The respiratory syncytial virus vaccine and monoclonal antibody landscape: the road to global access

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Respiratory syncytial virus (RSV) is the second most common pathogen causing infant mortality. Additionally, RSV is a major cause of morbidity and mortality in older adults (age ≥60 years) similar to influenza. A protein-based maternal vaccine and monoclonal antibody (mAb) are now market-approved to protect infants, while an mRNA and two protein-based vaccines are approved for older adults. First-year experience protecting infants with nirsevimab in high-income countries shows a major public health benefit. It is expected that the RSV vaccine landscape will continue to develop in the coming years to protect all people globally. The vaccine and mAb landscape remain active with 30 candidates in clinical development using four approaches: protein-based, live-attenuated and chimeric vector, mRNA, and mAbs. Candidates in late-phase trials aim to protect young infants using mAbs, older infants and toddlers with live-attenuated vaccines, and children and adults using protein-based and mRNA vaccines. This Review provides an overview of RSV vaccines highlighting different target populations, antigens, and trial results. As RSV vaccines have not yet reached low-income and middle-income countries, we outline urgent next steps to minimise the vaccine delay.

Introduction

Respiratory syncytial virus (RSV) is a leading cause of lower respiratory tract infections (LRTIs) globally and the second leading pathogen to cause infant mortality.[1] It is estimated that RSV accounted for more than 100 000 deaths among children younger than 5 years in 2019 of which more than 97% occurred in low-income and middle-income countries (LMICs).[2] In high-income countries (HICs), 1·8% of healthy term infants are hospitalised for RSV during the first year of life.[3] Underlying medical conditions, prematurity, and socioeconomic vulnerabilities increase the risk of RSV hospitalisation,[4–7] although three-quarters of hospitalised infants were previously healthy.[8] While RSV-LRTI incidence and hospital admission rates are highest in young infants, older infants (age 6–12 months), and toddlers (age 1–2 years) also bear a substantial burden.[2]

In older adults (age ≥60 years) and adults with underlying comorbidities, RSV is an important cause of severe respiratory illness, comparable with seasonal influenza.[9] The incidence of RSV-associated hospitalisation in HICs is estimated at 0·15–0·18%,[10,11] but adjusting for under-ascertainment due to diagnostic limitations in adults suggests the true burden might be twice as high.[10,12] The in-hospital case fatality rate might be as high as 7·1% in the general older adult population, and up to 11·7% in adults with comorbidities.[11]

Currently, there is no treatment for RSV infection, underscoring the need for preventive measures. The first paediatric RSV vaccine in the 1960s used formalin-inactivated RSV. Despite a surge in anti-RSV antibody titres, subsequent natural RSV infection led to hospital admission in 80% of the vaccinated children and the tragic deaths of two toddlers.[13,14] The mechanism of their deaths was identified as enhanced respiratory disease in which RSV-naive recipients were primed to produce non-neutralising antibodies and a T-helper 2-biased immune response causing airway hyper-reactivity and mucus hypersecretion.[15,16] Consequently, the trial was

Key messages

- A maternal vaccine (based on respiratory syncytial virus [RSV] prefusion F protein, RSVpreF) and monoclonal antibody (mAb, nirsevimab) have received regulatory approval in various high-income and upper-middle income countries to protect infants. First-year experience with nirsevimab showed greater than 80% effectiveness against RSV-associated hospitalisation.
- Vaccines based on the RSVpreF are available to protect older adults and an RSV mRNA vaccine is approved. Co-administration with vaccines against other pathogens and revaccination schedules are being studied in late-phase trials.
- An alternative mAb to nirsevimab (clesrovimab) is currently being studied in a phase 3 trial with possible market approval in 2026. One mAb (RSM01), specifically developed for low-income and lower-middle-income countries (LMICs) has completed a phase 1 trial. Additional mAbs on the market could affect supply and demand issues, LMIC access, and viral resistance.
- A live-attenuated RSV vaccine to reduce medically attended RSV infection among older infants and toddlers is currently in a phase 3 trial. It is unclear whether paediatric vaccines will have an effect on RSV transmission and could indirectly protect young infants and older adults (age >60 years).
- Access to infant RSV prevention in LMICs is at high risk of a minimum of 3 years delay for introduction compared with high-income countries. Closing the global vaccine gap is an urgent priority shared by multiple stakeholders.

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See Online for appendix

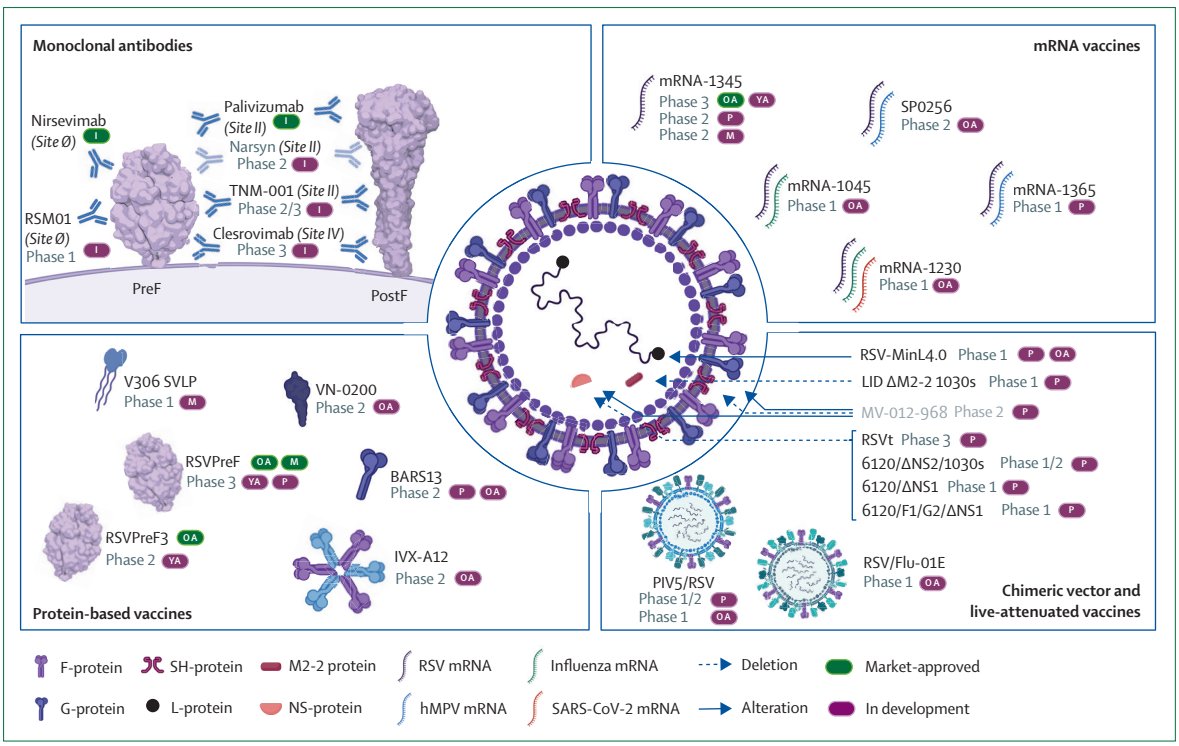

Figure 1: **Overview of RSV vaccine candidates by preventive approach**
Target population per vaccine candidate is indicated by green and purple ovals (I=infants age <12 months, P=paediatric age 1–18 years, M=maternal, OA=older adults age ≥60 years, YA=younger adults age 18–60 years). Narsyn and MV-012-968 are depicted in light grey as their development is halted. PreF protein was created with RCSB Protein Data Bank 4MMU[19,33] and postF protein was created with 3RRT.[34,35] F=fusion. G=glycoprotein. hMPV=human metapneumovirus. L=large polymerase. NS=non-structural. PIV5=parainfluenza virus 5. postF=post-fusion protein. preF=prefusion protein. RSV=respiratory syncytial virus. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. SVLP=synthetic virus-like particle.

stopped and RSV vaccine research was stalled for decades. In 1998, the development of palivizumab—a short-acting monoclonal antibody (mAb) against RSV fusion (F) protein—served as proof-of-principle of infant protection against RSV-LRTI via passively acquired antibodies.[17] However, due to its high costs and need for monthly injections, palivizumab use is reserved for high-risk infant and paediatric populations. The breakthrough stabilisation of F-protein in prefusion (preF) morphology was the tipping point in RSV vaccine development.[18,19] The preF antigen now serves as the basis of all five licensed vaccines and 11 of 30 vaccines and mAbs in clinical development.

In 2023, we conducted a review of the RSV vaccine and mAb landscape,[20] distilling the lessons learned from late-phase vaccine failures and identifying 33 candidates in clinical trials. This updated Review provides an overview of the drastic developments in the field over the past year. Of the 33 candidates, five have reached the market, 17 have continued development, 12 are no longer in development,[21–30] while 13 new candidates have expanded the field. Currently, RSV prevention is only available in HICs and upper-middle-income countries (UMICs) while the burden of life-threatening disease predominantly exists in LMICs. This inequitable distribution delays vaccine access for those who need a vaccine most. In this Review, we outline urgent next steps to reduce this delay.

Methods

Vaccine and mAb candidates that are market-approved or in clinical phases of development were identified using the PATH (centre for vaccine innovation and access) RSV Vaccine and mAb snapshot resource (last updated Jan 5, 2024).[31] Based on the PATH clinical trial tracker, trial registrations, and personal communications, 13 more candidates were identified and two are considered no longer in development.[32] A data collection template[20] was updated and filled out with targeted searches of PubMed, clinical trial registries, regulatory bodies, and pharmaceutical websites using the candidate names with no date or language restrictions (appendix p 2). 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. Information was selected by date and relevance. When available, peer-reviewed publications were preferred to information from trial registries or pharmaceutical websites. Additional data were collected from the RSV Vaccines for the World Conference organised by the Respiratory Syncytial Virus Network (ReSViNET) Foundation from Feb 13–16, 2024. During the meeting, information was systematically collected from scientific presentations, posters, and discussions using the data collection template. Preventive

	Antigen	Adjuvant	Mechanism of action	Registered population	Route of administration	Registration trial results	Real-world coverage and effectiveness results*	Examples of implementation†
RSVpreF3	PreF	$AS01_E$	Stabilised monovalent preF induces anti-preF IgG with neutralising activity and CD4+ T cells	Older adults (age ≥60 years)	Single dose, intramuscular	Efficacy of 94·1% (95% CI 62·4–99·9) against severe RSV-LRTI over one season; acceptable safety profile[36] (NCT04886596)	USA: effectiveness of both RSCpreF3 and RSVpreF of 73–82% against RSV hospitalisations in four studies[37] with general coverage of 24·4% in adults older than 60 years[38]	Year-round in general population age 60 years and older (Austria) or 75 years and older with shared decision making (USA, Australia, and UK);‡ additional use in high-risk population age 60 years and older (USA and Australia)
RSVpreF	PreF	None	Stabilised bivalent preF induces anti-preF IgG with neutralising activity and CD4+ T cells	Older adults (age ≥60 years)	Single dose, intramuscular	Efficacy of 85·7% (96·66% CI 32·0–98·7) against RSV-LRTI with three or more symptoms over one season;[39] acceptable safety profile[40] (NCT05035212)	USA: effectiveness of both RSCpreF3 and RSVpreF of 73–82% against RSV hospitalisations in four studies[37] with general coverage of 24·4% in adults older than 60 years[38]	Year-round in general population age 60 years and older (Austria) or 75 years and older with shared decision making (USA, Australia, and UK);‡ additional use in high-risk population age 60 years and older (USA and Australia)
RSVpreF	PreF	None	Stabilised bivalent preF induces anti-preF IgG with neutralising activity and CD4+ T cells; antibodies are transferred to the fetus across the placenta	Maternal; WGA varies based on registration body§	Single dose, intramuscular	Efficacy of 82·4% (95% CI 57·5–93·9) against severe MA-LRTI within 3 months after birth and 70·0% (95% CI 50·6–82·5) within 6 months after birth;[41] numerical imbalance in premature births, not statistically significant[42] (NCT04424316)	USA: 17·8% coverage[38]	Year-round at 28–36 WGA (UK and Australia); year-round at 32–36 WGA (Argentina); year-round at 32–36 WGA (USA)‡
mRNA-1345	PreF	None	Lipid nanoparticle contains mRNA encoding for stabilised RSV-A preF eliciting mAbs	Older adults (age ≥60 years)	Single dose, intramuscular	Efficacy of 83·7% (95% CI 66·0–92·2) against RSV-LRTI with at least two symptoms in primary analysis (NCT05127434)[40]	..	..
Nirsevimab	..	None	Passive neutralisation by mAb targeting RSV PreF site Ø with YTE mutation in Fc for extended half-life	Infants (age <12 months)	Single dose of 50 or 100 mg, intramuscular	Efficacy of 78·6% (95% CI 48·8–91·0) against very severe MA-LRTI and 76·8% (95% CI 49·4–89·4) against RSV hospitalisation;[43] no safety concerns within 6 months after vaccination[44] (NCT03979313)	Spain: effectiveness of 82·0–88·7% against RSV hospitalisation in four studies with reported coverage of 91·7–92·0%[45–48] and effectiveness of 81·0% against RSV-LRTI;[49] France: effectiveness of 83·5% against RSV bronchiolitis hospitalisation[50] and 75·9% against RSV PICU hospitalisation;[51] Luxembourg: 62% decrease in RSV-hospitalisation compared with the previous year in population with 84% coverage;[52] Italy: 0% RSV hospitalisations in nirsevimab group compared with 8·3% in no-nirsevimab group in a population with 69% coverage;[53] USA: effectiveness of 90% against RSV-associated hospitalisation[54] and coverage by jurisdiction between 2·4 and 22·8%[38]	Seasonally at birth and follow-up in children about to enter their first RSV season (Italy, Australia, Chile, Luxembourg, and France), children age 6 months and younger (Spain), and 8 months and younger (USA); additional use in high-risk children age 24 months and younger (Spain, Australia, and Luxembourg) or 8–19 months (USA); use in high-risk population and if available also seasonally in children age 3 months and younger (Finland)

..=not applicable or not available. mAb=monoclonal antibody. MA-LRTI=medically-attended lower respiratory tract infection. PICU=paediatric intensive care unit. preF=prefusion protein. RSV=respiratory syncytial virus. WGA=weeks gestational age. YTE=Met252Tyr, Ser254Thr, and Thr256Glu mutations. *It is important to note that these data only cover the first months after administration when effectiveness is expected to be at its highest. Real-world effectiveness data from prospective cohort studies covering the entire first year of life are necessary. †Non-exhaustive examples that are subject to change. ‡Although available year-round, a seasonal approach is recommended. §For example, 24–36 WGA (European Medicines Agency, Pharmaceuticals and Medical Devices Agency, and Anvisa), 28–36 WGA (Medicines and Healthcare products Regulatory Agency), or 32–36 WGA (US Food and Drug Administration).

Table: **Overview of recently market-approved RSV vaccines and mAbs**

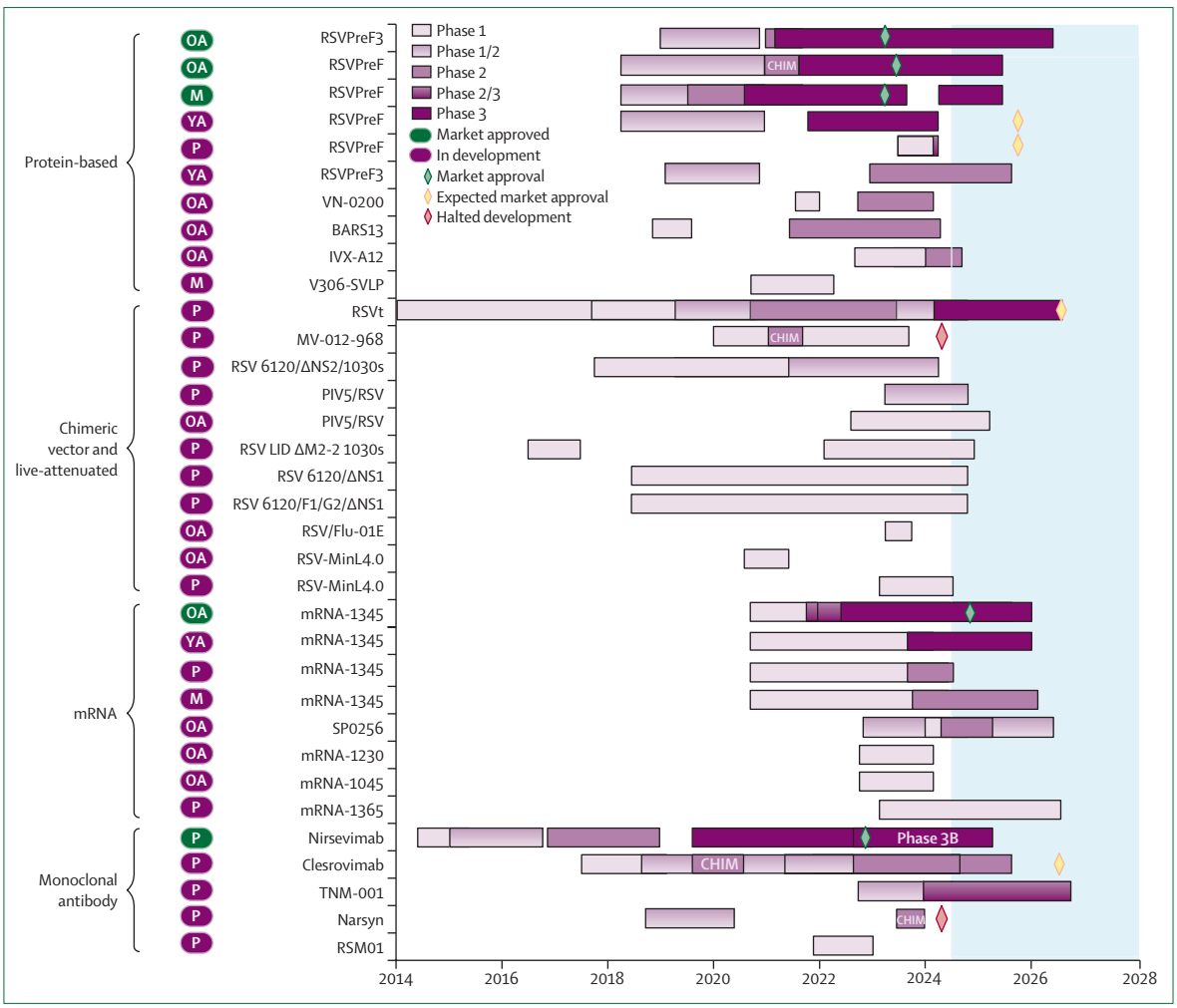

Figure 2: **RSV vaccine and monoclonal antibody clinical development over the last 10 years and expected market access**
All respiratory syncytial virus (RSV) vaccines and monoclonal antibodies that have recently been market-approved (green oval) or are still in clinical development (purple oval). As of May 2024, trials and market approval are projections based on the available information (blue background) and current development can be found on the PATH RSV vaccine and monoclonal antibody snapshot.[31] Trials of the same phase overlapping in time are compressed to one box for ease of reading. Detailed information on clinical trial timing can be found in the appendix (pp 3–9). Market approval is depicted as the first registration date and expected market-approval is projected as 1 year after (expected) interim phase 3 results or as publicly available intention of submission to regulatory bodies. CHIM=controlled human infection model. I=infants younger than 12 months. P=paediatric age 1–18 years. M=maternal. OA=older adults age 60 years and older. YA=younger adults age 18–60 years.

interventions were divided into four categories: protein-based, chimeric vector and live-attenuated, mRNA, and mAbs (figure 1). The table provides an overview of recently approved vaccines and mAbs, while figure 2 presents all candidates in clinical development. Detailed vaccine characteristics, such as mechanism of action, route of administration, and summary of trials have been compiled in the appendix (pp 3–9).

RSV vaccine and mAb landscape

Protein-based vaccines

Protein-based vaccines include subunits, such as RSV preF protein or glycoprotein (G) as single antigens and particle-based vaccines that might achieve increased immunogenicity by displaying multiple antigens. These proteins facilitate rational vaccine design by using structural information and protein engineering to preserve and optimally display antigenic sites most susceptible to neutralisation. Three subunit vaccines were market-approved in 2023 and seven other candidates are still in clinical development.

RSVPreF3 (Arexvy), a stabilised monovalent preF vaccine based on RSV-A F-protein adjuvanted with AS01E,[55] is approved for older adults (age ≥60 years) in the European Union (EU) and major HICs including the USA, Japan, the UK, Canada, and Australia (May, 2023–January, 2024). In clinical trials, RSVPreF3 showed a vaccine efficacy of 67·2% against RSV-LRTI and 78·8% against severe RSV-LRTI across two RSV seasons (ie, for 18 months).[36,56,57] Peak vaccine efficacy against RSV-LRTI

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was estimated at 88% with a monthly waning rate of –2·1%. Extrapolating these data, a single dose of RSVPreF3 might provide some protection after two seasons (efficacy 39·7% at 24 months follow-up).[58] Preliminary results show that revaccination after 2 years provides higher RSV-A and RSV-B neutralising antibody titres than annual revaccination.[59] Results from a phase 3 trial (NCT05590403) in younger adults (50–59 years) at increased risk of RSV disease due to comorbidities indicate non-inferior humoral responses compared with older adults (>60 years),[60] prompting label expansion to adults aged 50–59 years at increased risk.[59] Co-administration with quadrivalent influenza vaccine elicits non-inferior immune response.[61] Ongoing studies in older adults evaluate the safety and immunogenicity of co-administration with several influenza (NCT05568797 and NCT05559476) and herpes zoster vaccines (NCT05966090) and optimal revaccination schedules (NCT04732871).

Special attention for safety concerns in maternal RSV vaccination have centred on the potential for increased occurrence of preterm births and low birthweight, which arose from the halted RSVPreF3 maternal vaccine trial (NCT04605159) conducted during the COVID-19 pandemic. The statistically higher risk of preterm birth in the total RSVPreF3 group compared with placebo was driven by the increased risk in LMICs (relative risk [RR] 1·56, 95% CI 1·17–2·09), which was not found in HICs (RR 1·04, 95% CI 0·68–1·57).[62] Most premature births occurred 4 weeks or more after vaccination, were predominantly late preterm births, and were mostly coinciding with peaks of COVID-19, most strikingly during the Delta wave and remain unexplained.[30]

RSVpreF (Abrysvo), a non-adjuvanted bivalent preF vaccine based on currently predominant RSV-A and RSV-B strains, obtained market-approval for administration in older adults (August, 2023) and pregnant women (March–August, 2023) in the USA, Canada, Argentina, Japan, and the EU. The RENOIR phase 3 trial conducted in older adults showed a robust vaccine efficacy over two RSV seasons of 84·4% against RSV-LRTI with at least three symptoms and 56·8% efficacy against RSV-LRTI with at least two symptoms.[63] Co-administration studies of RSVpreF with inactivated influenza vaccine showed immunogenic non-inferiority without safety concerns.[64] Results from a phase 2 study on safety and efficacy of a combined RSV-COVID-19 vaccine when given with or without influenza vaccine are pending (NCT05886777). Efficacy in older people who are immunocompromised and those with major comorbidities remains uncertain as these populations were excluded from the trials.

RSVpreF for pregnant women induces polyclonal vaccine-specific antibodies that cross the placenta to protect infants up to 6 months after birth. The pivotal MATISSE phase 3 trial enrolled 7396 pregnant participants between 24 and 36 weeks of gestational age during two seasons across both the northern and southern hemispheres.[42] Final analysis revealed high efficacy against severe medically attended LRTI (MA-LRTI) of 82·4% within 3 months after birth and 70·0% for the first 6 months of life. Against less severe MA-LRTI, the vaccine showed an efficacy of 57·6% within the initial 3 months and 49·2% for the first 6 months after birth.[41] Efficacy wanes after 6 months for both severe and less-severe MA-LRTI.[41] There were no safety concerns as slight numerical imbalances in birth outcome lacked statistical significance (prematurity of 5·7% in the RSVpreF group *vs* 4·7% in the placebo group and low birthweight 5·1% in the RSVpreF group *vs* 4·3% in the placebo group).[41] The mean duration between vaccination and delivery was similar between groups (57·6 days for RSVpreF group and 57·9 days for placebo) and the mean gestational age at delivery was 39·1 weeks in both groups. The numerical imbalance was only seen in UMICs[65] and some maternal risk factors (COVID-19, previous history of preterm births, maternal adverse events, or hypertensive conditions) were reported more commonly in the RSVpreF group and among those with preterm births. The strict exclusion criteria for the RSVpreF MATISSE trial, which were similar to the RSVPreF3 maternal vaccine trial, resulted in lower prematurity rates in South Africa in the study population (5%) compared with the general population (15%).[66] Therefore, there is a need to assess risk of prematurity after vaccination in a population with high prematurity rates. A systematic review and meta-analysis of safety results of six randomised controlled trials describing three RSV maternal vaccines (n=17 991 pregnant women immunised with RSVPreF3, RSVpreF, or RSV-F nanoparticle compared with placebo) observed a potential higher risk of preterm births in the vaccine group and further investigation of the preterm safety signal is warranted.[67] For this reason, the Pan-American Health Organization and the US Food and Drug Administration have recommended the vaccine for use later in pregnancy (32–36 weeks gestational age) than the European Medicines Agency (24–36 weeks gestational age), and the regulatory bodies monitor outcomes in both maternal and infant populations in post-marketing safety studies. The WHO Strategic Advisory Group of Experts on immunisation (SAGE) will make policy recommendations on maternal vaccine use in LMICs in September, 2024. A phase 3 trial is ongoing in South Africa to establish the safety and immunogenicity in pregnant women living with HIV (NCT06325657). A phase 2 trial showed that co-administration of RSVPreF with the Tdap (tetanus, diphtheria, and polio) vaccine during pregnancy induced statistically non-inferior immune responses to those elicited by individual vaccinations, except for the pertussis component.[68] The clinical significance of the reduced antibody response to the pertussis component is uncertain. While 31% of data from the MATISSE study originated from LMICs, the

vaccine has so far received market-approval solely in the EU and HICs and UMICs (Argentina, Canada, Japan, the UK, and the USA). The USA introduced the maternal vaccine in the previous RSV season and Argentina has introduced it for the coming season. No early experience data are available yet.

There are five protein-based vaccines in clinical development that use the F-protein as antigens. The first is RSVPreF3 in phase 2 development for immunocompromised younger adults (≥18 years, NCT05921903). Second and third are RSVpreF vaacines in late-phase development for both children (age 2–18 years, phase 2/3, PICASSO trial, NCT05900154) and younger adults at high risk of severe RSV disease (age 18–60 years, phase 3, MONET trial, NCT05842967) with results expected at the end of 2024. The fourth is V306-SVLP, a particle-based vaccine designed with an F-protein antigenic site II epitope-focused approach rather than the entire fusion protein. The specific IgG response elicited was not translated to the expected increase in neutralising antibody (nAb) titres against RSV-A or RSV-B in the phase 1 trial. Future modifications of the vaccine (eg, generation of F-protein sites Ø and IV peptide mimetics) might improve the immunogenicity.[69] The fifth is the particle-based vaccine IVX-A12 that combines stabilised RSVpreF with human metapneumovirus (hMPV)-preF to induce an immune response against both pathogens.

The particle-based vaccine was well tolerated and immunogenic against RSV-A and RSV-B and hMPV-A and hMPV-B without immune interference in older adults.[70] Two subunit vaccines target other viral antigens: BARS13 and VN-0200. BARS13 is based on the RSV G-protein with cyclosporine A adjuvant to induce regulatory T cells. BARS13 was safe in a phase 1 trial and interim results of the phase 2 trial showed a dose-dependent and frequency-dependent antibody response.[71,72] VN-0200 uses VAGA-9001a as an antigen with MABH-9002b adjuvant, both of which have an undefined biological background. Phase 1 trial results are unpublished while the phase 2 trial is expected to be completed in February, 2024.

Chimeric vectors and live-attenuated vaccines

The paediatric RSV burden is highest in infants younger than 6 months, but substantial burden persists in older infants and toddlers, aged 6–24 months. There is an unmet need for protection, which can be fulfilled by chimeric live virus constructs and live-attenuated RSV vaccines (LAVs). Chimeric live virus vectors can replicate efficiently in the presence of pre-existing RSV immunity, while LAVs cannot. Such vectors are ideal for boosting RSV immunity after RSV vaccination or infection, but typically only express a single RSV protein. Both strategies are administered intranasally and provide a child-friendly solution for mucosal immune priming for future infections.

In the last three decades, the National Institute of Allergy and Infectious Diseases and National Institutes of Health have been dedicated to striking a delicate equilibrium between attenuation and immunogenicity within LAV formulations (appendix p 10). LAVs should be sufficiently attenuated to avert upper respiratory tract infections upon vaccination, while remaining resilient against reversion to wild type and yet immunogenic enough to confer protection upon future RSV exposure. Rational vaccine design informed by basic research has coalesced into three LAV families, each targeting distinct non-essential viral proteins namely M2-2, NS1, and NS2. The lead candidate RSVt (also known as SP0125, VAD0001, or RSV ΔNS2/Δ1313/I1314L) belongs to the ΔNS2 family. The phase 2 trial of two doses of RSVt in children aged 6–18 months showed a favourable safety profile, with transient rhinorrhoea and nasal congestion observed more frequently in vaccinees.[73] A robust four-fold rise in nAb titres was observed in 62–68% of toddlers,[73] which is associated with protection from disease.[74] Vaccine viral shedding decreased markedly following the second vaccination suggesting immune system priming. A global phase 3 efficacy trial is underway (NCT06252285) and submission for regulatory approval is expected in 2026.[73] In the meantime, the lead candidate is also in a head-to-head comparison with another candidate from the ΔNS2 family (RSV 6120/ΔNS2/1030s, NCT03916185). The two candidates of the ΔNS1 family (RSV 6120/ΔNS1 and RSV 6120/F1/G2/ΔNS1) are in a phase 1 head-to-head comparison trial (NCT03596801).

Five other candidates are in early phases of clinical development. PIV5/RSV, a chimeric vaccine based on live parainfluenza 5 (PIV5) encoding the RSV F antigen, is in phase 1/2a development for children aged 18–59 months. Preliminary results show no safety signals and 3·6-fold to 57-fold rise in nAbs over baseline levels in 80% of participants.[75] A phase 1 trial in older adults showed an acceptable safety profile and increased nasal RSV-specific IgA in 48% of participants.[76] RSV-MinL4.0, an LAV with four mutations in the L polymerase gene, is in phase 1 clinical development for both children and older adults (NCT04919108 and NCT04295070). RSV/Flu-01E, using an attenuated influenza vector displaying the RSV F-protein, is in phase 1 clinical development for older adults (NCT05970744). Little information about this candidate is available in the public domain. The development of MV-012-968, an LAV with attenuated NS1, NS2, and G proteins and SH-protein deletion, was recently halted to review the company's strategic options despite positive results from a phase 1c trial in seronegative toddlers.[77]

mRNA vaccines

mRNA-1345 (mRESVIA), leveraging the same lipid nanoparticle technology as the SARS-Cov-2 SpikeVax, aims to enhance immunogenicity by encoding for a

stabilised RSV-A preF protein. The pivotal phase 2/3 trial among older adults revealed efficacy of 63·3% against RSV-LRTI with at least two symptoms and 63·0% against RSV-LRTI with at least three symptoms after extended follow-up (median 8·6 months).[78] The efficacy was consistently higher against RSV-A compared with RSV-B, potentially due to fewer cases observed in the RSV-B subtype or due to the mRNA coding for RSV-A preF.[78] FDA approval was obtained for older adults on May 31, 2024, and regulatory approval is anticipated for the EU and various other countries (Switzerland, Australia, Canada, and the UK).[1–3,79–81] Ongoing trials seek to elucidate the durability of protection, revaccination strategies at both 1 and 2-year intervals, and co-formulation with seasonal influenza or SARS-CoV-2 vaccines (mRNA-1045 and mRNA-1230) to streamline older adult vaccination regimens (NCT05330975 and NCT06060457). mRNA-1345 is also in phase 3 clinical development for younger adults at high risk (age 18–60 years, NCT06067230), phase 2 for pregnant women (NCT06143046) and seropositive children (NCT06097299), and phase 1 as a co-formulation with mRNA encoding hMPV F-protein for seropositive children (mRNA-1365, NCT05743881).

Building upon the promising outcomes of a phase 1/2b trial with SP0256, an RSV mRNA vaccine with unknown viral antigens targeted at older adults, plans were announced for a combination mRNA vaccine targeting up to three respiratory pathogens (RSV, hMPV, and PIV).[82] Presently, SP0256 is undergoing evaluation in a phase 2b trial for older adults as a standalone RSV vaccine (NCT06251024) and phase 1 trials for its combination with hMPV (NCT06134648 and NCT06237296). The company announced a target regulatory submission in 2026.

Immunoprophylaxis with mAbs

Next generation mAbs targeting highly neutralisation-sensitive epitopes located on the RSV preF protein have been engineered with fragment crystallisable region mutations to extend the half-life for an entire RSV season (typically 4–5 months). Palivizumab, with limited potency and without extended half-life mutations,[83] was the only market-approved protection against RSV for infants for nearly 25 years. At present, nirsevimab is also in use, and four more mAbs are in clinical development.

Nirsevimab (Beyfortus) targets site Ø of the RSV preF protein and has a mean half-life of 68·7 days.[44] The MELODY registration trial showed an efficacy of 76·4% for MA-LRTI, 78·6% for very severe MA-LRTI, and 76·8% for RSV hospitalisations for 150 days post-dose.[43] In this trial, children followed into their second RSV season were found to remain unexposed to the theoretical risk of enhanced respiratory disease despite suboptimal nAb levels during this period.[84] The burden of disease did not shift to the second year of life as RSV events (MA-LRTI or hospitalisation) were balanced between treatment groups (1·8% in nirsevimab and 2·1% in placebo group).[84] Seroresponse rates to postF were similar between nirsevimab recipients (68–69%) compared with the placebo group (63–70%), suggesting that the presence of nirsevimab still allows an active immune responses upon RSV exposure.[85] In the HARMONIE pragmatic trial, efficacy against RSV hospitalisation was 83·2%.[86] More than 99% of RSV isolates from two clinical trials retained susceptibility against nirsevimab, escape variants were rare, and the binding site was highly conserved over the last 65 years.[87,88] Nirsevimab has been market-approved in the EU and in Argentina, Australia, Brazil, Canada, Chile, China, Saudi Arabia, Switzerland, the United Arabic Emirates, the UK, and the USA (October, 2022 to December, 2023) and is under review in several other countries. The demand was higher than anticipated and exceeded manufacturing capacity,[89] therefore some regions had to limit the use to children at high risk and other regions could not introduce at all.[90] The USA, France, Spain, Portugal, and Luxembourg had a rapid response in integrating nirsevimab into routine immunisation schedules for all children within one season of approval. Nirsevimab real-world early-effectiveness was 82·0% against RSV hospitalisation, 86.9% against severe RSV-LRTI requiring oxygen support, and 69·2% against all-cause LRTI hospitalisations in Galicia, Spain.[45,91] The universal prophylaxis programme showed notable coverage of 91·7% for combined in-seasonal and catch-up immunisation, with no severe adverse events reported among the 9408 administered doses.[45,92] RSV hospitalisations decreased by 89·8% compared with previous seasons (2016–23).[45,93] A population-based cohort study in Navarre, Spain, with 92·0% coverage showed early-effectiveness of 88·7% against RSV hospitalisations.[46] In line with this, a post-licensure, prospective case-control study in France found real-world effectiveness against RSV hospitalisations to be 83·5%.[50] Finally, Luxembourg had a coverage of 84%, with a 62% decrease in RSV hospitalisations compared with the same period the year before.[52] It is important to note that these data are from the first months after administration when effectiveness is at its highest. Notably, the reduction in hospitalisations primarily affected infants under 6 months (30% of admissions in 2023 *vs* 60% in 2022). As the number of hospitalisations among older infants remained similar, most hospitalisations are in older infants leading to an increased mean age at hospitalisation from 7·8 months to 14·4 months. The increase in age at RSV hospitalisation was also seen in France with a 75% coverage.[94] The real-world experiences recommend flexible appointments for parents, early negotiations to ensure supply, extensive parent education, and simple logistics for successful implementation and high coverage.[95]

Clesrovimab (MK-1654) primarily targets site IV of the RSV F-protein, featuring the same YTE mutation as nirsevimab to extend its half-life to 44·9 days in both

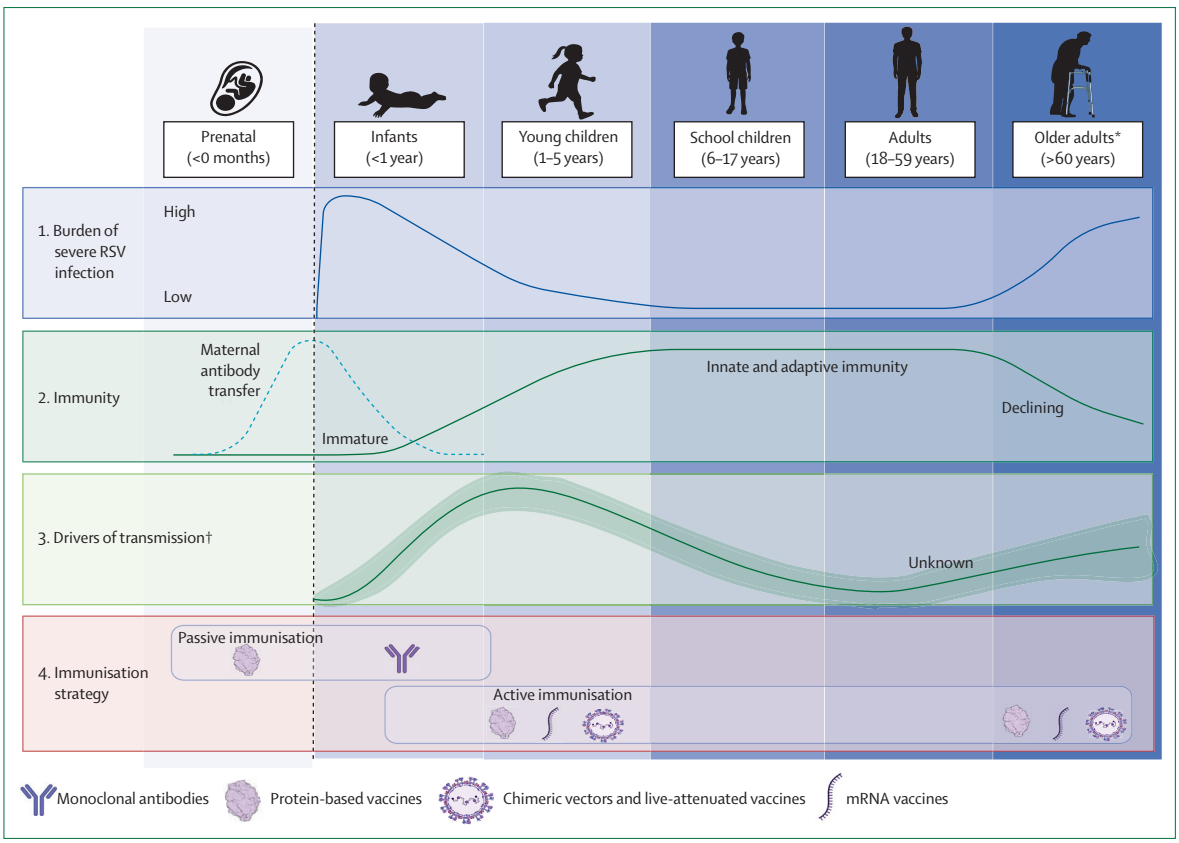

Figure 3: **Conceptual overview of RSV prevention strategies per target population**
The primary target populations for RSV immunisation include infants, young children, and older and high-risk adults. Active immunisation is the preferred strategy for the paediatric and adult population, whereas for infants, passive immunisation—either by monoclonal antibodies or maternal immunisation during pregnancy—is the preferred approach.RSV=respiratory syncytial virus.*Including younger adults (age 18–60 years) with underlying comorbidity at high risk for severe RSV infection. †Despite young children being recognised as major contributors to RSV transmission, the precise role of specific age groups in transmission remains uncertain. Also, the potential effect of vaccines targeting young children on RSV transmission and their indirect protective effect on infants and high-risk and older adults is yet unknown.

preterm and term infants.[96] The site IV epitope exhibits high conservation, with more than 99·9% identity observed among over 3058 reported complete RSV F-protein sequences.[97] Two phase 3 studies are ongoing: the results of a large phase 2b/3 trial are expected in 2024 (NCT04767373) alongside a head-to-head comparison with palivizumab (NCT04938830). Clesrovimab is characterised by improved penetration into the nasal epithelial lining fluid and neutralisation ex vivo in a controlled human infection model compared with other mAbs (with nasal concentrations ranging 1·4–3·3% of serum concentrations *vs* 1–2% in three other mAbs, including nirsevimab).[98] These data support the potential for improved local protection at the site of infection. The differences in pharmacokinetics between clesrovimab and nirsevimab regarding the potential of protection during the second season should be further clarified when the phase 3 trial efficacy results are available.

Three additional mAbs are currently in earlier stages of development. RSM01, a mAb against RSVpreF site Ø with YTE mutations, is developed by the Bill & Melinda Gates Medical Research Institute with a primary focus on addressing the needs of LMICs with a vaccine target price.[99] Preliminary findings from their phase 1 trial in healthy adults revealed an extended half-life of 79 days and a safety profile similar to placebo.[100] Modelling projections estimated that African infants aged 0–12 months might attain serum concentrations four-times higher than the protective threshold 150 days after intramuscular immunisation.[101] Narsyn (palivizumab administered intranasally) exhibits potential for increased accessibility and affordability due to child-friendly administration by parents, but encountered futility in the interim analysis of the phase 2b trial.[102] Timely interim analysis prevented further waste of resources and capital. Lastly, TNM-001 is an extended half-life mAb against RSVpreF with unknown target site. Little information is available in the public domain besides the neutralising capacity of at least 30-fold higher than palivizumab.[103] A phase 2/3 trial is planned but not yet recruiting (NCT06083623).

The alignment of multiple mAbs within the landscape of RSV prevention remains uncertain. Clesrovimab's

anticipated registration in 2025, alongside the already approved nirsevimab, begs the question how the two mAbs will coexist. Given the supply challenges encountered in the inaugural season,[89] there could be a need for two mAb producers to meet the increased global demand. Furthermore, having several options with distinct viral epitopes could prove advantageous if resistant mutants become predominant circulating strains under drug pressure. Global introduction of mAbs should be monitored with global genomic surveillance, such as the inclusion of RSV in the WHO Global Influenza Surveillance and Response System sentinel surveillance, to allow immediate action upon the occurrence of substantial resistance.

Vaccine strategy and implementation per target population

RSV immunisation strategies, their rationale, and implementation considerations vary among different target populations (figure 3; appendix pp 11–12). For infants, passive immunisation either by maternal vaccines or long-acting mAbs offers protection against severe RSV infections during the first months of life. With both strategies now available, it is important to consider their comparative advantages and implementation challenges, which are discussed in detail in the appendix (pp 11–12). The preferable immunisation strategy (ie, mAbs, maternal vaccine, or combined) and implementation approach (seasonal or year-round) is country-specific, depending on RSV seasonality, costs, sociocultural preferences, and health-care infrastructure. Toddlers and primary school children could be important drivers of RSV transmission,[104,105] but it is unclear whether paediatric RSV vaccines could indirectly protect infants and older adults. Adult RSV vaccination shows promise for protecting susceptible individuals, yet determining the specific target group requires careful consideration with current national guidelines ranging from vaccinating all adults older than 60 years (age-based strategy) to targeting specific groups based on comorbidities (high-risk strategy) and higher age thresholds.[106–108]

Public health effects

Cost-effectiveness of RSV immunisation is essential for country-level decision making, especially in lower-resource settings. RSV vaccination in older adults is estimated to be cost-effective in HICs.[109,110] The two strategies available for infants can be cost-effective in HICs,[111–113] but in LMICs affordability remains a barrier[114] although the clinical effect is expected to be substantially higher than in HICs. Reduction in RSV-LRTI is also expected to reduce all-cause LRTI, RSV and all-cause deaths, hospital bed occupancy, oxygen and antibiotic use, recurrent LRTIs and wheezing episodes in toddlers, and generally improve lung health.[46,115,116] The appendix (pp 12–14) provides a more detailed discussion on public health and cost-effectiveness considerations.

Implementation considerations and challenges in LMICs

Specific implementation considerations arise in LMICs additional to the general considerations (and outlined in the vaccine strategy and implementation per target population section and in the appendix pp 11–12), due to resource constraints, lack of RSV seasonality near the equator, limited vaccine access, and the potential effect of more prevalent maternal comorbidities (eg, HIV and malaria) unaddressed in clinical trials. Maternal vaccines are accessible due to pricing, although maternal vaccination programmes might not be well established in all LMICs. The relatively high prevalence of preterm births and HIV and malaria during pregnancy could affect maternal vaccination efficacy or the duration of protection. The numerical imbalances in preterm births observed with RSVpreF and RSVPreF3 were restricted to UMICs, necessitating further evaluation in LMICs and possibly delaying introduction in these settings potentially with initial use restricted to later gestational age, which has a major effect on feasibility due to challenges to assess gestational age in LMICs. Recent modelling showed that vaccination at 24 weeks gestational age could prevent 94% of in-hospital RSV mortality among infants younger than 6 months, while delaying it to 32 weeks gestational age could prevent 82% of RSV deaths.[117] The potential safety issues need to be carefully balanced with the potential reduction in the number of deaths caused by vaccinating mothers early in pregnancy using formal risk–benefit analysis. While the high burden of RSV in LMICs favours cost-effective interventions, pricing remains a crucial factor in implementation strategy for both mAbs and maternal vaccination. Seasonal approaches are cheaper as less product is used, but year-round immunisation with either mAb or maternal vaccination might be more achievable in countries with weaker health-care systems. In the end, cost and cost-effectiveness are likely to drive implementation strategy.

There is a high risk of an RSV vaccine gap between HICs and LMICs of several years (figure 4A) further increasing the already existing gap in disease burden. Stakeholders, such as pharmaceutical companies, the Global Alliance for Vaccines and Immunization (Gavi), WHO, the Bill & Melinda Gates Foundation (BMGF), PATH, regulatory and academic institutions, countries, health-care providers, families, patients, and other relevant health-care stakeholders can take steps to ensure RSV vaccine equity and overcome implementation challenges in LMICs (figure 4B). First, many LMICs have variable and prolonged regulatory pathways. Recognising this, the SAGE RSV working group evaluates available evidence to inform SAGE in making recommendations for LMICs, given that pivotal clinical trials might not always provide sufficient evidence for decision making in

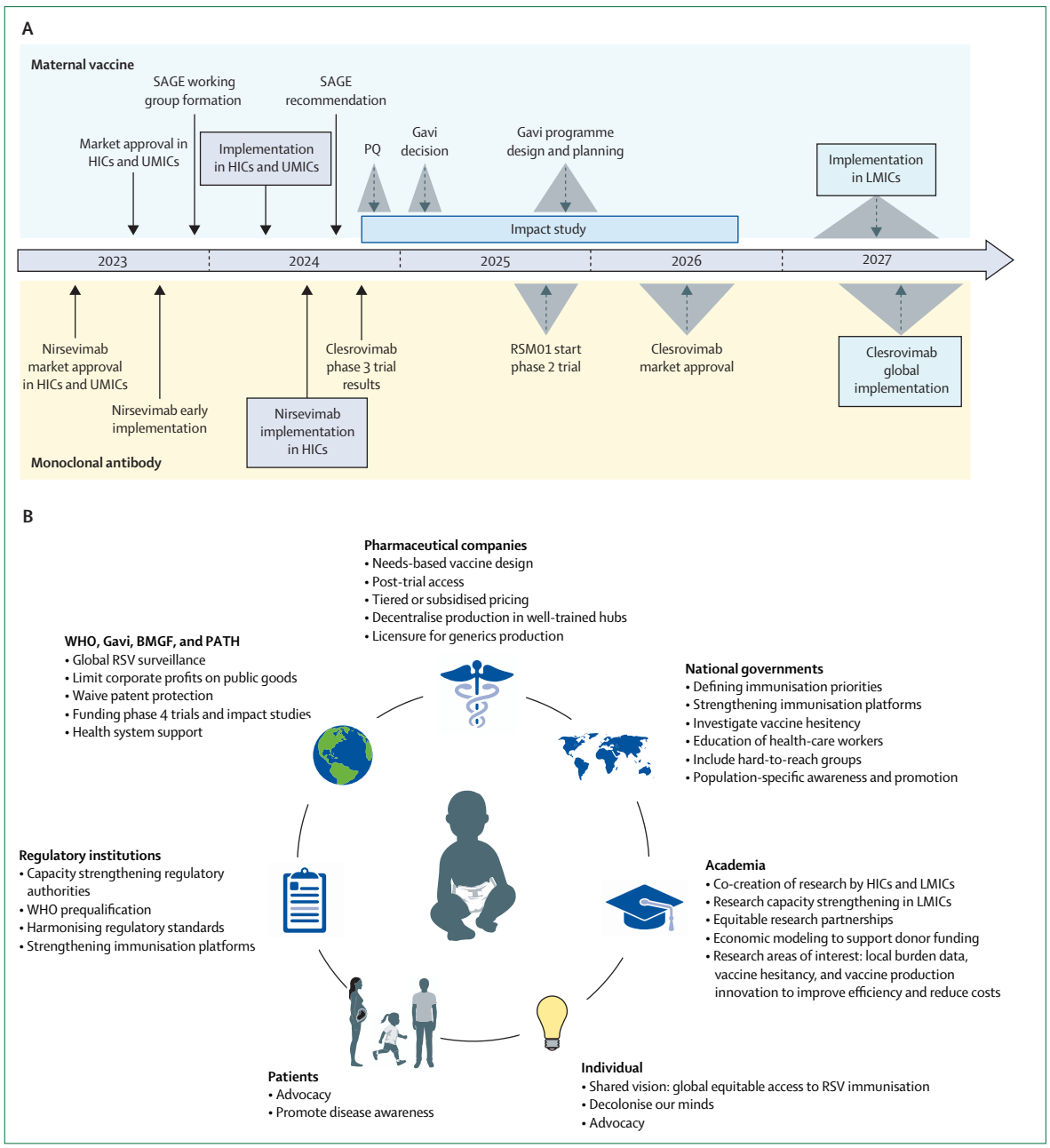

Figure 4: **The road to global access for infant RSV immunisation**
(A) Projected timeline for global access to RSV prevention for infants with planned (solid arrows) and projected (dashed arrows with uncertainty area) key actions. The WHO SAGE working group was formed in December 2023[118] to draft policy recommendations for RSV prevention in LMICs with a focus on maternal vaccination.[119] Depending on the outcome of SAGE recommendations, it is uncertain if or when following steps will take place. In case of positive SAGE recommendations and WHO prequalification, Gavi might decide to include RSV prevention in their portfolio allowing global access in 2027,[120] 3 years after HICs and UMICs.[121,122] If monoclonal antibodies are not included in the SAGE recommendations, inequitable access to highly effective and safe RSV prevention will remain. Although clesrovimab and RSM01 are dedicated to global affordability, the lag in clinical development delays access in LMICs until at least 2027: it will take at least 2 years to obtain market approval after the end of the clesrovimab phase 3 trial (NCT04767373) in 2024 and another year is estimated to be required to achieve global access. (B) Key actions per stakeholder needed for equitable global access to RSV prevention. BMGF=Bill & Melinda Gates Foundation. Gavi=Global Alliance for Vaccines and Immunisation. HICs=high-income countries. LMICs=low-income and middle-income countries. PATH=Centre for vaccine innovation and access. PQ=WHO prequalification. RSV=respiratory syncytial virus. SAGE=Strategic Advisory Group of Experts on Immunisation. UMICs=upper-middle-income countries.

LMICs. The SAGE recommendations expected in September, 2024 will be crucial for Gavi support for RSV vaccines. In parallel, SAGE is undertaking a real-world (ie, few exclusion criteria) impact study in three to four LMICs to better understand the effectiveness and effect of the maternal vaccine against RSV and all-cause

LRTI and hospitalisation and safety, including the risk of preterm births. The proposed study is anticipated to start in late 2024, will include two RSV seasons, and its results will be highly relevant to LMIC policy makers, although the trial might also delay vaccine introduction. However, SAGE should broaden their recommendations and impact trial to include mAbs for LMICs to increase the imperative to reduce mAb pricing and thus reduce global inequity. Second, vaccine pricing is prohibitively high for LMICs. Efforts to introduce clesrovimab beyond HICs and develop RSM01 specifically for LMICs at vaccine-like pricing offer promise in the future,[20,99] but high production costs prove difficult to keep prices to the level needed for global access, necessitating innovations to enhance production efficiency and lower costs for mAbs.[99] Gavi support is indispensable to ensure global accessibility of RSV prevention. Therefore, RSV vaccination was added to the vaccine investment strategy 5.0 (2021–25). SAGE recommendations will be crucial to develop a refined investment case for Gavi board decisions and programme design. Ways to keep pricing down for LMICs include licensure for generics-production, variable pricing mechanisms, and patent pooling. Third, RSV immunisation products would ideally be co-administered with other vaccines to reduce the strain on the health-care system. However, no data are available on the safety and immunogenicity of co-administration of RSV mAbs with the BCG vaccine at birth. Nonetheless, based on the mechanism of action and experience with palivizumab, nirsevimab is not expected to interfere with the immune response to other vaccines.[123] To date, insufficient data exist on the RSV maternal vaccine administered with the tetanus and pertussis vaccines. Fourth, LMICs experience competing immunisation priorities: not only are there new vaccines against major pathogens such as malaria, there is also a push to increase uptake of underutilised existing vaccines, such as measles, inactivated polio, and human papillomavirus. Fifth, inequity in immunisation within LMICs is already a major challenge, particularly affecting hard-to-reach populations, including those residing in remote rural areas, urban low-income communities, conflict-affected regions, and areas facing religion and gender-related barriers. Strengthening of immunisation platforms within countries to include all children and adults might be of higher priority to policy makers. Sixth, a lack of RSV awareness among both health-care policy makers, health-care providers, and the population in LMICs is a considerable barrier to overcome for successful vaccine implementation. Engagement to build political will is crucial to maximise vaccination uptake as the absence of RSV awareness among policy makers could lead to negative decisions regardless of SAGE recommendations. The RSV Roadshow was created by WHO and PATH as a communications toolkit[124] to advance the RSV prevention conversation to support global, regional, and country decision making around RSV prevention, policy, and implementation preparedness. WHO also generates country-specific burden data from their global surveillance data generation and packaging of existing global RSV data to inform country-level decisions. The perspective of health-care workers is crucial for successful vaccine acceptance,[125] so their education in RSV burden and vaccines could prove beneficial for vaccine uptake. Additionally, promoting awareness and understanding of RSV among the general population in LMICs, along with improving overall health literacy, should be important for successful uptake of immunisations when available. All in all, barriers including low awareness, lack of country-specific burden data, and cost of products preclude the successful delivery of RSV vaccines in LMICs. The crude birth rates in LICs are 3·5-times higher than in HICs, highlighting the necessity of rapid access to RSV prevention in LMICs.[126]

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

- Respiratory syncytial virus (RSV) transmission
- Necessity and optimal timing for booster vaccination
- Co-vaccination strategies
- Safety of maternal vaccination in lower-middle-income countries (LMICs)
- Additional real-world effectiveness data
- RSV genetic surveillance for viral resistance
- LMIC cost-effectiveness data, also driven by out-of-hospital mortality
- Definitive correlate-of-protection
- Effect of vaccination on long-term sequelae, antibiotic use, and microbiome
- Burden of RSV in older adult population
- Tools to increase RSV awareness and vaccine acceptance

Discussion

For the first time since the virus' discovery in 1956 and the tragic results of the first RSV vaccine trial in 1965, we now have effective RSV immunisations for infants and older adults in HICs. However, there is a high risk of years of vaccine gap between HICs and LMICs and urgent action is needed for global access to RSV vaccines. 30 RSV vaccine candidates are still in development, including an LAV in phase 3 for toddlers.

Remaining knowledge gaps in the RSV vaccine landscape include the long-term RSV vaccine effect on early LRTI-induced wheeze and lung health at later ages (panel). Real-world effectiveness data are currently restricted to first experiences with nirsevimab in HICs. However, as additional data emerge in the coming years, across various strategies and settings there is potential for insightful comparisons of real-world implementation, uptake, and effectiveness. As RSV has been associated with both viral and bacterial LRTIs, the protective aspect could be broader than generally

anticipated. Moreover, as nasal commensals protect against severe infection via immunomodulatory properties,[127,128] we should investigate how the commensal flora can be leveraged to increase vaccine impact. Although it is most effective to reduce the high RSV burden in infants and older adults using direct immunisation, it is uncertain if the transmission chain could be broken by reducing RSV in toddlers and school-going children (age 2–12 years). The cost-effectiveness of toddler and school-going children vaccination is unknown and would be incremental on previous maternal or infant immunisation. Finally, the potential effect of the introduction of RSV immunisation on the circulation patterns of other respiratory virus infections remains to be elucidated.

To conclude, the RSV vaccine and mAb landscape has come a long way since the first vaccine attempts with formalin-inactivated RSV in the 1960s. We can reduce the economic and clinical RSV burden in infants and older adults in HICs and major collaborative efforts need to be urgently undertaken to reduce the RSV vaccine gap to LMICs.

Contributors

All authors contributed to the Review and editing of the manuscript. JT contributed to the conceptualisation, original draft writing, data curation, and visualisation of the Review. SFH contributed to the data curation, visualisation, and original draft writing. YNL contributed to data curation and visualisation. LRN contributed to visualisation. NIM contributed to the conceptualisation, data curation, and supervision of the review.

Declaration of interests

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