>
<td>Monoclonal antibody</td>
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<tr>
<td>Older adults</td>
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<tr>
<td></td>
<td>RSV F nanoparticle (Novavax)</td>
<td>Nanoparticle</td>
</tr>
<tr>
<td></td>
<td>RSV BLP (Mucos)</td>
<td>Nanoparticle</td>
</tr>
<tr>
<td></td>
<td>MVA (Bavarian Nordic)</td>
<td>Vector</td>
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<tr>
<td></td>
<td>Adenovirus (Vaxart)</td>
<td>Vector</td>
</tr>
<tr>
<td></td>
<td>Adenovirus (Janssen)</td>
<td>Vector</td>
</tr>
<tr>
<td></td>
<td>DPX-RSV-SH Protein (Immunovaccine)</td>
<td>Subunit</td>
</tr>
<tr>
<td></td>
<td>RSV F protein (NIH/NIAID/VRC)</td>
<td>Subunit</td>
</tr>
</tbody>
</table>

Legend: m: months; y: years
### Table 3: Expected immune response and previous successes for vaccine candidates and monoclonal antibodies

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Target Population</th>
<th>Pre-F Immunity*</th>
<th>Immune response</th>
<th>Mucosal/Systemic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nanoparticle</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSV F Nanoparticle (Novavax)</td>
<td>M</td>
<td>Pre-F &lt; post-F</td>
<td>Broadly neutralizing antibodies</td>
<td>systemic</td>
</tr>
<tr>
<td>RSV F Nanoparticle (Novavax)</td>
<td>O</td>
<td>Pre-F &lt; post-F</td>
<td>Broadly neutralizing antibodies</td>
<td>systemic</td>
</tr>
<tr>
<td>RSV F Nanoparticle (Novavax)</td>
<td>P</td>
<td>Pre-F &lt; post-F</td>
<td>Broadly neutralizing antibodies</td>
<td>systemic</td>
</tr>
<tr>
<td>RSV BLP (Mucosics)</td>
<td>O &amp; P</td>
<td>unclear F confirmation</td>
<td>Activation of B &amp; T cells; local secretion of neutralizing IgA in the nose; production of IgG neutralizing IgG in the blood</td>
<td>mucosal &amp; systemic</td>
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<td><strong>Vector</strong></td>
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<td>MVA (Bavarian Nordic)</td>
<td>O</td>
<td>Pre-F &lt; post-F</td>
<td>B &amp; T cell response; antibodies against 5 RSV antigens</td>
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<tr>
<td>Adenovirus (GSK)</td>
<td>O</td>
<td>Pre-F &gt; post-F</td>
<td>B &amp; T cell response; neutralizing antibodies against F antigen; CD8 T cells against F, N and M2.1 antigens</td>
<td>systemic</td>
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<tr>
<td>Adenovirus (Vaxart)</td>
<td>O</td>
<td>Pre-F &lt; post-F</td>
<td>B &amp; T cell immunity, protection at mucosal surface</td>
<td>mucosal &gt; systemic</td>
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<tr>
<td>Adenovirus (Janssen)</td>
<td>P</td>
<td>Pre-F</td>
<td>B &amp; T cells</td>
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<td>Adenovirus (Janssen)</td>
<td>O</td>
<td>Pre-F</td>
<td>B &amp; T cells</td>
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<td>RSV F (GSK)</td>
<td>M</td>
<td>Pre-F</td>
<td>B &amp; T cell response</td>
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<tr>
<td>DPX-RSV (Dalhousie University)</td>
<td>O</td>
<td>none</td>
<td>B &amp; T cell response</td>
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<td>RSV F protein (NIH/NIAID/VRC)</td>
<td>O &amp; M</td>
<td>Pre-F</td>
<td>B &amp; T cell response</td>
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<td>BCG/RSV (Pontificia Universidad Catolica de Chile)</td>
<td>P</td>
<td>Pre-F &amp; post-F</td>
<td>B &amp; T cell response; Th1 polarized response; antibodies against N, F, G</td>
<td>systemic</td>
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<td>RSV D46 cp ΔM2-2 (Sanofi Pasteur/LID/NIAID/NIH)</td>
<td>P</td>
<td>Pre-F &amp; post-F</td>
<td>B &amp; T cell response; enhanced antibody production due to increased antigen production from M2-2 deletion</td>
<td>mucosal &amp; systemic</td>
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<td>RSV LID ΔM2-2 1030s (Sanofi Pasteur/LID/NIAID/NIH)</td>
<td>P</td>
<td>Pre-F &amp; post-F</td>
<td>B &amp; T cell response; enhanced antibody production due to increased antigen production from M2-2 deletion</td>
<td>mucosal &amp; systemic</td>
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<td>P</td>
<td>Pre-F &amp; post-F</td>
<td>B &amp; T cell response</td>
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<td>RSV D46 ΔNS2 N ΔM2-2 HindIII</td>
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<td>Pre-F &amp; post-F</td>
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Legend: Pre-F: prefusion conformation of the RSV F protein; Post-F: postfusion conformation of the RSV F protein; N: RSV nucleocapsid protein; F: RSV fusion protein; G: RSV attachment protein; O: older adults; M: maternal; P: pediatric.
Figure 1: Incidence is shown worldwide for children under 5 years of age unless otherwise stated. The hospital admission rate of 15.9 hospital admissions per 1000 neonates per year is in developing countries. The RSV ALRI hospitalization 63.9 among premature infants <1 year is reported per 1000 children per year globally. Legend: OR: odds ratio; LRTI: lower respiratory tract infection, RSV: respiratory syncytial virus, HIC: high income country, *: compared to children who survived RSV hospitalization and were mechanically ventilated. References: (a)(1) (b)(78) (c)(147) (d)(148) (e)(149) (f)(150)
Figure 2: Overview of Vaccine candidates and monoclonal antibodies in clinical trials per preventive approach including candidates for which development was recently halted.
Legend: For vaccine candidate names listed in gray development has been halted since the last RSV therapeutics review performed in 2015 (20). Abbreviations: PH I: phase I; PH II: phase II; PH III: phase III.
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<th>Live-att</th>
<th>Adjuvant/Adjuvants</th>
<th>Animal Model</th>
<th>Pre-F</th>
<th>Person Responsible</th>
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Response to comments

Dear editor,

We would like to thank you for the extensive comments, which have given us the chance to clarify and improve the manuscript. The manuscript has been revised addressing each of the recommended changes made by reviewers point-by-point. We hope the length of the manuscript is acceptable as we cover a broad range of issues related to RSV vaccine development. Actually, the reviewers encouraged us to expand on a few topics. Should you decide it needs shortening, we would welcome any editorial suggestion.

Kind regards,
Natalie Mazur, also on behalf of Louis Bont

Editor's comments:

Comment 1 [General]: Please be aware that the limit for the word count is 4500 words. 
Response: The current word count is 7,109 words. If the word count is absolute, we can consider moving part of the manuscript to supplemental materials. Please advise whether this is necessary.

Comment 2 [General]: Please be aware that the limit for the number of references is 150. 
Response: We are aware of this limit and the manuscript currently contains 150 references.

Comment 3 [General]: Please include, at the end of the main text, a "Contributors" section detailing the role of each author in the preparation of your paper. 
Response: We moved the “authors contributions” to the end of the main text and renamed it “contributors.”

Comment 4 [General]: Please include, at the end of the main text, a "Conflicts of interest" statement summarising key conflicts from the ICMJE forms. The standard wording, if there are no conflicts, is "We declare that we have no conflicts of interest." 
Response: We have summarized all relevant conflicts of interest in the manuscript using the conflict of interest forms sent in by all authors. 
Revised text: LJB and NIM were involved in the design and plan for this review. ACL and NH were involved in data collection. All authors contributed to the final manuscript.

Comment 5 [General]: Please consider the possibility of having a study group name. When a paper includes a study group name in the byline, we're now required to supply a separate list of the group members in a specific format if we want these names to be shown on PubMed. (This is in addition to the list of names and affiliations required by the journal to be listed at the end of the paper or in the appendix.)
To ensure that the information we supply to PubMed is accurate and complete, please email me a list of the study group members whose names should appear on PubMed in
Word table format, as follows:
First names (will be abbreviated on Pubmed) Surnames (not abbreviated)
David Villa Sanchez
Jackie Henrietta Davidson
This list will not be included in the paper itself - it's simply used to make sure that PubMed adds the names correctly. Please include the names of all study group members who need to be listed on PubMed. Names that do not need to be shown on PubMed do not need to be included.
Response: We have added “on behalf of ReSViNET” as a study group. Please find the list of names to be shown on PubMed as you suggest.

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José Melero has passed away since the original submission of the manuscript.
Comment 6 [General]: Please also include written consent of any cited individual(s) noted in acknowledgments or cited as personal communications.
Response: We have obtained written consent from all individuals listed in the acknowledgments section and as personal communications.

Comment 7 [General]: Reviews should include a brief section entitled "Search strategy and selection criteria" stating the sources (including databases, MeSH and free text search terms and filters, and reference lists from journals or books) of the material covered, and the criteria used to include or exclude studies. Citations to papers published in non-peer reviewed supplements are discouraged. Since these papers should be comprehensive, we encourage citation of publications in non-English languages.
Response: Search strategy and selection criteria
References for this review were identified through a search of PubMed for clinical trials with “syncytial” in the title published after January 1, 2013 with no language restrictions, through April 3, 2018. We did not intend to do a systematic review of the literature. No inclusion or exclusion criteria were used. Instead, we selected articles that were most relevant to the subheadings used in this review. The PATH RSV vaccine and mAb Snapshot was used as a reference to identify all vaccine and mAb candidates in clinical trials. ClinicalTrials.gov as well as the WHO vaccine pipeline tracker for RSV were used to identify all relevant trials for these vaccine candidates and mAbs. Additional data was collected during the RSV Vaccines for the World Conference on November 29-December 1, 2017 and through pharmaceutical websites for the respective vaccine and mAb candidates.

Comment 8 [General]: Please ensure that you provide your figures in an editable format and as separate files. For trial profiles a word file made of editable text boxes is the preferred format. For any statistical images (histograms, survival or time-to-even curves, line graphs, scatter graphs, forest plots, etc) you should provide editable vector files (ie, the original artwork generated by the statistical package used to make the image). Our preferred formats for these files are .ai, .eps, or .pdf. We cannot guarantee accurate reproduction of images without these files.
Response: We have sent all files in the correct format.

General editorial points that apply to all pieces in the Green section (please check each point):

Comment 9 [General]: Please see the end of this email for a list of signed statements from authors and people named in your paper that we will need before we can consider your paper further. Please scan and upload signed author statements and ICMJE conflict of interest forms for all authors with your revised submission.
Response: We have obtained all signed statements from authors and added them to the submission.
Comment 10 [General]: You will need to provide permission from the relevant publisher to include any material previously published that you wish to include in your paper.
Response: We understand this but have not reproduced any material for which we need permission.

Comment 11 [General]: Please provide: one preferred degree qualification per author and indicate any full professors; affiliation details (department, institute, city, state, country) for each author; full institutional correspondence address for corresponding author.
Response: We have provided a preferred degree for each author as well as affiliation details. We have marked full professors in the manuscript with an asterisk (*).

Comment 12 [General]: Please include, at the end of the main text, a "Contributors" section detailing the role of each author in the preparation of your paper.
Response: Please see comment 3 above

Comment 13 [General]: Please include, at the end of the main text, a "Conflicts of interest" statement summarising key conflicts from the ICMJE forms. The standard wording, if there are no conflicts is "We declare that we have no conflicts of interest."
Response: Please see comment 4 above.

Comment 14 [General]: For Reviews, Personal Views, Historical Reviews, and Grand Rounds please supply a 150-200 word unstructured summary of your manuscript. References should not be cited in the summary.
Response: We have added some information to the abstract (as summary) so it is now 160 words.
Revised text: The global burden of disease caused by respiratory syncytial virus (RSV) is increasingly recognized, not only in infants, but also in older adults. Advances in knowledge of the structural biology of the RSV surface fusion (F) glycoprotein have revolutionized RSV vaccine development by providing a new target for preventive interventions. The RSV vaccine landscape has rapidly expanded to include 19 vaccine candidates, including four approaches: (1) particle-based, (2) live-attenuated/chimeric, (3) subunit, (4) vector-based, as well as monoclonal antibodies (mAbs) in clinical trials, reflecting the urgency of reducing this global health problem and hence the prioritization of RSV vaccine development. Late phase RSV vaccine trial failures highlight gaps in knowledge regarding immunologic protection and provide lessons for future development. In this review we highlight promising new approaches to RSV vaccine design and provide a comprehensive overview of RSV vaccine candidates and mAbs currently in clinical development to prevent one of the most common and severe infectious diseases in young children and older adults worldwide.
Comment 15 [General]: Images that have been published previously should be accompanied by a statement indicating permission to reproduce the image. If required, further assistance can be obtained from the editorial team. If you have borrowed published images from colleagues, you must obtain permission from the publisher of the paper, not just from the authors. If all the figures are your own and have not been published before then this requirement does not apply. 
Response: We do not have any relevant images or figures.

Comment 16 [General]: Figure titles should be a maximum of 30 words. 
Response: We have kept our figure titles <30 words.

Comment 17 [General]: References should be in the Vancouver style and numbered in the order in which they first appear in the manuscript. References in figures, panels, and tables should be numbered in sequence with the references in the text where that figure, panel, or table is cited. Please ensure tables and figures are cited correctly in the body text to prevent the need for renumbering of references should the table and figure citations subsequently move. 
Response: We have kept references in Vancouver style and adhered to other guidelines regarding references as mentioned above.

Comment 18 [General]: For papers listed in references that are "in press" we need to see a galley proof and letter from the publisher stating that it is 'in press' as well as the full expected citation (ie, publication date/volume/issue etc). 
Response: We have included no references in press.

Comment 19 [General]: Please ensure that references are not inserted as Footnotes. 
Response: We have no references as footnotes.

Comment 20 [General]: For Reviews, Historical Reviews, and Grand Rounds, please supply a section entitled "Search strategy and selection criteria". This should state clearly the sources (databases, journals, or book reference lists, etc) of the material covered and the criteria used to include or exclude studies. Please state which search terms, languages and date ranges were used. 
Response: Please see comment 7 above.

Comment 21 [General]: Please include the signatures of any people whose names were on a previous version of this manuscript as an author but have now been deleted, or reclassified as an acknowledgment. Ex-authors should declare that they have agreed to have their names deleted or reclassified. 
Response: There has been no change of authors since the last version of the manuscript. One author (Dr. José Melero) has passed away since the previous submission. Is it possible to add a posthumous note in the manuscript?

Comment 22 [General]: If you have added to or changed the order of existing authors, we require signed statements from ALL authors that they are happy with these changes. 
Response: There is no change to author order since the previous manuscript.
Comment 23 [General]: Guidelines on electronic submission of text and figures are available at: http://ees.elsevier.com/thelancetid/. Please read these carefully; to ensure efficient preparation for publication, the text and figures should conform to these guidelines.
Response: We have adhered to your guidelines.

Comment 24 [General]: All authors are required to provide a Conflict of Interest Statement and should complete a standard form, which is available at http://download.thelancet.com/flatcontentassets/authors/icmje-coi-form.pdf. This form can be uploaded with the manuscript at submission. The form has been modified by the ICMJE following consultation with authors and editors. Further information is available in a joint ICMJE statement published on July 1, 2010. For more information see Lancet 2009; 374: 1395-96.
In summary, the signed statements we require are:
* Signed conflict of interest statements for ALL authors
Response: We have made sure that all authors have submitted conflict of interest forms.

Comment 25 [General]: All authors should complete and sign the author statement form and upload the signed copy. The form can be downloaded from the page (http://www.thelancet.com/lancet-infectious-diseases-information-for-authors/statements-permissions-signatures#conflicts-of-interest) from the fourth line of "Authors and contributions". The corresponding author must countersign manually the forms at the bottom of the page and send us the scanned version; electronic signatures are not accepted.
In summary, the signed statements we require are:
* Authors' contributions - signed by yourself and your co-authors indicating that you have all seen and approved the paper
Response: We have made sure that all authors have author statement forms, which have been countersigned by the corresponding author.

Reviewers' comments:

Reviewer #1:

Comment 1 [General]: The manuscript entitled "The Respiratory Syncytial Virus Vaccine Landscape" is an comprehensive review of vaccine and mABs candidates in clinical trials to prevent hRSV infection. They review from lessons of the failure of the first vaccines, explaining the different vaccines undergoing clinical trials that are reported according to PATH, the antigens use for vaccines against RSV and the target populations. The article describes the preventive strategies under clinical development addressing the problem caused by the RSV infection globally. It intends to provide updated information about the prophylactic and active immunization strategies currently under evaluation to prevent RSV infection. The manuscript includes bibliographic information, communications performed in the last RSV meeting in 2017 and information made public through several websites, such as clinicaltrials.gov. It also discussed strategies that have failed to meet clinical endpoints with the aim of providing information that should be considered for the current strategies under evaluation and future candidates moving to clinical evaluation. The manuscript is well organized and meets
the aim to provide the complete landscape of RSV vaccines and antibodies under clinical evaluation. However, there are several corrections that the authors need to perform before the manuscript be accepted for publication.

Response: Many thanks for thoroughly revising the manuscript. We have done our best to address all concerns mentioned.

Major comments:

Comment 2 [Reference]: Lack of references to support some statements throughout the text (For example, lines 108, 113, 153, 156, 280, 396, 430, 455, 463, 500, 520, 578, 600).

Referring to: 108, Motivazumab, a higher affinity variant of palivizumab, was developed in early 2000 but was withdrawn in 2010
Response: We have added a reference for this statement.
Revised text:

Referring to: 113, Without evidence of superiority for protection from RSV-related hospitalization, evidence of slightly higher side effects, and no plan for dose reduction or cost-saving, the product did not attain regulatory approval.
Response: We have added a reference for this statement.
Revised text:

Referring to: 153, The results of the preceding phase II RSV F nanoparticle trial suggested the candidate vaccine might have modest efficacy.
Response: We have added a reference for this statement.
Revised text:

Referring to: 156, In the phase III trial, 11,586 subjects ≥60 years of age were enrolled in 60 US sites in a double-blind placebo-controlled trial (RESOLVE) over a single season starting November 2015 with 330 days follow-up.
Response: We have added a reference for this statement.
Revised text:

Referring to: 280, A combined strategy that utilizes maternal vaccination to protect young infants followed by pediatric vaccination may be effective to prevent severe RSV infection in young children. 
Response: We have added a reference for this statement.
Revised text:

Referring to: 396, Assays of serum virus neutralization, RSV F-specific antibodies, palivizumab-competing antibodies and F-specific IgA indicated some immunogenicity, but the results did not reach the threshold set for continuation to viral challenge and the studies were suspended in 2017 (Openshaw and Chiu, personal communication). 
Response: Unfortunately there is no published material to support this statement but we feel it is valuable to include. We have received written consent from both authors for this personal communication to publish these results.

Referring to: 430, The anticipated use for this pediatric vaccine is to start immunization at two months of age, and to use two to three doses alongside the normal pediatric vaccination schedule, instead of seasonally. This vaccine candidate is currently being evaluated in 12-23 month old RSV seropositive children.
Response: We have added a reference for this statement.
Revised text:
Dieussaert I. GSK’s Pediatric RSV Vaccine Program. In: Presentation at Food and Drug Administration (FDA) 150th Meeting of the Vaccines and Related Biological Products Advisory Committee Meeting (VRBPAC). Silver Spring; 2017.

Referring to: 455, Preliminary results from the phase I trial, VRC 317, are promising and will soon be published.
Response: As this is also unpublished, we have softened the statement, as we cannot provide published sources to support it. However, we expect these results to be published based on their release at the RSV Vaccines meeting.
Revised text: Preliminary results from the phase I trial, VRC 317, are promising and are expected to be published soon.

Referring to: 463, Phase I results on safety and immunogenicity in the older adult population will soon be published from an investigator-initiated study.
Response: There is no published citation to support this statement. Since the phase I study has been completed and the data presented in a poster at the RSV Vaccines for the World meeting in Malaga, we expect that the data will soon be published. We have changed the phrasing to say that we expect a publication of this data soon. We hope this is acceptable.
Revised text: Phase I results on safety and immunogenicity in the older adult population have been released and are expected to be published from this investigator-initiated study.

Referring to: 500. Importantly, this candidate is the only vaccine candidate intended for administration to newborn infants.
Response: We have added a reference for this statement.

Revised text:

Referring to: 520. Other emerging approaches not yet in clinical development include nucleic acid-based vaccines.
Response: We have added a reference for this statement.

Revised text:

Referring to: 578. Given that the most severe RSV infection occurs in LMICs, information regarding LMIC target countries and potential pricing for vaccine candidates will be essential to facilitate access to vaccines worldwide, especially in areas where the mortality burden is highest.
Response: We have added a reference for this statement.

Revised text:

Referring to: 600. Viral interference, in which RSV inhibits infection by other viruses, is becoming an increasingly important concept to understand in the context of an approved RSV vaccine. RSV vaccination may conceivably result in an increased or decreased prevalence of other respiratory viruses.
Response: This sentence is used to introduce the following sentences, which mention evidence of viral interference after influenza vaccination, after RSV prevention and cross-sectionally in the absence of RSV during the RSV season. We have cited 5 peer-reviewed articles to support that viral interference exists and our interpretation is that this is an important concept in the context of RSV vaccination and could conceivable result in increased prevalence of other viruses.

Comment 3 [Reference]: References should be original articles or review but not oral communications (Lines 455 and 396)

Referring to:
396. The preliminary results of immunogenicity testing have been reported. The immunogenicity of this vaccine was evaluated after delivery as a nasal spray to healthy adult volunteers. Two intranasal doses of SynGEM were administered 28 days apart at low or high dose in 24 subjects per group (6 subjects in each group receiving placebo, double blinded). Assays of serum RSV F-specific antibodies, palivizumab-competing antibodies and F-specific IgA indicated some
immunogenicity, but the results did not reach the threshold set for continuation to viral challenge and the studies were suspended in 2017 (Openshaw and Chiu, personal communication).

455, Preliminary results from the phase I trial, VRC 317, are promising and will soon be published (Graham, personal communication).
Response: Unfortunately there is no published material to support this statement but we feel it is valuable to include. We have received written consent from both authors for this personal communication to publish these results.

Comment 4 [Other approaches]: The section "Other approaches not in clinical development" is too short and is not taking into account all the vaccine and Ab candidates that are reported under preclinical development in the PATH report (Line 520).
Response: The aim of the manuscript is to give a detailed overview of RSV vaccine candidates in clinical development. We have decided to mention other promising approaches to RSV vaccine development, however this is not an exhaustive coverage of all candidates in preclinical development as this is outside of the scope of the manuscript. We have mentioned only approaches that are not mentioned earlier in the rest of the manuscript to give a sense of other new approaches to developing an RSV vaccine: namely nucleic-acid based vaccines and biosimilars. The only approach we have not added that is not mentioned elsewhere is whole-inactivated vaccines but this is not a “new approach” which is why we had not mentioned it. However, we have now added whole-inactivated vaccines to this section so that all vaccine approaches in clinical and pre-clinical development are covered.
Revised text: Finally, another vaccine approach in preclinical development is a whole-inactivated vaccine to be delivered intranasally via a nanoemulsion technology for which development has been supported by the Bill & Melinda Gates Foundation(99).

Comment 5 [Table 1]: Some data are cited on the table 1 but not throughout the text (For example Line 500).
Referring to: Importantly, this candidate is the only vaccine candidate intended for administration to newborn infants.
Response: We have added the citations from the table into the text for the rBCG-N-hRSV vaccine candidate. However, table 1 provides a comprehensive overview of all vaccine candidates while the text highlights key elements. The length of the review does not allow us to mention every element of the table in the text. Please let us know if there are specific elements you feel are underrepresented.
Revised text:

Comment 6 [Table 1]: The status for clinical evaluation is outdated for some of the vaccines described. For example the following trial was omitted NCT03213405 (from www.clinicaltrials.gov) for a vaccine described in these references that should be added: Vaccine. 2017 Feb 1;35(5):757-766. doi: 10.1016/j.vaccine.2016.12.048. Proc Natl Acad Sci U S A. 2008 Dec 30;105(52):20822-7. doi: 10.1073/pnas.0806244105.
Response: The trial you mention was already in the table and the correct phase has been listed for this vaccine candidate (phase I). Both publications mentioned have also already been cited both in the text and in the table (please refer to comment 4 above, we have added these citations to the text as they were already in the table. The phases we list for all trials are up to date according to the PATH vaccine snapshot.

Response: Many thanks for these suggestions. We have added a sentence in immunologic endpoints regarding the opportunities and challenges with controlled human infection as well as the reference you mention: So far no vaccine candidates have been tested with experimental human infection model, but the model provides a unique opportunity to test vaccine candidates in the natural host despite practical and ethical challenges(81).
We have also added the first-in-human trial for MEDI7510:
The vaccine candidate showed safety and immunogenicity with elevated B and T cell responses in the vaccine group compared to the placebo group in phase I clinical trials(43) after safety and improved immunogenicity with an adjuvant was demonstrated in a first-in-human trial(44). The last reference you mention is a review of novel antibodies for the prevention and treatment of RSV. We have used this as a resource to cross-reference our own manuscript but have not cited this reference in the text as no information used primarily came from this manuscript.

Comment 8 [Introduction, Methods, RSV Vaccine History]: Some parts of the manuscript required edition for writing, gramma and spelling. For instance, from pages 5 to 8, most of the sentences are too long and some of them are not clear: line 12 "young infants passive immunization". The sentence is not clear. Should be "young infants through passive immunization"? Lines 34-36, the sentence is too long. Lines 50-54. Again, the sentence is too long, authors should either add colons or break the sentence in two.
Response: Thank you for bringing this to our attention. Line 12 was a typo and has been changed to read “young infants through passive immunization” as you suggest. We agree that the sentence for lines 34-36 was too long and not clear and have shortened and clarified it. We have also condensed the sentence in lines 50-54 and hope you will now find it reads more clearly.
Revised text:
Lines 34-36: Another challenge to RSV vaccine design is the lack of consensus regarding vaccine trial clinical endpoints though attempts have been made to define these for RSV prevention trials (14–16).

Referring to: Second, the discovery of the structure and stabilization of the prefusion (pre-F) conformation of the RSV F protein has advanced the field by showing that pre-F specific antibodies may be more potent in protecting against RSV LRTI than antibodies that also bind the postfusion (post-F) conformation and by thus providing a new target for vaccines and mAbs (21, 22).

Lines 50-54: Second, the discovery and stabilization of the prefusion (pre-F) conformation of the RSV F protein provided a new target for vaccines and mAbs (21, 22) as pre-F specific antibodies may be more potent than postfusion (post-F) antibodies in protecting against RSV LRTI.

Comment 9 [RSV Vaccine History]: Line 107. "Motivazumab" should be replaced for for "Motavizumab".
Response: We have changed this as suggested, thank you for pointing out this typo.

Comment 10 [RSV Vaccine History]: Line 125. For better fluidity and coherence, please add a brief comment about the clinical development of these live attenuated vaccines and a sentence indicating that additional information will be discussed in a following chapter.
Referring to: After reverse genetics techniques became available in the 1990s, it became possible to design vaccines with the appropriate level of attenuation, but with increased immunogenicity (32).
Response: To prevent the manuscript becoming too lengthy we have left the paper as is. Please let us know if additions are required.

Comment 11 [RSV Vaccine History]: Lines 9-8 "The mortality attributable to RSV in adults > 65 year of age is estimated to be 7.2 per 100,000 person year". Authors should clarify whether this is a global estimate or refers to data from the US.
Response: We agree this needs to be clarified and have added that this is an estimate from the US.
Revised text: The mortality attributable to RSV in adults ≥65 years of age is estimated to be 7.2 per 100,000 person years in the United States (3).

Comment 12 [Introduction]: Lines 18-24. The information provided here should be moved to "RSV vaccine history", line 96, to avoid redundancy through the text.
Referring to: ERD occurred in RSV-naïve infants who experienced infection with community-acquired wild-type RSV following receipt of FI-RSV. Decades of research have revealed that in these FI-RSV primed infants, natural RSV infection triggered a strong but non-neutralizing antibody response (5), followed by a T helper 2 (Th2) skewed immunologic response (6). The failure to mount a protective cytotoxic T lymphocyte (CTL) response was coupled with excess lung eosinophilia and neutrophilia, monocytic infiltration, and immune complex deposition in the lungs (7).
Response: We agree and have moved this section to RSV vaccine history as suggested.

Comment 13 [Introduction]: Lines 385-387. These sentences are not clear, it seems that some information is missing.
Referring to: The platform in which an antigen is presented by a bacterial particle has shown both local and systemic antibody responses for the influenza candidate in clinical trials using the same platform (79)
Response: We agree that this sentence was not clearly worded. We hope you will find the revision acceptable.
Revised text: The influenza vaccine candidate in clinical trials which uses the same vaccine platform, has shown both local and systemic antibody responses (85).

Comment 14 [References]: Some of the references are not properly cited and should be amended:
Several the links for the websites cited in the manuscript are not working (Ref 11, 74). These should be amended.

Referring to: 11
Response: The link to this website works, could you please clarify your comment? We have cited everything according to Vancouver citation style as a website.

Referring to: 17
Response: We believe you are referring to citation 74 instead of 17. In this case, the link works as well so we have undertaken no action. The link goes to the website at which one can download the NIBSC Antiserum to RSV WHO 1st international standard instructions for use.

Comment 15 [General]: Authors should include a brief discussion about the advantages and disadvantages of the enhanced disease models currently available as a pre-clinical test required for candidates to advance into clinical trials.
Response: We agree that this would be a valuable addition to the manuscript and have added a brief discussion as suggested to the section on immunologic endpoints.
Revised text: Animal models are important for preclinical development of vaccine candidates and assessing the possibility of enhanced disease. Alveolitis in the cotton rat and priming of a Th2 response in mice are considered markers to assess ERD; there is no consensus on the ability to reproduce ERD in calves (80). So far no vaccine candidates have been tested with experimental human infection model, but the model provides a unique opportunity to test vaccine candidates in the natural host despite practical and ethical challenges (81).

Reviewer #2:

Comment 1 [General]: This review article provides a good overview of the current state of the RSV vaccine field including an comprehensive overview of the vaccine candidates currently undergoing clinical trials. Overall, the review is well written and fairly comprehensive. It could benefit from an expanded discussion regarding what is known about the deficits in immunity following a natural RSV infection as this is critical for trying to develop an efficacious vaccine
as well as more discussion regarding the potential importance of developing vaccine approaches that will elicit both cell mediated immunity in addition to humoral immunity.

**Response:** We thank the reviewer for the comprehensive review of the manuscript. The aim of the manuscript is to focus on vaccine candidates in clinical development with a short overview of vaccine development history, important vaccine failures, target populations and immunologic endpoints. Unfortunately discussing cell-mediated immunity and deficits in immunity in detail is beyond the scope of this manuscript, as this would require a separate review. We hope the reviewer will find this acceptable. We realize this is a limitation of the manuscript and have mentioned this in the section on immunologic endpoints.

**Revised text:** Although we discuss several potential immunological correlates of protection for vaccine trials, we considered cell-mediated immunity beyond the scope of the manuscript.

**Specific comments:**

**Comment 2 [General]:** The discussion of ERD caused by the FI-RSV vaccine should include the study by Knudson et al PLoS Pathogens 2015 11(3):e1004757 as it demonstrates the critical role of CD4 T cells in mediating ERD as well as calling into question the implication that eosinophils contributed to the pathology.

**Response:** We have added this reference in the section on ERD as suggested.

**Revised text:** Other aspects of the immune response implicated in ERD include distinct subsets of CD4 cells(24) and memory CD8 T cells(25).

**Comment 3 [General]:** The section on the failure to license Motivazumab on page 7 does not really add to the review and could easily be cut to allow for additional focus on other areas.

**Response:** Thank you for this comment. Although we understand your objection, we believe the failure of motavizumab to gain FDA approval after 3 phase III trials is an important part of RSV vaccine history given the large investment, demonstrated efficacy and late-stage failure and have therefore decided to leave this part in.

**Comment 4 [Immunologic endpoints]:** The immunologic endpoints section should include an enhanced discussion of the potential importance of the induction of cell mediated immunity in combination with humoral immunity and how one may measure cell mediated immunity endpoints.

**Response:** Please refer to response to comment 1 above.

**Comment 5 [General]:** The authors should consider recent papers examining the role of T cell responses to RSV including Schmidt et al PLoS Pathogens 2018 14(1):e1006810, Scheible et al JCI Insight 2018 3(4) pit: 96724 [Epub ahead of print], and Mariani et al J Infect Dis 2017 216(8): 1027-1037.

**Referring to:** Schmidt et al PLoS Pathogens 2018 14(1):e1006810

**Response:** Thank you for this excellent suggestion, we have included this reference in the section on immunologic mechanisms of ERD.

**Revised text:** Other aspects of the immune response implicated in ERD include distinct subsets of CD4 cells(24) and memory CD8 T cells(25).
Referring to: Scheible et al JCI Insight 2018 3(4) pit: 96724 [Epub ahead of print]
Response: Although this reference is an important contribution to the body of knowledge regarding T cell development and abnormal health outcomes for infants, we feel that it does not fit the scope of the manuscript and have decided not to include it.

Referring to: Mariani et al J Infect Dis 2017 216(8): 1027-1037.
Response: Please see response above.

Reviewer #3:

General Comments to Authors:

Comment 1 [General]: This manuscript represents a review of an extremely important topic for the health of the world's pediatric and adult populations. The topic of advances in the prevention of respiratory syncytial virus is timely as well. Furthermore, the authors represent an august group with international experience and reputation on this particular subject.
Response: We are happy the reviewers agree that the manuscript is timely and written by a wide range of experts on the subject.

Comment 2 [General]: The manuscript could be improved in two important areas: first, the manuscript needs to have more attention devoted to RSV in adults, especially because this is the likely first population group for which vaccines will be developed.
Response: Thank you for this suggestion. Following the comments below we tried to devote more attention to RSV in adults as the reviewer suggests.

Comment 3 [General]: Second, the manuscript has a potentially very valuable section devoted to recent lessons learned from recent clinical trial failures. This section needs to be updated and expanded using all available publicly accessible evidence.
Response: Although, we understand the reviewers comments, we have tried to be complete. We welcome any missing information as we have indeed attempted to use all available information.

Comment 4 [General]: Third, the manuscript needs more attention devoted to an integrated discussion of monoclonal antibodies. More detailed line-specific comments are provided below.
Response: We have followed the reviewer’s suggestions below to devote more attention to the discussion of monoclonal antibodies.

Detailed Comments to Authors:

Comment 5 [Introduction]: Lines 14-15 This paragraph starts out lumping RSV vaccines and monoclonal antibodies together in the title sentence (which is a good idea). However, the discussion which follows is solely focused on vaccines and the problems encountered in their development. It is important to include a statement that monoclonal antibodies have avoided these issues.
Referring to: Development of effective RSV vaccines and monoclonal antibodies (mAbs) presents both opportunities and challenges.
Response: We agree that the introduction does not give a balanced introduction of both vaccine candidates and monoclonal antibodies and have revised the introduction to now include both.

Revised text:
We have added the following two sentences:
Despite these obstacles, there are several opportunities for RSV vaccine and monoclonal antibody development.
Monoclonal antibodies circumvent the problem of transient immunity to RSV and an immature immune response to vaccination in young infants at risk of severe disease.

Comment 6 [Introduction]: Lines 20-24 I believe that the authors may be inadvertently mischaracterizing the data from all of these referenced papers. The authors must make a clear delineation as to what they are talking about. Are they talking about the vaccine failing to do these things, or are they talking about the natural RSV infection after the vaccine failing to do these things.? The way it is written, the authors are talking about the natural infection (following the vaccine) which failed to do these things. This is a very important part of this review, and it needs to be explained correctly and well.

Referring to: Decades of research have revealed that in these FI-RSV primed infants, natural RSV infection triggered a strong but non-neutralizing antibody response(5), followed by a T helper 2 (Th2) skewed immunologic response(6). The failure to mount a protective cytotoxic T lymphocyte (CTL) response was coupled with excess lung eosinophilia and neutrophilia, monocytic infiltration, and immune complex deposition in the lungs(7).

Response: The intention of this statement is to talk about the response to natural RSV infection following priming with a FI-RSV However, we agree that it is unclear as written that the priming with FI-RSV results in low avidity antibodies and skews the immune system towards a Th2 response upon natural RSV infection. The 2010 Nature Medicine paper by Polack et al describes FI-RSV induction of low affinity antibodies which led to severe disease upon exposure to RSV. The 2006 Nature Medicine paper by Moghaddam et al boosts Th2 responses in mice. We hope the reviewer feels that the revision is clearer.

Revised text: ERD occurred in RSV-naïve infants who experienced infection with community-acquired wild-type RSV following receipt of FI-RSV. Decades of research have revealed that priming with FI-RSV triggered a strong but non-neutralizing antibody response(22), followed by a T helper 2 (Th2) skewed immunologic response(23) which may lead to ERD upon natural RSV infection.

Comment 7 [Introduction]: Lines 30-33 The failure of these referenced trials includes inadequacies in the study design, Logistics, and implementation. It is not necessarily the fault of gap in knowledge but rather the fault in implementation that drove the studies to fail. This statement needs to be softened so as to make it clear that in certain regards a Failure may just be logistic. This reviewer has personally evaluated the data sets for two of these three reference trials, and this evaluation is the basis for this reviewer's comment. Additionally, putting all of the blame on gaps in knowledge tends to inappropriately paralyze the vaccine and monoclonal antibody development pathways, which need to be open and active.

Referring to: Recently, three phase IIb/III trials (two vaccine trials in older adults(11,12) and one mAb trial in infants(13)) failed to meet clinical endpoints. The failure of these vaccine and mAb candidates demonstrates the continued gaps in knowledge regarding immunologic mechanisms of protection in the different target populations.
Response: We have rephrased this sentence to soften it and also acknowledge the importance of inadequacies of trial design.

Revised text: In addition to possible inadequacies in trial design and implementation, the failure of these vaccine and mAb candidates demonstrates the continued gaps in knowledge regarding immunologic mechanisms of protection in the different target populations.

Comment 8 [Introduction]: Lines 34-36 It is not clear what is meant buy endpoints of vaccine treatment trials. I think that the authors should limit the discussion to RSV prevention strategies, rather than therapeutic vaccines which are highly controversial.

Referred to: Another challenge to RSV vaccine design is the lack of consensus regarding clinical endpoints of vaccine trials though attempts have been made to define these for both prevention(14–16) and treatment trials(17).

Response: We agree with the reviewer and have revised the text so that only prevention is mentioned and not treatment trials.

Revised text: Another challenge to RSV vaccine design is the lack of consensus regarding vaccine trial clinical endpoints though attempts have been made to define these for RSV prevention trials(11–13).

Comment 9 [Introduction]: Lines 43-45 This is an ideal place to start talking about the advantages of passive antibody prophylaxis with monoclonal antibodies. In general, the discussion has been far too RSV vaccine focused and has neglected monoclonal antibodies in the discussion. The authors need to add a brief section here on the advantages of monoclonal antibodies which overcome this problem of in infants.

Referred to: An ideal RSV vaccine candidate should prevent severe disease in at risk populations.

Response: We agree that this is a good place to add a section on the advantages of monoclonal antibodies and have added this as per suggestion.

Revised text: Monoclonal antibodies circumvent the problem transient immunity to RSV and an immature immune response to vaccination in young infants at risk of severe disease.

Comment 10 [Introduction]: Lines 45 The authors need a reference to this statement. The prospect of herd immunity to RSV provided by a putative RSV vaccine has been modeled. I believe the paper is found in Proceedings of the National Academy of Sciences, Senior author: Galvani.

Referred to: Certain vaccines might also lessen person-to-person transmission and thereby provide secondary benefits in those who cannot benefit directly from vaccination.

Response: Thank you for this excellent suggestion, we have added the reference you suggest.


Comment 11 [Introduction]: Lines 64 This introduction continues to be too focused on vaccine to the exclusion of a discussion of monoclonal antibodies. Also, the authors focused too much on pediatrics to the relative amount of the discussion devoted to adult issues.
In the context of RSV as an increasingly recognized global health problem, these rapid changes and expansion show the prioritization of RSV vaccine development.

Response: We agree and have rephrased vaccine to vaccine and mAb for the “opportunities” paragraph at the end of the introduction. Although we only wrote vaccine, these opportunities are equally relevant for mAbs in clinical development. For the rest, we do not believe the introduction to be more focused on pediatric populations than adults as the focus of the introduction is to lay out the challenges and opportunities to RSV vaccine and mAb development. Please let us know if you find this acceptable as now written.

Revised text: In the context of RSV as an increasingly recognized global health problem, these rapid changes and expansion show the prioritization of RSV vaccine and mAb development.

Comment 12 [RSV Vaccine history]: Lines 104 The authors need to include the polyclonal RSV immune globulin manufactured by ADMA Biologics (RI-002) (ADMA Biologics, Ramsey, NJ, USA). This is-FDA approved as an immune globulin, and has been manufactured to mimic Respigam, but it did not receive the "FDA indication" of RSV preventing because the trials were not performed for that purpose (due to immense const). However, it is approved for use as a replacement for Primary Immune Deficiencies.

Referring to: Since its initial approval in 1998, palivizumab remains the only licensed preventive intervention against RSV(27).

Response: Although we understand that RI-002 is an approved polyclonal antibody with high RSV-neutralizing antibodies, we believe that RI-002 falls outside the scope of this manuscript as it was not developed as a strategy for RSV prevention specifically (but immunoglobulin supplementation in PIDD patients) and is not included in the PATH vaccine snapshot. The Phase III trial showed efficacy against serious bacterial infections but not against RSV. As a review of novel antibodies (Mejias et al, Vaccine 2017) mentioned “The role of RI-002 in preventing RSV infection in this population has not been reported.” The aim of this manuscript is to focus on prevention strategies in clinical development on the basis of the PATH snapshot. We have therefore decided not to include it in the manuscript. We hope the editor finds this acceptable.

Comment 13 [RSV Vaccine history]: Lines 106 The authors need to mention the efficacy of palivizumab in the various populations evaluated (including mentioning the approximately 80% reduction in RSV-hospitalizations in infants with milder degrees' prematurity and without chronic lung disease.

Referring to: Palivizumab has an excellent safety profile and is indicated for the prevention of severe RSV ALRI in children born prematurely, with congenital heart disease, or with chronic lung disease(28).

Response: We agree that adding some information about the efficacy of palivizumab IMPACT-RSV trial is informative and have mentioned the efficacy from this trial in premature children without BPD.

Revised text: Since its initial approval in 1998, palivizumab remains the only licensed preventive intervention against RSV after demonstrating a reduction of 39% to almost 80% reduction of RSV hospitalization in preterm infants < 35 weeks gestational age with and without chronic lung disease respectively(29).

Comment 14 [RSV Vaccine history]: Lines 111 The authors need to replace the word evidence with the words "sufficient evidence".
Referring to: Without evidence of superiority for protection from RSV-related hospitalization, evidence of slightly higher side effects, and no plan for dose reduction or cost-saving, the product did not attain regulatory approval.
Response: We have made the revision as suggested.
Revised text: Without sufficient evidence of superiority for protection from RSV-related hospitalization, evidence of slightly higher side effects, and no plan for dose reduction or cost-saving, the product did not attain regulatory approval.

Comment 15 [RSV Vaccine history]: Lines 118 I think it is important to mention that the other vaccine strategies were not allowed to be tried in infants (rather than they were tried and found to be unsafe) needs to be expanded. It was the regulators who haven't allowed this. Not necessarily the investigators. If I am mistaken on this point, please help me and the reader understand.
Referring to: With respect to vaccines for active immunization, many approaches targeted for RSV naive children were evaluated pre-clinically over the years. Only live-attenuated vaccine candidates were considered safe for clinical evaluation in these children(31).
Response: We have decided to remove this sentence.

Comment 16 [RSV Vaccine history]: Lines 139 So what is the lesson learned from this? The reasons for failure? Is there a new set of information from the Regeneron website? What about clin trials.gov? What about the half-life of the antibody with respect to the target dosing interval? Was it a failure of efficacy or a failure as safety? All these questions need to be addressed. We need to be able to learn a lesson, rather than have a bunch of questions still hanging.
Referring to: A phase III double-blind, placebo-controlled trial (NURSERY) evaluating REGN2222, a mAb against antigenic s V on the RSV pre-F protein, a major target for high-potency mAbs(37) was conducted.
Response: We agree upon the importance of learning a lesson from these large late-phase vaccine trial failures. Unfortunately, the lack of information available in the public domain (and lack of any peer-reviewed publication) make it very difficult to distil any lessons learned. This is exactly why we emphasize the importance of publishing these results and analyzing them in order to benefit future vaccine trials. Nevertheless, we have revisited clinicaltrials.gov, the Regeneron website, and any other published information to determine if we have missed any information. To address the question on whether it was a failure of efficacy or safety, we mentioned in the manuscript that the NURSERY trial did not meet its primary outcome to prevent medically-attended RSV infections which indicates that it was a failure of efficacy, not safety. The expected half-life of the antibody was not published. Only one or two doses were administered depending on the treatment arm. When two doses were administered, these were administered 8 weeks apart. It may be that this is not sufficient given the average half-life of antibodies to be was described in the poster as 32.0+/−8.79 and 34.4+/−11.9 days following IM administration of 3 mg/kg and 10 mg/kg doses, indicating the half life is longer than that of palivizumab. Unfortunately no new study results have been posted on the Regeneron website nor on clinicaltrials.gov. The only information in the public domain is a poster presentation from ID Week in 2015 on the phase 1 trial results (http://files.shareholder.com/downloads/REGN/0x0x853993/048D5B21-4FAD-4254-8299-6547853FCAC6/REGN2222_IDWeek_2015_poster_HIGH_RES.PDF). We have also written to Regeneron to inquire whether there were further analyses of this late-stage failure performed and whether there is a plan for publication of these results. Unfortunately, given the lack of
information we have only been able to speculate regarding the dosing interval and otherwise give
the lack of information have called upon the company to analyze and publish phase III results.
Revised text: A proposed explanation for the failure of this trial may be inadequate dosing
schedule in regard to the antibody half-life. Ultimately, the basis for failing to meet the primary
clinical endpoint is not known, as analyses of this late-stage failure have not yet been made
public.

Comment 17 [Lesson learned]: Lines 142 The authors need to add that these infants had to have
been rejected from receiving palivizumab. (Full list of inclusion and exclusion criteria can be
obtained at the Clintrials.gov website.
Referring to: REGN2222 was administered once or twice during the respiratory season in 1,149
healthy preterm infants < 6 months of age with a gestational age \( \leq 35 \) weeks and did not meet its
primary endpoint to prevent medically-attended RSV infections through day 150 of life.
Response: We agree that this is important information and have added this to the manuscript.
Revised text: REGN2222 was administered once or twice during the respiratory season in 1,149
healthy preterm infants < 6 months of age with a gestational age \( \leq 35 \) weeks who were not
eligible to receive palivizumab prophylaxis

Comment 18 [Lesson learned]: Lines 149. 2. The discussion of the second candidate is
inadequate. Additionally, the manufacturer/ sponsor (Novavax) (and the product name itself),
needs to be identified, so as to be parallel to the discussion of the first candidate, (Regeneron).
Referring to: The second candidate that failed to meet the predefined study endpoint in phase III
clinical trials was the RSV F nanoparticle vaccine candidate for older adults, a candidate based
on aggregates of full-length post-F.
Response: Throughout the entire manuscript text we have not mentioned the names of
pharmaceutical companies. The section on REGN2222 does not refer to Regeneron specifically
even though the name of the mAb includes “REGN.” The only section of the manuscript where
pharmaceutical names are mentioned is Table 1 under “Company/sponsor.” Furthermore, we
have addressed comments 18-20 and hope that this has led to a more adequate discussion of this
vaccine candidate.

Comment 19 [Lesson learned]: Lines 158 The authors might consider a brief discussion of the
appropriateness or inappropriateness of the controversial assay "palivizumab competing
antibody".
Referring to: Although the vaccine showed promising results in phase II and comparable
immunogenicity measures in the two phases as determined by neutralizing and palivizumab-
competing antibody induction, the vaccine candidate failed to show efficacy against RSV
moderate–severe lower respiratory tract disease (ms-LRTD) in phase III results(12).
Response: We agree that this is important to understand the Novavax phase III failure and have
added a sentence on PCA.
Revised text: For example, PCA titers may not correspond to effective immunity as non-
neutralizing antibodies also bind the palivizumab binding site and can interfere with the binding
of neutralizing antibodies(48).

Comment 20 [Lesson learned]: In this reviewer's recollection, the neutralizing antibodies were
not encouraging, But the PCA antibodies (Whatever that means) we're astoundingly high.
Referring to: Although the vaccine showed promising results in phase II and comparable immunogenicity measures in the two phases as determined by neutralizing and palivizumab-competing antibody induction, the vaccine candidate failed to show efficacy against RSV moderate–severe lower respiratory tract disease (ms-LRTD) in phase III results(12).

Response: We agree that in the public domain there is no clear data on increase of MN in the vaccination group compared to placebo (see for example: http://novavax.com/download/files/presentation/Novavax_RSV_Analyst_Day_7-24-17_PDF2.pdf). Reported immunogenicity measures include anti-F IgG as well as PCA. We have clarified this in the text.

Revised text: Another proposed explanation for failure of this vaccine candidate is that the quantity of the immune response to vaccination may not represent effective immunity. For example, PCA titers may not correspond to effective immunity as non-neutralizing antibodies also bind the palivizumab binding site and can interfere with the binding of neutralizing antibodies(48).

Comment 21 [Lesson learned]: Lines 170-173 This was the company's stated reason. However, it appears that the lack of a sufficient number of endpoints (RSV-MS-LT TD) was not the sole reason for the vaccine failure. Because the vaccine effect size was also shown to be too low. This needs to be brought out. Also, it needs to be pointed out and appropriately referenced that low micro neutralization responses may have been achieved (If this information is attainable in published form).

Response: Unfortunately, as stated earlier the MN titers for phase II and phase III are nowhere to be found in the public domain. Only the phase I results for the older vaccine candidate have been published (PMC5389002) which describes a 1.3-1.7 fold rise in neutralizing antibody titers in response to vaccination (see figure from manuscript included below).
The increase in RSV microneutralization response in vaccines compared to placebo is not available in the public domain for the phase III trial so it is difficult to draw a conclusion, but in the phase I trial there was only a modest (1.3-1.7 fold) increase in neutralizing antibody titers in response to vaccination(49).

Comment 22 [Lesson learned]: Lines 177 What was its primary objective? Phase 2 clinical trials are not usually having a primary objective of vaccine efficacy. Rather they usually have a primary objective of immunogenicity. What was the immunogenicity? The statement that the authors make that "93% of VAX recipients in these had an anti-F antibody seroresponse" is inadequate for the reader to understand what that quantitative level of seroresponse was.

Referring to: Development of the MEDI-7510 vaccine candidate, a subunit vaccine candidate for older adults, was discontinued after a phase IIb trial in North America, Europe, South Africa, and Chile in 1900 adults ≥60 years after the study failed to meet its primary objective.

Response: The primary outcome specified on clinicaltrials.gov (NCT02508194) was the percentage of participant who had a first episode of acute RSV-associated respiratory illness (ARA-RI) during the RSV season in season 1 for day 14 through the end of the surveillance period (approximately 7 months). Immunogenicity measures (GM fold change in Anti-F IgG, RSV microneutralization post dose geometric mean fold change, PCA post-dose GMC) were only included as secondary outcomes. We have clarified that this was the specified primary outcome of the phase IIb trial. Furthermore, we agree that the immunogenicity measures were not reported in enough detail and have now added this to the manuscript.

Revised text:
Development of the MEDI-7510 vaccine candidate, a subunit vaccine candidate for older adults, was discontinued after a phase IIb trial in North America, Europe, South Africa, and Chile in 1900 adults ≥60 years after the study failed to meet its primary objective, efficacy against RSV-associated respiratory illness between 14 days post-vaccination throughout the end of the surveillance period, approximately 7 months.

No efficacy was found in secondary subset analyses. On day 29, 93% of vaccinees had an anti-F IgG antibody seroresponse and there was a geometric mean fold rise in anti-F IgG titer of 4.6 at the end of the RSV season in vaccine recipients compared to the placebo group(50).

Comment 23 [Lesson learned]: Lines 187 The authors need to add information regarding the neutralizing antibody concentrations that were induced by the vaccine. This allows the reader to understand things about epitope specificity.

Referring to: One proposed explanation for the negative results may be that the choice of a post-F antigen induced antibodies without appropriate epitope specificity(40).

Response: We agree that this would be helpful to interpret whether epitope specificity played an important role in phase IIb failure. However, unfortunately the only data published show MN response at baseline and on day 29 after dosing in subjects who met the primary end point or were selected to match them (in a 1:6 ratio) or to match the sample size of a group that received the same formulation in the Phase Ib study. Thus, the MN data is not available for vaccine v placebo groups.

Comment 24 [Lesson learned]: Lines 191 Where are the authors going to mention the exciting preliminary results just announced for the maternal vaccination trial using nova VAX vaccine?
It may be appropriate to mention this here using proper soft and reserved language (beware of company-spin).

**Referring to:** Considerations for the future include selection of an older study population at higher risk of RSV infection.

**Response:** In accordance with the PATH vaccine snapshot we have considered the Novavax vaccine candidate for maternal immunization and older adults as separate candidates. Therefore we have decided to mention the results for the maternal vaccine in the section on particle-based vaccines and not together with this vaccine failure. The main aim of the section on the vaccine graveyard is to distil lessons learned from large late-phase RSV vaccine trial failures.

**Comment 25 [Vaccine antigens]:** Lines 201-203 Shouldn't the authors simply state that the energy of activation allowing pre-EF to change into post F is quite small, thus allowing "Spontaneous" conversion from pre-F to post F.

**Referring to:** There is no consensus on the trigger for the pre-F to post-F conformational change making it difficult to ensure a wild-type F vaccine antigen maintains a pre-F conformation, but stabilizing mutations have been identified that can preserve the pre-F-specific epitopes(41,43).

**Response:** We are not aware that the energy of activation is "quite small." We are left the statement as is which states that there is not yet consensus on a trigger for RSV F protein. A proposed mechanism that has been published is a reduction in buffer molarity (Chaiwatponsakorn, J Virol 2011). Other cellular receptors implicated in this triggering include TLR4 (Haynes et al, 2001), nucelolin (Tayyari et al, 2011), and ICAM-1 (Behera et al, 2001). Thus, ultimately there is no consensus as published in a review on the “Structure and function of RSV surface glycoproteins” (McLellan et al, Curr Top Microbiol Immunol, 2014). However we have consulted coauthors and rephrased the sentence to reflect this uncertainty.

**Revised text:** It remains unclear as to whether there is a trigger for the pre-F to post-F conformational change, but it does occurs spontaneously, making it difficult to ensure a wild-type F vaccine antigen maintains a pre-F conformation. However, stabilizing mutations have been identified that can preserve the pre-F-specific epitopes(53,55).

**Comment 26 [Vaccine antigens]:** Lines 205 Is it certain that these stabilizing mutations do not affect the conformation of the antibody binding sites? Is this still an open question? This reviewer does not know the answer to this but some of the authors probably do, and it would be appropriate to insert a simple sentence here describing the answer.

**Referring to:** There is no consensus on the trigger for the pre-F to post-F conformational change making it difficult to ensure a wild-type F vaccine antigen maintains a pre-F conformation, but stabilizing mutations have been identified that can preserve the pre-F-specific epitopes(41,43).

**Response:** We have consulted co-authors and added a sentence as the reviewer suggests.

**Revised text:** The antigenicity of some stabilized pre-F constructs has not been rigorously investigated, and it remains an open question as to whether certain stabilizing mutations affect the conformation of antibody binding sites

**Comment 27 [Vaccine antigens]:** Lines 231-233 This reviewer was expecting a brief discussion of the relevance of ADCC to RSV prevention, as well as the evidence or lack of evidence that T cell responses are important.
Referring to: The SH protein may be important for induction of antibody dependent cell-mediated cytotoxicity (ADCC), whereas non-membrane proteins are especially important to induce a robust T cell response(46)

Response: A more detailed discussion of ADCC and T cell immunity are unfortunately beyond the scope of this manuscript. This section focuses on vaccine antigens that are used in candidates in clinical developments. We only briefly highlight there relevance for different immune responses but do not provide an in depth discussion of the evidence and lack of evidence of importance of these immune responses in this section. In the section on immunologic endpoints we do briefly discuss the importance of T cell immunity as a marker for protection from clinical disease. We hope the reviewer understands these limitations.

Comment 28 [Target populations]: Lines 253 The authors need to mention at least one of the major limitations of maternal vaccination strategy to protect newborn infants: namely, that the elimination half-life of transplacental antibodies is naturally short, thus limiting the duration of protection even if passive antibody is transmitted to the infant in sufficient quantities.

Referring to: Passive transfer of antibodies to infants has been shown to be protective against severe RSV infection through the administration of high-titer polyclonal and monoclonal antibodies (RSV-IVIG and palivizumab) (26,27).

Response: We agree that we did not sufficiently highlight the limitations and have added this limitation.

Revised text: The duration of protection of maternal vaccination is defined by the antibody half-life.

Comment 29 [Target populations]: Lines 263 The authors need to define for the readers what the Word preterm means.

Referring to: Globally 10% of children are born preterm(62).

Response: We agree with this suggestion to clarify definition of preterm for the data from the systematic review we are referring to. However, in this systematic review, although there was a general consensus across the studies on a definition of less than 37 complete weeks of gestational age (75/92), some studies did not report a definition (14/92) and some had a different definition (3/92). Therefore, it would not be accurate to list a definition as different definitions were included in this systematic review.

Revised text: No change

Comment 30 [Target populations]: This review would be improved if specifics were given with respect to relative amounts of antibody transferred at different gestational age is. References do exist for this data. If preterm means less then 37 weeks, what percent of naturally transferred term antibody is present in these infants?

Response: We understand that this additional level of detail is interesting, however we also feel that it is beyond the scope of this review. We mention that the majority of IgG transfer occurs before 32 weeks gestational age to give an indication of the effect of preterm birth on the efficacy of maternal vaccination. Further detail goes beyond the scope of this manuscript. We hope the reviewer finds this acceptable.

Comment 31 [Target populations]: Lines 266 This reviewer believes that the reason that the premature infants do not receive passive antibody from mother is not because they are born
prematurely and therefore their umbilical cords are severed (thus cutting off flow). Rather it is because the maturation of the placenta does not occur to allow transfer of antibodies prior to being near-term. The wording here implies the different mechanism. And the concept is important with respect to the statements regarding improved efficacy of transfer if maternal vaccination occurs early or late within gestation. Lines 268-271 See my previous comment.

Referring to: Thus, a maternal vaccination strategy may not be sufficient to protect the high-risk preterm population if administered during the third trimester of pregnancy. Tetanus diphtheria acellular pertussis (Tdap) immunization in the second trimester is associated with higher antibody titers by time of birth as compared to third trimester immunization(64). A strategy of earlier vaccination could be considered for maternal RSV immunization to maximize protection to preterm infants.

Response: There is limited data on gestational age-related antibody transfer, the most relevant information is from Malek (Am J Reprod Immunol, 1996). To our knowledge, it has been shown that prolonged maternofetal transfer cumulatively results in higher transferred IgG than exposure at maximum transfer efficiency which occurs at 32-33 weeks gestation age (Eberhardt, CID 2016). We are not familiar with the statement above, that transfer of antibodies is “not allowed prior to being near-term. IgG transfer, although limited, is known to begin as early as 13 weeks gestational age, with transfer increasing in a linear fashion as pregnancy progresses (Palmeira et al, Clin Dev Immunol 2012). Regardless, the statement as now written does not indicate which mechanism underlies higher antibody titers associated with second trimester vaccination in comparison with third trimester vaccination. We have therefore decided to keep this section as is and hope the reviewer agrees. If this is not acceptable please let us know how this should be changed.

Comment 32 [Target populations]: Lines 278-286 This entire paragraph would greatly benefit from the addition of a perspective of monoclonal antibody administration to infants' afterbirth, Referring to: A combined strategy that utilizes maternal vaccination to protect young infants followed by pediatric vaccination may be effective to prevent severe RSV infection in young children. This strategy is estimated to avert at least twice as many admissions per 100 births and four times as many in-hospital deaths per 1000 births than maternal vaccination alone(66). A combined strategy will be particularly relevant to prevent morbidity and mortality in children with comorbidities who are at risk of severe RSV disease at older ages (67,68). A similar maternal and pediatric combined passive and active immunization strategy is currently employed for pertussis and influenza vaccination(65).

Response: We agree with the reviewer. We are trying to highlight a combination strategy in which young infants are protected via passive immunization (through maternal immunization or administration of mAbs) followed by pediatric active immunization. We have clarified this so that mAb administration after birth is equally well represented.

Revised text: A combined strategy that utilizes passive immunization to protect young infants, via maternal vaccination or mAbs, followed by pediatric active immunization may be effective to prevent severe RSV infection in young children(78).

Comment 33 [Target populations]: The extended half-life allowable by FC antibody alterations is a major potential improvement and needs appropriate coverage in this review. I have not seen it
discussed in this review yet. Information on these clinical trials which are ongoing, can be found in a few peer-reviewed publications, and clintrials.gov website. 

Response: We discuss FC alterations to extend antibody half-life in the section about MEDI-8897 as this is mAb candidate with the YTE technology. We agree on the importance of this technology and have therefore also added it earlier in the manuscript when we discuss the limitations the duration of protection due to antibody half-life in passive vaccination. 

Revised text: The duration of protection of maternal vaccination is defined by the antibody half-life. Administration of mAbs is an alternative form of passive vaccination that can circumvent this hurdle due to extended antibody half-life through Fc alterations (68).

Comment 34 [Immunologic endpoints]: Lines 317 The authors need to mention the well-defined serologic correlate of protection which has been repeatedly defined in phase 3 clinical trials in infants using both polyclonal and monoclonal antibodies. The actual level of protection in micro neutralization units needs to be mentioned in this review (immune experienced adults). This is a unique and important feature of RSV which can inform future vaccine development greatly.

Referring to: The mechanisms of protection may differ according to the type of vaccine, and therefore, many different immunologic assays are employed in clinical trials. 

Response: To our knowledge there is no well-defined serologic correlate of protection, nor is there an “actual level” of protection in micro neutralization units. All authors on this manuscript have read and approved this section which argues that there is no definitive immunologic correlate of protection and that there is no consensus in the field in this regard. If there is specific evidence on vaccine-specific correlates of protection, we will gladly add this to our manuscript. 

Comment 33 [Immunologic endpoints]: Lines 341 See my comment above. Is it really "elusive"?

Response: Please see response to comment 32 above.

Comment 35 [Immunologic endpoints]: Lines 357 some of them have been shown to be safe, but others have definitely NOT been shown to be safe. The authors need to modify this statement. Accordingly. This reviewer believes they did not show vaccine enhanced disease, but that is a separate issue than safety.

Replication deficient vectors, engineered to induce CD8 T cell responses expressing RSV antigens intracellularly, are considered more similar to 357 live-attenuated virus vaccines which have been shown not to cause ERD in this population. 

Referring to: Replication deficient vectors, engineered to induce CD8 T cell responses expressing RSV antigens intracellularly, are considered more similar to live-attenuated virus vaccines which have been shown to be safe in this population. 

Response: We agree that it has been shown that these are shown not to be associated in ERD. We have rephrased the wording as the reviewer suggests. 

Revised text: Replication deficient vectors, engineered to induce CD8 T cell responses expressing RSV antigens intracellularly, are considered more similar to live-attenuated virus vaccines which have been shown not to cause ERD in this population. 

Comment 36 [Particle-based]: Lines 393-396 Authors need to verify that this information is publicly releasable, or has already been released which necessitates a reference being placed here. 

Referring to: Assays of serum virus neutralization, RSV F-specific antibodies, palivizumab-competing antibodies and F-specific IgA indicated some immunogenicity, but the results did not
reach the threshold set for continuation to viral challenge and the studies were suspended in 2017 (Openshaw and Chiu, personal communication).

**Response:** We have obtained written consent from the two authors mentioned to release this information. It is otherwise not yet available in the public domain.

**Comment 37 [Vector-based]:** 410-413 This statement is confusing. How does a vaccine induction of a humoral response correct the impaired T cell immunity supposedly encountered in the elderly? Do the authors mean "cell mediated response rather than "humoral response"? 
**Referring to:** Given that severe disease in the older adult population is thought to be mediated by immunosenescence characterized by impaired T cell response, this vaccine candidate, which induces a humoral response, may be a promising intervention for the older adult population(81).

**Response:** In this case we do not mean humoral response. We expect a vaccine candidate not to be able to induce an adequate T-cell response but to be able to induce an adequate humoral response. For this reason, we expect this candidate to be able to induce a strong and effective immune response. However, we agree that the wording was confusing because we also wrote that severe RSV disease was mediated by impaired T-cell response. For this reason, we have rephrased this sentence for clarity.

**Revised text:** In the older adult population, immunosenescence may be characterized by impaired T cell responses to RSV(97,98). Thus, this vaccine candidate which induces a humoral response may be a promising intervention in this population.

**Comment 38 [Subunit]:** 461-463 Can this statement be updated with the reference now? What about a presentation at a publicly disclosed meeting?

**Referring to:** Phase I results on safety and immunogenicity in the older adult population will soon be published from an investigator-initiated study.

**Response:** Unfortunately these results are not yet in the public domain so we cannot update this with a reference. However, we have reworded the sentence because we agree that it can otherwise not stand without a reference.

**Revised text:** Phase I results on safety and immunogenicity in the older adult population have been released and are expected to be published from this investigator-initiated study.

**Comment 39 [mAbs]:** 509 The authors should briefly mention the effect of this YTE mutation on the functionality of the antibody with respect to antibody dependent Cellular cytotoxicity and other signaling pathways.

**Referring to:** Using the YTE technology for extending antibody half-life, the three-fold increase in half-life of MEDI8897(91) compared to palivizumab offers the possibility of passive protection for all infants for an entire season through a single intramuscular injection.

**Response:** We have added this statement as the reviewers suggest with an appropriate citation.

**Revised text:** Using the YTE technology which extends antibody half-life as well as modulates ADCC(111), the three-fold increase in half-life of MEDI8897(112) compared to palivizumab offers the possibility of passive protection for all infants for an entire season through a single intramuscular injection.

**Comment 40 [mAbs]:** 516 This section needs to be expanded to review the clinical development progress of this antibody as mentioned by Clintrials.gov

Section on monoclonal antibodies

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27
Referring to: Representatives of the pharmaceutical company have indicated that they expect vaccine-like pricing of MEDI8897. Given the increased potency, the extended half-life, and the required dose, it is expected that the cost to protect an infant during the RSV season can be kept relatively low(92).
Response: As far as we know the section on mAbs is up-to-date with clinicaltrials.gov. Please also see the mAbs in clinical development on the PATH snapshot we we used to define the scope of this manuscript. Please let us know if additional information is needed for the mAb paragraph.

Comment 41 [mAbs]: 517 The authors should also mention the major effect of improved manufacturing techniques of monoclonal antibodies which have been developed over the past decade which allows significantly less expensive production.
Referring to: Passive vaccination with an extended half-life antibody offers an approach to protecting infants that is safe and may be reasonably priced. Representatives of the pharmaceutical company have indicated that they expect vaccine-like pricing of MEDI8897. Given the increased potency, the extended half-life, and the required dose, it is expected that the cost to protect an infant during the RSV season can be kept relatively low(68).
Response: Although we agree with the reviewer, we felt that further analysis cost-related issues was beyond the scope of this review.

Comment 42 [References]: 1.there needs to be a mention of Galvani (sr. author) PNAS paper
Response: Please see response to comment 9 above.

Comment 43 [Table 2]: Overview of vaccines and MAbs by target population:
1.where are the MAbs mentioned?
Response: mAbs is the last category in the table.

Comment 44 [Table 3]: Expected immune response and precious successes for vaccine….1.do you need to mention RGN-2222? (MAb)?
Response: This table only contains mAbs that are in clinical development according to the PATH vaccine snapshot, which is why we have not included REGN-2222.

Comment 45 [Figure 1]: RSV global burden of disease in children: key facts and figures
This figure needs a lot of work and a greatly expanded footnote to add more detail to the various statements made. For example:

Comment 46 [Figure 1]: 1. is the 3.2 million hospitalization number from developed countries? If so, how does this fit with the fact that there are only 33.1 million RSV LRT eyes worldwide? A 10% hospitalization rate for RSP L RTI is quite hi depending on what age range are being evaluated. Likewise, the blue circle needs greater granularity also. I.e., which age range are we talking about?
Response: This concerns the hospitalization worldwide, we have clarified this in the legend.

Comment 47 [Figure 1]: 2. authors should explain the numerator and denominator of the 15.9 divided by 1000 new units per year. They also need to define the other rates mentioned in the green circles.
**Response:** 15.9 is the rate of neonates per year and this is also written inside of the green circle. We have added a clarifying sentence in the legend.

**Revised text:** The hospital admission rate of 15.9 hospital admissions per 1000 neonates per year is in developing countries. The RSV ALRI hospitalization 63.9 among premature infants <1 year is reported per 1000 children per year globally.

**Comment 48 [Figure 1]:** 3. might it be better to have a separate set of circles for infants in the developed world and another set for infants in the developing world? Might it be better to also include adults in this figure? As I understand, the review is not focused solely on children.

**Response:** We have decided to limit this figure to include only children. All rates have been specified inside of the green circles. We have also clarified in the legend which figures are global and which are for the developing world.

**Comment 49 [Figure 2]:** Overview of Vaccine candidates...(heading)

1. This figure seems to be limited to those that are in clinical trials rather than those that are in clinical development. There are a lot more of these in clinical development. I suggest renaming the title to show that you are listing only those Advanced into clinical trials.

**Response:** Figure 2, just as table 1 and table 2, and the entire manuscript focuses on vaccine candidates and mAbs for RSV in clinical trials only, not in preclinical testing. The only thing that has been added to this figure is candidates that are no longer in development since the review we published in the Lancet Respiratory Medicine. Nevertheless, we have changed the heading for this figure so that it is clearer what the scope of the figure entails.

**Revised text:** Figure 2: Overview of vaccine candidates and monoclonal antibodies in clinical trials per preventive approach including candidates for which development was recently halted.

**Comment 50 [Figure 2]:** Monoclonal:

The regeneron molecule needs to be placed here. Also, the polyclonal product respimmune. Also, palivizumab needs to be placed here.

**Response:** We agree that REGN-2222 needs to be added and have done so. However respimmune and palivizumab fall outside the scope of this figure as they are no longer in clinical development and we have therefore not added them.

**Revised text:** Addition of REGN-2222.

**Comment 51 [Figure 2]:** Vector-Based:

The Sendai virus backbone based vaccines need to be mentioned too since other phase ones have been mentioned.

**Response:** The vaccine candidate with a Sendai backbone, we believe you are referring to (PMID: 28250126) is not yet in clinical development and has therefore not been included in this figure.

**Comment 52 [Figure 2]:** I believe there are some G - protein-based subunits vaccines. If so, they should be mentioned. The black label F- protein stands out, but there is no balanced label for SH.

**Response:** Currently there are no G protein-based subunit vaccines in clinical development, which is why we have not included them in this figure. Please refer to the most recent PATH.
vaccine snapshot for an overview of vaccines and mAbs for RSV in clinical development. We hope we have addressed the reviewer’s concerns adequately.

Comment 53 [Figure 2]: I don't understand what the label inside the purple circle means. It looks like this label needs to be removed.
Referring to: Ad26/5; ChAd155, MVA
Response: The label inside the graphic represents vector-based vaccines are the vectors that are used for these vector-based vaccines. The idea was to give an overview of all vectors employed for this preventive approach. However, we agree that this is more confusing than it is helpful and have removed this label as the reviewer suggests.

Comment 54 [Figure 2]: It also looks like the label inside the blue circle needs to be removed (there are other live attenuated chimeric's other than BCG - based.
Referring to: RSV/BCG
Response: At this moment, there are no other chimeric vaccines in clinical development than the BCG vaccine. However, we agree that the figure is clearer with this removed and have done so. Please see response to comment 51 above.

Comment 55 [Figure 2]: Subunit: Colors need to be altered to allow better visualization. This is especially true of the lavender and peach colored approaches.
Response: We have changed the color to a darker color to allow for better visualization as the reviewer suggests.

Comment 56 [Figure 2]: Particle Based: (RSV F nanoparticle)
If this is the novaVAX vaccine, the company needs to be identified within the graphic. (in harmony with the other parts of this graphic.
Response: We understand the reviewer’s suggestion. However, we have not mentioned the company names anywhere in the manuscript besides Table 1 under the column “company/sponsor.” To avoid any commercial biases, we have decided to not use any pharmaceutical names but instead the index name of the vaccine candidate or mAb. Sometimes this includes an abbreviation of the company name but never the entire company name. For consistency, we have not added in “Novavax” in this figure.

Comment 57 [Figure 2]: Particle-Based: (SynGEM)
Since this particle based vaccine has been halted, shouldn't it be in gray?
Response: We understand your comment. Only vaccine candidates or mAbs that were previously halted have been made gray. All vaccine candidates and mAbs considered in clinical development according to the PATH snapshot are still in color. Likewise, the GSK adenovirus 26 preF vaccine has PhII has been halted and it is unclear whether development will continue. For SynGEM, this is the first publication, which will contain information in the public domain that mentions development being halted. For consistency, we have kept all 19 candidates in development according to the PATH snapshot in color in this figure and older candidates in grey. Please let us know if you feel a change is necessary.

Reviewer #4:
General comments:

Comment 1 [General]: This is a well-written review of the RSV vaccine candidates and Mabs currently in clinical development. In view of the considerable global burden of RSV and the urgent need for efficacious vaccines for the populations most severely affected by RSV, this review is very timely. In addition, with so many vaccine candidates in clinical development, and many more in pre-clinical stages, this provides an excellent reference.
Response: We thank the reviewer for recognizing the importance of this manuscript to the field of RSV vaccine development.

Specific Comments

Comment 2 [Lessons learned]: Line 178: What was the TLR4 agonist adjuvant and is this an optimal adjuvant based on pre-clinical studies, or could stronger ones be used that might promote higher levels of immunity?
Referring to: MEDI-7510 was a subunit vaccine using soluble (unaggregated) postfusion (post-F) conformation of the F protein with a TLR4 agonist adjuvant that showed safety and immunogenicity with elevated B and T cell responses in the vaccine group compared to the placebo group in phase I clinical trials(39).
Response: The adjuvant is a glucopyranosyl lipid adjuvant (GLA) which was administered in a squalene-based 2% emulsion (GLA-SE). Phase I clinical testing provided support for inclusion of the adjuvant in the vaccine candidate (Falloon et al, Vaccine 2016 and Falloon et al Clin Vaccine Immunol 2017). In the first-in-man trial the vaccine was tested with the adjuvant and unadjuvanted, no other adjuvants were tested. The adjuvant was found to increase both humoral and cellular immune responses. Thus, given available evidence the best possible adjuvant was selected to continue into phase II clinical trials. We hope this answers the reviewer’s question sufficiently.

Comment 3 [Lessons learned]: On line 179 the authors refer to induction of B and T cell responses in the group vaccinated with MEDI-7510; it is important to provide information about induction of VN antibodies, which are correlated to protection. Were they measured and if so, what were the levels?
Referring to: MEDI-7510 was a subunit vaccine using soluble (unaggregated) postfusion (post-F) conformation of the F protein with a TLR4 agonist adjuvant that showed safety and immunogenicity with elevated B and T cell responses in the vaccine group compared to the placebo group in phase I clinical trials(39).
Response: We agree that virus neutralization titers are most informative regarding the ability of the candidate to induce an effective immune response. VN titers were not reported for the IIb trial for vaccine v placebo groups. We have made this explicit in the manuscript.
Revised text: (50). Microneutralization, PCA and cell-mediated immunogenicity responses were only reported in subset analyses and therefore there is no data on microneutralization activity in the vaccine group versus the placebo group for this trial.

Comment 4 [Lesson learned]: Line 191: An alternative might be to increase the study population.
Referring to: Considerations for the future include selection of an older study population at higher risk of RSV infection
Response: Increasing the study population would have been necessary if this trial failure was due to an underpowered study. However, based on available knowledge from phase II the phase III trial was adequately powered. We mention extending enrolment by an additional RSV season since the pharmaceutical company has attributed the failure to a low attack rate and performing a trial over several seasons would have allowed for a more even distribution of attack rates from season to season, especially for a pivotal phase III trial. We hope this addresses the question.

Comment 5 [Immunologic endpoints]: Line 322: Would a ratio of fold-increase in RSV-binding antibodies to RSV neutralizing antibodies of 1 not be as effective?
Reffering to: A measure of functional antibody response can be elucidated by the ratio of fold-increase in RSV-binding antibodies to fold-increase in RSV-neutralizing antibodies (ELISA-to-neutralization response ratio).
Response: This statement described total antibodies to functional antibodies. The higher the amount of functional antibodies in proportion to total antibodies (when this ratio is <1), the greater the neutralizing activity. However, there is no consensus on this measure nor is there an exact cut off for optimal neutralizing activity. However, the lower the ratio the more effective so the answer is yes, a ratio of 1 would not be as effective.

Comment 6 [Vector-based]: Lines 406-413: This section should be deleted. The VXA-RSV-f is described under "five vector-based vaccines in clinical development" (line 399), but this vaccine candidate is not in clinical trials and thus does not fit within this manuscript - if the authors want to include RSV vaccines in pre-clinical development, there are many other promising candidates that should be discussed. More importantly, the information on results from the pre-clinical studies on VXA-RSV-f is not useful at all, as "enhanced IgA in the upper airways" does not mean anything unless supported by protection data. Furthermore, no reference is provided to support this statement. Reference 81 refers to a 2013 study on RSV viral shedding in adults, totally unrelated to this vaccine candidate.
Reffering to: The second vector-based vaccine candidate, VXA-RSV-f, uses an innovative platform with an adenovirus 5 based oral tablet delivery platform that is stable at room temperature. The results from preclinical studies show that mucosal immunization with the oral vaccine candidate enhanced mucosal IgA in the upper airways. Given that severe disease in the older adult population is thought to be mediated by immunosenescence characterized by impaired T cell response, this vaccine candidate, which induces a humoral response, may be a promising intervention for the older adult population(81).
Response: The Vaxart RSV vaccine candidate has entered phase I clinical trials in June 2016, please refer to the PATH Vaccine snapshot as well as clinicaltrials.gov (NCT02830932). In the manuscript text, we have focused only on candidates in clinical trials including this candidate. Unfortunately, since phase I is recruiting we can only mention data from preclinical testing. The reference to the 2013 paper was included in reference to immunosenescence mediated by impaired T cell function and was not supposed to be related to this vaccine candidate. We agree with the reviewer that references need to be added into this section regarding the vaccine candidate in question and have done so. The enhanced mucosal IgA in the upper airways was presented at the 2017 RSV vaccines for the World conference but is as of yet unpublished in a peer-reviewed journal. Therefore, we have decided to cite the phase I data from the influenza vaccine candidate using the same oral platform and vector. Furthermore, we have included the preclinical data which are mentioned in a press release on the company website.
Revised text: Using the same oral adenovirus vaccine delivery platform, a phase I trial for influenza has been conducted, which showed a neutralizing antibody responses against influenza in the vaccine group and no interference of pre-existing vector immunity. Preclinical studies for the RSV vaccine candidate in the cotton rat model showed an increase in anti-F antibodies and protection against RSV challenge.

Comment 7 [Vector-based]: Line 415: The phrase "The candidate uses pre-F antigen" is unclear; the authors likely mean: "In this vaccine candidate, pre-F antigen is expressed in… etc".
Referring to: The candidate uses pre-F antigen expressed in the human adenovirus strain 26, a vector with a favorable safety profile when used for other infectious diseases.
Response: We have revised this according to reviewer’s comments and agree that this is clearer.
Revised text: In this candidate pre-F antigen is expressed in the human adenovirus strain 26, a vector with a favorable safety profile when used for other infectious diseases.

Comment 8 [Live-attenuated]: Lines 469-474: There is ample evidence that live-attenuated vaccines are often inhibited by maternal/circulating antibodies. What is the evidence that live-attenuated RSV vaccines generate a strong enough immune response in the presence of maternal antibodies (how robust were those responses), and if so, why would such a vaccine then be expected to be inhibited by the presence of RSV-specific circulating antibodies in older adults?
Referring to: Another benefit of live-attenuated vaccines in the pediatric population is their ability to generate an immune response despite the presence of maternally acquired antibodies, and to elicit a more broad antibody and cellular response.
Response: We agree that this is not accurately written as there is evidence of interference due to pre-existing immunity for live-attenuated vaccines. We have rephrased this sentence to clarify that there is empirical evidence for live-attenuated RSV vaccines that they are able to replicate in the upper respiratory tract of young infants despite pre-existing maternally acquired antibodies. This is indeed not true of ALL live-attenuated vaccines in ALL populations. We hope the reviewer will find this modification acceptable. The evidence for this statement comes from two RSV live-attenuated vaccine candidates which have been tested in 1-2 month old infants in which viral peak titers in nasal wash specimens demonstrated equal or higher viral replication when compared to seronegative 6-24 month children (presumed to have no residual maternally-acquired antibodies).
Revised text: Another benefit of live-attenuated vaccines against RSV in young infants is their ability to replicate in the respiratory tract despite the presence of maternally-acquired antibodies, and to elicit a broad humoral and cellular response.

Comment 9 [Live-attenuated]: Lines 480-493: Of the five live-attenuated vaccine candidates in Phase I clinical trials, the results for only one, MEDI <DELTA>M2-2, are provided. What is the developmental stage of the other four and what are they?
Referring to: Five live-attenuated vaccine candidates in phase I clinical trials are being developed in partnership with the National Institutes of Health (NIH). Live-attenuated vaccines face the challenge of achieving sufficient attenuation to be safe while remaining immunogenic enough to induce a protective immune response, but improved understanding of the RSV viral genome has
informed the development of new vaccine candidates that may overcome this challenge. Two main modifications to the RSV genome have been engineered through reverse genetics: the ΔM2-2 deletion which attenuates viral replication and upregulates antigen expression\(^{(32)}\) as well as the ΔNS2 deletion which reduces viral suppression of host interferon thereby boosting the innate immune response. RSV MEDI ΔM2-2 strongly reduced viral replication while inducing a strong primary serum neutralizing antibody as well as potent anamnestic response in RSV-seronegative infants and children\(^{(32)}\). Further results from phase I clinical trials with live-attenuated vaccines are expected.

**Response:** The other four candidates are in Phase I clinical trials. We have not provided the results as they are not yet available in the public domain, this is also why we write “further results from phase I clinical trials with live attenuate vaccines are expected.” We have rephrased this for clarity.

**Revised text:** Further results from phase I clinical trials with the other live-attenuated vaccine candidates are expected.

**Comment 10 [Discussion]:** Line 573: Typo: plans
Referring to: We attempted to collect data regarding expected plan for access to a preventive intervention in LMICs and expected pricing for all vaccine candidates, however this information was not publicly available.

**Response:** We have changed this as suggested by the reviewer.

**Revised text:** We attempted to collect data regarding expected plans for access to a preventive intervention in LMICs and expected pricing for all vaccine candidates, however this information is not publicly available.

**Comment 11 [Table 1]:** Page 32: Typo: ectodomain
Referring to: SHE: small hydrophobic protein ectodomain

**Response:** Thank you for the observant correction. We have fixed the typo.

**Revised text:** SHE: small hydrophobic protein ectodomain

**Comment 12 [Figure 1]:** Page 36, Fig 1: Add ALRI explanation to legend.
Referring to: all ALRI mortality

**Response:** Instead of adding ALRI to the legend we have decided to consistently use LRTI throughout the figure.

**Revised text:** all LRTI mortality

**Comment 13 [General]:** Supplementary Table 1: only the first column is useful, the rest contains no heading or information, so can be deleted. Typo: Adjuvants

**Response:** We agree that the rest of the template contains no useful information. However, we have added the column headings so that it is clear which template was used for data collection as this is key to the systematic collection of data for this manuscript. We have also fixed the typo you mention, many thanks for the observant correction.
28% LRTI due to RSV

33.1 million RSV LRTI worldwide

94,600 – 149,400 deaths children <5 years

4 – 7 months median age at RSV-related death

48 – 50% out of hospital

15.9/1000 neonates/year in developing countries

Highest hospitalization rate <6 months

45% hospitalizations occur <6 months of age

79% of hospitalized children previously healthy

OR: 119.4 of death for infants with sepsis

OR: 65.5 of death for infants with pneumothorax

70% children who died had comorbidity in HICs

3.2 million RSV LRTI requiring hospitalization

Mortality Burden

Mortality

Risk Factors

GLOBAL INCIDENCE RSV LRTI

Figure 1 & 2
PARTICLE-BASED MONOCLONAL ANTIBODIES

VECTOR-BASED

RSV D46/NS2/N/ΔM2-2-HindIII

RSV LID cpΔM2-2

RSV LID ΔNS2Δ1313 I1314L

RSV D46 cpΔM2-2

RSV cps2

MEDI-559

RSV001

ChAd155-RSV

Ad26.RSV.preF

VXA-RSVf

MVA-BN RSV

MEDI-534

DPX-RSV-SH

GSK RSV F

PHASE II HALTED

PHI/II/III

PHI

PHI

PHI/II/HALTED

PH I

PH II

PH II

PH II

PARTICULAR

SUBUNIT

REGN-2222

MEDI8897

PH II

F-protein

PHI

PH I

PH II

PH II

PH I

PHI

HALTED

DEVELOPMENT

HALTED
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