Respiratory syncytial virus prevention within reach: the vaccine and monoclonal antibody landscape

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Respiratory syncytial virus is the second most common cause of infant mortality and a major cause of morbidity and mortality in older adults (aged >60 years). Efforts to develop a respiratory syncytial virus vaccine or immunoprophylaxis remain highly active. 33 respiratory syncytial virus prevention candidates are in clinical development using six different approaches: recombinant vector, subunit, particle-based, live attenuated, chimeric, and nucleic acid vaccines; and monoclonal antibodies. Nine candidates are in phase 3 clinical trials. Understanding the epitopes targeted by highly neutralising antibodies has resulted in a shift from empirical to rational and structure-based vaccine and monoclonal antibody design. An extended half-life monoclonal antibody for all infants is likely to be within 1 year of regulatory approval (from August, 2022) for high-income countries. Live-attenuated vaccines are in development for older infants (aged >6 months). Subunit vaccines are in late-stage trials for pregnant women to protect infants, whereas vector, subunit, and nucleic acid approaches are being developed for older adults. Urgent next steps include ensuring access and affordability of a respiratory syncytial virus vaccine globally. This review gives an overview of respiratory syncytial virus vaccines and monoclonal antibodies in clinical development highlighting different target populations, antigens, and trial results.

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Introduction

In the past decade, the substantial burden of respiratory syncytial virus (RSV) has received increasing recognition globally. RSV is the second leading cause of infant mortality after the neonatal period[1] with more than 99% of childhood deaths occurring in low-income and middle-income countries (LMICs).[2] Nevertheless, the RSV burden in children is likely underestimated, and major gaps in knowledge regarding RSV disease burden have been addressed only recently. More than 50% of pediatric RSV mortality occurs out of hospital (as opposed to in hospital) in LMICs[3] with poverty as a substantial risk factor (figure 1). Infants at highest risk of RSV disease in high-income countries (HICs) include the very young infants born prematurely and those with underlying congenital heart or chronic lung disease,[8] Down's Syndrome,[9] and neuromuscular disorders.[10] Maternal vaccination is insufficient to protect infants with extreme prematurity as transplacental antibody transfer only reaches mature levels towards the end of the third trimester.[11]

In older adults (aged >60 years), the burden of morbidity and mortality due to RSV was also underestimated until recently. Modelling studies now estimate that the RSV burden is similar to the burden of seasonal influenza in adults older than 65 years.[12–14] Preliminary economic evaluations have highlighted the potential value of a vaccine for older adults, especially in HICs. Key economic drivers of cost-effectiveness include RSV incidence, risk of death, and level and duration of protection.[15,16]

Natural immunity to RSV is incomplete and reinfection occurs throughout life.[17] A concern in the development of RSV vaccines is the potential for enhanced respiratory disease in which more severe illness occurs upon natural infection after vaccination of RSV-naive infants as was observed with formalin-inactivated RSV in the 1960s.[18] Enhanced respiratory disease was associated with induction of poorly neutralising antibodies in vaccine recipients[19] and animal models of enhanced respiratory disease show a T helper type 2 (Th2) biased T-cell response.[20] For this reason, an RSV vaccine for RSV-naive recipients ideally elicits potent neutralising antibodies without a Th2 bias. Although a definitive correlate of protection against RSV infection remains elusive, cell-mediated immunity,[21] mucosal IgA,[22] and neutralising antibodies[23–26] have been associated with protection from RSV infection.

Key messages

- Knowledge of neutralisation-sensitive viral epitopes informed a shift from empirical to structure-based vaccine and monoclonal antibody design
- Market access for an extended half-life respiratory syncytial virus monoclonal antibody for prophylaxis in all infants is within reach in 2023 and will likely be followed by approval of a maternal vaccine to protect all infants
- No vaccine or monoclonal antibody is within reach for resource poor areas with the highest paediatric mortality burden
- Subunit, vector-based, and nucleic acid vaccine approaches are in late-phase trials for older adults (older than 60 years)

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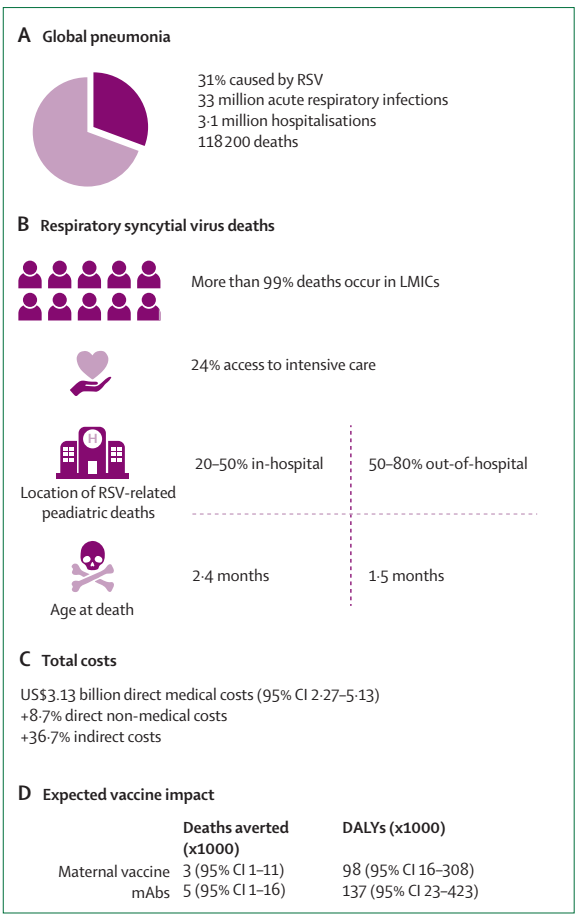

Figure 1: **Paediatric RSV disease burden key facts and figures**
(A) Contribution of RSV to worldwide pneumonia: approximately one-third of worldwide pneumonia is caused by RSV. (B) Deaths related to RSV: more than 99% of the global burden of paediatric mortality due to RSV occurs in low-income and middle-income countries.[1] Access to care is likely a key factor of the inequitable distribution of the mortality burden as less than one fourth of these children have access to an intensive care.[4] At least half of this burden was previously hidden, these deaths occur out out-of-hospital.[3] Recently the out-of-hospital burden has been characterised and is distinct from the in-hospital mortality burden which has implications for global vaccine development: children who die out of hospital die at a younger age and risk factors are linked to poverty instead of underlying conditions.[5] (C) Total costs: estimated direct associated with RSV exceed US$3 billion in low-income and middle-income countries, with additional direct non-medical and indirect costs.[6] (D) Expected vaccine impact: the cost-effectiveness and potential impact of maternal immunisation versus monoclonal antibodies has been estimated in deaths averted and discounted disability adjusted life-years.[7] RSV=respiratory syncytial virus.

Stabilisation of the pre-Fusion (pre-F) conformation of the RSV fusion (F) protein has led to the determination of viral epitopes that elicit highly neutralising antibodies. Antibodies that recognise pre-F provide most of the neutralising activity in human RSV-immune sera[27] supporting development of vaccine candidates and monoclonal antibodies (mAbs) based on stabilised pre-F antigens (figure 2).

There are three different target populations for RSV prevention: paediatric, maternal, and older adult (figure 3).[32] Leading strategies for the paediatric population include passive immunoprophylaxis with mAbs for young infants (aged <6 months) and live-attenuated vaccines (LAVs) for active immunisation of older infants (aged >6 months). Young infants might also be protected by passively transferred antibodies in immunised pregnant women. Stabilised pre-F subunit vaccines are in late-phase development for maternal vaccination. Finally, for older adults three vaccination approaches (nucleic acid, subunit, and vector-based vaccines) that employ pre-F antigen are in late phase trials.

In 2018, we did a comprehensive review of the RSV vaccine landscape in which we distilled lessons learned from late-phase vaccine failures and identified 19 vaccine candidates and monoclonal antibodies in clinical trials.[33] The review might have provided vaccine developers with guidance for future vaccine development by endorsing pre-F as a new target for RSV preventive interventions. The pre-F antigen is now the basis of six vaccine candidates and two mAbs in phase 3 trials.[34–37] Furthermore, we endorsed controlled human infection models as a unique tool to generate rapid proof of concept of protection and extensive immunological characterisation. This approach has been adopted into clinical development for six current RSV vaccine candidates (MV-012–968, RSVPre-F, MVA-BN-RSV, palivizumab biosimilar, clesrovimab, and Ad26.RSV.Pre-F). This updated review shows that 11 (58%) of 19 candidates from 2018 (and three [30%] of ten candidates from our 2015 review)[38] have continued development, with simultaneous expansion of the field with 19 additional candidates having entered clinical trials (figure 2, figure 4). Finally, after the success of mRNA SAR-CoV-2 vaccine development, vaccines delivered as mRNA are a novel preventative approach that has been rapidly accelerated to late-phase trials.

Methods

Vaccine and monoclonal antibodies (mAb) candidates in clinical phases of development were identified using the PATH (centre for vaccine innovation and access) RSV Vaccine and mAb snapshot (last updated Sept 28, 2021).[32] The data collection template from previous reviews[33] was updated (appendix p 1) and filled out by searching PubMed, clinical trial registries, WHO, European Medicines Agency, and pharmaceutical websites for each vaccine candidate, with no date or language restrictions. We did not intend to conduct a systematic review of the peer-reviewed literature but instead provide an update on the current development by capturing all recent publicly available information. No inclusion or exclusion criteria were used. Instead, for each vaccine candidate or mAb in clinical development, information was selected by date (with preference for more recent literature) and by relevance (with preference for trial data). When available, peer-reviewed publications were preferred to information from trial registries or pharmaceutical websites. To supplement the data collected and the identified gaps in

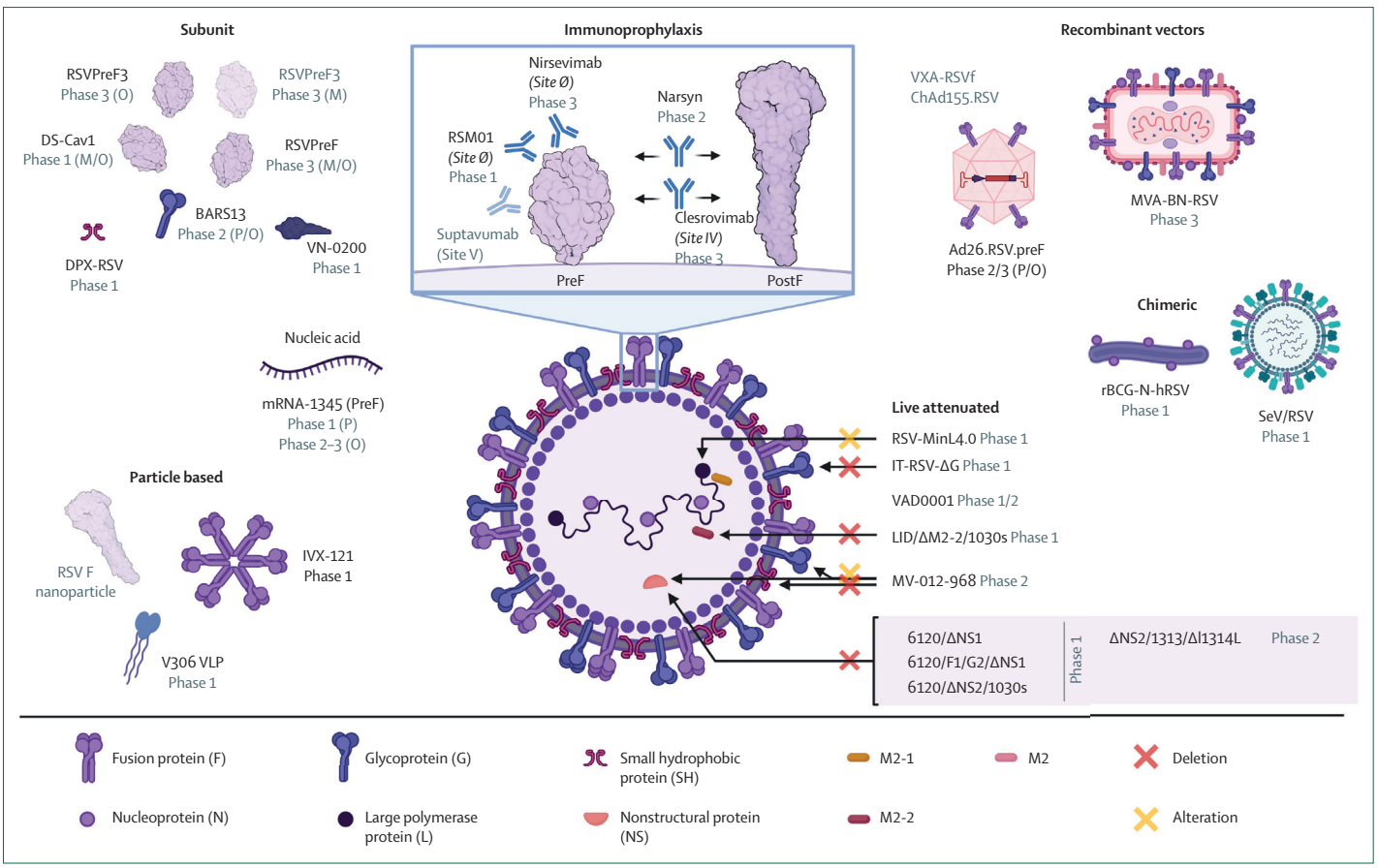

Figure 2: **Overview of vaccine candidates by preventive approach**
Pre-F protein was created with Protein Data Bank RCSB PDB 4MMU[28,29] and post-F protein was created with 3RRT.[30,31] Light grey indicates vaccine development halted or discontinued. RSV=respiratory syncytial virus. PreF=prefusion protein. PostF=postfusion protein. Ad=adenovirus. MVA=modified vaccinia Ankara virus. BCG=mycobacterium bovis. SeV=sendai virus.

knowledge, data for this review were systematically collected using the data collection template (appendix p 1) at the virtual RSV Vaccines for the World Conference organised by the Respiratory Syncytial Virus Network from Nov 10–12, 2021. The goal of this meeting was to share scientific data and expertise on RSV vaccine development, and to connect stakeholders involved in RSV research. During the meeting, information was collected from scientific presentations, posters, and discussions. Any publicly available data from this meeting has been included in this manuscript. Vaccines were divided into six major groups: recombinant vector, subunit, particle based, live attenuated, chimeric, and nucleic acid. Immunoprophylaxis with mAbs was included as a seventh category. Vaccine characteristics such as mechanism of action, adjuvants, route of administration, and summary of trial results have been compiled in the table.

Lessons learned

We examine lessons learned from three late phase clinical trial failures since our last review. The PREPARE trial[39] was a milestone: the first phase 3 trial of an RSV maternal vaccine. More than 4000 pregnant women received an RSV F nanoparticle vaccine or placebo (2:1 ratio) during the third trimester. RSV maternal vaccination was determined to be safe. Although the vaccine did not meet the primary endpoint, the candidate is the first proof-of-concept demonstration for efficacy of RSV maternal immunisation against severe RSV infection in infants. Efficacy was shown through day 90 in South Africa, where more than 50% of participants were enrolled: 56% (95% CI 33–71) against medically significant RSV lower respiratory tract infection (LRTI) and 74% (50–86) against RSV LRTI with severe hypoxemia. Moreover, there was 49% efficacy against all-cause infant pneumonia through 1 year after vaccination.[39] The difference in efficacy might be explained by hospitalisation for less severe disease and lower background rates of severe RSV infection in HICs. compared with LMICs. Lessons learned include geographical heterogeneity of RSV disease burden and potential efficacy between different countries, and the importance of timing of vaccination in relation to RSV season and gestational age.[39] Furthermore, it was shown that RSV neutralising antibodies and F surface

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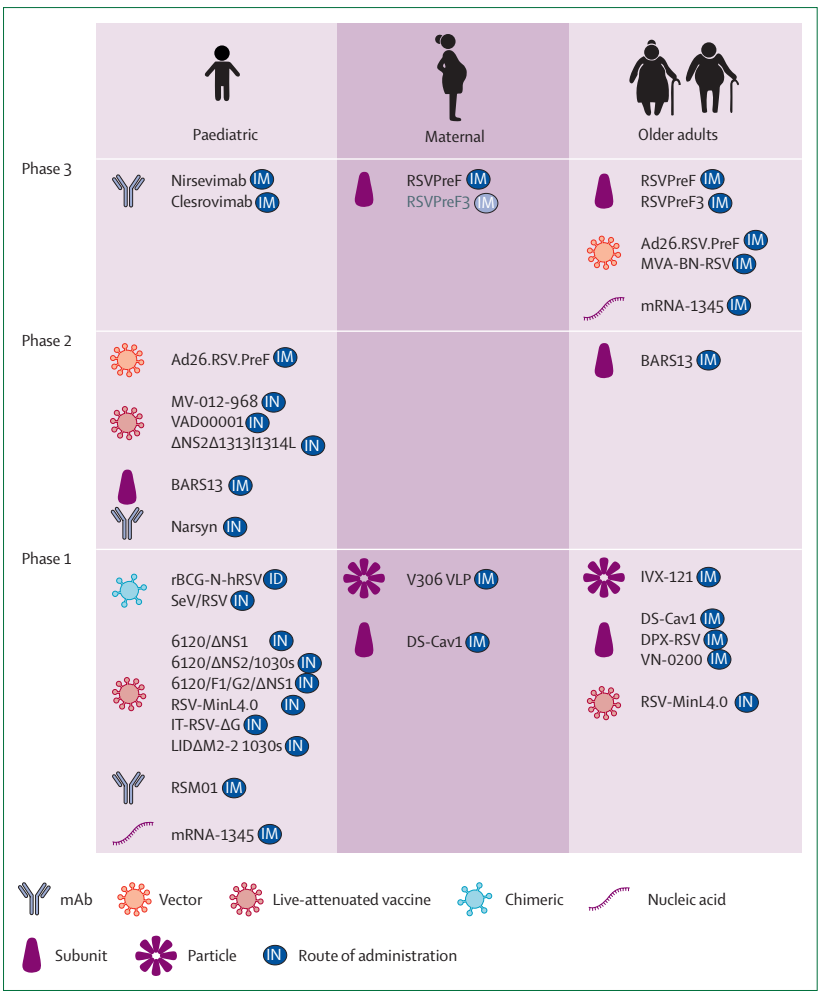

Figure 3: **RSV vaccine and monoclonal antibody agents by target population**
Vaccine candidates and monoclonal antibidies are categorised into three different target populations: paediatric, maternal, and older adults (aged >60 years) and clinical phase of development (ie, phase 1, 2, or 3). Different immunisation approaches are indicated by the key. Light grey text indicates development halted. IM=intramuscular. IN=intranasal. ID=intradermal. RSV=respiratory syncytial virus. PreF=prefusion protein. PostF=postfusion protein.

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glycoprotein binding antibodies were correlated with protection against RSV LRTI with severe hypoxemia (eg, a vaccine-induced maternal antiF IgG 16 times increase from maternal enrollment to day 14 was associated with a baseline covariate-adjusted vaccine efficacy of 75%).[40] Proven efficacy poses an ethical dilemma that a potentially life-saving vaccine might not become available in these countries as drug development was discontinued because prespecified criteria for efficacy were not met.[41] A rollover trial might be considered to confirm efficacy and develop this vaccine for LMICs.

At the time of our last review in 2018,[42] analysis of the late-stage clinical trial failure of suptavumab (REGN2222), an antigenic site 5 mAb, which did not meet its primary endpoint, had not yet been made public. In a phase 3 study[42] in 18 countries, it was shown that suptavumab did not reduce RSV hospitalisation or outpatient RSV LRTI due to a natural mutation in the predominant circulation strain of RSV subgroup B that resulted in loss of antibody binding and neutralisation. There were no changes in circulating RSV A strains and negligible anti-suptavumab antibody responses. Post-hoc analyses suggested the antibody was relatively effective against the subgroup A strains but not the new circulating B strain; the relative risk for RSV subgroup A hospitalisation or outpatient LRTI versus placebo was 0·38 (95% CI 0·17–0·86). These findings highlight the importance of characterisation of the viral fitness of monoclonal antibody resistant viral mutants in clinical development and the risk associated with targeting a single viral epitope as well as more potential variability of certain targeted antigenic sites.

Finally, ChAd155.RSV, a recombinant chimpanzee adenovirus vector vaccine expressing RSV f, N, and M2–1 proteins, was in development for the paediatric population. Development was halted after preliminary analyses of a phase 2 trial in infants aged 3–7 months showed that the target efficacy profile was unlikely to be met.[43] The published first-in-human trial in healthy adults showed adequate safety as well as increased specific humoral and cellular immune responses.[44] The results of the phase 2 study have not yet been published so further lessons learned and analysis of the results are pending. Potentially the choice of vaccine antigens was not optimal for an effective immune response.

LAVs

LAVs are designed to generate a potent immune response, including a local mucosal antibody and cellular response, by mimicking natural infection while being attenuated for reduced virulence. Genetic stability is important to limit the chance of reversion to wildtype virus. A better understanding of the RSV genome and reverse genetics has allowed the rational design of LAV candidates by deleting or modifying proteins known to be important in RNA synthesis regulation or interference with host-immune responses (eg, M2-2, NS2, SH, L, and G proteins) leading to restricted viral replication.[45]

An analysis of the compiled results of seven phase 1 trials using intranasal LAV (n=239; children aged 6–24 months) provides information on vaccine safety, efficacy, and duration of protection of RSV LAV candidates.[45] LAVs are considered safe after first exposure, because vaccine-enhanced disease has not been detected after LAV immunisation, although LAV have the potential to induce upper respiratory illness if attenuation is insufficient.[45] Estimated efficacy from compiled data of five vaccine candidates was 67% (95% CI 24 to 85) against medically-attended RSV acute-respiratory illness and 88% (–9 to 99) against medically-attended RSV LRTI. On an immunological level, a four times rise in RSV-plaque reduction neutralising antibody titre was predictive of vaccine efficacy and responses were durable through 1 year after vaccination.[45]

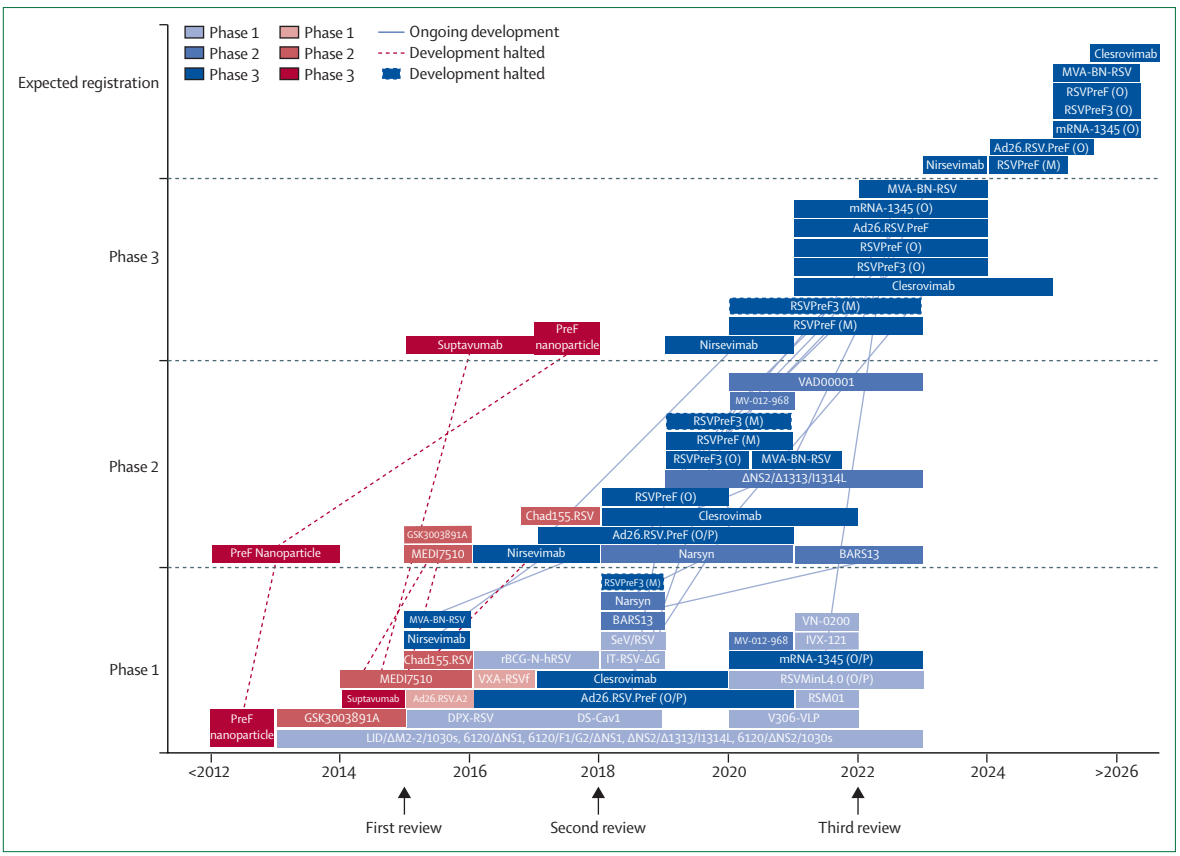

Figure 4: **Historical perspective of RSV vaccine and immunoprophylaxis development over the last 10 years and expected market access**
Candidates that are in ongoing development (blue) or no longer in development (red) are presented at the timing of the clinical trials rounded off to full years. The darkness of the colour represents the furthest development (phase 1, 2, or 3) of the candidate. Candidates with multiple clinical trials are connected with full or dotted lines to show the speed of development. Live attenuated viruses by the same manufacturer are summarised in one box as development of these candidates largely overlaps. The timing of current and previous RSV vaccine landscape reviews is shown at the bottom. RSV=respiratory syncytial virus. PreF=prefusion protein. The development of RSVPreF (M) was not discontinued but instead halted (dotted box). Expected registration was estimated by adding 1 year after published interim results, or if not available by adding 1 year to the estimated completion year published on ClinicalTrials.gov. In case of a phase 1/2 or 2/3 trial, the trial has only been placed in the furthest developed stage.

There are six phase 1 trials and four candidates that have progressed to phase 2 trials. The National Insitute of Health and National Insitute of Allergy and Infectious Disease and others are developing LAV candidates with an NS2 deletion and temperature sensitivity mutation: RSV ΔNS2/Δ1313/I1314L (phase 2);[46] and RSV 6120/ΔNS2/1030s (phase 1).[47,48] MV-012–968 (altered NS1 and NS2 and G proteins, SH deletion, and ablation of secreted G protein)[49] has been shown to be safe and to generate a mucosal IgA response in seropositive adults and children.[50] A safety trial in seronegative children and a human challenge trial in healthy adults to show efficacy are being conducted for this vaccine candidate.[51–53] IT-RSV-ΔG (absent G protein) was safe in seropositive healthy adults. However, the serum neutralising antibody response was low, and nasal IgA antibodies were below the level of detection; immunogenicity needs to be further studied in children and eventually in seronegative infants.[54] Other candidates include LIDΔ M2–2/1030s,[55] 6120/ΔNS1 and 6120/F1/G2/ΔNS1 (NCT03596801) in phase 1 trials, and VAD00001 (NCT04491877) in phase 2 trial. RSV-MinL4·0 (altered polymerase gene) showed a humoral and cellular immune response similar to wildtype infection in non-human primates and is in phase 1 trials.[56,57]

Overall, LAVs provide an important needle-free tool for active intranasal immunisation of older infants who will not be sufficiently protected by a mAb or maternal vaccine. Moreover, a relatively small sample size (n=540) is needed for a phase 3 trial in this population.[45] Further clinical development using this vaccination approach might affect paediatric health directly by reducing paediatric infections and infections in older adults indirectly through herd immunity.

Chimeric

Chimeric live virus vaccine candidates express RSV proteins in related attenuated viruses with favourable safety profiles. In contrast to vectored vaccine candidates, chimeric vaccines show favourable antigen presentation

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See **Online** for appendix

For **Vaccines for the World Conference** see https://www.resvinet.org/rsvvw21.html

	Manufacturing process	Antigen	Adjuvant	Mechanism of action	Target population	Route of administration	Clinical phase	Animal models	Phase 1 trial	Phase 2 trial	Phase 3 trial	Results
Subunit vaccine												
VN-0200, Daiichi Sankyo	..	VAGA-9001a	MABH-9002b	..	O	IM	1	..	June, 2021, to January, 2022; NCT04914520; 48 participants	..	..	..
DS-Cav1, National Insitute of Health and National Insitute of Allergy and Infectious Disease	Structure-based vaccine design	Stabilised preF DS-Cav1	None or alum	RSV preF	O	IM	1	Cotton rats, calves, mice, macaques	February, 2017, to October, 2019; NCT03049488; 95 participants	..	..	Phase 1: safe and well-tolerated; vaccination elicited robust neutralising Ab response sustained at 44 weeks
DPX-RSV, Immunovaccine	DepovaxTM, a lipid-in-oil delivery system	SHe	DepoVax (DPX-RSV[A]), DPX, or aluminum hydroxide	SHe generate a non-neutralising Ab and CD4+ T-cell response	O	IM	1	Cotton rats, mice	May, 2015, to June, 2017; NCT02472548; 40 participants	..	..	Phase 1: safe and well-tolerated, no serious adverse events, antigen-specific Ab response durable >6 months
BARS13, Advaccine	..	G	None or cyclosporine A	RSV G; immuno–suppressant	P and O	IM	2	..	October, 2018, to August, 2019; NCT04851977 and ACTRN12618–000948291; 60 participants	May, 2021, to June, 2023; NCT04681833; 120 participants	..	Phase 1: safe and well tolerated, substantial Ab response (90% in low dose groups *vs* 100% in high-dose groups)
RSVPre-F3/ GSK3844766A, GlaxoSmithKline	..	PreF3	None	Induce immune response with stabilised preF	P and O	IM	3	..	January, 2019, to November, 2020; NCT04090658, NCT03814590, and NCT04657198; 1055 participants	January, 2019, to November, 2020; NCT04090658 and NCT04657198; 1055 participants	February, 2021, to May, 2024; NCT04886596; 25000 participants February, 2021, to May, 2024; NCT04732871; 1720 participants February, 2021, to May, 2024; NCT05059301; 750 participants	Phase 1 and 2: humoral and cellular immune responses in all vaccines; older adults had higher humoral response (mostly neutralising) with higher dosage and higher cellular response with adjuvant Phase 3: interim analysis showed efficacy and the effect was consistent among RSV A and B strains

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	Manufacturing process	Antigen	Adjuvant	Mechanism of action	Target population	Route of administration	Clinical phase	Animal models	Phase 1 trial	Phase 2 trial	Phase 3 trial	Results
(Continued from previous page)												
RSVPreF3/ GSK3888550A, GlaxoSmithKline	..	PreF3	None	Induce immune response with stabilised preF	M	IM	3, halted	..	October, 2018, to September, 2019; NCT03674177; 502 participants	July, 2020, to May, 2021; NCT04126213; 534 participants	November, 2020, to February, 2024; NCT04605159; 20 000 participants September, 2021, to May, 2022; NCT05045144; 1541 participants	Phase 1 and 2: robust increase in maternal RSV-specific Ab responses and RSV-A and RSV-B neutralising Ab titres; successful Ab transfer to foetus until 6 months after birth
RSVPreF, Pfizer	Bivalent stabilised preF, sequence based on contemporary RSV A and B strains	pre-F	None or Al(OH)3 or alum adjuvanted	Induce immune response with stabilised preF	M	IM	3	Animal studies, specifics unknown		April, 2018, to December, 2020; NCT03529773; 1235 participants November, 2020, to August, 2021; NCT04785612 (controlled human infection model); 62 participants October, 2019, to December, 2019; NCT04071158; 713 participants; August, 2019, to September, 2021; NCT04032093; 1153 participants	June, 2020, to November, 2023; NCT04424316; 10000 participants	Phase 1 and 2: patients were aged 18–49 years; safe and well tolerated; immunisation elicited ten to 20 times increases in neutralising Ab titres
RSVPreF, Pfizer	Bivalent stabilised preF, sequence based on contemporary RSV A and B strains	preF	None	Induce immune response with stabilised preF	O	IM	3	Animal studies, specifics unknown		April, 2018, to December, 2020; NCT03529773; 1235 participants November, 2020, to August, 2021; NCT04785612; 62 participants October, 2019, to December, 2019; NCT04071158; 713 participants August, 2019, to September, 2021; NCT04032093; 1153 participants	August, 2021, to June, 2024; NCT05035212; 30000 participants	Phase 1 and 2: patients were aged 18–49 years; safe and well tolerated; immunisation elicited ten to 20 times increases in neutralising Ab titres

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	Manufacturing process	Antigen	Adjuvant	Mechanism of action	Target population	Route of administration	Clinical phase	Animal models	Phase 1 trial	Phase 2 trial	Phase 3 trial	Results
(Continued from previous page)												
Particle-based vaccine												
V306-SVLP, Virometix	Synthetic peptides conjugated to a synthetic nanoparticle made from self-assembling lipopeptides	V-306	Pam2Cys	Synthetic virus-like particle displays a universal T-helper epitope, lipid component (Pam2C) and mimetic of the Palivizumab epitope (FSIIm)	M	IM with skin patch boosters	1	Mice and rabbits	September, 2020, to March, 2022; NCT04519073; 60 participants	..	..	..
IVX-121, Icosavax	Self-assembling virus-like particle platform technology to deliver stabilized trimeric preF proteins	Stabilised Pre-F DS-Cav1	None or alum	Presentation of DS-Cav1 on computationally designed virus-like particle generates a neutralising Ab response against preF	O	IM	1	Mice	2021; 90 participants	..	..	..
Nucleic acid vaccine												
mRNA-1345, Moderna	Lipid nanoparticle containing optimised protein and codon sequences	preF	None	mRNA encodes for a stabilised preF glycoprotein eliciting neutralising antibodies	O	IM	2 and 3	..	September, 2020, to September, 2023; NCT04528719; 100 healthy adults, 300 older adults, 180 women, and 40 children	Phase 2 and 3; November, 2021, to November, 2024; NCT05127434; 34000 participants	Phase 2 and 3; November, 2021, to November, 2024; NCT05127434; 34000 participants April, 2022, to January, 2023; NCT05330975; 1350 people	Phase 1: well tolerated at doses up to 200 µg; geometric mean concentration ≥9·8 times rise in neutralising Abs at 1 month for RSV A and ≥5·3 times rise in neutralising Abs at 1 month for RSV B; three doses helped maintain peak titers through month 5 in younger adults
mRNA-1345, Moderna	Lipid nanoparticle containing optimised protein and codon sequences	preF	None	mRNA encodes for a stabilised preF glycoprotein eliciting neutralising antibodies	P	IM	1	..	September, 2020, to September, 2023; NCT04528719; 40 children aged 12–59 months	..	..	..

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	Manufacturing process	Antigen	Adjuvant	Mechanism of action	Target population	Route of administration	Clinical phase	Animal models	Phase 1 trial	Phase 2 trial	Phase 3 trial	Results
(Continued from previous page)												
Recombinant vectors vaccine												
MVA-BN RSV, Bavarian Nordic	MVA-BN platform technology	F, G (A & B subtype), and N and M2	None	Simulate robust T-cell response against 5 RSV antigens and moderate humoral response against both RSV subtypes	O	IM	3	BALB, c mice, and cotton rats	August, 2015, to May, 2016; NCT02419391; 63 participants	September, 2016, to December, 2018; NCT02873286; 420 participants February, 2021, to June 2021; NCT04752644; 73 participants	To be announced end 2021	Phase 2: broad and durable Ab and T-cell response, substantial booster response after 1 year; phase 2: controlled human infection model; substantial reduction in viral load and no vaccine-related serious adverse events
AD26.RSV.PreF, Johnson & Johnson	Human cell line, PERC6 (Ad26) encoding RSV F from RSV-A2 strain	preF	None	Replication-incompetent Adenovirus 26 containing DNA for RSV-A2 F protein stabilised in preF conformation	O	IM	3	Neonatal and adult mice	November, 2016, to January, 2021; NCT02926430; 73 participants November, 2016, to January; NCT03795441; 24 participants November, 2016, to January; NCT04354480; 36 participants	October, 2017, to June, 2022; NCT04453202, 459 participants October, 2017, to June, 2022; NCT03502707; 669 participants October, 2017, to June, 2022NCT03–303625; 48 participants October, 2017, to June, 2022; NCT03334695; 64 participants October, 2017, to June, 2022; NCT03339713; 180 participants October, 2017, to June, 2022; NCT03982199; 5815 participants	July, 2021, to January, 2024; NCT04908683; 23000 participants	Phase 1: safe in older adults and sustained immune responses after 2 years Phase 2: 80% vaccine efficacy and robust cellular and humoral immune response; phase 2 controlled human infection model: lower viral load and lower infection rate and disease severity in intervention group
AD26.RSV.PreF, Johnson & Johnson	Human cell line, PERC6 (Ad26) encoding RSV F from RSV-A2 strain	PreF	None	Replication-incompetent adenovirus 26 containing DNA for RSV-A2 F protein stabilised in preF conformation	P	IM	1 and 2	Neonatal and adult mice	November, 2017, to April, 2020; NCT03303625; 48 participants January, 2019, to November, 2021; NCT03606512; 38 participants	November, 2017, to April, 2020; NCT03303625; 48 participants January, 2019, to November, 2021; NCT03606512; 48, and 38 participants	..	Phase 1 and 2: well-tolerated and elicited both humoral and cellular immune responses

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	Manufacturing process	Antigen	Adjuvant	Mechanism of action	Target population	Route of administration	Clinical phase	Animal models	Phase 1 trial	Phase 2 trial	Phase 3 trial	Results
(Continued from previous page)												
Immunoprophylaxis vaccines												
Narsyn, UMC Utrecht	Intranasal formulation of humanised mouse mAb	..	None	mAb targeting site 2 of the RSV F protein; neutralisation	P	IN	2	Balb/c mice	October, 2018, to November, 2018; NTR7378; 20 participants	November, 2018, to April, 2020; NTR7403; 408 participants	..	Phase 1: safe in healthy adults
Clesrovimab (MK 1654), Merck	In-vitro optimised human mAb with three YTE mutations in Fc-domain	..	None	mAb targeting site 4 of the RSV F protein with extended half-life; neutralisation	P	IM or IV	1, 2, and 3	Cotton rats	June, 2017, to February, 2019; 152 adults September, 2018, to September, 2022; NCT03524118; 180 infants	September, 2018, to September, 2022; NCT03524118; 180 infants March, 2020, to August, 2020; NCT04086472 (controlled human infection model); 80 participants	November, 2021, to August, 2025; NCT04938830; 1000 high-risk infants April 2021, to September, 2024; NCT04767373; 3300 healthy infants	Phase 1: safe in adults; controlled human infection model efficacy 0·62 (95% CI −0·05 to 0·86) for prevention of RSV lower tract respiratory infection
Nirsevimab, (MEDI8897), Astra Zeneca, MedImmune LLC	In-vitro optimised human mAb with YTE mutation in Fc	..	None	mAb targeting site Ø of the RSV F protein with an extended half-life; neutra–lisation	P	IM	3	Cotton rats, cynomolgus, and monkeys	April, 2015 to June, 2015; NCT0211426; 342 participants January, 2015 to September, 2016; NCT0229034; 151 participants	November, 2016, to July, 2018; NCT02878330; 1453 participants August, 2020, to January, 2023; NTC04484935; 100 immuno–compromised children	July, 2019, to May, 2022; NCT03959488 (MEDLEY); 925 high-risk children July, 2019, to March, 2023; NCT03979313 (MELODY); 3000 healthy children	Phase 2b: safety and tolerability similar to palivizumab in 25 countries worldwide; Phase 3 interim: 75% efficacy against medically attended RSV LRTI
RSM01, Gates Medical Research Institute	In-vitro optimised human mAb with YTE mutation in Fc	..	None	mAb targeting site x of the RSV F protein with an extended half-life; neutra–lisation	P	IM or IV	1	..	November, 2021, to February, 2022; NCT05118386; 56 participants	..	..	..
Chimeric vaccine												
SeV/RSV, National Insitute of Allergy and Infectious Disease	Modified mouse parainfluenza virus type 1	F	None	SeV expressing RSV F protein	P	IN	I	African green monkey	May, 2018, to February, 2019; NCT03473002; 21 participants	..	..	..
rBCG-N-hRSV, Pontificia Universidad Católica de Chile	Live-attenuated recombinant *Mycobacterium bovis* (rBCG) based on Danish strain 1331 that expresses N	N	None	Recombinant BCG used as a vector to deliver RSV N	P	IN	1	Mice and holstein calves	June, 2016, to June, 2018; NCT03213405; 24 participants	..	..	Phase 2: safe and well tolerated; no serious adverse events; humoral and cellular response against N and purified protein derivative

(Table continues on next page)

	Manufacturing process	Antigen	Adjuvant	Mechanism of action	Target population	Route of administration	Clinical phase	Animal models	Phase 1 trial	Phase 2 trial	Phase 3 trial	Results
(Continued from previous page)												
Live-attenuated vaccine												
RSV-MinL4·0, Codagenix	Reverse engineering of 4 mutations in the L protein	All viral proteins	None	L alterated for attenuation	O	IN	1	Non-human primates	July, 2020, to May, 2021; NCT04295070; 36 participants	..	..	..
RSV-MinL4·0, Codagenix	Reverse engineering of 4 mutations in the L protein	All viral proteins	None	L alterated for attenuation	P	IN	1	Non-human primates	March, 2022, to February, 2023; NCT04919109; 36 participants	..	..	..
IT-RSVΔG, Intravacc	Reverse genetics to delete G protein from the RSV genome	All viral proteins	None	Severely impaired binding to host cells due to absent G-protein reducing infectivity	P	IN	1	Cotton rats	May, 2018, to March, 2019; NTR7173; 48 participants	..	..	Phase 1: safe and well tolerated; neutralising antibody response absent in seropositive adults
MV-012–968, Meissa	Codon deoptimisation of NS1/NS2/G, SH deletion and ablation of secreted G through AttenuBlock synthetic biology platform	All viral proteins	None	Reduced NS1 and NS2 expression for enhanced immuno–genicity, SH deletion and G de-optimisation for attenuation	P	IN	1 and 2	BALB/c mice; cotton rats	January, 2020, to August, 2020; NCT04227210; 20 participants June, 2020, to May, 2021; NCT04444284; 20 participants June, 2021, to October, 2022; NCT04909021; 45 participants	December, 202 to May, 2021; NCT04690335; 60 participants	..	Phase 1: well tolerated, heavily attenuated, and induces an RSV-specific mucosal IgA response in healthy seropositive 0 and P participants
RSV ΔNS2/ Δ1313 / I1314L, National Insitute of Allergy and Infectious Disease (Sanofi)	Reverse genetics: NS2 deletion, L stabilisation; I1314L stabilising mutation via reverse genetics	All viral proteins	None	NS2 deletion bolsters innate response, deletion at position 1313 of L protein, and I1314L stabilisation confers moderate temperature sensitivity	P	IN	1 and 2	Mice and chimpanzees	June, 2013, to April, 2023; NCT03227029; 65 participants June, 2013, to April, 2023; NCT03422237; 80 participants June, 2013, to April, 2023; NCT03916185; 160 participants June, 2013, to April, 2023; NCT01893554; 105 participants	May, 2019, to April, 2023; NCT03916185; 160 participants	..	Genetically stable; attenuated yet immunogenic in RSV seronegative P

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	Manufacturing process	Antigen	Adjuvant	Mechanism of action	Target population	Route of administration	Clinical phase	Animal models	Phase 1 trial	Phase 2 trial	Phase 3 trial	Results
(Continued from previous page)												
RSV LID/ΔM2–2/1030s, National Insitute of Allergy and Infectious Disease (Sanofi)	Reverse genetics: M2-2 deletion and L mutation at position 1030s	All viral proteins	Non-adjuvanted	Inefficient replication yet high immunogenicity due to ML2-2 deletion ; moderate temperature sensitivity due to L mutation	P	IN	1	Mice, African green monkeys	September, 2020, to April 2022; NCT04520659; 81 patients	..	..	85% of vaccinees shed LID/ΔM2–2/1030s vaccine and ≥4 rise in serum-neutralising Abs
RSV 6120/ΔNS2/1030s, National Insitute of Allergy and Infectious Disease (Sanofi)	NS2 gene deletion and temperature sensitivity mutation (1030s) of L	All viral proteins	Non-adjuvanted	NS2 deletion bolsters innate response, sensitivity mutation (1030s) of L	P	IN	1	..	May, 2019, to April, 2023; NCT03916185; 160 patients October, 2017, to May, 2021, NCT03387137; 45 patients		..	..
RSV 6120/F1/G2/ΔNS1, National Insitute of Allergy and Infectious Disease (Sanofi)	Optimised NS1 deletion	All viral proteins	Non-adjuvanted	NS1 gene-deletion; increased F and G expression by moving to first and second genome positions	P	IN	1	..	June, 2018, to December, 2023; NCT03596801; 75 patients	..	..	..
RSV 6120//ΔNS1, National Insitute of Allergy and Infectious Disease (Sanofi)	Optimised NS1 deletion	All viral proteins	Non-adjuvanted	NS1 gene-deletion	P	IN	1	..	June, 2018, to December, 2023; NCT03596801; 75 patients	..	..	..
VAD00001 (SP0125), National Insitute of Allergy and Infectious Disease (Sanofi)	..	..	Non-adjuvanted	..	P	IN	1 and 2	Mice	September, 2020, to April, 2023; NCT04491877; 300 patients	September, 2020, to April, 2023; NCT04491877; 300 patients	..	..

Ab=antibody. mAb=monoclonal antibody. preF=prefusion protein. RSV=respiratory syncytial virus. ..=not applicable or not available. ID=Intradermal. IM=Intramuscular. IN=Intranasal. M=Maternal. O=Adults and older adults (aged ≥65 years). P=Pediatric.

Table: **Overview of RSV vaccines and mAbs in clinical development**

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which activates an adaptive immune response.[58,59] There are two chimeric RSV vaccine candidates in phase 1 trials. One of these candidates uses a replication-deficient Sendai virus modified to express RSV F protein (SeV/RSV)[58] and the other uses a live-attenuated recombinant BCG vector expressing RSV N protein (rBCG-N-hRSV)[60] administered via the intradermal route. The latter vaccine candidate was found to be safe in phase 1 trial.[60]

Subunit

Subunit vaccines are protein based; this approach has been avoided in RSV-naive children due to the formalin-inactivated-RSV experience with enhanced respiratory disease in which it became clear enhanced respiratory disease is a concern for people not primed with live virus infection.[61] In parallel to the phase 3 trail[39] failure of a post-F subunit vaccine candidate, five vaccine candidates have adopted pre-F as vaccine antigen. Eight subunit candidates are in development for two different target populations: pregnant women and older adults. We discuss vaccine candidates using fusion antigens first, followed by candidates employing nonfusion antigens.

The phase 1 results of DS-Cav1, a subunit vaccine using stabilised pre-F developed by the National Insitute of Health and National Insitute of Allergy and Infectious Disease, provide proof-of-concept of structure-based vaccine design. Vaccination resulted in more than ten times increase in serum neutralising activity[62] and is sustainable for an entire RSV season.[63] Two other candidates use a stabilised pre-F protein as vaccine antigen. RSVpre-F (PF-06928316) is a bivalent (subtype A and B) stabilised pre-F without adjuvants. A phase 2 trial[64] was done in non-pregnant women with RSVpreF. co-administered with diphtheria toxoid and acellular pertussis vaccine, which showed safety and noninferiority relative to RSV pre-F alone.[64] The anti-pertussis response was inferior (geometric mean concentration between 0·59 and 0·8 for pertussis antigens compared with diphtheria toxoid and acellular pertussis alone) yet the clinical significance of these findings is still unclear and did not differ when adjusted for age.[65] The phase 3 MATISSE trial[66] in women who were pregnant was started in 2020 and is expected to be unblinded in the fourth quarter of the trial in 2023.[67] A human challenge trial[66] showed 75% efficacy of RSV pre-F against RSV infection and informed dose and formulation selection for the maternal vaccine candidate.[68] The phase 3 RENOIR trial[60] using the same vaccine candidate has started in the fall of 2021, in 30 000 older healthy and high-risk adults.[69] Another pre-F subunit vaccine, RSVpreF3, is in phase 3 clinical trials without adjuvant (GSK3888550A) for RSV maternal immunisation to protect infants (GRACE trial)[70] and with AS01 adjuvant (GSK3844766A)[72] to protect the older adult population. Development was halted for the maternal vaccine candidate in Feb 18, 2022, due to a safety signal. The older adult candidate was safe and induced approximately a ten times increase in pre-F IgG and IgA antibodies (48 adults aged 18–40 years; 1005 adults aged 60–80 years) in phase 1 to 2 clinical trials.[72–74] Interim analysis of the phase 3 trial for the older adult candidate showed efficacy against RSV lower respiratory tract infection (NCT04886596). For the maternal candidate, phase 1 and 2 studies showed a 14 times increase in RSV A and B neutralising antibody titers 1 week after vaccination and maintained a six times increase or more after 91 days in healthy women who were not pregnant (n=502).[74] In the phase 3 study[75] of the maternal vaccine candidate, the immune response was durable as antibody levels for vaccinees remained elevated against RSV A and RSV B for 6 months after birth. Registration of RSVpreF maternal vaccine is expected in 2024, and RSVpreF older adult and both RSV pre-F3 vaccine candidates in 2025, assuming registration is obtained within 1 year after phase 3 completion date according to the clinical trial registry.

There are three protein-based vaccines in clinical development that use non-F viral antigens. First, BARS13 uses RSV G protein as an antigen and cyclosporine A (CSA) immunosuppressant to induce regulatory T cells. BARS13 was safe and immunogenic in phase 1[76] and is now in phase 2[77] trials. Second, DPX-RSV, uses the ectodomain of RSV-A-SHe protein as a vaccine antigen formulated in depot-based lipid-in-oil delivery platform to allow for prolonged antigen and adjuvant exposure. The proposed mechanism of action against this antigen is generation of SHe-specific antibodies, which promote clearance of RSV-infected cells by alveolar macrophage phagocytosis. DPX-RSV showed safety and immunogenicity in a phase 1 first-in-human trial in adults aged 50–64 years.[78,79] Finally, VN-0200, uses VAGA-9001a as antigen and an MABH-9002b adjuvant (phase 1).[80] We were not able to define the biological background of VAGA-9001a.

Particle-based

Particle-based vaccines harness the immunogenical potential of displaying multiple antigens via particle assembly. IVX-121 uses a self-assembling synthetic virus-like particle platform technology to deliver 20 copies of stabilised trimeric pre-F proteins (DsCav-1). The computationally designed nanoparticle allows for stabilisation of the pre-F protein and in-vitro adjustment of antigen density. IVX-121 showed 10 times higher neutralising antibody responses than did DSCav1 alone in preclinical studies.[81] A phase 1 trial[82] started in 2021, with first results expected in 2022. After completion of the monovalent RSV candidate trial, the company plans to shift to development of a bivalent virus-like particle vaccine with both RSV and human metapneumovirus antigens.

A second particle-based vaccine candidate, V306-VLP, uses a synthetic virus-like particle to display a site 2 F

protein epitope. The vaccine platform uses conformationally constrained synthetic peptides conjugated to a synthetic nanoparticle made from self-assembling lipopeptides containing a T-helper epitope and toll-like receptor ligand.[83] The vaccine candidate aims to boost pre-existing immunity in pregnant women or older adults.[84] A phase 1 trial is being done in healthy women.[85] The needle-free intradermal delivery route via an epicutaneous patch is being explored for boosters and has shown similar antibody titers for pertussis as a commercial vaccine in a phase 1 trial[84] but might require a delivery enhancement procedure to optimise vaccine delivery. Overall, particle-based vaccines are still in early development but have the potential to elicit a powerful immune response for pregnant women and the elderly.

Nucleic acid

mRNA vaccines have shown safety and high efficacy against SARS-CoV-2 infection and were developed based on previous work for RSV.[86] Both mRNA COVID-19 vaccines express stabilised versions of SARS-CoV-2 pre-F spike protein patterned after the success of RSV pre-F as a vaccine antigen. The extensive work on RSV vaccine-associated enhanced respiratory disease was also important for the rapid development of COVID-19 vaccines and provided regulatory guidelines for vaccine safety. Because of the successful scale-up and establishment of a robust supply chain, mRNA will be a new vaccine modality available for other purposes including RSV vaccines. An mRNA vaccine (mRNA-1345) encodes stabilised RSV pre-F and uses the same lipid nanoparticle formulation as for the SARS-CoV-2 vaccine SpikeVax (Moderna) that is known to induce and boost antibody and T-cell responses, including CD8+ T cells, Th1 cells, and T follicular helper cells. The interim results of the phase 1 trial in younger and older adults showed favourable safety and potent boosting of neutralising activity.[87] A phase 2/3 trial (ConquerRSV) started on Nov 17, 2021, with 34 000 adults older than 60 years.[88] The company intends to combine mRNA-1345 with mRNA-1653 (an mRNA vaccine against two other pediatric viruses, hMPV and parainfluenza virus type 3 intended for use in the pediatric population). A phase 1 trial is ongoing (NCT04144348) in women of childbearing age and seropositive children.

Recombinant vectors

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

Firstly, MVA-BN-RSV uses a poxvirus vector, modified vaccinia Ankara virus, to express RSV surface antigens (F and G) and intracellcular proteins (M2 and N).[89] In a phase 1 trial cellular and humoral immune responses were similar in younger and older adults.[89] Results of a phase 2a human challenge study (n=61) showed 79% reduction in symptomatic RSV infection and a reduction in viral load.[90] The phase 2 trial[91] in older adults showed elevated antibody responses for 6 months which can be safely boosted at 12 months. After dose selection from the phase 2 trial, preparations for a phase 3 trial are ongoing.[92]

Ad26.RSV.pre-F is being developed for two different target populations: paediatric (phase 2 trial; NCT03303625 and NCT03606512) and elderly (phase 3 trial; NCT04908683). Ad26.RSV.pre-F vaccine candidate uses an adenoviral vector to express the RSV F protein in the pre-F conformation.[93] The vaccine candidate showed improved immunogenicity in comparison to the previous vaccine candidate with post-F RSV protein (Ad26.RSV.FA2). In neonatal mice, the vaccine candidate showed a biased reponse to a Th1-biased response cells.[94] A durable humoral and cellular immune response was shown for at least 2 years after immunisation in the first-in-human study in adults aged 60–81 years.[95] Proof-of-concept was obtained in the first RSV vaccine human challenge study.[96] In the primary efficacy results from the proof-of-concept CYPRESS study,[97] Ad26.RSV.pre-F showed 80% (95% CI 52 to 93) efficacy against RSV LRTI through the first RSV season in the older adult population. Ad26.RSV.pre-F was found to be safe and well-tolerated[98] and showed efficacy in adults aged 65 years or older with or without risk factors (68% [–27 to 95] *vs* 85% [50 to 97]).[99] Furthermore, there was no interference when an RSV vaccine was co-administered with seasonal influenza vaccine in older adults in a phase 2 trial,[100] and the vaccine candidate was shown to have an acceptable safety profile although showing increased reactogenicity compared to influenza vaccination. In 2019, this candidate was granted US Food and Drug Administration breakthrough therapy designation. Subsequently, the phase 3 EVERGREEN trial[101] was started on July 21, 2021 and will examine efficacy across two RSV seasons in 23 000 adults aged 60 years and above. For the paediatric vaccine candidate a phase 1/2b trial in seropositive infants aged 12–24 months showed Ad26.RSV.Pre-F was well-tolerated and elicited both humoral and cellular immune responses.[102] Of note, a SARS-CoV-2 adenovirus vector vaccine candidate uncovered new safety concerns with adenoviral vector vaccines, including vaccine-induced immune thrombotic thrombocytopenia which was observed for at least two of the COVID-19 adenoviral vector vaccines.[103]

MAbs

MAbs have been labelled as the magic bullet against infection because of their high pathogen specificity.[104] For RSV, increased knowledge of the structure and immunogenicity of the RSV fusion protein has resulted in next generation antibodies targeting highly neutralisation-sensitive epitopes located on the RSV pre-F protein. Furthermore, next generation RSV antibodies have been

engineered with Fc mutations to extended half-life and enable protection of all infants against lower respiratory tract disease for an entire RSV season.

The leading candidate is nirsevimab (formerly MEDI-8897), a human mAb targeting site Ø of the F protein with a YTE mutation in the Fc portion to allow for an extended half-life. In phase 2 trial[105] results (n=1453) nirsevimab showed 70% (95% CI 52 to 81) efficacy against medically-attended RSV LRTI and 78% (52 to 90) against RSV hospitalisation in preterm infants,[105] which is similar to the phase 3 trial interim results: 75% (50 to 87) against RSV lower tract respiratory infection and 62% (–9 to 87) against RSV hospitalisation among healthy late preterm and full-term infants (n=1490).[106] The safety profile of nirsevimab is similar to that of the current standard of care, monthly palivizumab, administered to infants with congenital heart or lung disease (n=310) and preterm infants between 29 and 35 weeks gestational age (n=615).[106] RSV monoclonal antibody resistant mutants were generated and were shown not to have an effect on viral replication and had a low natural frequency amongst circulating strains.[107] The most prominent advantages of nirsevimab in contrast to the approved palivizumab are that a single intramuscular injection protects infants for an entire season compared with monthly doses, and reduced costs (vaccine-like pricing expected) allowing for administration to all infants compared with only high-risk children.

Clesrovimab (MK-1654), an extended half-life mAb with the same YTE mutation as nirsevimab, targets site IV (although preferentially binding pre-F due to partial targeting of site V of the RSV F protein). This mAb is in phase 2b/3 trials (NCT04767373) and phase 3 trials (NCT04938830) in infants. This mAb has shown high potency against RSV clinical isolates in vitro and is equipotent against RSV subgroup A and B strains.[108] A human challenge trial[109] (n=80) showed reduced viral load after viral challenge and reduced RSV symptomatic infection rates. A meta-analysis[110] was done to assess the relationship between serum neutralising antibodies and clinical endpoints; the study estimated a single 75 mg dose would have more than 75% efficacy lasting 5 months in term infants. The company developing this agent has committed to helping navigate uncertainty and improving issues of access through ongoing research and innovation to help address the burden of potentially preventable childhood diseases (Andrew W Lee, Merck, personal communication).

Affordability remains a key consideration for mAb development as it is a potential barrier to global access. There are three different clinical development efforts underway to circumvent this problem: (1) an affordable extended half-life site Ø mAb, (2) local administration, and (3) a biosimilar. First, a phase 1 trial of RSM01,[111] a site Ø mAb, intended for LMICs has a target price of less than US$5 per dose.[112] Second, local needle-free administration of palivizumab, a market-approved site II mAb, via nose drops might significantly reduce costs by reducing the drug dose needed.[113] Results of a phase 1 and 2b trial will soon be published for intranasal palivizumab administration to prevent RSV infection. Finally, a biosimilar for palivizumab is being developed in a public-private partnership with the Utrecht Center for Affordable Biotherapeutics, Utrecht, the Netherlands, for which a human challenge trial was done in 2020 (n=56), but the results of this trial have not yet been made publicly available.[114]

Important considerations for the development of next-generation mAbs are affordability, which can be achieved by investing in higher efficiency production or developing biosimilars or potentially through local administration. Likewise, viral resistance needs to be monitored and might be prevented through administration of a cocktail of mAbs targeting multiple epitopes. Monthly administration of intranasal mAbs or a palivizumab biosimilar might have a programmatic limitation in most LMICs. Potentially, a combination of mAbs targeted to different epitopes might provide a solution to loss of efficacy due to viral resistance. However, practical barriers exist to this solution as the combination would have to consist of separately registered antibodies. Thus far, the epitopes for mAbs being developed are highly conserved with minimal naturally occurring antibody-resistant strains, which have shown similar or lower viral fitness when compared with non-resistant viral strains in vitro.

Discussion

In the last decade, the RSV vaccine landscape has had a major transition from empirical to rational vaccine design. In two previous reviews[33,38] we characterised the dynamics of the RSV vaccine landscape, which included multiple late-phase failures. These failures have laid the foundation for future success by guiding development of vaccines: supporting pre-F as a vaccine antigen, highlighting the importance of conducting vaccine trials over more than one RSV season, providing knowledge of a protective immune response, emphasising the importance of monitoring viral resistance to mAbs, and highlighting the value of controlled human infection model to decrease the risk of RSV vaccine development. The number of candidates in late-phase development is expanding: only one mAb and one maternal vaccine candidate were in phase 3 development as of 2015 and 2018, respectively. Development was halted for both after failure to meet the primary endpoints of the trials, but important lessons learned have been incorporated into current trials. A better understanding of RSV neutralising epitopes has resulted in rapid expansion to the nine vaccine candidates in phase 3 trials (figure 4).

RSV prevention appears to be on the horizon with market access expected for nirsevimab within the next 12 to 24 months as of July, 2022. This approval might be followed shortly by approval of a maternal vaccine and

a vaccine for older adults (subunit, vector-based, and nucleic vaccines in late phase trials). In this case a situation will emerge in which multiple RSV vaccine candidates are approved. If all the ongoing phase 3 trials generate positive results, relative efficacy and safety trial data, delivery strategies, and costs might determine vaccine uptake for different maternal and older adult candidates. Despite the approval of next-generation antibodies, palivizumab might remain on the market until there is global market access of extended half-life mAbs and because mAb supply might not meet global demand. RSV has shown negligible viral resistance against palivizumab after 20 years on the market.[115] For this reason, despite multidose schedule and costs, palivizumab might act as a back-up prophylaxis strategy while waiting for global real-time viral resistance data upon mAb implementation in HICs.

With both infant immunoprophylaxis and maternal vaccines on the market, it is important to consider how these two prevention strategies aiming to protect young infants will coexist. Maternal vaccines and infant immunoprophylaxis might have a complementary role in the prevention of severe RSV infection during infancy. There is a clear use-case for mAbs even if a maternal vaccine is approved: mAbs are expected to protect premature and full term infants, might be able to provide a longer duration of protection than maternal vaccines,[116,117] can be applied flexibly where RSV seasonality is variable, and can be implemented in cases where maternal immunisation did not occur. There is also a use case for a maternal vaccine in coexistence with an approved mAb. Active maternal vaccination provides broad protection; however, it is still unclear if maternal vaccination persists until a subsequent pregnancy and whether booster vaccination provides even stronger protection. Maternal vaccination might also provide an alternative for parents preferring not to vaccinate their babies. Finally, maternal vaccines serve as a backup in the case of viral resistance to mAbs or prohibitively high costs related to the production of biologicals that limit administration only to select populations.

In LMICs, there is a use case for mAbs to protect young infants: if there is a substantial time gap until a vaccine becomes available, if their mothers are not immunised, and if there is insufficient time for an immune response after vaccination (ie, premature infants).[112] LMICs might even prefer mAbs over maternal immunisation due to potential higher coverage and ease of implementation into the Expanded Programme on Immunisation. However, there are several challenges to LMIC implementation, including (1) year-round RSV circulation (mAb administration at birth might be more cost-effective than seasonal), (2) scalability dependent upon use of multi-dose vials and stability at ambient temperature, (3) scarcity of data on both RSV burden and health-care use in LMICs to have a case for implementation, (4) trial design in the case nirsevimab reaches the market (requiring a large sample size), and (5) potential limitations of surveillance of viral resistance in LMICs (though potentially enhanced since COVID-19). Thus, mAbs could have a high impact in LMICs, but implementation challenges remain.

Panel: **Future RSV vaccine and monoclonal antibodies landscape research priorities**

- Generating knowledge of RSV awareness
- Understanding cost-effectiveness of RSV prevention in different parts of the world
- Defining a correlate of protection for RSV
- Defining efficacy of RSV prevention in low-income to middle-income countries
- RSV genetic surveillance

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

Although the approval of multiple RSV vaccines is within reach, several obstacles to worldwide access remain. Globally representative trials are needed and vaccine trials need to be done in countries with the highest disease burden as efficacy can differ between LMICs and HICs as observed for vaccines against RSV[39] and other pathogens.[118] Access in LMICs might be delayed due to a scarcity of trial data in populations with a high incidence of HIV and malaria and regulatory drug lag between time of regulatory submission and approval in sub-Saharan Africa.[119] GAVI's (the Vaccine Alliance's) vaccine investment strategy includes RSV and will be important in making RSV prevention available in countries eligible for GAVI support. Differential pricing might be an important consideration for countries not eligible for GAVI support. Other challenges to global access include measuring protection in the case maternal vaccine boosters are indicated. A correlate of protection for RSV is absent as well as a simple tool to measure protection after RSV vaccination. It will be important to assess the sustainability of RSV prevention via ongoing genetic surveillance. The development of viral resistance is most relevant for infant immunoprophylaxis with mAbs. A cocktail of mAbs targeting different epitopes might help prevent the emergence of viral resistance. However, there are currently no ongoing clinical trials with multiple mAbs which might hamper approval of a drug cocktail by regulatory bodies such as the approved mAb cocktail to prevent SARS-CoV-2. Finally, awareness

of RSV is low amongst patients, policy makers and health-care providers and further cost-effectiveness studies of products are needed.[7] These knowledge gaps related to global vaccine implementation are important future research priorities (panel).

Overall, we are at an exciting phase of vaccine and mAb development in which RSV prevention is within reach. It is likely that multiple immunisation strategies with complementary value, unique advantages and use-case scenarios will shape the RSV prevention landscape. To guarantee worldwide access, urgent steps are required to surmount challenges of measuring protection, monitoring viral resistance, and prioritising LMIC access and affordability.

Contributors

LB and NIM contributed to the review design and plan. NIM, JT, and YL contributed to the data collection, extraction, and quality assessment. JT created the figures for the manuscript with Biorender.com. All authors contributed to the writing of the manuscript. The manuscript was written in collaboration with the ReSViNET Foundation.

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References

1 Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380:** 2095–128.

2 Nair H, Brooks WA, Katz M, et al. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. *Lancet* 2011; **378:** 1917–30.

3 Srikantiah P, Vora P, Klugman KP. Assessing the full burden of respiratory syncytial virus in young infants in low- and middle-income countries: the importance of community mortality studies. *Clin Infect Dis* 2021; **73:** S177–79.

4 Scheltema NM, Gentile A, Lucion F, et al. Global respiratory syncytial virus-associated mortality in young children (RSV GOLD): a retrospective case series. *Lancet Glob Heal* 2017; **5:** e984–91.

5 Clinical Infectious Diseases. Supplement 3: community mortality burden associated with respiratory syncytial virus in low- and middle-income countries. *Clin Infect Dis* 2021; **73**.

6 Zhang S, Akmar LZ, Bailey F, et al. Cost of respiratory syncytial virus-associated acute lower respiratory infection management in young children at the regional and global level: a systematic review and meta-analysis. *J Infect Dis* 2020; **222:** S680–87.

7 Li X, Willem L, Antillon M, Bilcke J, Jit M, Beutels P. Health and economic burden of respiratory syncytial virus (RSV) disease and the cost-effectiveness of potential interventions against RSV among children under 5 years in 72 Gavi-eligible countries. *BMC Med* 2020; **18:** 82.

8 Bulkow LR, Singleton RJ, Karron RA, Harrison LH. Risk factors for severe respiratory syncytial virus infection among Alaska Native children. *Pediatrics* 2002; **109:** 210–16.

9 Beckhaus AA, Castro-Rodriguez JA. Down syndrome and the risk of severe RSV infection: a meta-analysis. *Pediatrics* 2018; **142:** e20180225.

10 Resch B, Manzoni P, Lanari M. Severe respiratory syncytial virus (RSV) infection in infants with neuromuscular diseases and immune deficiency syndromes. *Paediatr Respir Rev* 2009; **10:** 148–53.

11 Omer SB. Maternal immunization. *N Engl J Med* 2017; **376:** 1256–67.

12 Ackerson B, Tseng HF, Sy LS, et al. Severe morbidity and mortality associated with respiratory syncytial virus versus influenza infection in hospitalized older adults. *Clin Infect Dis* 2019; **69:** 197–203.

13 Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory syncytial virus infection in elderly and high-risk adults. *N Engl J Med* 2005; **352:** 1749–59.

14 Korsten K, Adriaenssens N, Coenen S, et al. Burden of respiratory syncytial virus infection in community-dwelling older adults in Europe (RESCEU): an international prospective cohort study. *Eur Respir J* 2021; **57:** 2002688.

15 Herring WL, Zhang Y, Shinde V, Stoddard J, Talbird SE, Rosen B. Clinical and economic outcomes associated with respiratory syncytial virus vaccination in older adults in the United States. *Vaccine* 2021; **40:** 483–93.

16 Zeevat F, Luttjeboer J, Paulissen JHJ, et al. Exploratory analysis of the economically justifiable price of a hypothetical RSV vaccine for older adults in the Netherlands and the United Kingdom. *J Infect Dis* 2021; published online Sept 15. https://doi.org/10.1093/infdis/jiab118.

17 Johnson KM, Bloom HH, Mufson MA, Chanock RM. Natural reinfection of adults by respiratory syncytial virus. Possible relation to mild upper respiratory disease. *N Engl J Med* 1962; **267:** 68–72.

18 Kim HW, Canchola JG, Brandt CD, et al. Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine. *Am J Epidemiol* 1969; **89:** 422–34.

19 Killikelly AM, Kanekiyo M, Graham BS. Pre-fusion F is absent on the surface of formalin-inactivated respiratory syncytial virus. *Sci Rep* 2016; **6:** 34108.

20 Knudson CJ, Hartwig SM, Meyerholz DK, Varga SM. RSV Vaccine-enhanced disease is orchestrated by the combined actions of distinct CD4 t cell subsets. *PLoS Pathog* 2015; **11:** e1004757.

21 Jozwik A, Habibi MS, Paras A, et al. RSV-specific airway resident memory CD8+ T cells and differential disease severity after experimental human infection. *Nat Commun* 2015; **6:** 10224.

22 Habibi MS, Jozwik A, Makris S, et al. Impaired antibody-mediated protection and defective iga b-cell memory in experimental infection of adults with respiratory syncytial virus. *Am J Respir Crit Care Med* 2015; **191:** 1040–49.

23 Chu HY, Steinhoff MC, Magaret A, et al. Respiratory syncytial virus transplacental antibody transfer and kinetics in mother-infant pairs in bangladesh. *J Infect Dis* 2014; **210:** 1582–89.

24 Glezen WP, Paredes A, Allison JE, Taber LH, Frank AL. Risk of respiratory syncytial virus infection for infants from low-income families in relationship to age, sex, ethnic group, and maternal antibody level. *J Pediatr* 1981; **98:** 708–15.

25 Stensballe LG, Ravn H, Kristensen K, et al. Respiratory syncytial virus neutralizing antibodies in cord blood, respiratory syncytial virus hospitalization, and recurrent wheeze. *J Allergy Clin Immunol* 2009; **123:** 398–403.

26 Piedra PA, Jewell AM, Cron SG, Atmar RL, Paul Glezen W. Correlates of immunity to respiratory syncytial virus (RSV) associated-hospitalization: establishment of minimum protective threshold levels of serum neutralizing antibodies. *Vaccine* 2003; **21:** 3479–82.

27 Ngwuta JO, Chen M, Modjarrad K, et al. pre-F F-specific antibodies determine the magnitude of RSV neutralizing activity in human sera. *Sci Transl Med* 2015; **7:** 309ra162.

28 Joyce MG, McLellan JS, Stewart-Jones GBE, et al. Crystal structure of pre-F-stabilized RSV F variant DS-Cav1 at pH 5·5: pdb4MMU. 2013. https://www.rcsb.org/structure/4MMU (accessed July 20, 2022)

29 McLellan JS, Chen M, Joyce MG, et al. Structure-based design of a fusion glycoprotein vaccine for respiratory syncytial virus. *Science* 2013; **342:** 592–98.

30 McLellan JS, Yang Y, Graham BS, Kwong PD. Structure of respiratory syncytial virus fusion glycoprotein in the postfusion conformation reveals preservation of neutralizing epitopes. *J Virol* 2011; **85:** 7788–96.

31 McLellan JS, Yongping Y, Graham BS, Kwong PD. Structure of the RSV F protein in the post-fusion conformation: pdb3RRT. 2015. https://www.rcsb.org/structure/3RRT (accessed July 20, 2022).

32 PATH. RSV Vaccine and mAb Snapshot. PATH. 2021. https://www.path.org/resources/rsv-vaccine-and-mab-snapshot/ (accessed April 12, 2022).

33 Mazur NI, Higgins D, Nunes MC, et al. The respiratory syncytial virus vaccine landscape: lessons from the graveyard and promising candidates. *Lancet Infect Dis* 2018; **18:** e295–311.

34 ClinicalTrials.gov. Identifier: NCT03959488, a study to evaluate the safety of MEDI8897 for the prevention of medically attended respiratory syncytial virus (RSV) lower respiratory track infection (LRTI) in High-risk Children. May 22, 2019. https://clinicaltrials.gov/ct2/show/NCT03959488 (accessed April 12, 2022).

35 ClinicalTrials.gov. Identifier: NCT03979313, a study to evaluate the safety and efficacy of MEDI8897 for the prevention of medically attended lower respiratory tract infection due to respiratory syncytial virus in healthy late preterm and term infants (MELODY). June 7, 2019. https://clinicaltrials.gov/ct2/show/NCT03979313 (accessed April 12, 2022).

36 ClinicalTrials.gov. Identifier: NCT04938830, MK-1654 in infants and children at increased risk for severe respiratory syncytial virus (RSV) disease (MK-1654–007). June 24, 2021. https://clinicaltrials.gov/ct2/show/NCT04938830 (accessed April 12, 2022).

37 ClinicalTrials.gov. Identifier: NCT04767373, efficacy and safety of MK-1654 in Infants (MK-1654–004). Feb 23, 2021. https://clinicaltrials.gov/ct2/show/NCT04767373 (accessed April 12, 2022).

38 Mazur NI, Martinón-Torres F, Baraldi E, et al. Lower respiratory tract infection caused by respiratory syncytial virus: current management and new therapeutics. *Lancet Respir Med* 2015; **3:** 888–900.

39 Madhi SA, Polack FP, Piedra PA, et al. Respiratory syncytial virus vaccination during pregnancy and effects in infants. *N Engl J Med* 2020; **383:** 426–39.

40 Fong Y, Borate B, Zhang W, van der Laan L, Huang Y, Gilbert P. Immunologic biomarker correlates of severe RSV disease in a vaccine efficacy trial. In: Presentation at RSVVW'21. Virtual: 6th ReSViNet Conference: November 10–12, 2021. Avaiable from: https://www.resvinet.org/uploads/2/2/2/7/22271200/_virtual__rsvvw21_information_brochure_v3·0.pdf, 2021 (accessed April 12, 2022).

41 Mazur NI, Bont LJ, van Delden JJM, Omer SB. An ethics framework and practical guidance for post-trial access to an RSV maternal vaccine. *Lancet Respir Med* 2019; **7:** 474–76.

42 Simões EAF, Forleo-Neto E, Geba GP, et al. Suptavumab for the prevention of medically attended respiratory syncytial virus infection in preterm infants. *Clin Infect Dis* 2021; **73:** e4400–08.

43 Taylor NP. Biotech GSK culls phase 2 RSV vaccine in kids, as feladilimab flops again in lung cancer. Fierce Biotech. 2021. https://www.fiercebiotech.com/biotech/gsk-drops-phase-2-viral-vector-rsv-vaccine-pediatric-ages#:~:text=Biotech-,GSK culls phase 2 RSV vaccine in kids%2C as,flops again in lung cancer&text=GlaxoSmithKline is shutting down development,become severe in some (accessed Dec 1, 2021).

44 Cicconi P, Jones C, Sarkar E, et al. First-in-human randomized study to assess the safety and immunogenicity of an investigational respiratory syncytial virus (RSV) vaccine based on chimpanzee-adenovirus-155 viral vector-expressing RSV fusion, nucleocapsid, and antitermination viral proteins. *Clin Infect Dis* 2020; **70:** 2073–81.

45 Karron RA, Atwell JE, McFarland EJ, et al. Live-attenuated Vaccines Prevent Respiratory Syncytial Virus-associated Illness in Young Children. *Am J Respir Crit Care Med* 2021; **203:** 594–603.

46 Karron RA, Luongo C, Mateo JS, Wanionek K, Collins PL, Buchholz UJ. Safety and Immunogenicity of the Respiratory Syncytial Virus Vaccine RSV/ΔNS2/Δ1313/I1314L in RSV-Seronegative Children. *J Infect Dis* 2020; **222:** 82–91.

47 ClinicalTrials.gov. Identifier: NCT03227029, Evaluating the Infectivity, Safety, and Immunogenicity of Recombinant Live-Attenuated RSV Vaccines RSV ΔNS2/Δ1313/I1314L or RSV 276 in RSV-Seronegative Infants 6 to 24 Months of Age - Full Text View - ClinicalTrials.gov. Bethesda Natl. Libr. Med. (US). 2022 Jan 8. https://clinicaltrials.gov/ct2/show/NCT03227029 (accessed April 12, 2022).

48 ClinicalTrials.gov. Identifier: NCT03916185, safety and immunogenicity of a single dose of the recombinant live-attenuated respiratory syncytial virus (RSV) vaccines RSV ΔNS2/Δ1313/I1314L, RSV 6120/ΔNS2/1030s, RSV 276 or placebo, delivered as nose drops to RSV-seronegative C. Apr 16, 2019. https://clinicaltrials.gov/ct2/show/NCT03916185 (accessed April 12, 2022).

49 Stobart CC, Rostad CA, Ke Z, et al. A live RSV vaccine with engineered thermostability is immunogenic in cotton rats despite high attenuation. *Nat Commun* 2016; **7:** 13916.

50 Meissa Vaccines I. Meissa vaccines provides a pipeline update on vaccine candidates for COVID-19 and RSV. June 30, 2020. https://www.meissavaccines.com/post/meissa-vaccines-provides-a-pipeline-update-on-vaccine-candidates-for-covid-19-and-rsv (accessed April 12, 2022).

51 ClinicalTrials.gov. Identifier: NCT04227210, safety and immune response to an investigational vaccine against respiratory syncytial virus in healthy adults. Jan 13, 2020. https://clinicaltrials.gov/ct2/show/NCT04227210 (accessed April 12, 2022).

52 ClinicalTrials.gov. Identifier: NCT04909021, safety and immunogenicity of an intranasal vaccine for respiratory syncytial virus in seronegative children 6–36 months. June 1, 2021. https://clinicaltrials.gov/ct2/show/NCT04909021 (accessed April 12, 2022).

53 Vaccines M. Meissa announces 1st dosing in phase 2 study of intranasal live attenuated vaccine candidate for RSV. Jan 21, 2021. https://www.meissavaccines.com/post/meissa-announces-1st-dosing-in-phase-2-study-of-intranasal-live-attenuated-vaccine-candidate-for-rsv (accessed April 12, 2022).

54 Verdijk P, van der Plas JL, van Brummelen EMJ, et al. First-in-human administration of a live-attenuated RSV vaccine lacking the G-protein assessing safety, tolerability, shedding and immunogenicity: a randomized controlled trial. *Vaccine* 2020; **38:** 6088–95.

55 McFarland EJ, Karron RA, Muresan P, et al. Live-attenuated respiratory syncytial virus vaccine with M2–2 deletion and with small hydrophobic noncoding region is highly immunogenic in children. *J Infect Dis* 2020; **221:** 2050–09.

56 Mueller S, Stauft CB, Kalkeri R, et al. A codon-pair deoptimized live-attenuated vaccine against respiratory syncytial virus is immunogenic and efficacious in non-human primates. *Vaccine* 2020; **38:** 2943–48.

57 Nouën C Le, McCarty T, Brown M, et al. Genetic stability of genome-scale deoptimized RNA virus vaccine candidates under selective pressure. *Proc Natl Acad Sci* 2017; **114:** e386–95.

58 Wiegand MA, Gori-Savellini G, Gandolfo C, et al. A respiratory syncytial virus vaccine vectored by a stable chimeric and replication-deficient sendai virus protects mice without inducing enhanced disease. *J Virol* 2017; **91:** e02298–16.

59 Scaggs Huang F, Bernstein DI, Slobod KS, et al. Safety and immunogenicity of an intranasal sendai virus-based vaccine for human parainfluenza virus type I and respiratory syncytial virus (SeVRSV) in adults. *Hum Vaccin Immunother* 2021; **17:** 554.

60 Abarca K, Rey-Jurado E, Muñoz-Durango N, et al. Safety and immunogenicity evaluation of recombinant BCG vaccine against respiratory syncytial virus in a randomized, double-blind, placebo-controlled phase I clinical trial. *EClinicalMedicine* 2020; **27:** 100517.

61 Anderson LJ, Dormitzer PR, Nokes DJ, Rappuoli R, Roca A, Graham BS. Strategic priorities for respiratory syncytial virus (RSV) vaccine development. *Vaccine* 2013; **31:** B209–15.

62 Crank MC, Ruckwardt TJ, Chen M, et al. A proof of concept for structure-based vaccine design targeting RSV in humans. *Science* 2019; **365:** 505–09.

63 Ruckwardt TJ, Morabito KM, Phung E, et al. Safety, tolerability, and immunogenicity of the respiratory syncytial virus pre-F F subunit vaccine DS-Cav1: a phase 1, randomised, open-label, dose-escalation clinical trial. *Lancet Respir Med* 2021; **9:** 1111–20.

64 ClinicalTrials.gov. Identifier: NCT04071158. A study of a RSV vaccine when given together with TDap in healthy nonpregnant women aged between 18 to 49 years - Full Text View - ClinicalTrials.gov. Bethesda Natl. Libr. Med. (US). 2019 Aug 28. https://clinicaltrials.gov/ct2/show/NCT04071158 (accessed April 12, 2022).

65 Peterson JT, Zareba AM, Fitz-Patrick D, et al. Safety and Immunogenicity of a Respiratory Syncytial Virus pre-F F Vaccine When Coadministered With a Tetanus, Diphtheria, and Acellular Pertussis Vaccine. *J Infect Dis* 2021; **jiab505:** 1–10.

66 ClinicalTrials.gov. Identifier: NCT04785612, study of RSVpre-F vaccination and RSV challenge in healthy. Mar 8, 2021. https://clinicaltrials.gov/ct2/show/NCT04785612 (accessed April 12, 2022).

67 ClinicalTrials.gov. Identifier: NCT04424316, a trial to evaluate the efficacy and safety of RSVpre-F in infants born to women vaccinated during pregnancy. June 9, 2020. https://clinicaltrials.gov/ct2/show/NCT04424316 (accessed April 12, 2022).

68 ClinicalTrials.gov. Identifier: NCT04032093, a phase 2b placebo-controlled, randomized study of a respiratory syncytial virus (RSV) vaccine in pregnant women. July 25, 2019. https://clinicaltrials.gov/ct2/show/NCT04032093 (accessed April 12, 2022).

69 ClinicalTrials.gov. Identifier: NCT05035212, study to evaluate the efficacy, immunogenicity, and safety of RSVpre-F in adults. Sept 5, 2021. https://www.clinicaltrials.gov/ct2/show/NCT05035212 (accessed April 12, 2022).

70 ClinicalTrials.gov. Identifier: NCT04605159, a phase III double-blind study to assess safety and efficacy of an RSV maternal unadjuvanted vaccine, in pregnant women and infants born to vaccinated mothers. Oct 27, 2020. https://clinicaltrials.gov/ct2/show/NCT04605159 (accessed April 12, 2022).

71 ClinicalTrials.gov. Identifier: NCT04886596, efficacy study of GSK's investigational respiratory syncytial virus (RSV) vaccine in adults aged 60 years and above. May 14, 2021. https://clinicaltrials.gov/ct2/show/NCT04886596 (accessed April 12, 2022).

72 Tica J, Guiñazú JR, Andrews CP, et al. 119. A respiratory syncytial virus pre-F F protein (RSVPre-F3) candidate vaccine administered in older adults in a phase I/II randomized clinical trial is well tolerated. *Open Forum Infect Dis* 2020; **7:** S187–S188.

73 Guiñazú JR, Tica J, Andrews CP, et al. 121. A respiratory syncytial virus pre-F F protein (RSVPre-F3) candidate vaccine administered in older adults in a phase I/II randomized clinical trial is immunogenic. *Open Forum Infect Dis* 2020; **7:** S188–89.

74 GSK. GSK presents positive clinical data on maternal and older adults RSV candidate vaccines, GSK. Oct 21, 2020. https://www.gsk.com/en-gb/media/press-releases/gsk-presents-positive-clinical-data-on-maternal-and-older-adults-rsv-candidate-vaccines/ (accessed April 12, 2022).

75 Kantele A. CS-7: investigational maternal respiratory syncytial virus vaccine (rsvpre-F3) boosts maternal immunity against RSV-A and RSV-B, with transplacentally acquired antibodies persisting in infants until six months post-birth. In: RSVVW'21 Abstract Booklet. Virtual: RSVVW'21: 6th ReSViNet Conference: November 10–12, 2021 (abstr CS-7).

76 ClinicalTrials.gov. Identifier: NCT04851977, A first in human study to evaluate the safety and immune response to a vaccine for the treatment of a respiratory virus, when administered into the arm in healthy adult participants. Apr 21, 2021. https://clinicaltrials.gov/ct2/show/NCT04851977 (accessed April 12, 2022).

77 ClinicalTrials.gov. Identifier: NCT04681833, safety and efficacy of BARS13 in the elderly. Dec 23, 2020. https://clinicaltrials.gov/ct2/show/NCT04681833 (accessed April 12, 2022).

78 Langley JM, MacDonald LD, Weir GM, et al. A respiratory syncytial virus vaccine based on the small hydrophobic protein ectodomain presented with a novel lipid-based formulation is highly immunogenic and safe in adults: a first-in-humans study. *J Infect Dis* 2018; **3:** 378–87.

79 Torrey HL, Kaliaperumal V, Bramhecha Y, et al. Evaluation of the protective potential of antibody and T cell responses elicited by a novel preventative vaccine towards respiratory syncytial virus small hydrophobic protein. *Hum Vaccin Immunother* 2020; **16:** 2007–17.

80 ClinicalTrials.gov. Identifier: NCT04914520, study of VN-0200 in Japanese healthy adults and elderly subjects. June 4, 2021. https://clinicaltrials.gov/ct2/show/NCT04914520 (accessed April 12, 2022).

81 Marcandalli J, Fiala B, Ols S, et al. Induction of potent neutralizing antibody responses by a designed protein nanoparticle vaccine for respiratory syncytial virus. *Cell* 2019; **176:** 1420–31.e17.

82 Icosavax Inc. Icosavax Provides corporate update and anticipated. Globe Newswire. Jan 7, 2020. https://www.globenewswire.com/news-release/2022/01/07/2363089/0/en/Icosavax-Provides-Corporate-Update-and-Anticipated-Milestones-for-2022.html (accessed April 12, 2022).

83 Zuniga A, Rassek O, Vrohlings M, et al. An epitope-specific chemically defined nanoparticle vaccine for respiratory syncytial virus. *NPJ vaccines* 2021; **6:** 85.

84 Hervé PL, Dhelft V, Zuniga A, et al. Epicutaneous immunization using synthetic virus-like particles efficiently boosts protective immunity to respiratory syncytial virus. *Vaccine* 2021; **39:** 4555–63.

85 ClinicalTrials.gov. Identifier: NCT04519073, phase 1 study to evaluate the safety and immunogenicity of a candidate vaccine against respiratory syncytial virus. Aug 19, 2020. https://clinicaltrials.gov/ct2/show/NCT04519073 (accessed April 12, 2022).

86 Corbett KS, Edwards DK, Leist SR, et al. SARS-CoV-2 mRNA vaccine design enabled by prototype pathogen preparedness. *Nature* 2020; **586:** 567–71.

87 Chen GL, Mithani R, Schaefers K, et al. VT&T-53: safety and immunogenicity of mRNA-1345 , an mRNA-based vaccine against respiratory syncytial virus in adults. In: RSVVW'21 Abstract Booklet. Virtual: RSVVW'21: 6th ReSViNet Conference: November 10–12, 2021. (abstr VT&T-53).

88 ClinicalTrials.gov. Identifier: NCT05127434, a study to evaluate the safety and efficacy of mRNA-1345 vaccine targeting respiratory syncytial virus (RSV) in adults ≥60 years of age. Nov 19, 2021. https://clinicaltrials.gov/ct2/show/NCT05127434 (accessed April 12, 2022).

89 Samy N, Reichhardt D, Schmidt D, et al. Safety and immunogenicity of novel modified vaccinia Ankara-vectored RSV vaccine: a randomized phase I clinical trial. *Vaccine* 2020; **38:** 2608–19.

90 Weidenthaler H, Schultz S, Sanos S, et al. VT&T-77: efficacy, safety and immunogenicity of the recombinant MVA-BN-RSV vaccine against respiratory syncytial virus (RSV) infection in a human challenge trial (HCT) in healthy adult participants. In: RSVVW'21 Abstract Booklet. Virtual: RSVVW'21: 6th ReSViNet Conference: November 10–12, 2021 (abstr VT&T-77).

91 Jordan E, Lawrence SJ, Meyer TPH, et al. Broad antibody and cellular immune response from a phase 2 clinical trial with a novel multivalent poxvirus-based respiratory syncytial virus vaccine. *J Infect Dis* 2021; **223:** 1062–72.

92 ClinicalTrials.gov. Identifier NCT05238025, phase 3 MVA-BN-RSV vaccine efficacy trial. Feb 14, 2022. https://clinicaltrials.gov/ct2/show/NCT05238025 (accessed April 12, 2022).

93 Krarup A, Truan D, Furmanova-Hollenstein P, et al. A highly stable pre-F RSV F vaccine derived from structural analysis of the fusion mechanism. *Nat Commun* 2015; **6:** 8143.

94 van der Fits L, Bolder R, Heemskerk-van der Meer M, et al. Adenovector 26 encoded pre-F conformation stabilized RSV-F protein induces long-lasting Th1-biased immunity in neonatal mice. *NPJ vaccines* 2020; **5:** 49.

95 Williams K, Bastian AR, Feldman RA, et al. Phase 1 Safety and immunogenicity study of a respiratory syncytial virus vaccine with an adenovirus 26 vector encoding pre-F F (Ad26.RSV.pre-F) in adults aged ≥60 years. *J Infect Dis* 2020; **222:** 979–88.

96 Sadoff J, De Paepe E, DeVincenzo J, et al. Prevention of respiratory syncytial virus infection in healthy adults by a single immunization of Ad26.RSV.pre-F in a human challenge study. *J Infect Dis* 2021; published online Jan 5. https://doi.org/10.1093/infdis/jiab003.

97 Falsey AR, Williams K, Gymnopoulou E, et al. Efficacy and immunogenicity of an Ad26.RSV.pre-F-based vaccine in the prevention of RT-PCR-confirmed RSV-mediated lower respiratory tract disease in adults aged ≥65 years: a randomized, placebo-controlled, phase 2b study. *Open Forum Infect Dis* 2021; **8:** S812–12.

98 Falsey AR, Williams K, Efi G, et al. VT&T-58. Safety and tolerability of an Ad26.RSV.pre-F-based vaccine: a randomized, double-blind, placebo-controlled, phase 2b study in adults aged >65 years. In: RSVVW'21 Abstract Booklet. Virtual: RSVVW'21: 6th ReSViNet Conference: November 10–12, 2021 (abstr VT&T-58).

99 Falsey AR, Williams K, Efi G, et al. VT&T-57: Efficacy, safety, and immunogenicity of AD26.RSV.pre-F-based vaccine in adults aged >65 years with or without addditional risk factors for RSV-mediated lower respiratory tract disease. In: RSVVW'21 Abstract Booklet. Virtual: RSVVW'21: 6th ReSViNet Conference: November 10–12, 2021 (abstr VT&T-57).

100 Sadoff J, De Paepe E, Haazen W, et al. Safety and immunogenicity of the Ad26.RSV.pre-F investigational vaccine coadministered with an influenza vaccine in older adults. *J Infect Dis* 2021; **223:** 699–708.

101 ClinicalTrails.gov. Identifier: NCT04908683, a study of an adenovirus serotype 26 pre-fusion conformation-stabilized F protein (Ad26. RSV. pre-F) based respiratory syncytial virus (RSV) vaccine in the prevention of lower respiratory tract disease in adults aged 60 years and O. June 1, 2021. https://clinicaltrials.gov/ct2/show/NCT04908683 (accessed April 12, 2022).

102 Snape M. Phase 1 safety and immunogenicity study of a respiratory syncytial virus vaccine with an adenovirus 26 vector encoding pre-F F (Ad26.RSV.pre-F) in adults aged ≥60 years. In: ISIRV RSV Webinar Series: RSV Vaccines and Therapies. Virtual: Available from: https://isirv.org/site/index.php/9-events/514-rsv-webinar-series, 2022. DOI:10.1093/infdis/jiaa193 (Feb 22, 2022).

103 Klok FA, Pai M, Huisman M V, Makris M. Vaccine-induced immune thrombotic thrombocytopenia. *Lancet Haematol* 2022; **9:** e73–80.

104 Brodsky FM. Monoclonal antibodies as magic bullets. *Pharm Res* 1988; **5:** 1–9.

105 Griffin MP, Yuan Y, Takas T, et al. Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants. *N Engl J Med* 2020; **383:** 415–25.

106 Hammitt LL, Dagan R, Yuan Y, et al. Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants. *N Engl J Med* 2022; **386:** 837–46.

107 Zhu Q, Lu B, Mctamney P, et al. Prevalence and Significance of Substitutions in the Fusion Protein of Respiratory Syncytial Virus Resulting in Neutralization Escape From Antibody MEDI8897. *J Infect Dis* 2018; **218:** 572–80.

108 Tang A, Chen Z, Cox KS, et al. A potent broadly neutralizing human RSV antibody targets conserved site IV of the fusion glycoprotein. *Nat Commun* 2019; **10:** 4153.

109 Maas BM, Lommerse J, Plock N, et al. VT&T-65: forward and reverse translational approaches to predict efficacy of the neutralizing respiratory syncytial virus (RSV) antibody MK-1654. In: RSVVW'21 Abstract Booklet. Virtual: RSVVW'21: 6th ReSViNet Conference: November 10–12, 2021 (abstr VT&T-65).

110 Maas BM, Lommerse J, Plock N, et al. Forward and reverse translational approaches to predict efficacy of neutralizing respiratory syncytial virus (RSV) antibody prophylaxis. *EBioMedicine* 2021; **73:** 103651.

111 ClinicalTrials.gov. Identifier: NCT05118386, safety, tolerability, and pharmacokinetics of RSV monoclonal antibody RSM01 in healthy adults. Nov 12, 2021. https://clinicaltrials.gov/ct2/show/NCT05118386 (accessed April 12, 2022).

112 Ananworanich J, Heaton PM. Bringing preventive RSV monoclonal antibodies to infants in low- and middle-income countries: challenges and opportunities. *Vaccines* 2021; **9:** 961.

113 Jones RGA, Martino A. Targeted localized use of therapeutic antibodies: a review of non-systemic, topical and oral applications. *Crit Rev Biotechnol* 2016; **36:** 506–20.

114 ClinicalTrials.gov. Identifier: NCT04540627, exploratory study to estimate the prophylactic efficacy of palivizumab in healthy adult participants inoculated with RSV. https://clinicaltrials.gov/ct2/show/NCT04540627 (accessed April 12, 2022).

115 DeVincenzo JP, El Saleeby CM, Bush AJ. Respiratory syncytial virus load predicts disease severity in previously healthy infants. *J Infect Dis* 2005; **191:** 1861–68.

116 Chu HY, Englund JA. Maternal immunization. *Clin Infect Dis* 2014; **59:** 560–68.

117 Nunes MC, Cutland CL, Jones S, et al. Duration of infant protection against influenza illness conferred by maternal immunization secondary analysis of a randomized clinical trial. *JAMA Pediatr* 2016; **170:** 840–47.

118 Lee B. Update on rotavirus vaccine underperformance in low- to middle-income countries and next-generation vaccines. *Hum Vaccin Immunother* 2021; **17:** 1787–802.

119 Ahonkhai V, Martins SF, Portet A, Lumpkin M, Hartman D. Speeding access to vaccines and medicines in low- and middle-income countries: a case for change and a framework for optimized product market authorization. *PLoS One* 2016; **11:** e0166515.