The respiratory syncytial virus vaccine landscape: lessons from the graveyard and promising candidates

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The global burden of disease caused by respiratory syncytial virus (RSV) is increasingly recognised, not only in infants, but also in older adults (aged ≥65 years). Advances in knowledge of the structural biology of the RSV surface fusion glycoprotein have revolutionised 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 prioritisation of RSV vaccine development. The candidates include mAbs and vaccines using four approaches: (1) particle-based, (2) live-attenuated or chimeric, (3) subunit, (4) vector-based. Late-phase RSV vaccine trial failures highlight gaps in knowledge regarding immunological protection and provide lessons for future development. In this Review, we highlight promising new approaches for RSV vaccine design and provide a comprehensive overview of RSV vaccine candidates and mAbs in clinical development to prevent one of the most common and severe infectious diseases in young children and older adults worldwide.

Introduction

Acute lower respiratory infection (ALRI) caused by respiratory syncytial virus (RSV) 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).[1] Although often characterised as a paediatric disease, RSV infection in adults represents a substantial health burden. Mortality attributable to RSV in adults aged 65 years or older is estimated to be 7·2 per 100 000 person-years,[7] and 8% of RSV ARLI among older adults admitted to hospital was reported to result in death[8] in the USA. RSV vaccine candidates aim to protect at least three target populations that are at risk for severe RSV disease: (1) young infants (0–6 months), (2) older infants and young children (2 months or older) through active immunisation, and (3) older adults (65 years or older).

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.[9] Second, an absolute correlate of protection against a clinically relevant RSV infection remains elusive, although cell-mediated immunity,[10] mucosal IgA,[11] and potent neutralising antibodies[12] have been associated with decreased disease severity.

Between 2016, and 2017, three phase 2b or phase 3 trials (two vaccine trials in older adults[13,14] and one mAb trial in infants[15]) did not meet clinical endpoints. In addition to possible inadequacies in trial design and

implementation, the failure of these candidates shows the continued gaps in knowledge regarding immunological mechanisms of protection in the different target populations. Another challenge to RSV vaccine design is the lack of consensus regarding clinical endpoints, which might 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,[16] although the most severe RSV disease is usually observed during the primary infection. mAbs 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 and might also lessen person-to-person transmission.[17]

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 WHO[18] and the Bill & Melinda Gates Foundation, based on better estimates of RSV-associated mortality worldwide.[19] Second, the discovery and stabilisation of the prefusion (pre-F) conformation of the RSV surface fusion (F) glycoprotein provided a new target for vaccines and mAbs[20,21] as pre-F specific antibodies might be more potent than postfusion (post-F) antibodies in protecting against RSV ALRI. Third, pharmaceutical companies have recognised the urgent unmet need of RSV prevention and prioritised the development of RSV vaccines and mAbs.

In 2015, RSV prevention and therapeutic strategies were reviewed, identifying ten vaccines in clinical

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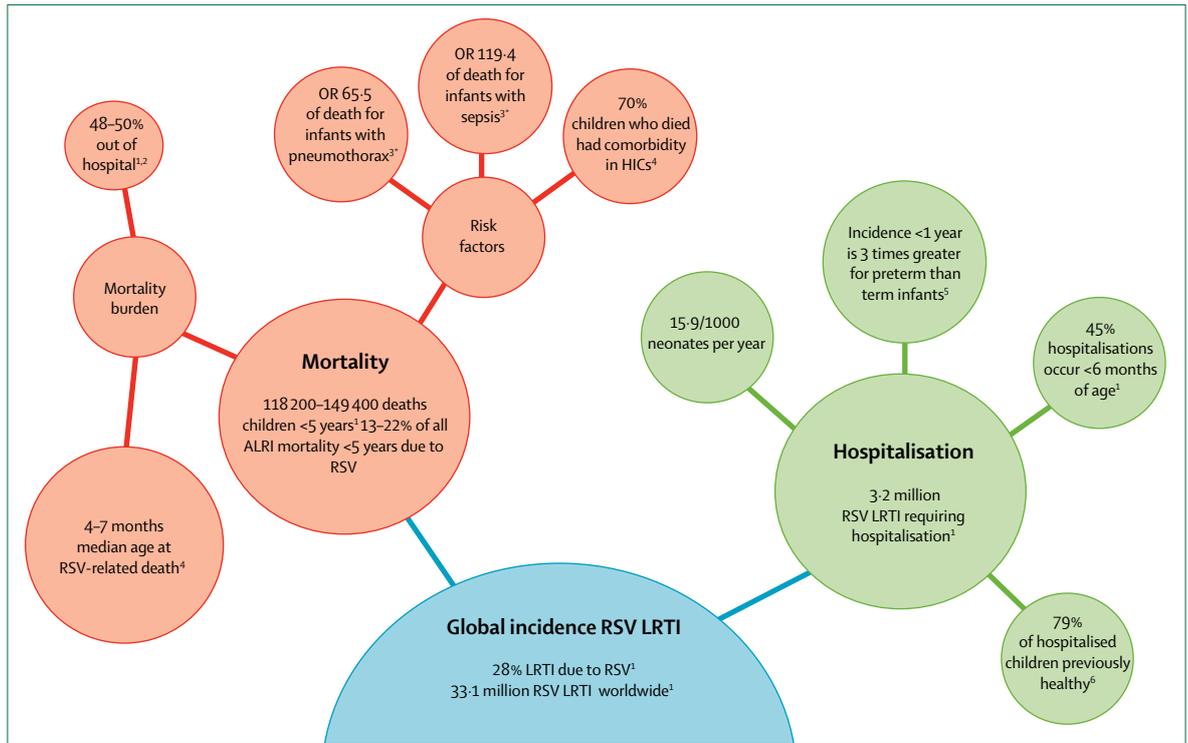
Figure 1: Global burden of RSV in children under 5 years of age[1–6]
Incidence is shown worldwide for children less than 5 years of age unless otherwise stated. The hospital admission rate of 15·9 hospital admissions per 1000 neonates per year is in developing countries. The RSV ALRI hospital admission rate of 15·9 among neonates is reported per 1000 individuals per year in developing countries. OR=odds ratio. LRTI=lower respiratory tract infection. RSV=respiratory syncytial virus. HIC=high-income country. *Compared with children who survived RSV hospitalisation and were mechanically ventilated.
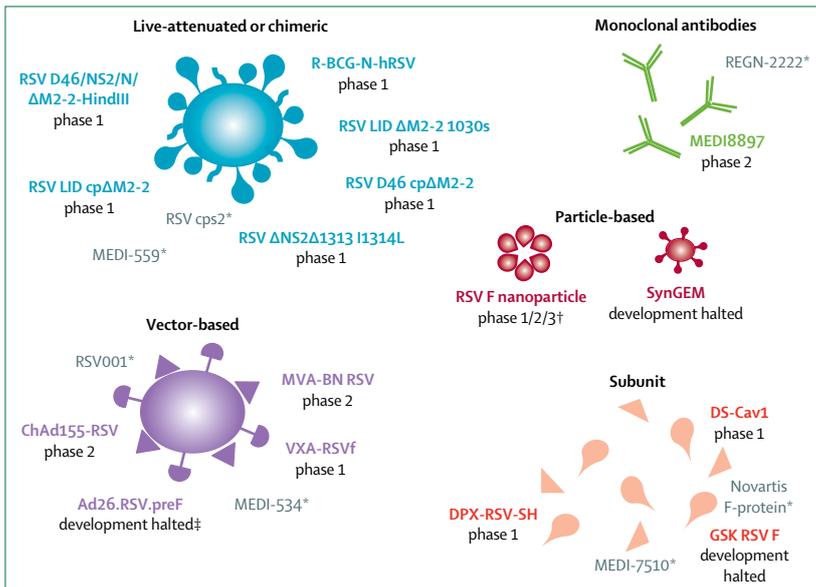

Figure 2: Overview of vaccine candidates and monoclonal antibodies in clinical trials per preventive approach including candidates for which development was halted
RSV=respiratory syncytial virus. *Development has been halted since the last RSV therapeutics review performed in 2015.[22] Candidates for which development is halted but are not indicated with an asterisk are still listed in clinical development according to the PATH snapshot.[23] †Three candidates. ‡Two candidates.

development.[22] An update of the 2015 review is necessary in light of the recent failures and new candidates in the years since 2015. In this Review, we show that only 40% (four of ten) of the vaccine candidates from 2015 are continuing in clinical trials and 14 additional new vaccine candidates have entered clinical trials (figure 2). A single vaccine candidate can be in clinical development both in different populations and in different clinical phases; in these instances, they are considered to be additional candidates. Therefore, the RSV F nanoparticle is considered to be three candidates and Ad26.RSV.preF to be two. Throughout the manuscript we have adhered to the 19 vaccine candidates and mAbs in clinical development according to the PATH Vaccine Snapshot.[23]

RSV vaccine history

RSV vaccine development started shortly after the first identification of the virus in humans in 1957.[24] However, ERD upon natural RSV infection after vaccination with a FI-RSV candidate in a series of trials in the 1960s severely hindered inactivated virus and subunit vaccine develop-ment for many years. Nevertheless, work continued on the development and human testing of live-attenuated RSV vaccine candidates. In the following 60 years, only two products were licensed for prevention of RSV: (1) RSV

intravenous immunoglobulin (RSV-IVIG) and (2) palivizumab. 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.[23] The history of RSV vaccine development is discussed in more detail in the appendix.

Lessons from the vaccine and mAb graveyard

There have been three late-phase vaccine and mAb trial failures between 2016, and 2017 (table 1). It is important to distil lessons learned from these results to inform future vaccine development. First, a phase 3 trial in 1149 healthy preterm infants was done to evaluate REGN2222 (suptavumab), a mAb against antigenic site V on the RSV pre-F protein.[25] The trial did not meet its primary efficacy endpoint to prevent medically attended RSV infections up until day 150 of life.[26] REGN2222 was accelerated from phase 1 to phase 3 because of promising results and the US Food and Drug Administration (FDA) granted fast-track designation in October, 2015. 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.

Second, an RSV F nanoparticle vaccine candidate based on aggregates of full-length post-F did not meet the predefined study endpoint in older adults. The results of the preceding phase 2 trial showed modest efficacy[27] and promising immunogenicity measures, as identified by a rise in geometric mean titre for IgG antibodies against the F protein and palivizumab competing antibodies (PCA).[28] The trial was granted fast-track designation by the FDA in 2016.[29] In the phase 3 trial, 11850 participants were enrolled over a single season. However, the vaccine candidate did not show efficacy against RSV moderate–severe lower respiratory tract disease (ms-LRTD) in phase 3 results.[14] Compared with the previous season, RSV acute respiratory disease (RSV-ARD) and ms-LRTD attack rates were lower than expected in the 2015–16 season (RSV-ARD 2·0% vs 4·9% and RSV-msLRTD 0·4% vs 1·8% during the vaccine and previous season, respectively). The vaccine manufacturer speculates that the difference in vaccine efficacy observed might in part be due to this lower attack rate and high pre-existing immunity in the study population.[27] Another proposed explanation for failure of this vaccine candidate is that the quantity of the immune response to vaccination might not represent effective immunity. PCA titres might not correspond to effective immunity as non-neutralising antibodies can also bind the palivizumab binding site and can interfere with the binding of neutralising antibodies.[30] In a post-hoc subgroup analysis, the vaccine candidate showed efficacy against hospital admissions for all-cause chronic obstructive pulmonary disease (COPD) exacerbations.[27] There was a non-statistically significant trend towards higher RSV microneutralisation titres in adults without RSV-ARD when compared with adults with RSV-ARD.

Company/ sponsor	Vaccine type	Mechanism of action	Clinical trial phase	NCT	Trial design, name	Dates	Study population	Administration/ dosing	Location	Clinical endpoint
REGN2222 (suptavumab)	mAb	mAb against antigenic site V	3	NCT02325791	Double-blind, placebo-controlled trial (NURSERY)	July, 2015–July, 2017	1149 healthy preterm infants <6 months of age with a gestational age ≤35 weeks, not eligible to receive palivizumab prophylaxis	Administered once or twice during the RSV season	250 sites in 19 countries	Medically attended RSV infections through day 150 of life
RSV F nanoparticle for older adults	Particle-based	Aggregates of full-length post-F	3	NCT02608502	Double-blind placebo-controlled trial (RESOLVE, RSV-E-301)	Nov, 2015–Dec, 2016	11850 participants ≥60 years of age	135 μg via IM injection	60 US sites	RSV ms-LRTD for 182 days follow-up
MEDI-7510	Subunit	Soluble (unaggregated) postfusion (post-F) conformation of the F protein with a TLR4 agonist adjuvant	2b	NCT02508194	Double-blind placebo-controlled trial	Sept, 2015–Nov, 2016	1900 adults ≥60 years	Single IM injection	61 study sites in 7 countries (North America, Europe, South Africa, and Chile)	RSV-associated respiratory illness between 14 days post vaccination throughout the end of the surveillance period, approximately 7 months

IM=intramuscular. ms-LRTD= moderate–severe lower respiratory tract disease. RSV=respiratory syncytial virus. mAb=monoclonal antibody.

Table 1: Recent vaccine candidates that failed to meet efficacy endpoints in late-phase clinical trials

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	Target Population	Pre-F Immunity[35]	Immune response	Mucosal/systemic
Particle-based				
RSV F nanoparticle (Novavax)	M	Pre-F<post-F	Broadly neutralising antibodies	Systemic
RSV F nanoparticle (Novavax)	O	Pre-F<post-F	Broadly neutralising antibodies	Systemic
RSV F nanoparticle (Novavax)	P	Pre-F<post-F	Broadly neutralising antibodies	Systemic
SynGEM (Mucosis)	O and P	Unclear F conformation	Activation of B and T cells; local secretion of neutralising IgA in the nose; production of IgG neutralising IgG in the blood	Mucosal and systemic
Vector-based				
MVA-BN RSV (Bavarian Nordic)	O	Pre-F<post-F	B and T cell response; antibodies against 5 RSV antigens	Systemic
ChAd155-RSV (GSK)	O	Pre-F>post-F	B and T cell response; neutralising antibodies against F antigen; CD8 T cells against F, N and M2-1 antigens	Systemic
VXA-RSVf oral (Vaxart)	O	Pre-F<post-F	B and T cell immunity, protection at mucosal surface	Mucosal>systemic
Ad26.RSV.preF (Janssen)	P	Pre-F	B and T cells	Systemic
Ad26.RSV.preF (Janssen)	O	Pre-F	B and T cells	Systemic
Subunit				
GSK RSV F (GSK)	M	Pre-F	B and T cell response	Systemic
DPX-RSV (Dalhousie University, Immunovaccine, and VIB)	O	None	B cell response specific to SHe antigen	Systemic
RSV F DS-Cav1 (NIH/NIAID/VRC)	O and M	Pre-F	Pre-F-specific serum neutralising antibodies, and CD4 T cells	Systemic
Live-attenuated				
rBCG-N-hRSV (Pontificia Universidad Catolica de Chile)	P	Pre-F and post-F	B and T cell response; Th1 polarised response; antibodies against N, F, G	Systemic
RSV D46 cp ΔM2-2 (Sanofi Pasteur/LID/NIAID/NIH)	P	Pre-F and post-F	B and T cell response; enhanced antibody production due to increased antigen production from M2-2 deletion	Mucosal and systemic
RSV LID ΔM2-2 1030s (Sanofi Pasteur/LID/NIAID/NIH)	P	Pre-F and post-F	B and T cell response; enhanced antibody production due to increased antigen production from M2-2 deletion	Mucosal and systemic
RSV ΔNS2 Δ1313/I1314L (Sanofi Pasteur/LID/NIAID/NIH)	P	Pre-F and post-F	B and T cell response	Mucosal and systemic
RSV D46 ΔNS2 N ΔM2-2-HindIII (Sanofi Pasteur/LID/NIAID/NIH)	P	Pre-F and post-F	B and T cell response; enhanced antibody production due to increased antigen production from M2-2 deletion	Mucosal and systemic
RSV LID cp ΔM2-2 (Sanofi Pasteur/LID/NIAID/NIH)	P	Pre-F and post-F	B and T cell response; enhanced antibody production due to increased antigen production from M2-2 deletion	Mucosal and systemic
Monoclonal antibody				
MEDI8897 (MedImmune)	P	NA	NA	NA

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=paediatric. VIB=Flemish Institute of Biotechnology. NIH=National Institutes of Health. NIAID=National Institutes of Allergy and Infectious Diseases. VRC=Vaccine Research Center. LID=Laboratory of Infectious Diseases. RSV=respiratory syncytial virus. NA=not applicable or not available. BLP=bacterium-like-particle. MVA=modified vaccinia Ankara.

Table 2: Expected immune response for vaccine candidates and monoclonal antibodies

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.

Third, development of the MEDI-7510, a subunit vaccine candidate using soluble (unaggregated) post-F conformation of the F protein with a TLR4 agonist adjuvant, was discontinued after a phase 2b trial in 1900 adults aged 60 years or older. Safety and increased B and T cell responses in the vaccine compared with the placebo group were shown in a phase 1 clinical trial[31] after safety and improved immunogenicity with an

adjuvant was demonstrated in a first-in-human trial.[32] The study did not meet its primary efficacy objective; 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 of –7·1.[31] On day 29, 93% of vaccinees had an anti-F IgG antibody seroresponse and there was a 4·6 geometric mean times rise in anti-F IgG titre at the end of the RSV season in vaccine recipients compared with the placebo group.[31] One proposed explanation for the negative results could be that the selected post-F antigen induced antibodies without appropriate epitope specificity.[33] 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 severe RSV infection.

Vaccine antigens

Vaccine antigens included in RSV vaccine candidates are diverse. The majority of vaccines in clinical trials (11 of 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, and stabilisation of the pre-F soluble forms, has resulted in advances in vaccine antigen design.[21,34] Current vaccine candidates use pre-F and post-F as vaccine antigens (table 2). The predominant conformation displayed on the FI-RSV vaccine candidate was the post-F conformation.[36] 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 wildtype F vaccine antigen maintains a pre-F conformation. However, stabilising mutations have been identified that can preserve the pre-F-specific epitopes.[34,37] The antigenicity of some stabilised pre-F constructs has not been rigorously investigated, and remains an open question as to whether particular stabilising mutations affect the conformation of antibody binding sites. Assays to assess antigen conformation are needed. There is no consensus on cellular receptors that determine viral tropism.[38]

Other less frequent vaccine antigens, used alone or in combination with other antigens, include the RSV envelope associated glycoproteins G (one of 18) and small hydrophobic (SH) protein (one of 18), as well as internal proteins: nucleocapsid (N) (three of 18), M (one of 18), and M2-1 (one of 18). Besides the F protein, the G protein is the only other target for neutralising antibodies on the viral surface. The G protein is most important for viral attachment and is less frequently used as a vaccine antigen due to high variability across RSV strains,[39] and little knowledge of its surface structure.[40] 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.[41] There is evidence that the soluble form of the G protein can act as a decoy that helps the virus to evade the antibody response.[42] Another possible vaccine target, the SH protein, is not well understood, but data suggest that it has a role in viral replication in vivo[38] and inflammasome activation.[43] The SH protein contains transmembrane and extracellular domains;[44] the latter has been used as a vaccine antigen.[45] Internal proteins are particularly relevant to induce T cell-mediated immunity.[40] 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.[46] The M2-1 and M2-2 proteins are specific to RSV and other pneumoviridae. M2-1 is essential for viral transcription,[47] and M2-2 deletion is used in live vaccine candidates for viral attenuation. Finally, the M protein is a membrane-associated protein that gives virions their filamentous shape.[48,49] In summary, different viral proteins are being used as antigens in RSV vaccine design. Viral surface glycoproteins such as F and G are known to induce antibodies with differing neutralisation capacity. The SH protein might be important for induction of

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See **Online** for appendix

	Vaccine type
Pregnant mothers	
RSV F nanoparticle (Novavax)	Particle-based
GSK RSV F (GSK)	Subunit
RSV F DS-Cav1 (NIH/NIAID/VRC)	Subunit
Paediatric	
RSV F nanoparticle (Novavax)	Particle-based
ChAd155-RSV (GSK)	Vector-based
SynGEM (Mucosis)	Particle-based
Ad26.RSV.preF (Janssen)	Vector-based
rBCG-N-hRSV (Pontificia Unversidad Catolica de Chile)	Chimeric
RSV D46 cp ΔM2-2 (Sanofi Pasteur/LID/NIAID/NIH)	Live-attenuated
RSV LID ΔM2-2 1030s (Sanofi Pasteur/LID/NIAID/NIH)	Live-attenuated
RSV ΔNS2 Δ1313 I1314L(Sanofi Pasteur/LID/NIAID/NIH)	Live-attenuated
RSV D46/NS2/ N/ΔM2-2-HindIII (Sanofi Pasteur/LID/NIAID/NIH)	Live-attenuated
RSV LID cp ΔM2-2 (Sanofi Pasteur/LID/NIAID/NIH)	Live-attenuated
MEDI8897 (MedImmune)	Monoclonal antibody
Older adults	
RSV F nanoparticle (Novavax)	Particle-based
SynGEM (Mucosis)	Particle-based
MVA-BN RSV (Bavarian Nordic)	Vector-based
VXA-RSVf oral (Vaxart)	Vector-based
Ad26.RSV.preF (Janssen)	Vector-based
DPX-RSV-Protein (Immunovaccine, VIB and Dalhousie University)	Subunit
RSV F DS-Cav1 (NIH/NIAID/VRC)	Subunit

NIH=National Institutes of Health. NIAID=National Institutes of Allergy and Infectious Diseases. LID=Laboratory of Infectious Diseases. VIB=Flemish Institute of Biotechnology. VRC=Vaccine Research Center. RSV=respiratory syncytial virus.

Table 3: **Overview of vaccines and monoclonal antibodies by target population**

antibody dependent cell-mediated cytotoxicity (ADCC), whereas non-membrane proteins are especially important to induce a robust T-cell response.[40]

Target populations
RSV prophylactic interventions are designed to protect at least two populations most susceptible 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 owing to an increased understanding of RSV burden in this population. An overview of all RSV vaccine candidates per target population is shown in table 3 and strategies to prevent RSV in different target populations are discussed in more detail in the appendix.

Immunological endpoints
Antibodies are thought to be the key players in limiting RSV ALRI as evidenced by proven protection in immunoprophylaxis trials in children.[50–52] Evidence from experimental human infection in adults suggests a protective role for nasal RSV-specific IgA against RSV infection,[11] underscoring the importance of mucosal immunity. A limited ability to generate memory IgA responses after RSV infection could be in-part responsible for incomplete immunity and subsequent RSV re-infection. Antibodies directed against different antigenic sites of the F protein display different neutralisation capacities with the most neutralisation-sensitive epitopes exclusive to the pre-F conformation. Antibodies with specificity for antigenic sites ø and V show high neutralising activity and are exclusive to the pre-F conformation.[25,53] Antigenic site ø is located at the apex of the pre-F conformation, the most variable region of the highly conserved F protein.[21] Antibodies against antigenic site III prefer the pre-F conformation and have high neutralising activity.[54] Antibodies directed against site II and IV, present on both pre-F and post-F, have medium to high neutralisation potency.[53,55] Finally, antibodies against antigenic site I, present primarily on post-F, show weak or no neutralisation. 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 could differ according to vaccine type, and, therefore, many different immuno-logical assays are used in clinical trials. Neutralising activity of serum is a frequent immunological endpoint of vaccine trials. A measure of functional antibody response can be elucidated by the ratio of times-increase in RSV-binding antibodies to times-increase in RSV-neutralising antibodies (ELISA-to-neutralisation response ratio). A ratio of less than 1 might be an important correlate of protection.[56] Furthermore, rather than a definitive protective threshold for antibodies, times-rise in antibody titre could be a relevant correlate of protection for live-attenuated vaccines, since that might be the best indicator of B-cell priming. In 2017, efforts by PATH, WHO, and the National Institute for Biological Standards and Control (NIBSC) examined the variability of RSV neutralisation assays across laboratories and recommended steps for improved standardisation globally,[57] resulting in the development of a new WHO International Standard for Antiserum to RSV with 1000 IU of RSV subtype A neutralising activity per vial now available through the NIBSC.[58] Standardisation of other frequently used immunological 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 part in viral clearance.[35] 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 develop-ment 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. However, there is no consensus on the ability to reproduce ERD in calves.[59]

Although we discuss several potential immunological correlates of protection for vaccine trials, we considered cell-mediated immunity beyond the scope of the manu-script. The different aspects of the expected immune response for all 19 vaccine candidates and mAbs in clinical development are highlighted in table 2. 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.[60] Ultimately, the outcome of large-scale vaccine trials will inform which immunological 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 or chimeric vaccines.[24] We have also included mAbs in clinical development for the prevention of RSV ALRI. In the snapshot there are 43 vaccines and four mAbs in development, of which 19 are in clinical stage development. In table 4 we provide a comprehensive overview and more detailed comparison of all characteristics of the 19 vaccine candidates and mAbs in clinical development. Other approaches, which

	Manufacturing process	Antigen, adjuvant	Mechanism of action	Target population	Animal models	Phase 1	Phase 2	Phase 3	Result summary
Particle-based vaccines									
RSV F nanoparticle, Novavax, phase 3*	Sf9/BV recombinant technology	Stabilised F protein exhibiting post-F morphology, aluminium phosphate	F forms nanoparticle in multimeric micelle format	Maternal	Cotton rats[61,62], baboons[63] guinea pigs[64]	Dec, 2010–Dec, 2011 NCT01290419 (n=150)	Oct, 2012–May, 2013 NCT01704365 (n=330) Oct, 2013–April, 2014 NCT01960686 (n=720) Sept, 2014–July, 2016 NCT02247726 (n=50)	Dec, 2015–June, 2020 NCT026249 47 (n=8618)	Phase 2: all formulations well tolerated and immunogenic; most robust Ab response with 120 μg and 0·4 mg aluminium formulation, peak day 14 and persistence through day 91; RSV infection measured by western blot was reduced by 52% (p=0·009) in healthy women of childbearing age (n=720)[65] Vaccine safe, immunogenic, and reduced RSV infection in healthy women of childbearing age (n=330)[66]
RSV F nanoparticle, Novavax, phase 2*	Sf9/BV recombinant technology	Stabilised F protein exhibiting post-F morphology, aluminium phosphate and Matrix M	F forms nanoparticle in multimeric micelle format	Older adults	Cotton rats[61,62] baboons[63]	Oct, 2012–March, 2014 NCT01709019 (n=220)[67]	Oct, 2014–March, 2016 NCT02266628 (n=1599) Oct, 2015–Nov, 2016 NCT02593071 (n=1330) Jan, 2017–July, 2018 NCT03026348 (n=1329)	Nov, 2015 – Dec, 2016 NCT02608502 (n=11850)	Phase 2: safe, VE: 41% vs RSV-ARD, 64% VE vs RSV-msLRTD[88] Phase 3: safe, no efficacy vs RSV-ARD and RSV-msLRTD; post-hoc efficacy vs all-cause hospitalisation (n=11 850) Phase 2 rollover; second immunisation protective against RSV-ARD and msLRTD (n=1329)[14]
RSV F nanoparticle, Novavax, phase 1*	Sf9/BV recombinant technology	Stabilised F protein exhibiting post-F morphology, aluminium phosphate/ Matrix M-1	F forms nanoparticle in multimeric micelle format	Paediatric	Cotton rats[61,62] baboons[63]	Nov, 2014–April, 2016 NCT02296463 (n=32)	NA	NA	Phase 1: well tolerated; anti-F IgG and PCA increase day 14, peak day 28, elevated to day 56; 10-times increase PCA and anti-F IgA adjuvanted 6-times increase in unadjuvanted (n=32)
SynGEM, Mucosis, phase 1†	BLP mimopath technology carrying F proteins	F protein, unclear which conformation, BLP	BLP allows presentation of F protein and elicits mucosal IgA	Older adults and paediatric	Mice	July, 2016–Dec, 2017 NCT02958540 (n=48)	NA	NA	Phase 1: some immunogenicity in healthy adults but did not meet threshold; development suspended
Vector-based vaccines									
MVA-BN RSV, Bavarian Nordic, phase 2‡	MVA-BN technology (antigens expressed in attenuated modified vaccinia Ankara)	F, G (subtype A and B), N, M2, no adjuvant	Virus replication blocked at a late stage	Older adults	Cotton rats, BALB/c mice[69]	*Aug, 2015–May,2016 NCT02419391 (n=63) †Sept, 2018–Aug, 2019 NCT02864628 (n=96)	Sept, 2016–Aug, 2018 NCT02873286 (n=400)	NA	Phase 1; safe, 2-times increase IgG and IgA; 3–5-times increase in T cell responses (n=63)[69] Phase 2 interim results: well tolerated; broad Ab and T cell response in older adults after single vaccination (n=421)[70]
VXA-RSVf oral, Vaxart, phase 1§	Antigen and adjuvant expressed in non-replicating adenovirus vector (Ad5)	F, dsDNA that activates TLR3 receptor	Vector delivers directly to gut (ileum)	Older adults	Cotton rat	June, 2016–Dec, 2017 NCT02830932 (n=66)	2018?	NA	Preclinical: systemic anti-F Abs and protection against RSV infection in cotton rat model[71]

(Table 4 continues on next page)

	Manufacturing process	Antigen, adjuvant	Mechanism of action	Target population	Animal models	Phase 1	Phase 2	Phase 3	Result summary
(Continued from previous page)									
Ad26.RSV.preF, Janssen, phase 2*	Antigen expressed in human adenovirus type 26 produced in PER.C6 human cell line	Pre-F (previously FA2), no adjuvant	Ad26 vector is replication incompetent but expresses immunogenic F antigen	Older adults	Mice, cotton rats[72]	Nov, 2016–Dec, 2018 NCT02926430 (n=73)	Dec, 2017–July 2018 NCT03339713 (n=180)	NA	Phase 2: well tolerated; durable humoral and cellular immune response for FA2 candidate; comparable or higher for preF candidate in older adults[73]
Ad26.RSV.preF, Janssen, phase 1*	Antigen expressed in human adenovirus type 26 produced in PER.C6 human cell line	Pre-F (previously FA2), no adjuvant	Ad26 vector is replication incompetent and expresses immunogenic F antigen	Paediatric	Mice, cotton rats[72]	Nov, 2017–March, 2019 NCT03303625 (n=60)	Nov, 2017–March, 2019 NCT03303625 (n=60)	NA	NA
ChAd155-RSV, GSK, phase 2*	Chimpanzee adenovirus ChAd155-RSV with F, N, M2-1 insert and E1 deletion	F, N, M2-1, no adjuvant	Intracellular RSV antigen expression; replication incompetent vector	Paediatric	Mouse, cotton rat, calves[74]	July 2015–Feb, 2017 NCT02491463 (n=73)	Jan, 2017–Sept, 2020 NCT02927873 (n=96)	Plan to start post 2020 with age de-escalation seronegative infants	Phase 1: safe, B cell and RSV-neutralising antibodies in RSV-seropositive adults (n=73)[75]
Subunit vaccines									
GSK RSV F, GSK, phase 2*	Pre-F produced in CHO cells	Pre-F, with or without aluminium hydroxide	Pre-F antigen induces neutralising antibodies that are transferred to infant	Maternal	Mice, cotton rats, guinea pigs, cows	Dec, 2014–March, 2017 NCT02298179 (n=288) July 2013–March, 2015 NCT01905215 (n=128)[76]	March, 2015–June, 2016 NCT02360475 (n=507) April, 2016–June, 2016 NCT02753413 (n=102) Nov, 2016–March, 2018 NCT02956837 (n=406) July, 2017–Jan, 2021 NCT03191383 Halted due to instability of pre-F antigen during manufacturing	NA	Phase 1: safe, RSV-A neutralising Ab titres increased 3·2–4·9 times; remained high to day 60, decreased on day 180 and 360 in healthy men (n=128)[76] Phase 2: increased RSV-A neutralising Ab 30 days post-vaccination in healthy non-pregnant women[7]
DPX-RSV, Immunovaccine and VIB, Dalhousie University, phase 1*	DepovaxTM delivery in 100% oil-based platform preventing release at injection site	SHe, DepovaxTM or aluminium hydroxide	Depovax gives controlled and prolonged exposure of antigen and adjuvant	Older adults	Mice, cotton rats	May, 2015–June, 2017 NCT02472548 (n=40)	NA	NA	Phase 1: well tolerated, antigen-specific Ab response durable to day 421, low immunogenicity with alum adjuvant in healthy older adults[78]
RSV F DS-Cav1, NIH/NIAID/VRC, phase 1*	Prefusion stabilised trimeric RSVF expressed in CHO cell line	Pre-F, alum/ TLR4 agonist (E)	Pre-F antigen elicits highly neutralising antibodies against pre-F epitopes	Maternal and older adults	Cotton rats,[79] mice, calves,[37] macaques[37]	Feb, 2017–Jan, 2020 NCT03049488 (n=100)	NA	NA	Preclinical: induction of highly neutralising Abs and differential adjuvant-induced enhancement[79] Immunisation of mice and macaques induces RSV-neutralising Ab many times protective threshold[37]

(Table 4 continues on next page)

(Continued from previous page)

Live-attenuated or chimeric vaccines

	Manufacturing process	Antigen, adjuvant	Mechanism of action	Target population	Animal models	Phase 1	Phase 2	Phase 3	Result summary
rBCG-N-hRSV, Pontificia Universidad Catolica de Chile, phase 1¶	Recombinant BCG expressing N antigen	N, no adjuvant	Paired BCG and RSV vaccine induces Th1 response	Paediatric	Mice[80–83]	June, 2017–May, 2018 NCT03213405 (n=24)	NA	NA	Preclinical: protective T cell immune response and recruitment of Th1 cells[81,82]
RSV D46 cpΔM2-2, Sanofi Pasteur/LID/NIAID/NIH, phase 1†	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	Native RSV, no adjuvant	Deletion of regulatory factor M2-2 causes inefficient replication but high immunogenicity; further attenuation with cp mutations	Paediatric	African green monkeys	Oct, 2015–May, 2018 NCT02601612 (n=45)	NA	NA	NA
RSV LID ΔM2-2 1030s, Sanofi Pasteur/LID/NIAID/NIH, phase 1†	M2-2 deletion via reverse genetics and temperature sensitivity mutation 1030s	Native RSV, no adjuvant	Deletion of regulatory factor M2-2 causes inefficient replication but high immunogenicity; temperature sensitive mutation at position 1030 of L gene	Paediatric	Mice, African green monkeys	June, 2016–July, 2017 NCT02794870, NCT02952339 (n=33)	NA	NA	NA
RSV ΔNS2 Δ1313 I1314L, Sanofi Pasteur/LID/NIAID/NIH, phase 1†	NS2 and 1313 deletion via reverse genetics, I1314L substitution	Native RSV, no adjuvant	NS2 deletion bolsters innate response; deletion at position 1313 of L protein, and I1314L substitution confers moderate temperature sensitivity	Paediatric	Mice and chimpanzees	June, 2013–May, 2017 NCT01893554 (n=75) Aug, 2017–May, 2019 NCT03227029 (n=80)	NA	NA	NA
RSV D46/NS2/N ΔM2-2 HindIII, Sanofi Pasteur/LID/NIAID/NIH, phase 1†	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	Native RSV, no adjuvant	Deletion of regulatory factor M2-2 causes inefficient replication but high immunogenicity	Paediatric	African green monkeys	March, 2017–April, 2019 NCT03102034, NCT03099291 (n=33)	NA	NA	NA

(Table 4 continues on next page)

	Manufacturing process	Antigen, adjuvant	Mechanism of action	Target population	Animal models	Phase 1	Phase 2	Phase 3	Result summary
(Continued from previous page)									
RSV LID cp ΔM2-2, Sanofi Pasteur/LID/NIAID/NIH, phase 1†	M2-2 deletion via reverse genetics, and cp mutation	Native RSV, no adjuvant	Deletion of regulatory factor M2-2 causes inefficient replication but high immunogenicity; further attenuation with cp mutations	Paediatric	African green monkeys	Sept, 2016–April, 2018 NCT02890381 (n=17)	NA	NA	NA
Monoclonal antibody (mAb)									
MEDI8897, Medimmune, phase 2||	In vitro–optimised human mAb with YTE mutation in Fc	NA	Antibody targeting site Ø of the F protein of RSV with an extended half-life	Paediatric	Cotton rats, cynomolgus monkeys[84]	April, 2014–June, 2015 NCT02114268 (n=342) Jan, 2015–Sept, 2016 NCT02290340 (n=151)	Nov, 2016–Nov, 2018 NCT02878330 (n=1454)	NA	Phase 1; well tolerated, mean half-life 85–117 days; time to max concentration 5–9 days; bioavailability 77% in healthy adults (n=136)[85]

RSV=respiratory syncytial virus. NA=not applicable or not available. ARD=acute respiratory disease. PCA=palivizumab-competing antibodies. SHe=small hydrophobic protein ectodomain. RSV ARD=all symptomatic respiratory disease due to RSV. msLRTD=moderate-severe RSV-associated lower respiratory tract disease. VIB=Flemish Institute of Biotechnology. NIAID=National Institutes of Allergy and Infectious Diseases. VRC=Vaccine Research Center. NIH=National Institutes of Health. LID=Laboratory of Infectious Diseases. Ab=antibody. aa=aminoacid. BLP=Bacterium-like-particle. *Intramuscular. †Intranasal. ‡Intramuscular or intranasal. §Oral. ¶Intradermal. ||Intravenous or intramuscular.

Table 4: Overview of RSV vaccines and monoclonal antibodies in clinical development

are still in preclinical development, including nucleic acid-based vaccines, whole-inactivated vaccines, and biosimilars, are discussed in the appendix.

Particle-based vaccines
The RSV F nanoparticle-based vaccine platform is 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 aged 60 years or older. These vaccine candidates use aggregates of a modified stabilised F protein which has the post-F morphology.[86] 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 3 trial to enrol up to 8618 pregnant women at 80 sites in 11 countries.[27] In January, 2018, an informational analysis of the phase 3 trial was announced in which the vaccine candidate successfully targeted an efficacy threshold against the primary endpoint in infants at day 90 of more than 40%.[87] Second in clinical development is the RSV F nanoparticle vaccine for older adults. Despite the absence of efficacy in a phase 3 trial (RESOLVE) with a non-adjuvanted vaccine candidate, development was continued in a phase 2 study initiated in January, 2017, in Australia in 300 adults. The aim of this trial is to establish whether two dose regimens with an adjuvant (Matrix-M, a saponin-based adjuvant, or aluminium phosphate) could 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.[27] Finally, the phase 1 trial was completed in young children 24–72 months of age in 2016, but no data have been published yet.[88]

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 that uses the same vaccine platform has shown both local and systemic antibody responses[89] but further optimisation is needed for RSV vaccination. The preliminary results of immunogenicity testing of SynGEM 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 a low or high dose in 24 individuals per group (six participants 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 (P J Openshaw, Imperial College London; and C Chiu, Department of Laboratory Medicine, University of California San Francisco, personal communication).

Vector-based vaccines

Five vector-based vaccines are in clinical development. The first uses a modified vaccinia Ankara (MVA) virus, a replication-defective smallpox viral vector, and the remaining four vaccine candidates use an adenovirus vector to display viral antigens. The MVA vector has been safely used in vaccines for other infectious diseases.[90] 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 2 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 1 trial for influenza has been conducted, which showed neutralising antibody responses against influenza and no interference of pre-existing vector immunity.[91] Preclinical studies for the RSV vaccine candidate in the cotton rat model showed an increase in anti-F antibodies and protection against RSV challenge.[71] In the older adult population, immunosenescence can be characterised by impaired T-cell responses to RSV.[92,93] This vaccine candidate, which induces a strong humoral response, could be a promising intervention in this population.

Third and fourth, Ad26.RSV.preF, is a vaccine candidate being developed for older adults and the paediatric population. In this candidate, pre-F antigen is expressed in the human adenovirus strain 26, a vector with a favourable safety profile when used for other infectious diseases.[94,95] Previously, the vaccine candidate vector expressed post-F as antigen (FA2) but has now been changed to stabilised pre-F conformation. The stabilised pre-F protein has five aminoacid changes from wildtype, and is stable at 4°C and heat-stable.[34] With the expectation that this vaccine candidate will induce highly neutralising antibodies against pre-F, phase 2 trials will be conducted in RSV-seropositive children. In December, 2017, a phase 2 trial began comparing concomitant admixtion of RSV vaccine and seasonal influenza vaccine versus seasonal influenza vaccine alone in healthy older adults.[96]

Fifth, ChAd155-RSV, the replication-incompetent chimpanzee adenovirus 155 has been used as a vector for the F, N, and M2-1 proteins. The anticipated use for this paediatric vaccine is to start immunisation at 2 months of age, and to use two doses alongside the normal paediatric vaccination schedule, instead of seasonally.[74] This vaccine candidate is 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-naive populations. Results of phase 2 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 already in phase 2 trials.

Subunit vaccines

Owing 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. Results from a phase 1 trial showed safety and immunogenicity as evidenced by RSV neutralising antibody response in healthy men.[76] However, a phase 2 trial scheduled for 2017 was halted because of instability of the pre-F antigen during manufacturing.

DPX-RSV is a vaccine candidate with a unique choice of vaccine antigen: the extracellular domain of the SH protein of RSV.[45] The DepoVax technology allows for a prolonged exposure of antigen and adjuvant, and aims to induce ADCC using a liposome and oil-based depot.[97] The antigen and adjuvant are encapsulated in a liposome, lyophilised and suspended in oil, and the process is expected to produce vaccines with long shelf-life stability.[97] Phase 1 results on safety and immunogenicity in the older adult population have been released and are expected to be published from this investigator-initiated study.

Structure-guided stabilisation of the pre-F conformation has yielded a subunit vaccine candidate, RSV F DS-Cav1. The stabilisation includes a foldon trimerisation domain, the introduction of cysteine residues to form a disulphide bond, and cavity-filling hydrophobic residues.[37] The vaccine is able to preserve neutralisation-sensitive epitopes on a functional pre-F form of the viral surface protein. In preclinical studies, the subunit vaccine induced high amounts of RSV-neutralising antibodies in mice and non-human primates.[37] Preliminary results from the phase 1 trial, VRC 317, are promising and are expected to be published soon.

Finally, another stabilised pre-F subunit vaccine candidate, which has been optimised for antigen design after screening 360 candidates with cryo-electron microscopy, is expected to enter phase 1 clinical trials soon.[99]

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 wildtype RSV after vaccination.[100] 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.[101] Live-attenuated vaccines are probably limited to the

paediatric population under 2 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 might be increased rates of rhinorrhoea, similar to what has been observed with the live-attenuated influenza vaccines.

Five live-attenuated vaccine candidates in phase 1 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, and 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 could 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,[102] and 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 neutralising antibody and potent anamnestic response in RSV-seronegative infants and children.[102] Further results from phase 1 clinical trials with the other live-attenuated vaccine candidates are expected.

The only chimeric vaccine candidate in clinical development, rBCG-N-hRSV, is delivered via a BCG strain. BCG has a safe profile in newborn babies and infants, induces a Th1 response,[81,82] 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[83] but the candidate also induces a humoral response. The antigen presented by this vaccine candidate is the RSV N protein.[103] So far, this candidate is the only vaccine candidate intended for administration to newborn babies.[103]

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 optimised from the human antibody D25 that targets antigenic site ∅ on the pre-F conformation, which is more neutralisation sensitive than the palivizumab epitope, antigenic site II. Using the YTE (aminoacid substitutions Met252Tyr/Ser254Thr/Thr256Glu) technology, which extends antibody half-life and modulates ADCC,[104] the three-times increase in half-life of MEDI8897,[105] compared with palivizumab offers the possibility of passive protection for all infants for an entire season through a single intramuscular injection. The intended use is for 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 can 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.[84]

Considerations by regulatory agencies and WHO

Considerations in population selection for vaccine trials mentioned by the European Medicines Agency (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 that included guidance regarding trial design, assessment of efficacy, and safety.[106] The draft guidelines will be revised after a period of public consultation based on comments and new publications.

WHO has recognised 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 has developed RSV vaccines preferred product characteristics and research and development technical roadmap documents.[107,108] Further guidance for development will contribute to adequate policy making. WHO standardisation 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 the consultation with regulators, manufacturers, and academia in 2018, with the aim of finalisation 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 and WHO prequalification.

Finally, the WHO is now doing 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.[109]

Discussion

Challenges in RSV vaccine design include concerns of ERD post-vaccination, lack of definitive immunological correlates

of protection, lack of consensus regarding clinical endpoints, and little natural immunity following RSV infection. Despite these challenges, 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 low-income and lower middle-income countries (LMICs) and expected pricing for all vaccine candidates; however, this information is not publicly available. Given that the most severe RSV infection occurs in low-income and LMICs,[19] 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. 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.[110]

A vaccine trial can be considered a probe study to establish whether a causal relationship exists between RSV infection and asthma, a long-standing 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 is a missed opportunity 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 effect 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 could conceivably result in an increased prevalence of other respiratory viruses. There is evidence supporting viral interference for influenza vaccination,[111,112] for RSV prevention,[113,114] and during the RSV season in the absence of RSV.[115] It is important for vaccine trials to examine this effect by evaluating the prevalence 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 (2b or 3) and aim to prevent the disease burden in infants. Despite some failures, RSV vaccine candidates and mAbs in clinical development hold promise that a preventive intervention for RSV is on the horizon.

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