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ABSTRACT

Respiratory syncytial virus (RSV) is the predominant cause of acute lower respiratory infection (ALRI) in young children worldwide, yet no licensed RSV vaccine exists to help prevent the millions of illnesses and hospitalizations and tens of thousands of young lives taken each year. Monoclonal antibody (mAb) prophylaxis exists for prevention of RSV in a small subset of very high-risk infants and young children, but the only currently licensed product is impractical, requiring multiple doses and expensive for the low-income settings where the RSV disease burden is greatest. A robust candidate pipeline exists to one day prevent RSV disease in infant and pediatric populations, and it focuses on two promising passive immunization approaches appropriate for low-income contexts: maternal RSV vaccines and long-acting infant mAbs. Licensure of one or more candidates is feasible over the next one to three years and, depending on final product characteristics, current economic models suggest both approaches are likely to be cost-effective. Strong coordination between maternal and child health programs and the Expanded Program on Immunization will be needed for effective, efficient, and equitable delivery of either intervention.

This 'Vaccine Value Profile' (VVP) for RSV is intended to provide a high-level, holistic assessment of the information and data that are currently available to inform the potential public health, economic and societal value of pipeline vaccines and vaccine-like products. This VVP was developed by a working group of subject matter experts from academia, non-profit organizations, public private partnerships and multilateral organizations, and in collaboration with stakeholders from the WHO headquarters. All

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contributors have extensive expertise on various elements of the RSV VVP and collectively aimed to identify current research and knowledge gaps. The VVP was developed using only existing and publicly available information.

1. The global public health need for immunization

Respiratory syncytial virus (RSV) is the predominant cause of acute lower respiratory infection (ALRI) in young children worldwide, yet no licensed RSV vaccine exists to help prevent the millions of episodes and hospitalizations and tens of thousands of young lives taken each year. Monoclonal antibody (mAb) prophylaxis exists for prevention of RSV in a small subset of very high-risk infants and young children, but the only currently licensed product is impractical and expensive for low-income settings, where the RSV disease burden is greatest [1]. Globally, in 2019, there were an estimated 33.0 million episodes of RSV-induced ALRI in children under five years of age, resulting in 3.6 million hospital admissions and 26,300 in-hospital deaths. Overall, RSV-attributable deaths were estimated to be 101,400, with more than 95 % of RSV ALRI episodes and 98 % of RSV deaths occurring in low- and middle-income countries (LMICs) among children under five years old [2]. Infants aged six months or younger are at higher risk for RSV-associated severe outcomes. In 2019, there were 1.4 million hospital admissions and 13,300 in-hospital deaths for RSV ALRI in infants under six months of age globally [2]. In addition, recent RSV community mortality studies reveal a high unmeasured burden of RSV deaths outside hospitals in LMICs, particularly among infants [3,4]. See Table 1. Given this substantial morbidity and mortality burden, RSV prevention interventions are needed for young children, especially infants under six months of age, who have the highest incidence and most severe disease burden.

This analysis focuses on two passive immunization[1] approaches that target protecting newborns and young infants from severe RSV disease. One approach is maternal RSV vaccination and the other is a mAb for immunoprophylaxis, both mediated via passive protection through RSV antibodies. Since the intent of this document is to describe vaccines and vaccine-like products in late-stage development for use in LMICs, and the overwhelming burden of RSV disease in these settings occurs in children less than six months of age, information will primarily focus on this population. Indications for older children and older adult populations will not be addressed here but may be included in subsequent versions.

Post-submission update: please note, since the RSV vaccine value profile included in this special edition was submitted in June 2022, several significant developments have occurred in the field including: a long-acting mAb licensed in late 2022; an RSV vaccine for older adults licensed in early 2023; and a maternal vaccine under regulatory review in 2023. These updates are not included in this profile.

1.1. Current methods of surveillance, diagnosis, prevention, and treatment

The current standard of care for RSV remains supportive management. This includes hydration and nutritional support (e.g., intravenous fluids and nasogastric feeding), oxygen therapy, and noninvasive and invasive ventilation [52]. Prevention with a licensed monoclonal antibody, palivizumab (PVZ; SYNAGIS®) is recommended among very high-risk infants and young children and its use is almost exclusively limited to high-income countries (HICs) due to its high cost and challenges in delivery (five monthly doses needed during the RSV season). Virological testing for RSV is not recommended for routine use in case management by most existing guidelines [52].

RSV surveillance is available mostly in HICs and in some middle-income countries (MICs) but in LMICs, it is limited. In 2016, the World Health Organization (WHO) piloted Phase 1 of a three-year RSV surveillance strategy that leverages the capacities of existing surveillance infrastructure in the Global Influenza Surveillance and Response System [53]. Phase 2 began in November 2018 with a three-year extension of the strategy, expansion to a total of 25 countries, and testing for RSV in patients meeting a modified severe acute respiratory infection or influenza-like illness case definition, with a focus on children under two years of age.

1.2. Summary of knowledge and research gaps in epidemiology, potential indirect public health impact, and economic burden

Priority knowledge

- RSV represents a substantial morbidity and mortality burden among children younger than five years old globally, particularly infants aged six months or younger in LMICs.
- Recent RSV community mortality studies reveal a high and previously unmeasured burden of RSV deaths outside hospitals in LMICs.
- RSV infection can lead to secondary consequences—in the short term, RSV infection can predispose to bacterial pneumonia; in the long term, early-life RSV infection is associated with later wheezing/asthma episodes and recurrent lower respiratory infections, although a causal role has not been demonstrated.
- RSV infection contributes to the development of antimicrobial resistance through the inappropriate prescription and use of antibiotics (intended for treating bacterial infections) as well as the use of antibiotics in secondary bacterial pneumonia.
- RSV imposes a substantial economic burden on health systems, governments, and society.
- Given the high disease burden of RSV in infants aged six months or younger, RSV maternal immunization or mAb use in newborns or young infants has the potential for substantial public health impact globally.

Research gaps

- Data from LMICs on RSV burden of disease stratified by narrow age bands for infants.
- Additional evidence on the effect of maternal RSV vaccine against severe RSV disease in infants.
- Evidence from studies in LMICs designed and powered to evaluate the effect of RSV prevention in early infancy, including secondary outcomes such as repeat ALRI episodes and subsequent wheezing illness.

2. Potential target populations and delivery strategies

While maternal RSV vaccines and mAbs both offer protection for young infants, their target populations differ and thus will require different strategies for delivery. Whereas the target popu-

[1] Passive immunization is defined as the transfer of humoral immunity in the form of ready-made antibodies to provide temporary protection against a microbial agent or toxin.

Table 1
Summary of epidemiology and potential indirect public health impact of respiratory syncytial virus.

Feature	Summary and evidence
Epidemiology	
Reservoir	• No known animal reservoir. • No specific human populations identified as transmission reservoirs outside the RSV season, although there is suggestion that humans with persistence of RSV (e.g., chronic obstructive pulmonary disease [COPD] patients) could serve as a possible reservoir. [5]
At-risk populations	*Identified at-risk subpopulations or indicated general population* • Young children (especially infants under 6 months). • Preterm infants; healthy, full-term infants also at risk. • Older adults (≥65 years). • Children and adults (>40 years) with comorbidities. • Those born premature or with comorbidities also at risk for poor outcomes following RSV-associated ALRI, including prolonged hospital stay, oxygen supplementation, mechanical ventilation, and intensive care unit admission. [2,6–11]
Mortality	• In-hospital CFR for children aged 0 ≤ 60 months: 0.1 % in HICs, 0.6 %–0.8 % in LMICs, and 1.4 % in LICs. • In-hospital CFR for older adults aged ≥ 65 years: 1.6 % in HICs and 9.1 % in LMICs. • Recent RSV community mortality studies reveal a high and previously unmeasured burden of RSV deaths in young children in LMICs; for example, in rural India, the CFR for infants aged 0–5 months was estimated to be 7.1 % and 2.8 % in the community and in hospital, respectively. [2–4,6,8]
Morbidity	• Acute presentation in children: ranging from mild upper respiratory tract symptoms to life-threatening lower airway involvement, including bronchiolitis and pneumonia. • Sequelae in children: children with early-life RSV infection are reported to have higher risks for wheezing/asthma, although it is not clear whether RSV causes wheezing/asthma or if an increased susceptibility for respiratory dysfunction (e.g., genetic predisposition) leads to both severe RSV disease and wheezing/asthma. Early-life RSV infection is also found to be associated with recurrent lower respiratory infections. • Acute presentation in adults: mild upper respiratory symptoms for the majority; older adults or adults with comorbidities are more likely to experience lower airway involvement. • Sequelae in adults: RSV might lead to deterioration of underlying cardiorespiratory and cardiovascular diseases (e.g., COPD, myocardial infarction, and stroke). [12–18]
Geographical and seasonal distribution	• Over 95 % of RSV ALRI episodes and 98 % of RSV mortality occurs in LMICs among children < 5 years; in LMICs, RSV ALRI annual incidence rate ranges from 24 to 55 per 1,000 under among children < 5 years. • RSV hospitalization rate in children < 5 years fluctuates between 0.5 and 2-fold of its median yearly rate (i.e., variations of 4-fold) in most years. • Seasonal RSV activity observed in most areas: circulating during autumn/winter season in temperate regions and during rainy/wet season in tropics. [2,6,19,20]
Gender distribution	• Males more likely (odds ratio: 1.23 [1.13–1.33]) to have RSV ALRI than females. • No differences in transmission between males and females. • Very limited data on RSV infection during pregnancy or breastfeeding. [7,21]
Socioeconomic status vulnerability(ies) (equity/wealth quintile)	• Higher RSV incidence in socioeconomically disadvantaged areas. • Earlier RSV seasonal epidemics in socioeconomically disadvantaged areas and those with high population densities. [22–24]
Natural immunity	• Natural immunity is not fully protective from RSV infection; repeated lifelong infections occur. Most infants have RSV-specific antibodies from their mothers, but neutralizing antibody level declines rapidly with a half-life of approximately-one month. • Although protection occurs from maternal transfer of antibodies, RSV was found to be a common cause of serious infections among young infants in the first 2 months of life in Asia. [25–30]
Pathogenic types, strains, and serotypes	• One serotype, further divided into two subtypes: RSV-A and RSV-B, based on antigenic variability. • Nine genotypes in RSV-A and 15 genotypes in RSV-B, based on systematic intergenotypic and intragenotypic sequence analysis. [31–33]
Potential indirect impact	
Antimicrobial resistance threat	• As the main cause of bronchiolitis and pneumonia among young children, RSV poses an AMR threat through the inappropriate use of antibiotics (intended for treating bacterial infections). A study from Finland reported that 54 % of the study population of children younger than 14 years and 66 % of children younger than 3 years with confirmed RSV infection received antibiotic treatment. Similar data (though lower proportion) of antibiotic use in bronchiolitis have been reported from the United States and China. • A recent study of a maternal RSV vaccine found a 12.9 % reduction in antibiotic prescribing among infants in the first 3 months of life. [34–37,38]
Epidemic and outbreak potential	• Seasonal epidemics occur every year in the general population in most locations globally. • Nosocomial RSV is under-recognized/under-detected in LMIC health care settings with outbreaks reported in several health care settings, including pediatric/neonatal intensive care units, adult stem cell transplant units, and adult hematology/oncology units. • RSV outbreaks reported in older adults in long-term care facilities. [20,39–43]

Table 1
Summary of epidemiology and potential indirect public health impact of respiratory syncytial virus.

Feature	Summary and evidence
Transmission route/potential	• RSV is primarily spread by two mechanisms: 1) large particle droplet aerosols (10–100 μm) which are propelled short distances (≤0.9 m) by sneezing, coughing, and even quiet breathing; and 2) by infectious secretions contaminating environmental surfaces followed by self-inoculation. [44]
Acquired/herd immunity	• Acquired immunity from RSV infection not fully protective from reinfection; no effective herd immunity from natural infection of RSV. [26]
Co-associated mortality	• RSV ALRI could predispose individuals to subsequent bacterial pneumonia, which could be lethal. [13,45–49]
Economic burden	
Health facility costs/out-of-pocket costs/productivity costs	• Data on RSV-associated costs are limited in LMICs (refer to Section 7). • Existing data, mainly from Europe, North America, and Australia show that: o Inpatient average management cost per episode in children < 5 years old: €3452 without follow-up and €8591 with follow-up until 2 years after the initial event. o Outpatient average management cost per episode in children < 5 years old: €299 without follow-up and €2191 with follow-up until 2 years after the initial event. o Direct nonmedical costs (mainly food and transportation) reported to be 2.3 %–3.8 % of the total management cost per patient. o Indirect costs representing productivity losses reported to be 5.8 %–31.6 % of the total management cost per patient. o Children hospitalized for RSV with known risk factors for severe disease (e.g., preterm birth, congenital heart disease, chronic lung disease, intensive care unit admission, and ventilator use) had €4160 increased cost of hospitalization. • The direct and indirect costs of RSV-associated, long-term respiratory sequelae are likely to be substantial, although the causal role of RSV remains unclear. [50,51]

ALRI: acute lower respiratory infection; AMR: antimicrobial resistance; CFR: case-fatality rate; HICs: high-income countries; LICs: low-income countries; LMICs: low- and middle-income countries; RSV: respiratory syncytial virus.

lation for maternal vaccines are individuals in the second or third trimester of pregnancy, mAbs would be provided to neonates at birth or during early infancy. Delivery strategies are likely via two platforms: the maternal and child health programs for maternal vaccines through antenatal care (ANC) services and the Expanded Program on Immunization (EPI) for mAbs. The path to introduction of either intervention in a country will vary widely based on the choice of intervention, delivery platform selected, and contextual factors specific to the country and hierarchy of care. Since the effectiveness of a maternal vaccination strategy is limited to the very young and would not provide protection for children beyond approximately-four to six months of age, a hybrid approach, employing both interventions, may be considered by some countries that also want to protect older infants [54]. Use of either passive RSV antibody approach may require non-interference evidence on infants' subsequent active immunization response to EPI and forthcoming RSV vaccines. Given that the EPI program was designed for reaching older infants, there are unique delivery challenges to achieving desired levels of coverage for the unconventional target populations of pregnant women or neonates, as described below.

Variations in RSV seasonality may also affect the approach to vaccine delivery [55]. Studies have demonstrated seasonal trends in RSV incidence, even in tropical geographies. Despite increasing the complexity of delivery, seasonal approaches to delivery of RSV immunization might be considered in some places. In areas with distinct seasonality, the effectiveness of interventions will rely on their pre-seasonal use, although more local data on seasonal variations in burden from LMICs are needed to inform appropriate approaches for programmatic implementation.

2.1. Delivery of maternal RSV vaccines through ANC

This platform assumes an integrated delivery model wherein the maternal vaccine is delivered via routine ANC services and as part of the ANC contact. It assumes that the EPI program manages the forecasting, storage, stock management, and transport of the vaccine with administration by ANC staff to pregnant women. Maternal and child health channels manage staff training, handle advocacy and communications, and report both adverse events following immunization (AEFI) and vaccination coverage. ANC serves as a potential platform for delivering a wide range of health services, including health screenings, behavior change communication, and disease prevention and management. ANC therefore provides a means for a holistic approach to disease control and health promotion and offers the potential to maximize health impact. WHO's 2016 *Recommendations on Antenatal Care for a Positive Pregnancy Experience* provides for a total of eight visits, four of which coincide with the likely gestational age vaccination window for maternal RSV vaccines—between 24 and 36 weeks [56]. Models estimate a median vaccination coverage of 65 % (range 16 %–94 %) among women attending ANC within this gestation window across a range of LMICs [57]. Efforts to include ANC providers as informed stakeholders can improve perceptions and uptake of vaccines by pregnant women given provider recommendations have been shown to significantly influence vaccine acceptance [58–61]. While levels of vaccine acceptance among pregnant women are reported to be medium to high based on provider recommendations, this acceptance can also be influenced by interventions tailored to the contextual drivers in any given setting [61–63].

Expanding vaccine delivery into ANC services has the potential to strengthen collaborations between often siloed EPI and maternal and child health programs in ways that go beyond delivering RSV vaccine. Experiences from integrating previously siloed programs, such as malaria control (intermittent preventive treatment in pregnancy with sulfadoxine/pyrimethamine) and prevention-of-mother-to-child-transmission of human immunodeficiency virus (HIV), into ANC illuminate the potential for greater sustainability and program efficiency when leveraging broader health care systems with vertical programs [64–66]. Offering vaccines during ANC to protect infants may also have

positive benefits for ANC coverage and uptake. Conversely, integration of maternal RSV vaccines into ANC has the potential to disrupt routine services and require substantial financial support for building or improving reliable logistics, cold chain, waste management, monitoring, and reporting systems, particularly where providing ANC and EPI have been historically siloed efforts or in areas where ANC is delivered through outreach programs. ANC staff (particularly outreach staff) may require training to safely provide vaccines, assess AEFIs, and record and report vaccination coverage and may be overburdened by the extra responsibilities unless additional personnel are provided. Country advisory groups for ANC services and National Immunization Technical Advisory Groups (multidisciplinary groups of national experts who provide independent advice to policymakers on issues related to immunization and vaccines) will need to work together and plan for potential disruptions caused by vaccine introduction.

2.2. Delivery of mAbs through EPI

This delivery platform assumes logistics and delivery of mAbs via routine EPI, including coordination and management of training and advocacy and communication efforts. The intervention would be administered to newborns along with other birth-dose vaccines, via the avenues and locations that routinely provide vaccines to this population. Safety events and vaccination coverage would be managed primarily through EPI; mAbs may also be given to infants during EPI visits, possibly just prior to the onset of the RSV season.

This platform is particularly attractive for the delivery of mAbs in LMICs given this could be done concomitantly with recommended EPI vaccines. While reported coverage for birth-dose vaccines (e.g., hepatitis B) is generally higher than uptake of postnatal care for neonates in LMICs, there are differences across countries, and those with higher coverage generally have higher rates of institutional delivery [67–69]. Vaccines intended to be given at birth are more often provided after seven days, regardless of institutional delivery status [67,68]. For countries with low rates of institutional delivery, the costs for scaling up birth-dose vaccination can be high, and birth-dose vaccines are often administered with the first dose of diphtheria-tetanus-pertussis (DTP) vaccine. This visit could be leveraged in countries with low birth-dose coverage to reach the children missed at birth; however, early EPI visits already include multiple injectable vaccines and parents and/or health staff may find the addition of another intramuscular injection unacceptable. Timely first EPI visits (i.e., six to eight weeks of age) would be needed to protect against RSV, as incidence rises after the first month of life when transplacentally acquired antibodies start to wane. An overview of potential targets for RSV vaccine is provided in Table 2.

3. RSV and its consideration as a public health priority by global, regional, or country stakeholders

RSV lower respiratory tract infection (LRTI) is recognized as an important cause of early childhood morbidity and mortality in both HICs and LMICs. As stated in Section 1.1, use of the only currently licensed RSV preventive intervention, PVZ, recommended for some very high-risk infants and young children, is limited by its high costs and monthly dosing.

Next-generation RSV preventive interventions for young infants, including long-acting mAbs and vaccines for use during pregnancy, are being evaluated in clinical trials with the goal of licensure for the broader indication of prevention of severe RSV disease among general populations. In HICs, the market demand for such products is expected to be high if licensure for use by general populations is achieved and demand is generated sufficiently ahead of product introduction. In LMICs, the market demand will be driven by the indication for use, programmatic suitability, and product affordability.

It is not anticipated that the leading pipeline RSV prevention candidates will be affordable for low-income countries without subsidies; however, Gavi, the Vaccine Alliance, has already committed to support RSV immunization products in eligible countries once a suitable product is WHO prequalified, recommended by WHO, and meets specified financial assumptions [71]. Leading pipeline candidates may not be affordable for national programs in MICs without subsidies or tiered pricing by manufacturers. Next-generation interventions will have dual market demand if affordable products are available for LMIC purchase or with Gavi support. Licensed products meeting WHO preferred product characteristics are likely to be cost-effective, although the costs of leading pipeline candidates may be higher than many LMIC governments are willing to pay and RSV awareness at regional and country levels must be increased to support demand for prod-

Table 2
Overview of potential target and key populations for respiratory syncytial virus vaccine and associated delivery strategies.

Target and key populations	Delivery strategies
Pregnant women	Maternal RSV vaccine delivered via immunization services integrated into the ANC platform prior to and through the RSV season. Optimally, a single-dose vaccine timed to coincide with ANC visits in the second and third trimester. Given challenges around timing and uptake of ANC visits and difficulties in accurately determining gestational age in LMICs, vaccines that can be delivered in a wide window during the gestational period would be preferred. Assumes: • No challenges in delivery with other maternal vaccines in the schedule. • A high level of acceptability for the proposed vaccine among pregnant women and key influencers, including health care providers. • Known and/or little variation in disease seasonality. • Low or no barriers to systems integration. [54,70]
All infants up to 6 months of age (some countries may also target older infants)	Optimally, mAbs are delivered to infants born during the RSV season as a single birth dose. If born outside the RSV season, mAbs to be administered to infants under 6 months of age just prior to or at the onset of RSV season in tandem with routine EPI vaccines. Assumes: • No challenges in delivery with other birth-dose or routine EPI vaccines. • A high level of acceptability of provision of mAbs concomitantly with EPI vaccine(s). • Known and/or little variation in disease seasonality. [54]

ANC: antenatal care; EPI: Expanded Program on Immunization; LMICs: low- and middle-income countries; mAbs: monoclonal antibodies; RSV: respiratory syncytial virus.

Table 3
Overview of non-commercial stakeholders engaged, their interest, and potential demand for a respiratory syncytial virus vaccine.

Stakeholders engaged	Summary of position/interest	Potential demand, uptake, and resources
World Health Organization	WHO SAGE asked for preparations to be made to support global policies for RSV maternal immunization as well as passive immunization with long-acting mAb. SAGE emphasized the need to link maternal immunization platform strengthening with influenza, tetanus, and pertussis vaccines along with preparations for potential country introductions of RSV vaccines/mAbs [72,73]. A WHO RSV Technical Advisory Group meets regularly to monitor progress of vaccine clinical trials.	WHO prequalifies products for procurement by United Nations agencies, ensuring that the vaccines supplied through these agencies are consistently safe and effective under conditions of use in national immunization programs. WHO makes vaccine policy recommendations through SAGE to Member States. Typically, WHO prequalification and policy recommendations are necessary for national vaccine program implementation in LMICs.
Gavi, the Vaccine Alliance	Will support RSV immunization products contingent on availability of a licensed product, WHO prequalification, and SAGE recommendation, and will support pre-introduction activities (including demand generation) [54].	Gavi supports the immunization of almost half the world's children. Gavi funding is critical for demand generation in countries eligible for vaccine support. Gavi included RSV interventions in its 2018 investment case, which included demand forecast estimates [54].
UNICEF	The world's leading procurement agency of vaccines to LMICs. UNICEF works with governments to ensure that children can access efficient, safe, and sustainable immunization services.	UNICEF provides country support to immunization programs and procures vaccines for LMICs. UNICEF support is critical to facilitate program implementation in LMICs [74].
PAHO Revolving Fund for Access to Vaccines	Provides access to safe and quality vaccines at affordable prices for Member States and Territories throughout the WHO Region for the Americas [75].	The PAHO Revolving Fund assists countries in demand forecasting, purchases vaccines at bulk prices through open tenders, and monitors shipments to countries.
International nongovernment organizations	Monitors and makes publicly available a vaccine candidate development pipeline. Fills vaccine delivery and health economics data gaps to inform maternal immunization platform decision-making and implementation [76].	• RSV Clinical Trial Tracker [77] • RSV Vaccine and mAb Snapshot [78] • A Roadmap for Advancing RSV Maternal Immunization [79].
Bill & Melinda Gates Foundation	Leading funder for RSV research in LMICs, including product development and pre-implementation. The Gates Foundation has tremendous clout as an advocate for public health and the resources to facilitate product uptake within LMICs.	• Bill & Melinda Gates Foundation website, Pneumonia page [80]
RSV research consortia	Several research consortia, such as ReSViNET, RESCEU, and ISIRV, conduct critical research to understand RSV disease burden and the potential impact of prevention in LMICs.	• RESCEU website [81] • ISIRV website [82]
Clinical and public health professional societies	Numerous professional societies have identified RSV prevention as a global unmet need and advocate for development of safe, effective, and affordable preventive interventions.	Advocate for pediatric pneumonia prevention in LMICs and will be an important coalition partner once RSV prevention interventions are supported by Gavi. • World Academy of Science, Engineering and Technology website [83] • World Society for Pediatric Infectious Diseases [84] • International Federation of Gynecology and Obstetrics [85] • International Confederation of Midwives [86]
Pneumonia charities, action groups, and parent voices	These groups advocate for the prevention and treatment of pneumonia as a major cause of disease burden in young children.	Advocate for pediatric pneumonia prevention in LMICs and will be an important coalition partner once RSV prevention interventions are supported by Gavi. • The Critical Role of Pneumonia-Fighting Vaccines in an Era of Respiratory Pandemics [87] • Save the Children website, Fighting for Breath page [88]

ANC: antenatal care; EPI: Expanded Program on Immunization; ISIRV: International Society for Influenza and other Respiratory Virus Diseases; LMICs: low- and middle-income countries; mAbs: monoclonal antibodies; PAHO: Pan American Health Organization; RESCEU: Respiratory Syncytial Virus Consortium in Europe; ReSViNET: Respiratory Syncytial Virus Network; RSV: respiratory syncytial virus; SAGE: Strategic Advisory Group of Experts on Immunization; UNICEF: United Nations Children's Fund; WHO: World Health Organization.

ucts once they are available. An overview of public health stakeholders, their interest, and potential demand for RSV vaccine is provided in Table 3.

4. Existing guidance on preferences/preferred product attributes for vaccines and monoclonal antibodies against RSV

WHO has guidance on preferred product characteristics for high-quality, safe, affordable, and effective maternal RSV vaccines and mAbs that prevent severe RSV disease and RSV-related deaths in young children globally [89,90].

The currently licensed mAb, PVZ, is recommended in some HICs and MICs for very premature, immunosuppressed, or otherwise severely ill infants with significant underlying cardiac or pulmonary disease for prevention of severe RSV disease, but its high cost and multiple dosing regimen make it unsuitable for LMICs [91,92]. Priority attributes for maternal vaccines and infant mAbs for global use are described in Tables 4a and 4b.

5. Vaccine development

5.1. Probability of technical and regulatory success

Currently, there is no approved vaccine against RSV. For the protection of young infants), passive immunization is the strategy under evaluation, either through maternal immunization with RSV fusion (F) glycoprotein vaccines in the prefusion conformation, or through administration of extended half-life mAbs that target RSV prefusion. Currently, two maternal RSV vaccine candidates and two extended half-life RSV mAb candidates are in Phase 3 trials. Although not the focus of this review, active immunization is the strategy being evaluated for protection of older infants and young children; live-attenuated vaccines, adenovirus vectored vac-

Table 4a
Summary of existing guidance on preferred product characteristics of maternal respiratory syncytial virus vaccines intended for use in low- and middle-income countries.

Product attribute	Preferential characteristic	Publishing entity	Notes
Indication	Active immunization of women during pregnancy for prevention of severe RSV disease in offspring during the neonatal period and early infancy.	WHO [89]	Preferred endpoint case definitions for use in LMIC settings have been published [93].
Target population	Women in the second or third trimester of pregnancy.	WHO [89]	Vaccination timing in pregnancy should maximize antibody transfer to the fetus and protection of the offspring, including for those born preterm, who are at increased risk of severe RSV disease. Vaccination during early pregnancy should be avoided, as the first months of pregnancy are associated with an increased risk of spontaneous abortion and could confound vaccine safety assessments. Given the difficulties related to access to obstetric care and the determination of precise gestational age in many LMICs, vaccines that can be delivered over a range of gestational ages are preferred. HIV infection should not be a contraindication to vaccination.
Outcome measure(s) and target efficacy	Greater than 70 % vaccine efficacy against confirmed severe RSV disease in the offspring, from birth to age 4 months (and preferably more).	WHO [89]	A vaccine with 50 % vaccine efficacy against confirmed severe RSV disease in the offspring, from birth to age 3 months, may be considered as acceptable for use. Proposed priority study endpoint case definitions have been published [76]. The dynamic of protection over time throughout infancy should be described, taking seasonality patterns into account. Vaccine efficacy against other endpoints of public health interest should also be evaluated, including: • Non-severe RSV respiratory disease. • Recurrent wheezing, hyper-reactive airway disease, and asthma. • RSV-related morbidity in vaccinated women. • Reduction of antibiotic use in infants. [93]
Strain specificity	Vaccination protects against both RSV A and B subtypes.	WHO [89]	
Immunogenicity	Established correlate/surrogate of protection based on a validated assay measuring antibody levels in the mother and/or the neonate.	WHO [89]	A detailed quantitative profiling of passively transferred antibodies and relationship to timing of vaccination in pregnancy is desirable. Longevity of vaccine-induced maternal antibodies in infants should be characterized and the relationship to duration of protection should be investigated. The fine specificity of vaccine antigen neutralizing epitopes should be characterized, as they may have a significant influence on binding and functionality of the antibody induced. The generation of clinically relevant validated neutralization assay data, ideally using high-throughput formats, is an important goal. Quantitative assays measuring the ability of vaccine-induced antibodies to compete with monoclonal neutralizing antibodies (such as palivizumab or motavizumab) are interesting but may not be reflective of all effector functions of vaccine-induced immunity and should not replace the need to evaluate neutralization. The role of antibody transferred through breastfeeding should be investigated. The influence of maternal HIV infection and malaria in pregnancy should be evaluated. Collaborative efforts to establish relevant nonclinical assays, using open-source reference reagents with international standards of quality, may greatly contribute to comparability assessments. The generation of a correlate of protection acceptable for regulatory purposes will support immune bridging steps, simplify clinical development plans, and accelerate the pathway to licensure.
Safety profile	Safety and reactogenicity profile at least as favorable as current WHO-recommended routine vaccines for use during pregnancy (influenza, tetanus toxoid, acellular pertussis). No indication of enhanced RSV disease in the offspring.	WHO [89]	
Number of doses and schedule	A 1-dose regimen is highly preferred.	WHO [89]	A 2-dose regimen, with a first priming dose possibly delivered prior to pregnancy, is not a preference but may need to be considered. The role of additional doses in successive pregnancies should be evaluated, possibly post-licensure.
Route of administration	Injectable (intramuscular, intradermal, or subcutaneous) using standard volumes for injection as specified in programmatic suitability for WHO prequalification or needle-free delivery.	WHO [89]	

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Table 4a (*continued*)

Product attribute	Preferential characteristic	Publishing entity	Notes
Co-administration	Demonstration of favorable safety and immunologic noninterference upon co-administration of other vaccines recommended for use in pregnancy.	WHO [89]	In LMICs, investigation of co-administration with tetanus vaccine should be investigated as a priority. Co-administration with Tdap, influenza, and possibly group B *Streptococcus* (if a vaccine for maternal use is available) should also be considered. The possible interference with specific pediatric EPI vaccines, particularly if a pediatric RSV vaccine is available, should be considered.
Registration, prequalification, and programmatic suitability	The vaccine should be prequalified according to the process outlined in procedures for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies. WHO-defined criteria for programmatic suitability of vaccines should be met.	WHO [89]	[94,95]
Vaccine platform and adjuvant requirements	Well-characterized platforms with established favorable safety profiles, evaluated in pregnancy, and no known safety concerns for pregnant women. Live viral vaccines are not favored, given the potential risk of adverse effects on the fetus. Preference for the absence of an adjuvant.	WHO [89]	A formulation including an aluminum salt or other adjuvant with an extensively demonstrated favorable safety profile in pregnancy may be acceptable.

EPI: Expanded Program on Immunization; HIV: human immunodeficiency virus; LMICs: low- and middle-income countries; RSV: respiratory syncytial virus; Tdap: tetanus, diphtheria & acellular pertussis vaccine; WHO: World Health Organization.

cines, and mRNA vaccines are currently in Phase 1 and 2 clinical trials [98]. For all products, see Fig. 1.

Several observations support the biological feasibility of RSV vaccine development, as well as some developmental challenges, including the following:

- Primary RSV infection occurs in most children in the first two years of life, with virtually all children infected by three years of age. Infections recur throughout life but, as natural immunity increases and airways mature, disease severity lessens so that older children and healthy younger adults typically experience upper respiratory illness. Preventing RSV-associated ALRI in the youngest populations, therefore, may be an achievable goal.
- The ability of RSV-specific functional antibodies to neutralize virus has been demonstrated in vitro, and protection has been shown in numerous preclinical models (i.e., murine, guinea pig, calf, and primate), including a well-established cotton rat infection model [99]. Furthermore, monoclonal and polyclonal RSV antibodies delivered prophylactically to children reduce the incidence of severe RSV disease [100]. Serum neutralizing antibody clearly protects against RSV-associated ALRI, although other types of immunity (e.g., mucosal antibody, cell-mediated immunity) may be induced by certain vaccines and may also contribute to protection.
- A reduced incidence of RSV ALRI during the first months of life correlates with higher concentrations of RSV-specific maternal antibody [101].
- RSV F and G surface glycoproteins are targets for neutralizing antibodies. Antibodies to F protein are generally cross-reactive across RSV A and B subtypes, while antibodies to G protein are much less so. In the last five years, identification and stabilization of the F glycoprotein in the prefusion conformation has provided a new target antigen for vaccines and mAbs, and prefusion specific antibodies may be more potent than postfusion antibodies in protecting against RSV ALRI [102,103].
- Data from several late clinical stage trials provide proof of concept for RSV maternal vaccines and mAbs. A Phase 3 trial of postfusion F protein maternal RSV vaccine demonstrated an antibody half-life of 49.1 days with 44.4 % efficacy (95 % confidence interval [CI]: 19.6 %–61.5 %) against RSV LRTI associated with hospitalization in the first three months of life [104]. Although this study failed to meet its primary efficacy endpoint (perhaps related to F antigenic conformation), it provided important lessons for subsequent maternal immunization studies. A Phase 3 trial of a mAb targeting a single epitope on RSV-preF failed as a result of 2 amino acid mutations in the mAb epitope found on all circulating RSV-B strains, rendering the mAb unable to bind and neutralize. This study highlights the potential need for a cocktail of nonoverlapping mAbs to reduce the risk of failure due to either escape viral variants during treatment or the circulation of a new variant in future RSV seasons [105].
- More recently, a maternal RSV prefusion F protein vaccine showed 84.7 % efficacy (95 % CI: 21.6 %–97.6 %) against medically attended RSV LRTI in a Phase 2b trial [106]. Prophylaxis with an extended half-life mAb targeting the prefusion F protein conformation given to late-preterm and healthy, full-term infants showed 74.5 % efficacy (95 % CI: 49.6 %–87.1 %) against medically attended RSV LRTI through the first five months of life in a Phase 3 trial [107].
- Recently, following a recommendation from the Independent Data Monitoring Committee of their large Phase 3 maternal RSV vaccine study (NCT04605159), GSK made the decision to stop enrolment and vaccination in their maternal RSV vaccine studies but continues to follow participants to fully evaluate any safety signals. Details have not yet been provided on the safety signal observed; so relevant trial results will be included in subsequent versions of the RSV Value Profile [108].

Issues and evidence to inform development of an RSV vaccine for LMICs are provided in Table 5.

5.2. Overview of the vaccine candidates in the clinical pipeline

A robust pipeline of clinical-stage vaccine candidates to prevent RSV disease in infant and pediatric populations has been developed over the last several years. These candidates leverage a variety of vaccine platforms that target either active immunization or passive protection via maternal immunization or immunoprophylaxis with mAbs [78]. The focus of this paper being the protection of infants, there are currently-four Phase 3 trials underway evaluating the efficacy of two protein-based maternal RSV vaccine candidates and two mAb candidates. Licensure of one or more of these candidates is feasible over the next one to three years.

PATH periodically updates a snapshot of the RSV vaccine and mAb technology landscape, which includes the platforms, develop-

Table 4b
Summary of existing guidance on preferred product characteristics of respiratory syncytial virus monoclonal antibodies intended for use in low- and middle-income countries.

Product attribute	Preferential characteristic	Publishing entity	Notes
Indication	Prevention of severe RSV disease during early infancy, the period of highest risk of severe RSV disease and mortality.	WHO [90]	While manufacturers may choose to use medically attended disease as the primary endpoint for licensure, secondary endpoints measuring severe disease should be included, because severe RSV disease is most important from a public health impact perspective in LMICs. To allow for evaluation of severity in different settings and products, objective measures of severity such as elevated respiratory rate by age group and documented hypoxemia (by oxygen saturation) should be used. These should be measured on a continuous scale. Clinical signs of hypoxia or increased work of breathing (e.g., central cyanosis, nasal flaring, grunting, severe lower chest indrawing, inability to feed) can also be collected.
Target population	All infants in the first 6 months of life.	WHO [90]	Rates of RSV severe disease and mortality peak within the first 6 months of life but continue to be elevated throughout infancy, after which they decline gradually throughout childhood. The aim of the target population attribute is to protect most infants during their first RSV season. Policymakers may consider including (i) all infants in the first 12 months of life, and/or (ii) children < 2 years of age with risk factors (e.g., chronic lung disease, chronic heart disease, or other factors) entering their second RSV season, based on local epidemiology and context.
Outcome measure(s) and target efficacy	At least 70 % efficacy against RSV-confirmed severe disease for 5 months following administration (the median length of the RSV season).	WHO [90]	A mAb with a lower efficacy and shorter duration of protection could still have a significant public health impact, depending on the epidemiological setting, product-attributable disease reduction, and cost-effectiveness. Other efficacy endpoints of public health significance are: • Hospitalized RSV. • Medically attended RSV LRTI. • All-cause severe LRTI, up to 1 year. • Recurrent wheezing and asthma (would require follow-up for several years (2–6 years). • All-cause mortality. • Antibiotic use.
Strain specificity	Protects against both RSV A and B subtypes.	WHO [90]	Prior to efficacy trials, mAbs should demonstrate neutralization capacity in vitro against circulating contemporary A and B subtypes. Potential escape mutants should be mapped, based on known epitope structures, and mAb-binding characteristics from in vitro studies and sequences of circulating strains should be tracked. RSV F protein structure determination, from clinical case surveillance, should be undertaken pre- and post-licensure; identification of emerging F sequence variations should prompt in vitro neutralization studies to determine whether F sequence variations alter susceptibility to anti-RSV mAbs.
Safety profile	Safety and reactogenicity comparable to other WHO-recommended vaccines given at the same age (e.g., hepatitis B birth dose).	WHO [90]	While the age of first infection is expected to shift to older ages with the use of mAbs, evidence should be provided indicating an overall reduced risk of severe RSV disease compared to no intervention. If more than one dose of mAb is to be given, then the impact of anti-drug antibodies should be evaluated.
Number of doses and schedule	A 1-dose regimen is highly preferred. A single dose can be given as a birth dose or at any health care visit during the first 6 months of life.	WHO [90]	Both seasonal and year-round dosing can be considered: • In settings with clearly defined RSV seasonal circulation, dosing can occur in the few months before the onset of, and during, the RSV season. • Year-round dosing might be preferred in settings with continuous and/or inconsistent peaks of RSV circulation. mAb administration, either alone or in combination with other vaccines, can be done at the following time points:

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Table 4b (*continued*)

Product attribute	Preferential characteristic	Publishing entity	Notes
			• Birth dose (or soon after) is preferred for newborns likely to have their first RSV exposure in the first 5 months of life. • It can be done during any health care contact, such as the scheduled primary series EPI visits (e.g., with DTP1, DTP2, or DTP3) during the first 6 months of life. Policymakers should select a delivery strategy based on local context and programmatic feasibility. A mAb requiring more than one dose to protect throughout the RSV season may be considered, based on local cost-effectiveness analyses and programmatic suitability.
Route of administration	Single intramuscular or subcutaneous dose using standard volumes for injection, as specified in programmatic suitability for prequalification.	WHO [90]	0.5 ml dose preferable for young infants, but up to and including 1.0 ml is considered suitable for WHO prequalification [94].
Co-administration	RSV mAbs are not expected to interfere with any current co-administered childhood vaccines.	WHO [90]	Potential interference with any RSV vaccines licensed in the future will need to be evaluated.
Duration of protection	Five months following administration (the median length of the RSV season).	WHO [90]	
Registration, prequalification, and programmatic suitability	Must be licensed and approved by national regulatory authorities in countries of use. WHO-defined criteria for prequalification and programmatic suitability of vaccines, and recommendations on presentation, packaging, thermostability, storage volume, and disposal should be met, where applicable to mAbs.	WHO [90]	Many principles and criteria of vaccine prequalification will apply to preventive mAbs [94,95]. Specific requirements for prequalification of mAbs are outlined in the pilot procedure for prequalification of biotherapeutic products and similar biotherapeutic products, though WHO guidance on prequalification of preventive mAbs for infectious diseases has not yet been issued at this time but is under development (2022) [96]. WHO Guidelines for the production and quality control of monoclonal antibodies and related products for medicinal use were published in 2022 [97] Prequalification by WHO will facilitate approval and ability to purchase products in LMICs [94].
Access and affordability	RSV mAb should be accessible and affordable to LMICs in order to allow broad protection of the most vulnerable infants.	WHO [90]	The impact of RSV mAbs on health systems (such as reduction of hospitalization burden and decrease in antibiotic use) and the immunization program (such as cold storage capacity) and on quality-adjusted life-years and/or disability-adjusted life-years should be evaluated pre- and/or post-licensure, as practicable. The mAb price should be similar to other new vaccines for feasibility of use in LMIC settings, and cost-effectiveness analyses should support use. The mAb price should be acceptable to Gavi investment case for use in Gavi-eligible countries [54]. Price considerations should also consider those LMICs that are not Gavi-eligible and their ability to pay.

DTP: diphtheria-tetanus-pertussis; EPI: Expanded Program on Immunization; LMICs: low- and middle-income countries; LRTI: lower respiratory tract infection; mAb: monoclonal antibody; RSV: respiratory syncytial virus; WHO: World Health Organization.

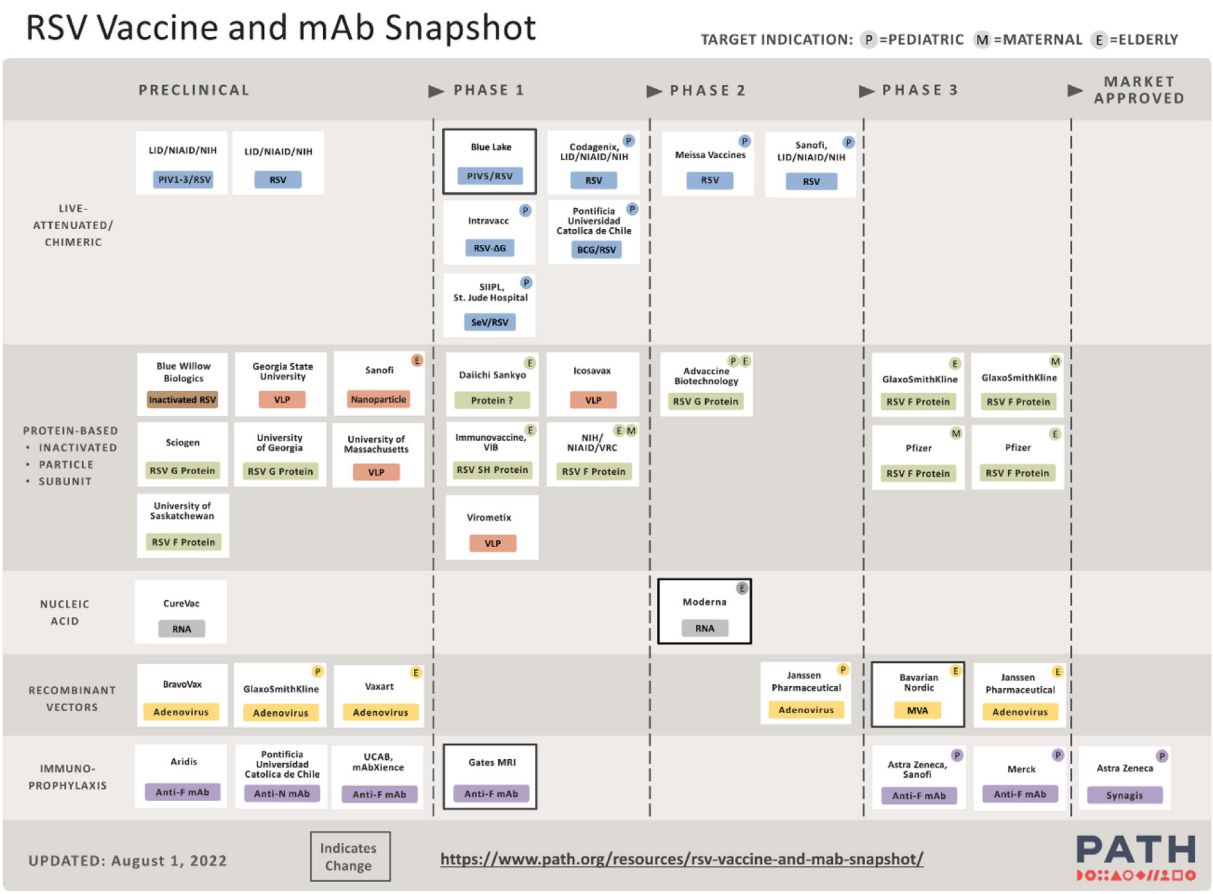

Fig. 1. Overview of respiratory syncytial virus vaccine and mAb candidates in clinical trials.

ment stages, and target populations of approaches being worked on worldwide [78].

PATH also maintains an RSV Clinical Trial Tracker, which provides publicly available information on clinical trials of RSV candidate vaccines and mAbs, including a link to the clinical trial registry for each study, the trial phase, study start dates, and populations, among other information [77].

6. Health impact of a vaccine on burden of disease and transmission

This section summarizes available evidence on the impact of vaccines on vaccine-preventable RSV disease among young children. Given no intervention currently exists, the evidence is derived from model-based studies. The policy questions addressed by individual studies along with the methods used for assessment of impact, key assumptions used to inform the models, and the key findings and interpretation from source papers are listed in Table 6. Apart from the individual model-based studies, for completeness we have also identified and summarized in the table two relevant review articles.

6.1. Summary of knowledge and research gaps in modeling health impact on disease burden and transmission

Priority knowledge

- Maternal RSV vaccines and infant mAbs have the potential to substantially reduce disease burden in young infants and will likely be impactful in averting more severe RSV outcomes. Newer-generation vaccines (using prefusion technology) may be more efficacious and impactful.
- Modeled estimates of vaccine impact on health may be high as data used for efficacy and duration of protection in some studies are optimistic compared to some trial outcomes.
- There is uncertainty in health impact estimation due to limited data on disease burden (especially by granular age band), case fatality rates, varied geographies, and product characteristics such as efficacy and duration of protection.
- Seasonal rather than year-round interventions are likely to be most efficient in reducing RSV infections per dose administered in areas with distinct RSV seasonality.
- The health impact of interventions is likely greatest in areas with the highest burden, such as LMICs. For mAbs specifically, targeting high-risk infants might be more cost-efficient, though programmatic feasibility of reaching this population might pose challenges to applicability of this approach.
- Recent data demonstrate an effect of RSV immunization on decreasing RSV-related hospitalization and all-cause pneumonia hospitalizations.

Research gaps

- Additional data on seasonal distribution of RSV disease burden, particularly in LMICs.
- Information on programmatic challenges of RSV immunization delivery in LMICs.

Table 5
Overview of parameters that inform scientific feasibility of developing an effective vaccine or mAb for respiratory syncytial virus for low- and middle-income country public market use.

Parameter	Issues and evidence
Diagnosis/case ascertainment	As no RSV-specific treatment exists, diagnosis in routine clinical practice in both HICs and LMICs is often based on clinical findings in the outpatient setting (wheezing illness in infancy during recognized season). In inpatient settings in HICs and MICs, diagnosis may be made using nucleic acid technology or immunochromatography. These methods are rarely used in LMIC settings owing to the expense of the assays and the absence of specific treatment.
Biomarkers/ correlates of risk and/or protection	Neutralizing antibody is the mechanism of protection for maternal RSV vaccines and mAbs used for prophylaxis; however, a specific titer that correlates with protection against RSV LRTI has not been established. Neutralization assay formats vary, but results can and should be harmonized across laboratories and studies by using the WHO RSV Antiserum International Standard, with results reported as IU/mL [109,110].
Sero-epidemiological data	Currently there is no immune correlate of protection for RSV that could be used to infer efficacy; however, research is ongoing to establish one [111–113]. The European Medicines Agency has published guidelines on the clinical evaluation of RSV prophylaxis [114]. In addition, WHO has published guidelines on the quality, safety, and efficacy of RSV vaccines [115].
Clinical endpoints	The most relevant primary clinical endpoint is severe LRTI associated with laboratory-confirmed RSV infection, for which WHO proposed the following case definition [93]: *Laboratory criterion* • RSV infection confirmed by fit-for-purpose, fully validated polymerase chain reaction assay with high specificity and sufficient sensitivity on upper respiratory samples; *Clinical criteria* • Respiratory infection defined by cough or difficulty breathing; AND • LRTI defined as fast breathing by WHO criteria or oxygen saturation < 95 %; AND at least one of the following features of severe disease: • Pulse oximetry < 93 %. • Lower chest wall indrawing. However, case definitions for outcomes according to these clinical criteria differ somewhat between studies. Primary endpoints in clinical trials have focused more on medically attended or medically significant LRTI defined in one Phase 3 publication [104] as: • At least one manifestation of LRTI (cough, nasal flaring, indrawing of the lower chest wall, subcostal retractions, stridor, rales, rhonchi, wheezing, crackles or crepitations, or observed apnea); • PLUS hypoxemia (peripheral oxygen saturation of < 95 % at sea level or < 92 % at an altitude of >1800 m); • OR tachypnea (≥70 breaths per minute from 0 to 59 days of age and ≥ 60 breaths per minute at 60 days of age or older); • AND the presence of RSV in nasal swab samples confirmed by a validated molecular assay. It has been suggested that data be collected in a manner to allow comparisons between studies and across geographies.
Controlled human infection model	Previously used predominantly for antiviral and drug development, the existing CHIM is increasingly being used to assess proof of concept for RSV vaccines and mAbs in older adults [116]. In contrast to all adults who are partially immune to RSV, CHIMs are of limited utility for assessment of vaccines and mAbs intended for RSV-naïve children as live-attenuated RSV vaccines in development are highly attenuated and do not replicate in toddlers who have likely experienced only one or two RSV infections. Indeed, the RSV mAbs and vaccines in late-stage clinical trials for children have all proceeded without data from CHIM.
Opportunity for innovative clinical trial designs	Pivotal efficacy study size for RSV maternal vaccines has increased 2- to 4-fold (from approximately 4,500 to 10,000–20,000) based on previous experience. Studies are event-driven and may be unblinded early. Monitoring not just for RSV LRTI but also for all-cause LRTI should be included in late-stage clinical trials given the potential additional benefit that prevention of RSV in early life might have. Phase 3 trials for both maternal RSV vaccines and mAbs are global with follow-up for minimally 1 year, and ideally 2 years to assess longer-term outcomes.
Regulatory approach(es), including potential accelerated approval strategies	Several companies (including multinational corporations developing RSV vaccines or mAbs) have received fast-track designation by the US Food and Drug Administration and/or European Medicines Agency [117–119]. The ultimate goal is licensure through a stringent national regulatory authority followed by WHO prequalification for Gavi markets of interventions targeted to pediatric populations. At this time, efficacy trials will be required for licensure/registration; however, if a correlate of protection is identified (e.g., a neutralizing antibody titer using the WHO international standard), subsequent similar products could conceivably be registered based on safety and immunogenicity.
Potential for combination with other vaccines	For maternal RSV vaccines, a combination vaccine strategy may be feasible, particularly if mRNA advances as a maternal vaccine candidate (e.g., influenza + RSV, or SARS-CoV-2 + RSV, or all three) [120], depending on the relevance in LMICs. Otherwise, use of a combination vaccine is improbable in LMICs, as administration timing is unlikely to be as flexible as with maternal tetanus toxoid-containing vaccination. For mAb, there is no potential for combination with other vaccines.
Feasibility of meeting presentation and stability requirements	To be determined. Long-acting mAbs would likely be delivered within EPI systems, whereas maternal immunizations would be delivered within antenatal care systems. Vial size and doses/vials are being actively considered for the latter. Both lead candidates in development, RSV prefusion (Pfizer's maternal vaccine which is lyophilized) [121] and the anti-F mAb (Nirsevimab) are able to be stored within the normal cold chain at 2 °C–8 °C [122].
Vaccine platform	Ease of implementation for large-scale manufacturing and technology transfer to be determined. Regarding vaccine platform adaptability to alternate strains, RSV F does not evolve as quickly as major protective antigens for other respiratory viruses (e.g., influenza and SARS-CoV-2), so at this time strain changes are not anticipated but would need to be monitored [123].
Large-scale manufacturer capacity/interest	Several multinational pharmaceutical companies are in the process of scaling and prepping for commercializing maternal RSV vaccines and RSV mAbs, including for the Gavi market [78].

CHIM: controlled human infection model; EPI: Expanded Program on Immunization; Gavi: Gavi, the Vaccine Alliance; HICs: high-income countries; LMICs: low- and middle-income countries; LRTI: lower respiratory tract infection; mAb: monoclonal antibody; MICs: middle-income countries; RSV: respiratory syncytial virus; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; WHO: World Health Organization.

Table 6
Overview of modeling studies that measure health impact on disease burden and transmission.

Policy question	Assessment method/measure	Additional information specific to models	Assumptions	Outcomes/interpretation
1. Review articles				
What is the current evidence on the effectiveness of potential vaccination strategies against RSV?	Systematic review of evidence (published between 2000 and 2020) on the effectiveness (and cost-effectiveness) of potential RSV vaccination strategies. Strategies include MI, infant mAbs, PI, and older adult immunization.	Included 22 model-based studies.	Qualitative synthesis of evidence. Study-specific key assumptions and inputs are listed in Tables 2 and 3 in the review paper.	On average, a potential 27 % reduction in RSV hospitalizations among infants due to maternal vaccine, and a 50 % reduction among infants directly immunized. Vaccination of children is likely to contribute more protective benefits to children than maternal vaccination. The higher health impact is mainly driven by assumptions of long-lasting, vaccine-induced immunity. RSV vaccines with anticipated characteristics ("high values of efficacy and duration of protection") may reduce a "sizeable" proportion of the RSV burden. The results are subject to substantial uncertainty because of the limited epidemiological and clinical data. R1 [124]
What is the current evidence on RSV transmission dynamics, population-level effectiveness, and cost-effectiveness of RSV interventions in LMICs?	Interventions focused on young infants (MI and mAbs) not expected to impact disease transmission. Systematic review of evidence (published between 2000 and 2020) on the transmission dynamics, and population-level effectiveness and cost-effectiveness of potential RSV vaccination strategies. Strategies include MI, mAbs, and PI.	Included 15 model-based studies. 10 studies on RSV transmission/natural history; 8 studies on impact of RSV vaccines and mAbs; 3 studies on cost-effectiveness of RSV interventions.	Qualitative synthesis of evidence. Study-specific key assumptions and inputs are listed in tables in the review paper.	Studies from LMICs (considered in this review) demonstrate the potential effectiveness of RSV vaccines and mAbs. Paucity of literature from geographically diverse settings (most health impact studies from LMICs are based on a few countries). Insufficient evidence at this time to draw definitive conclusions about what strategy will be most effective. Highlights the importance of incorporating seasonality of RSV into mathematical models of transmission. Additionally, studies included in the review demonstrated the importance of weather, nutritional status, school schedules, and social contact rates as factors that can affect seasonal outbreak patterns of RSV in LMICs. The role of school-aged children as index case for infection in the household; partial immunity derived from prior infection also impacts disease transmission. R2 [125]
2. Individual articles not included in the review articles				
What is the health impact and cost-effectiveness of RSV maternal immunization and mAbs to prevent childhood RSV across 131 LMICs?	**Method:** Vaccine and mAb impact modeling. **Measure:** Reduction of infections, hospitalizations, deaths, and DALYs.	**Model type:** Static population-based cohort model. **Data fit:** Model parameterized using country- and age-specific demographic data. **Time period:** 10 years **Seasonality:** not considered **Waning effects:** not considered **Herd effects:** not considered **Model transparency:** high **Granularity:** 131 LMICs.	**Disease burden:** Retrieved from published systematic review (incidence of RSV ALRI across countries: 35.3–65.6 per 1,000 children under 5 years per year; hospital CFR: 2.2 %–2.4 %). **Intervention efficacy:** MI: At baseline, 40 %–60 % mAb: At baseline, 60 %–70 %. Considered a range of efficacy 30 %–60 % for both interventions in scenario analysis. **Duration of protection:**	Under baseline assumptions, **RSV MI** is estimated to avert 2.97 million non-severe cases, 2.63 million severe cases, 2.03 million hospitalizations, 126,552 deaths, and 3.73 million DALYs (discounted) among children younger than 6 months of age across all countries over 10 years. Globally, about 25 % of RSV-related deaths among infants under 6 months of age would be averted by RSV maternal vaccine, equivalent to approximately 13 deaths averted per

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Table 6 (*continued*)

Policy question	Assessment method/measure	Additional information specific to models	Assumptions	Outcomes/interpretation
			MI: 3 months (range: 3–6 months). mAb: 6 months (range: 3–6 months). **Intervention and target population:** MI: Single dose given to all pregnant women attending any ANC during 24–36 gestation weeks (modeled estimates). mAb: Single dose given to all newborns during EPI. **Intervention coverage:** MI: Derived from ANC coverage during appropriate gestation window (24–36 weeks) (range 40 %–96 %). mAb: Assumed at BCG coverage levels (range: 48 %–98 %).	100,000 vaccinated pregnant women. **RSV mAb** is expected to avert 19.47 million cases of non-severe disease, 7.18 million severe cases, 5.40 million hospitalizations, 276,933 deaths, and 8.19 million DALYs (discounted) among children younger than 6 months of age across all countries over 10 years. Globally, about 55 % of RSV deaths among infants younger than 6 months of age would be averted with RSV mAbs, equivalent to approximately 28 averted deaths per 100,000 newborns receiving the intervention. More than 80 % of the vaccine impact would occur among countries in sub-Saharan Africa and South Asia, the regions that comprise the largest estimated disease burden as well as countries receiving Gavi, the Vaccine Alliance support. [126]
What is the potential health effect of seasonal and year-round passive immunization strategies against RSV for infants in LICs and LMICs?	**Method:** Vaccine and mAb impact modeling. **Measure:** Reduction of infections, hospitalizations.	**Model type:** Mathematical model. **Data fit:** Model parameterized using country- and age-specific demographic, epidemiological data. **Time period:** N/A **Seasonality:** yes **Waning effects:** considered in sensitivity analysis **Herd effects:** not considered **Model transparency**: high **Granularity:** 52 LMICs.	**Disease burden:** Retrieved from literature review (aggregate regional-level proportion of RSV cases among infants < 1 year: RSV ALRI incidence share: <1 month: 14.91; 1–3 months: 10.40; 3–<6 months: 25.26; 6–<9 months: 22.98; 9–<12 months: 26.45. RSV ALRI hospitalization share: <1 month: 15.10; 1–3 months: 33.32; 3–<6 months: 23.92; 6–<9 months: 16.58; 9–<12 months: 11.08. **Intervention efficacy:** MI: 70 % (range: 50 %–90 %) mAb: 70 % (range: 50 %–90 %) **Duration of protection:** MI: 5 months (3–6 months) mAb: 6 months (4–8 months) **Intervention and target population:** MI: Single dose given to all pregnant women attending ANC services. mAb: Single dose given to newborn during EPI. **Intervention coverage:** MI: proportion of women receiving 4 or more ANC visits. mAb: Assumed at BCG coverage levels for each country.	For **RSV MI**, a seasonal approach had the highest relative efficiency. The median effectiveness of the year-round approach was 19.4 % (IQR: 13.1–21.1) and 23.6 % (with 100 % coverage). For **RSV mAb**, the effectiveness was highest in the year-round approach, followed by seasonal approaches. The median effectiveness of the year-round approach was 58.1 % (IQR: 51.3–63.8) and 66.2 % (with 100 % coverage). In countries with clear seasonality, the effectiveness of **RSV mAb** against hospital admission ranges from 25.8 % to 49.4 % across various seasonal approaches. The effectiveness of **RSV MI** against hospital admission ranges from 11.1 % to 13.7 % across various seasonal approaches. In countries with clear RSV seasonality, seasonal approaches to **mAb** and **MI** administration might optimize disease prevention by dose given, compared with year-round administration. [127]
What are the key epidemiological parameters and the cost-effective, affordable maximum purchase price for a comprehensive suite of next-generation RSV interventions? Strategies include PVZ, long-acting mAbs, PI, MI, and childhood and older adult vaccinations.	**Method:** Effectiveness and cost-effectiveness modeling. Estimated epidemiologic parameters (GP visits, hospitalizations, deaths) then incorporate into a cost-effectiveness analysis. **Measure:** Hospitalizations averted, GP consultations averted, deaths averted,	**Model type:** Individual transmission model with an economic analysis. **Data fit:** Calibrate model using RSV surveillance data in England collected via the Respiratory DataMart System between July 2010 and June 2017. **Time period:** 10 years	**Disease burden:** RSV surveillance data from England between July 2010 and June 2017 (model calibrated to RSV surveillance data predicted between 68 % and 81 % of infants experience an RSV infection in their first year of life; probability of hospitalization in infants (0.010–0.097); average probability of deaths is < 3 per 100,000 infections).	Seasonal administration of long-lasting **RSV mAb** to very high-risk and high-risk infants prevents 36–51 hospitalization per 1,000 doses administered. Seasonal **RSV MI** prevents 8.5 (95 % CI: 7.4–10.3) hospitalized cases per 1,000 vaccine courses administered, with 22 %–30 % of the hospitalized cases prevented in infants

Table 6 (*continued*)

Policy question	Assessment method/measure	Additional information specific to models	Assumptions	Outcomes/interpretation
	QALYs gained.	**Seasonality:** Yes, for risk of infection seasonally and for administration of each intervention (year-round administration was also evaluated). **Waning effects**: yes **Herd effects**: yes **Model transparency**: high **Granularity:** UK with broader application.	**Intervention efficacy:** PVZ: 33.8 % mAb: 70.1 %–78.4 % PI: 83 % MI: 41.4 %–53.5 % **Duration of protection:** PVZ: 150 days mAb: 275 days PI: 359 days MI: 133.5 days **Intervention and target population:** PVZ: Given to very high-risk infants at birth. mAb: Single dose at birth (considers all infants, high-risk, and very high-risk infants under different strategies). PI: All infants aged 2 months. MI: All pregnant women at 28–32 weeks of gestation. **Intervention coverage:** PVZ: 90 % mAb: 90 % PI: 90 % MI: 60 %	<1 year of age attributable to indirect protection from vaccinated mothers. Maternal protection of infants is seasonal, with 38 %–62 % of infants born with protection against RSV. Up to 12 % of annual symptomatic cases averted, depending on the strategy. Up to 24 % RSV hospital admissions averted depending on the strategy. In seasonal RSV transmission settings, seasonal programs rather than year-round intervention programs are always optimal. [128]
3. Individual articles from LMICs included in the review articles				
What is the health impact and cost-effectiveness of RSV MI and mAbs to prevent childhood RSV in Gavi-eligible countries?	**Method:** Vaccine and mAb impact and cost effectiveness. modeling **Measure:** Reduction of infections, hospitalizations, deaths, and DALYs.	**Model type:** Static population-based cohort model. **Data fit:** Model parameterized using country- and age-specific demographic, epidemiological data. **Time period:** 5 years **Seasonality:** not considered **Waning effects:** not considered **Herd effects:** not considered **Model transparency**: high **Granularity:** 72 Gavi countries.	**Disease burden:** Input values were not reported but were retrieved from a published systematic review and data were interpolated to generate monthly disease burden. **Intervention efficacy:** MI: 70 % (range: 50 %–90 %) mAb: 70 % (range: 50 %–90 %) **Duration of protection:** MI: 5 months (range: 3–6 months) mAb: 6 months (range: 4–8 months) **Intervention and target population:** MI: Single-dose vaccine targeted to all pregnant women attending any ANC services. mAb: Single dose given to newborn during EPI. **Intervention coverage:** Assumed at BCG coverage levels for 2016 for each country for both interventions.	Across 72 Gavi countries, **RSV MI** could avert 1.186 million cases (95 % prediction interval: 0.6–1.9 million), 104 thousand hospital admissions (95 % PI: 19–309 thousand), 3 thousand deaths (95 % prediction interval: 1–11 thousand), and 98 thousand discounted DALYs. Across all countries, it translated to about 15.6 % of RSV-related hospitalizations and 16.7 % of RSV-related deaths averted among infants under 1 year of age. Similarly, an **RSV mAb** could avert 1.721 million cases (95 % prediction interval: 0.98–2.7 million), 151 thousand hospital admissions (95 % prediction interval: 29–443 thousand), 5 thousand deaths (95 % prediction interval: 1–15 thousand), and 137 thousand discounted DALYs. Across all countries, it translated to about 22.6 % of RSV-related hospitalizations and 27.8 % of RSV-related deaths averted among infants under 1 year of age. **RSV mAb** is assumed more effective and of longer duration of protection than **RSV MI** but likely more costly. Age-specific hospitalization and death rates drive most uncertainty in results. R1 [124] R2 [125,129]

(*continued on next page*)

Table 6 (*continued*)

Policy question	Assessment method/measure	Additional information specific to models	Assumptions	Outcomes/interpretation
What is the potential health impact of maternal RSV vaccine on infant health in 73 Gavi-supported countries?	**Method:** Vaccine impact modeling. **Measure:** Reduction of infections, hospitalizations, deaths, and DALYs.	**Models:** Comparison of two independent vaccine impact models for cross validation, static population-based cohort models. **Data fit:** Harmonized model inputs and assumptions in consultation with expert groups and stakeholders. **Time period:** 2023–2035 **Seasonality:** not considered **Waning effects:** not considered **Herd effects:** not considered **Model transparency:** high **Granularity:** 73 Gavi countries.	**Disease burden:** Retrieved from published systematic review (incidence of RSV ALRI across countries: 35.3–65.6 per 1,000 children under 5 years per year; hospital CFR: 2.2 %–5.3 %). **Intervention efficacy:** 60 % (range: 30 %–90 %) at baseline, range considered in sensitivity. **Duration of protection:** 5 months (range: 3–6 months) at baseline, range considered in sensitivity. **Intervention and target population:** Single-dose vaccine targeted to all pregnant women attending ANC during the appropriate gestation window (24–36 weeks). **Intervention coverage:** Average of 69 % (range: 21 %–96 %). Modeled estimates of pregnant women attending ANC clinics using DHS data and WHO guidance.	**RSV MI** with 60 % efficacy and 5 months of protection implemented across 73 LMICs could avert 10.1–12.5 million cases, 2.8–4.0 million hospitalizations, 123.7–177.7 thousand deaths, and 8.5–11.9 million DALYs among infants under 6 months of age for the duration of analysis (2023–2035). Under baseline assumptions, **RSV MI** was projected to avert 27 % of RSV deaths per year among infants under 6 months of age. The health impact of **RSV MI** is dependent on the input values of efficacy and duration of protection. Under a conservative assumption of 30 % efficacy and 4 months of protection, the MI was projected to avert 11 % of RSV deaths among infants under 6 months, and under a more optimistic scenario assuming 90 % efficacy and 6 months of protection, MI was projected to avert 46 % of RSV deaths among infants under 6 months of age. **RSV MI** can substantially reduce mortality and morbidity among young infants. More than 80 % of the vaccine impact would occur among countries in sub-Saharan Africa and South Asia, the regions that comprise the largest estimated disease burden. R1 [124,130]
What is the impact of maternal RSV vaccination on hospital admissions and mortality?	**Method:** Mathematical model for maternal vaccine-induced antibody dynamics. **Measure:** Reduction (%) of hospitalizations and deaths.	**Model type:** Maternal antibody transfer model. **Data fit:** Three datasets (A) PICU cohort from UK from 2002 to 2014 (n = 370), (B) PICU cohort from the Netherlands from 2008 to 2015 (n = 167) and (C) global mortality cohort (n = 211). **Time period:** not stated **Seasonality** not considered **Waning effects:** yes **Herd effects:** not considered **Model transparency**: medium **Granularity:** UK, Netherlands, and countries worldwide (RSV GOLD countries).	**Disease burden:** Data was fit to PICU data from UK and Netherlands and a global mortality cohort (RSV GOLD study); specific burden data values not reported. **Intervention efficacy:** Used vaccine efficiency factor values of 5 and 10 (rather than efficacy of a vaccine). **Duration of protection:** Assumed full protection as long as the antibody remains above the threshold of 40 μg/ml (with assumed antibody half-life of 41 days). **Intervention and target population:** Single-dose vaccine to pregnant women at 30 weeks of gestation. Model applied to measure impact on the global cohort of infants hospitalized with severe RSV. **Intervention coverage:** 100 % (used Phase 3 trial data on maternal vaccine trial data).	**RSV MI** could prevent 29 %–48 % of deaths among infants hospitalized with RSV at global level and at least 62 % of hospitalizations (62 %–75 %) in the UK and 76 %–87 % in the Netherlands). Preterm children and children with comorbidities were predicted to benefit less than healthy, full-term children. **RSV MI** has the potential to substantially decrease life-threatening RSV infections in infants in the first few months of life. R2 [125,131]
What is the effectiveness of maternal RSV vaccination combined with vaccination of household members in reducing RSV hospitalization among newborns?	**Method:** Epidemiological effectiveness assessment. **Measure:** Reduction (%) of hospitalizations and infections.	**Model type:** Individual (agent-based) model that captures both within household and within community transmission. **Data fit:** District hospital monthly admissions data between 2000 and 2016 (Kilifi County Hospital, Kenya).	**Disease burden:** Sourced from literature and inferred from hospitalizations at Kilifi County Hospital, Kenya. **Intervention efficacy:** Not explicitly specified. **Duration of protection:** Range of 15–90 days (75 additional days to 21.6 days of	**RSV MI** offering up to 75 additional days of protection to newborns could reduce 50 % of RSV hospitalizations combined with a 75 % coverage of their population co-inhabitants. **RSV MI** has the potential to substantially decrease life-threatening RSV infections in infants.

Table 6 (*continued*)

Policy question	Assessment method/measure	Additional information specific to models	Assumptions	Outcomes/interpretation
		Time period: 10 years **Seasonality:** Seasonal variation in transmission. **Waning effects:** yes **Herd effects:** yes **Model transparency:** high **Granularity:** Model parameterized using data from Kenya and applied to a generic LMIC setting.	natural protection). **Intervention and target population:** Single-dose vaccine delivered to pregnant women in third trimester. **Intervention coverage:** MI coverage of 50 % and 100 %, household member coverage range from 0 % to 100 %.	R1 [124] R2 [125,132]
What is the optimal target profile for RSV interventions?	**Method**: Epidemiological effectiveness analysis of the optimal target profile for RSV interventions, including infant vaccine and maternal vaccine. **Measures:** Reduction of multiple effect measures of the intervention (i.e., risk of infection, duration of infection, infectiousness, reduced upper respiratory tract infection, reduced LRTI, reduced severe LRTI).	**Model type:** Two distinct age-specific deterministic compartmental models.* **Data fit:** District hospital monthly admissions data (Kilifi County Hospital, Kenya). **Time period:** N/A **Seasonality:** Yes, for infection risk but not intervention administration. **Waning effects:** yes **Herd effects:** yes **Model transparency**: medium **Granularity:** Kenya. *(Model 1: Models sequential infection that leads to lifelong partial immunity. Model 2: Models partial immunity maintained by repeated or boosting infections).*	**Disease burden:** Monthly hospitalization data on RSV among children from 2004 to 2011 in Kenya. **Intervention efficacy:** Variable, 50 %–90 % against risk of ALRI. **Duration of protection:** Infant vaccine: 1 year; maternal vaccine: 3 months (up to 6). In assessing impact, children born to mothers receiving MI would be protected from birth to 3 months (baseline) or 6 months. **Intervention and target population:** Infant vaccine (2- or 3-dose vaccine) given between 0 and 6 months; maternal vaccine: single dose (vaccine delivery time not explicit). **Intervention coverage:** Range of 25 %–90 %.	**RSV MI and neonatal vaccine** could reduce up to 70 % RSV hospitalizations among children under 5 years depending on vaccine characteristics. Vaccine characteristics that reduce the duration and infectiousness of infections are projected to have the greatest impact on hospitalized RSV and should be considered important for product development. R1 [124] R2 [125,133]
What are the characteristics of RSV transmission parameters in LMICs? What is the impact of multiple vaccine schedules (i.e., children 3 months age, school-age children, and MI) on reduction in RSV occurrence in infants?	**Method**: Epidemiological effectiveness analysis. **Measures:** Reduction of infections.	**Model type:** Individual transmission model. **Data fit:** Kenya DHS data (2002–2005) **Time period:** 10 years **Seasonality**: yes **Waning effects:** yes **Herd effects:** yes **Model transparency:** medium **Granularity:** Kenya.	**Disease burden:** Kenya DHS data 2002–2005. **Intervention efficacy:** Not clear. **Duration of protection:** 4, 6, and 12 months for pediatric vaccine, 4 months for MI. **Intervention and target population:** Infant vaccination at 3 months of age, with and without a catch-up campaign targeting 3 months and 15 years of age. Pediatric vaccination: one-off vaccination at first school enrollment, with and without catch-up campaign in the first year targeting primary school students. Also explored annual repeated vaccination. MI: Vaccination of pregnant women. **Intervention coverage**: 100 %, 80 %, and 60 % modelled.	Household transmission was found to be responsible for 39 % of RSV infant infections; school-age children were the main source of infection within the household, causing around 55 % of cases. **RSV MI** that is able to offer additional 4 months of antibody protection to infants can reduce up to 31.5 % of RSV infections in infants. R1 [124] R2 [125,134]
4. Individual articles from UMICs/HICs (not exhaustive) included in the review articles				
What is the potential impact of RSV vaccination strategies on children's health in Turkey?	**Methods:** Vaccine impact modeling. **Measure:** Reduction of GP visits, hospitalizations, and deaths.	**Model type:** Multi-cohort static Markov model with cycles of 1 month. **Data fit:** 2014 birth cohort in Turkey (111,459 newborns) and hospital data from multicenter hospital study.	**Disease burden:** Hospital data from multicenter hospital study from Turkey (RSV-related hospitalizations as a proportion of total hospitalizations = 17.78, RSV-related mortality as a proportion of hospitalization among < 1 years = 0.0068 and among 1–	RSV MI would prevent 16.8 % of RSV-related hospitalizations and 19.49 % of RSV deaths among children < 2 years of age. Infant vaccination at 2 and 4 months of age would prevent about 42 % of RSV-related hospitalizations and 41 % of RSV-related

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Table 6 (*continued*)

Policy question	Assessment method/measure	Additional information specific to models	Assumptions	Outcomes/interpretation
		Time period: 2-year time horizon with monthly cycle. **Seasonality:** Yes (effects of seasonal vaccination). **Waning effects:** yes **Herd effects:** not considered **Model transparency**: medium **Granularity:** Hospital-level data in Bursa, Turkey.	2 years = 0.00026). **Intervention efficacy:** MI: 60 % PI: Infants 2 months of age 60 %. PI: Infants 4 months of age 75 %. **Duration of protection:** MI: 3 months. PI: 5 months. **Intervention and target population:** PI: Vaccinating infants at 2 and 4 months of age on a seasonal basis. MI: vaccinating pregnant women. Combination: vaccinating pregnant women and infants at 2 and 4 months of age. **Intervention coverage:** 85 % for all vaccinations.	deaths among children < 2 years. RSV MI + infant vaccination would prevent 54 % of RSV-related hospitalizations and deaths among children < 2 years. Health impact is sensitive to duration of protection. R1 [124] R2 [125,135]
What is the impact of a maternal RSV vaccination in reducing RSV hospital admissions among young children in a high-income country?	**Method:** Vaccine impact modeling. **Measure:** Reduction of RSV hospitalizations.	**Model type:** Deterministic compartmental disease transmission model. **Data fit:** Birth cohort in separate study in Western Australia 1996–2012. **Time period:** 2 years **Seasonality:** Yes, in changing risk of infection by season, but no seasonal vaccination. **Waning effects:** yes **Herd effects:** yes **Model transparency:** high **Granularity**: Western Australia.	**Disease burden:** Population-based linked data on RSV hospitalizations between 2000 and 2013, Western Australia. **Intervention efficacy:** 80 % (varied to 60 %, 70 %, 90 %, and waning effectiveness). **Duration of protection:** 6 months protection (varied 3 and 4 months). **Intervention and target population:** Single-dose vaccine given to pregnant women in third trimester of pregnancy. **Intervention coverage:** 50 % (varied 30 % and 70 %). Modeled with mixing between age groups using contact matrices.	**RSV MI** could reduce RSV hospitalizations by 26 % (range: 3 %–37 %) for 0–2-month-old children and 40 % (30 %–46 %) for 3–5-month-old children. Under high effectiveness and high coverage scenarios, hospitalization reductions can be up to 51 % and 63 % among 0–2 months old and 3–5 months old, respectively. No impact of maternal vaccine among > 6 months old (indicating no herd immunity). RSV MI with reasonable efficacy and protection be an effective option in reducing RSV hospitalizations in children up to 6 months of age. R1 [124,136]
What is the impact of maternal and pediatric RSV vaccination strategies in reducing RSV disease severity among children?	**Method:** Epidemiological effectiveness modeling. **Measure:** Reduction in infection attack rate.	**Model type:** Dynamic disease transmission model. **Data fit:** Hospitalizations and general practitioner visits data from the Netherlands (2012–2017). **Time period:** 20 years **Seasonality:** Yes, in risk of infection. **Waning effects:** yes **Herd effects:** yes **Model transparency:** high **Granularity:** Netherlands.	**Disease burden:** RSV hospitalizations and general practitioner visits (2012–2017) from the Netherlands. **Intervention efficacy:** 100 % **Duration of protection:** 6 months protection for MI; for PI, 6 months to 4 years for infants, with immunity waning at 5 years of age. **Intervention coverage:** 50 % for both maternal vaccines and infant vaccines.	**RSV MI** reduced the attack rate in infants by 27 % but led to an increased rate in 1–4-year-old children of 10 %. **Infant vaccination** reduced the attack rate in infants by 30 %, in 1–4-year-old children by 24 %, and in 5–9-year-old children by 8 %. Assuming a vaccination coverage of 50 % and perfect vaccine efficacy, both maternal vaccination and pediatric vaccination were able to reduce the attack rate in infants. By shifting the age at first infection upward, however, maternal vaccination is expected to increase the infection attack rate in older children, while the severity is reduced. R1 [124,137]
What is the potential impact of immunization strategies on RSV-associated medically attended LRTIs among infants < 12 months in the US? Strategies considered: PVZ, other mAb, MI	**Method:** Vaccine and monoclonal antibody impact modeling. **Measure:** Reduction in hospitalizations, emergency department visits, outpatient visits, and infections.	**Model type:** Decision tree. **Data fit:** US birth cohort. **Time period:** 12 months. **Seasonality:** Considered for intervention administration but not infection risk.	**Disease burden:** Assumed 0.98 % of all births as high risk who are eligible to receive PVZ, rates of medically attended RSV per 1,000 births: hospitalization (8.4), emergency department visits (66.2), outpatient clinic visits (230.9); case fatality ratio 0.10 %.	A **mAb** targeting all infants prevented the most LRTIs among infants: 48 % of outpatient clinic visits, 51 % of emergency department visits, 55 % of hospitalizations. A strategy combining **RSV MI** and **PVZ** prevented 14 % of outpatient visits for LRTI,

Table 6 (*continued*)

Policy question	Assessment method/measure	Additional information specific to models	Assumptions	Outcomes/interpretation
		Waning effects: yes **Herd effects:** not considered **Model transparency:** high **Granularity:** US.	**Intervention efficacy:** PVZ 51 %, mAb 80 % (73 %–85 %), MI 80 % (73 %–85 %). **Duration of protection:** PVZ 150 days (120–180 days), mAb 150 days (120–180 days), MI 90 days (60–120 days). **Intervention and target population:** US birth cohort, PVZ: given to high-risk infants during RSV season (monthly doses for 5 months). mAb: given to all infants up to 6 months age during RSV season (single doses). MI: given to all pregnant women (year-round) single dose during third trimester. **Intervention coverage:** PVZ 38 %, antibody low-risk infants 71 % and 80 % high-risk infants, MI 56 %.	13 % in emergency department visits, and 25 % of hospitalizations among infants. Of the candidates evaluated, administering **mAb** to all infants born during the season, and at the start of the season for those born outside the season, prevents the most medically attended LRTIs. This strategy may avert approximately 2 times the hospitalizations than a strategy in which a maternal vaccine candidate is offered to mothers year-round (in addition to PVZ use per current US recommendations). R1 [124,138]

Notes on reading Table 6:

– The studies listed in the table are organized in the following order: 1. Review articles, 2. Individual articles not included in the review articles, 3. Individual articles from LMICs included in the review articles, and 4. Individual articles from upper-middle-income countries (UMICs) or HICs (not exhaustive) included in the review articles. Review articles are numbered R1 [124] and R2 [125]. Individual studies included in the review are referenced.

– The column "Policy question" states the main question that each article in the literature is addressing, which may not necessarily address the general policy question in the field.

– Model transparency in the "Additional information specific to models" column is qualitatively rated as high, medium, or low based on availability of parameter values in the article, supplemental files available, and level of detail provided by authors.

ALRI: acute lower respiratory infection; ANC: antenatal care; BCG: Bacille Calmette-Guérin; CFR: case-fatality rate; CI: confidence interval; DALY: disability-adjusted life year; DHS: Demographic and Health Survey; EPI: Expanded Program on Immunization; GP: general practitioner; IQR: interquartile range; LICs: low-income countries; LMICs: low- and middle-income countries; LRTI: lower respiratory tract infection; mAb: monoclonal antibody; MI: maternal immunization; N/A: not applicable; PI: pediatric immunization; PICU: pediatric intensive care unit; PVZ: palivizumab; QALY: quality-adjusted life year; RSV: respiratory syncytial virus; UK: United Kingdom; UMICs: upper-middle-income countries; US: United States; USD: United States dollar; WHO: World Health Organization.

Table 7
Overview of modeling studies that measure anticipated socioeconomic impact of the vaccine.

Policy question	Assessment method/measure	Additional information specific to models	Assumptions	Outcomes/interpretation
Cost effectiveness				
1. Review articles				
What is the current evidence on the cost-effectiveness of potential active vaccination strategies against RSV?	Systematic review of evidence (published between 2000 and 2020) on the effectiveness and cost-effectiveness of potential RSV vaccination strategies. Strategies include MI, infant mAb, childhood vaccinations, and older adult vaccinations.	Includes 22 model-based studies.	Qualitative synthesis of evidence. Study-specific key assumptions and inputs are listed in Tables 2 and 3 in the review paper.	Most studies included in this review used static models to estimate cost-effectiveness and evaluated a wide range of vaccination scenarios. Overall, the RSV vaccination of different groups is demonstrated to be cost-effective. Higher values for vaccine effectiveness, duration of protection, and vaccine uptake increased the benefits. Disease burden, distribution of disease among age groups, and product costs were important parameters determining uncertainty of cost-effectiveness estimates. Infant vaccination is associated with higher cost-effectiveness ratios in LMICs. Vaccination of neonates born before the RSV season was the most cost-effective in high-income settings. The cost-effectiveness is highly dependent on the WTP threshold, and a competitively priced intervention could be considered a good value. R1 [124]
What is the current evidence on RSV transmission dynamics and population-level effectiveness and cost-effectiveness of RSV interventions in LMICs?	Interventions focused on young infants (MI and mAbs) not expected to impact disease transmission. Systematic review of evidence (published between 2000 and 2020) on the transmission dynamics and population-level effectiveness and cost-effectiveness of potential RSV vaccination strategies. Strategies include MI, infant mAb, and PI.	Includes 15 model-based studies. Ten studies on RSV transmission/natural history; 8 studies on impact of RSV vaccines and mAbs; 3 studies on cost-effectiveness of RSV interventions.	Qualitative synthesis of evidence. Study-specific key assumptions and inputs are listed in tables in the review paper.	Studies from LMICs demonstrate the potential effectiveness of RSV vaccines and mAbs. Paucity of literature from geographically diverse setting (most of the health impact studies from LMICs are based on a few countries). Not enough evidence at this time to draw definitive conclusions about what strategy will be most effective. R2 [125]
2. Individual articles not included in the review articles				
What is the health impact and cost-effectiveness of RSV maternal immunization and monoclonal antibodies to prevent childhood RSV in 131 LMICs?	**Method:** Vaccine and mAb impact and modeling. **Measure:** Reduction of infections, hospitalizations, deaths, DALYs, and cost per DALY averted.	**Model:** Static population-based cohort model. **Data fit:** Model parameterized using country- and age-specific demographic data. **Time period:** 10 years **Seasonality:** not considered **Waning effects:** not considered **Herd effects:** not considered **Model transparency:** high **Granularity:** 131 LMICs.	**Disease burden:** Retrieved from published systematic review (incidence of RSV ALRI across countries: 35.3–65.6 per 1,000 children under 5 years per year; hospital CFR: 2.2 %–2.4 %). **Intervention efficacy:** MI: At baseline, 40 %–60 %. mAb: At baseline 60 %–70 %. Considered a range of efficacy 30 %–60 % for both interventions in scenario analysis. **Duration of protection:** MI: 3 months (range: 3–6 months). mAb: 6 months (range: 3–6 months). **Intervention and target population:** MI: Single dose given to all pregnant women attending any ANC during 24–36 gestation weeks (modeled estimates). mAb: Single dose given to all newborns during EPI.	The average ICER per DALY averted was United States dollars (USD)* 1,342 (range USD 800–1,866) for **RSV MI** and USD 431 (range USD 167–692) for **RSV mAbs**. At a 50 % GDP per capita threshold, maternal vaccine and mAbs were cost-effective in 60 and 118 countries, respectively. **RSV mAbs**, with assumed higher efficacy and duration of protection, are expected to be more cost-effective than **RSV MI** at similar prices. Final product characteristics (efficacy and duration of protection) and product prices are important parameters that will determine the relative cost-effectiveness of RSV interventions. *USD in 2016 units. [126]

Table 7 (*continued*)

Policy question	Assessment method/measure	Additional information specific to models	Assumptions	Outcomes/interpretation
			Intervention coverage:MI: Derived from ANC coverage during appropriate gestation window (24–36 weeks) (range 40 %–96 %).mAb: Assumed at BCG coverage levels (range: 48 %–98 %). **Product cost:** USD 3 per dose and USD 5 per dose for Gavi, the Vaccine Alliance, and non-Gavi countries respectively, for both MI and mAb.	
What is the likelihood of RSV prevention interventions to be cost-effectiveness in Mali?	**Method:** Cost-effectiveness modeling. **Measure:** cost per DALY averted, ICERs.	**Model type:** Probability-based outcome tree model simulating monthly birth cohorts for the first 6 months in life. **Data fit:** Calibrate model using data from Mali. **Time period:** 1 year **Seasonality:** Yes, evaluated both seasonal and year-round delivery strategies. **Waning effects:** not considered **Herd effects:** not considered **Model transparency**: high **Granularity:** Mali.	**Disease burden:** Mali-specific granular disease burden derived from infant cohort enrolled in clinical trial of maternal influenza vaccination in Mali (incidence of RSV among children 1–6 months: 141.61 to 1,046.8 per 1,000 life year; probability of hospitalization among RSV patients: 0.29; CFR among hospitalized: 0.016 %). **Intervention efficacy:** MI: 56 % Short-acting mAb: 78 % Long-acting mAb: 70 % **Duration of protection:** MI: 3 months Short-acting mAb: 1 month Long-acting mAb: 5 months **Intervention and target population:** MI: Single dose given to all pregnant women attending any ANC during third trimester at any time of year. Short-acting mAb: Intra-seasonal monthly administration of vaccine during EPI. Long-acting mAb: Pre-seasonal birth-dose administration. **Intervention coverage:** MI: 35.5 % based on ANC. Short-acting mAb: 77 % based on DTP3 coverage. Long-acting mAb: 83 % based on BCG coverage. **Product cost**: USD 3 per dose for all interventions.	The ICERs per DALY averted at baseline, from societal perspective, were: **RSV MI**: USD* 8,020 (USD 3,501 to 47,047) **Short-acting mAb**: USD 4,280 (USD 1,892 to 122,434) **Long-acting mAb**: USD 1,656 (USD 734 to 9,091) For reference, the GDP per capita for Mali is USD 891. In Mali, **long-acting mAb** is likely to be cost-effective at USD 3 per dose, from a donor perspective at a WTP above USD 1,521 per DALY. **RSV MI** would need higher efficacy over that measured by a recent trial in order to be considered cost-effective. Seasonal delivery of **RSV MI** would be relatively more cost-effective than year-round vaccination. Disease burden (inpatient case fatality rate) was the most influential parameter of cost-effectiveness across all interventions. *USD in 2019 units. [139]
What is the cost effectiveness of RSV prevention strategies in China?	**Method:** Cost effectiveness modeling. **Measure:** TSC*, defined as the maximum costs per child for a strategy to be cost-effective (defined as 1 national GDP per capita per QALYs gained). **Threshold strategy cost allows for comparison of different strategies without specifying price of each intervention.*	**Model type:** Static cohort model. **Data fit:** 12 hypothetical monthly birth cohorts of Chinese newborns. **Time period:** 5 years **Seasonality:** Yes, evaluated both seasonal and year-round delivery strategies. **Waning effects:** yes **Herd effects:** not considered **Model transparency**: high **Granularity:** China.	**Disease burden:** China RSV- severe acute respiratory infection sentinel surveillance data (probability of RSV outpatient cases among children 0–11 months: 23.9 to 165.9 per 1,000 per year; probability of RSV inpatient (including RSV death) among children 0–11 months: 4.0 to 35.8 per 1,000 per year). **Intervention efficacy**: MI: 71.6 %, mAb: 100 % PI: 100 % efficacy day 0 and decay to 70 % efficacy year 5 **Duration of protection**: MI: 4 months mAb: Efficacy decay rate 0.5x10^-2/day	At a 1x GDP per capita WTP threshold (GDP per capita *USD 10,267 in 2019), the TSC of seasonal delivery was: **MI**: USD 2.4 to 14.7 **mAb**: USD 19.9 to 144.2 **PI**: USD 28.7 to 201.0 **MI + PI**: USD 31.1 to 220.7 **mAb + PI**: USD 41.3 to 306.2 TSC of year-round **RSV mAb** plus **PI** is the highest among all the year-round strategies, indicating that earlier and longer protection with high efficacy is desirable. Moreover, maternal vaccines would need to be priced very competitively in comparison to RSV PI, in order to offer equivalent value for money.

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Table 7 (*continued*)

Policy question	Assessment method/measure	Additional information specific to models	Assumptions	Outcomes/interpretation
			PI: Decay to 70 % efficacy in year 5 **Intervention and target population:** MI: Single dose given to pregnant women during ANC. mAb: Single dose given to newborn. PI: Single dose given to infant at 3 months. Combination strategy (MI + PI) and (mAb + PI) are also considered. **Intervention coverage:** 100 % (inferred) **Product cost**: N/A	Seasonal administration of RSV interventions could be more cost-effective than their year-round counterpart. The future market price of infant mAbs was assumed to be more expensive compared to vaccines, but the future price of mAbs would need to be equivalent to that of paediatric vaccines to make mAbs a competitive and cost-effective option. *USD in 2019 units. [140]
What is the cost-effective, affordable maximum purchase price for a comprehensive suite of next generation of RSV interventions? Strategies include PVZ, long-acting mAbs, PI, MI, childhood vaccinations, and older adult vaccinations.	**Method:** Impact and cost-effectiveness modeling. **Measure:** Maximum purchase price for cost-effectiveness assuming a cost-effectiveness threshold of £20,000/QALY.	**Model type:** Individual transmission model with an economic analysis. **Data fit**: Calibrate model using RSV surveillance data in England collected via the Respiratory DataMart System between July 2010 and June 2017. **Time period:** 10 years. **Seasonality:** Yes, for risk of infection seasonally and for administration of each intervention (year-round administration was also evaluated). **Waning effects:** yes **Herd effects:** yes **Model transparency**: high **Granularity:** UK with broader application.	**Disease burden:** RSV surveillance data from England between July 2010 and June 2017 (model calibrated to RSV surveillance data predicted between 68 % and 81 % of infants experience an RSV infection in their first year of life; probability of hospitalization in infants (0.010–0.097), average probability of deaths is < 3 per 100,000 infections). **Intervention efficacy:** PVZ: 33.8 % mAb: 70.1 %–78.4 % PI: 83 % MI: 41.4 %–53.5 % **Duration of protection:** PVZ: 150 days mAb: 275 days PI: 359 days MI: 133.5 days **Intervention and target population:** PVZ: Given to very high-risk infants at birth. mAb: Single dose at birth (considers both all infants, high-risk and very high-risk infants under different strategies). PI: All infants aged 2 months. MI: All pregnant women between 28 and 32 weeks gestation. **Intervention model and coverage:** PVZ: 90 % mAb: 90 % PI: 90 % MI in combination with PVZ, seasonal, and year-round vaccination: 60 % **Product cost:** N/A.	The purchase price per dose of long-acting mAbs would have to be less than around £4,350 (USD 5,577) to be cost-effective but dropping to £200 (USD 256) for vaccinated heightened-risk infants or £90 (USD 115) for all infants. A seasonal maternal vaccine would have to be priced less than £85 (USD 109) to be cost-effective and affordable. Vaccinating infants at 2 months seasonally would be cost-effective and affordable if priced less than £80 (USD 103). For a country with seasonal RSV dynamics, seasonal vaccination rather than a year-round intervention program is always optimal. *Exchange rate: USD 1 = £0.78; Currency year: 2020; Source: World Bank* [128]
3. Individual articles from LMICs included in the review articles				
What is the health impact and cost-effectiveness of RSV maternal immunization and monoclonal antibodies to prevent childhood RSV in Gavi, the Vaccine Alliance–eligible countries?	**Method:** Vaccine and mAb impact and cost-effectiveness modeling. **Measure:** Reduction of infections, hospitalizations, deaths, and DALYs; cost per DALY averted, optimal strategy (strategy that maximize the expected net benefits) for a range of societal WTP.	**Model:** Static population-based cohort model that follows RSV-related events monthly from birth to age 60 months. **Data fit:** Model parameterized using country- and age-specific demographic, epidemiological data.	**Disease burden:** Retrieved from published systematic review, and interpolated data to generate monthly disease burden (actual input values not available). **Intervention efficacy:** MI: 70 % (range: 50 %–90 %) mAb: 70 % (range: 50 %–90 %) **Duration of protection:**	The average ICER at baseline assumptions (*not reported but calculated based on reported values*) was USD* 1,893/DALY averted for **RSV MI** and USD 2,769/DALY averted for **RSV mAb**. The most cost-effective strategy would be **RSV MI** at WTP value range between USD 1,000–8,000 for LMICs; **RSV mAb** at WTP value range between USD 3,500–8,000.

Table 7 (*continued*)

Policy question	Assessment method/measure	Additional information specific to models	Assumptions	Outcomes/interpretation
		Time period: 5 years **Seasonality:** not considered **Waning effects:** not considered **Herd effects:** not considered **Model transparency**: high **Granularity:** 72 Gavi countries.	MI: 5 months (range: 3–6 months) mAb: 6 months (range: 4–8 months) **Intervention and target population:** MI: Single-dose vaccine targeted to all pregnant women attending any ANC services. mAb: single dose given to newborn during EPI. **Intervention coverage:** Assumed at BCG coverage levels for 2016 for each country for both interventions. **Product cost**: MI: USD 3 per dose mAb: USD 6 per dose	Price scenario analysis demonstrates that when the incremental intervention cost per dose between maternal and mAb strategy is USD 1 (USD 3 versus USD 4, respectively), the mAb is the optimal strategy. In other words, an extra month of protection is worth more than USD 1. For all countries, uncertainty in disease burden (age-specific RSV hospitalization, incidence rate, CFR, etc.) are the top influential factors for choice of the optimal strategy at all WTP values. *USD in 2016 units. R1 [124] R2 [125,129]
4. Individual articles from UMICs/HICs (not exhaustive) included in the review articles				
What is the potential health impact of RSV vaccination strategies in Turkey? Strategies included: (1) vaccinating infants at 2 and 4 months of age on a seasonal basis, (2) vaccinating pregnant women, and (3) vaccinating pregnant women and infants at 2 and 4 months of age.	**Methods:** Vaccine impact and cost-effectiveness modeling. **Measure:** Reduction of general practitioner (GP) visits, hospitalizations, and deaths, cost per QALY gained.	**Model type:** Multi-cohort static Markov model with cycles of 1 month. **Data fit:** 2014 birth cohort in Turkey (111,459 newborns) and hospital data from multicenter hospital study. **Time period:** 2-year time horizon with monthly cycle. **Seasonality:** Yes, considered effects of seasonal vaccination. **Waning effects:** yes **Herd effects:** not considered **Model transparency**: medium **Granularity:** Turkey.	**Disease burden:** Hospital data from multicenter hospital study from Turkey (RSV-related hospitalization as a proportion of total hospitalization = 17.78, RSV-related mortality as a proportion of hospitalization among < 1 years = 0.0068 and among 1–2 years = 0.00026). **Intervention efficacy:** MI: 60 % PI: infants 2 months of age 60 % PI: infants 4 months of age 75 % **Duration of protection:** MI: 3 months PI: 5 months **Intervention and target population:** PI: Vaccinating infants at 2 and 4 months of age on a seasonal basis. MI: Vaccinating pregnant women. Combination: Vaccinating pregnant women and infants at 2 and 4 months of age. **Intervention coverage:** 85 % for all vaccinations **Product cost:** 60 TL per dose or USD 31.5 per dose.	**PI** at 2 and 4 months of age would result in 51,969 (95 % CI: 35,313– 68,244) TL/QALY or 27,295 (95 % CI: 18,547–35,842) USD/QALY. **MI** would result in 60,638 (95 % CI: 45,154–76,806) TL/QALY or 31,848 (95 % CI: 23,715–40,339) USD/QALY. **MI plus PI** at 2 and 4 months of would result in 61,653 (95 % CI: 44,347–79,799) TL/QALY or 32,381 (95 % CI: 23,291–41,911) USD/QALY. At a WTP threshold of 61,821 TL (USD 32,469), PI had the highest probability of being cost-effective followed by MI and then the combination strategy). Vaccine efficacy and disease burden (incidence and mortality) were the most influential parameters of cost effectiveness. RSV vaccination of infants and/or pregnant women has the potential to be cost-effective in Turkey. A 2-dose infant schedule is the most desirable in terms of cost-effectiveness, though MI strategy becomes more desirable if the duration of protection is sufficiently long. *Exchange rate: USD 1 = TL 1.904; Currency year: 2013; Source: World Bank* R1 [124] R2 [125,135]
What is the impact and cost effectiveness of childhood RSV interventions in the US?	**Method:** Decision tree model on cost and outcomes. **Measure:** Cost per QALY gained.	**Model type:** Decision tree. **Data fit:** Hypothetical cohort of newborn infants in the US, 2007–2009. **Time period:** 5 years after birth for hospitalizations, 10 years for asthma effects, lifetime for productivity. **Seasonality:** not considered	**Disease burden:** Informed by literature from the US (mortality due to RSV 5.1 per 100,000 children among < 1 year, and 0.9 per 100,000 children among 1–5 years; incidence of hospitalization per 1,000 children 11.5 to 32 among < 1 year). **Intervention efficacy:** Base case 50 %. **Duration of protection:** Half-life of 12 months, assume protective effect starting at birth.	RSV vaccination intervention could avert 23,069 hospitalizations (24.1 %), 66 deaths (17.3 %), and gain 4,735 QALYs per birth cohort in the US. Assuming a vaccine cost per course USD* 232 (including administration fees), the cost per QALY gained would be USD 93,401 (95 % CI: USD 65,815–126,060) from the health care system perspective and USD 65,115 (95 % CI: USD 41,003–93,679) from the societal perspective.

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Table 7 (*continued*)

Policy question	Assessment method/measure	Additional information specific to models	Assumptions	Outcomes/interpretation
		Waning effects: Yes **Herd effects:** not considered **Model transparency**: high **Granularity:** US.	**Intervention and target population:**Evaluated a theoretical 2-dose vaccine that can be given to infant (or pregnant women) and assuming p*rotection effective at birth either from MI or mAb*. **Intervention coverage**: 69 % **Product cost:** USD 90.27 (based on Rotarix price per dose), USD 232 per course (including injection and other supplies).	Immunization against RSV could reduce the burden of RSV infection if we assume a vaccine with 50 % efficacy combined with fast waning of protection. *USD in 2011 units. R1 [124,141]
What is the potential impact and cost effectiveness of different RSV immunization strategies? Strategies considered: targeting vaccination for infants, or pregnant women, or prophylactic antibodies for neonates	**Method:** Vaccine impact modeling using statistical regression models. **Measure:** Reduction of hospitalizations, QALYs gained, maximum cost-effective price.	**Model type:** Regression-based model followed by a static cohort model for economic analysis. **Data fit:** GP attendance and hospital admissions data from the United Kingdom (UK). **Time period:** 1 year **Seasonality:** yes **Waning effects:** not considered **Herd effects:** not considered **Model transparency:** high **Granularity:** UK.	**Disease burden:** Retrieved from database on clinical attendance and laboratory test data from UK (incidence of RSV among < 6 months old: 21.42, among < 5 years old: 11.99, per 100 population; deaths among < 6 months old: 0.00248, among < 5 years old: 0.00085, per 100 population; *estimated values*). **Intervention efficacy:** 70 % for all interventions. **Duration of protection:** **MI:** 3 months mAb: 6 months PI: 6 months, **Intervention and target population:** MI: Pregnant population. mAb and PI: All newborns and eligible infants pre-RSV season. **Intervention coverage:** not stated (assumed 100 %) **Product cost:** N/A (calculated maximum price per fully protected person).	The maximum price per fully protected person for the infant, newborn, and maternal strategies without seasonal restrictions was £192 (95 % UI 168–219) or USD 246 (95 % UI 215–281), £81 (76–86) or USD 104 (100–110), and £54 (51–57) or USD 69 (65–73), respectively. The most cost-effective strategy was to selectively immunize all children born before the start of the RSV season (maximum price of £220 [95 % UI 208–232] per vaccine, for an ICER of £20,000 per QALY or maximum price of USD 282 [95 % UI 267–297] per vaccine, for an ICER of USD 25,641 per QALY). RSV vaccine and antibody strategies are likely to be cost-effective if they can be priced below around £200 (USD 256) per fully protected person. A seasonal vaccination strategy is likely to provide the most direct benefits. In settings of high RSV seasonality, the most cost-effective strategy would be to deliver seasonal RSV interventions. *Exchange rate: USD 1 = £0.78; Currency year: 2017; Source: World Bank* R1 [124,142]
What is the cost-effectiveness of potential vaccination against RSV infection?	**Method:** Cost-effectiveness modeling. **Measure:** hospitalizations averted, deaths averted, QALYs gained, ICER per QALY.	**Model type:** Markov cohort-based decision model. **Data fit:** Derived from the literature regarding GP visits in the Netherlands and a few other high-income countries. **Time period:** 1 year **Seasonality:** yes **Waning effects:** not considered in baseline **Herd effects:** not considered **Model transparency:** high **Granularity:** Netherlands.	**Disease burden:** Derived from GP visit data from the literature (probability of RSV-related GP visit among 0–12 months: 0.16; RSV-related hospitalization as a % of GP visits: 0.0562; RSV-related mortality as a % of hospitalizations: 0.002778). **Intervention efficacy:** 30 %/60 %/75 % for doses 1/2/3 for a 3-dose schedule given at ages 0, 1, 3 months; 30 %/70 % for doses 1/2 for a 2-dose schedule given at ages 0 and 3 months. **Duration of protection:** Infant vaccination offers 5 months of protection. **Intervention coverage:** 96 % **Intervention and target population:** Infant vaccine given at a 2- or 3-dose schedule between 0 and 3 months. **Product cost:** €37.50 per dose.	Under a year-round vaccination scenario and 3 doses of vaccine, the model estimated to avert 66 % of hospitalizations and deaths due to RSV among 0- to 1-year olds. The cost-effectiveness was estimated at €34,142 (USD 43,772) per QALY. Vaccinating all infants with 3 doses at the age of 0, 1, and 3 months of age would result in a cost per QALY of €34,142 (95 % CI: €21,652–€87,766) or USD 43,772 (95 % CI: USD 27,759–112,520). Vaccinating all infants with 3 doses at a 1-month delay schedule (0, 2, and 4 months of age), would result in a higher cost per QALY of €40,900 (USD 52,436). Assumption of waning protection leads to higher cost per QALY estimates. Lower disease burden and vaccine protection

Table 7 (*continued*)

Policy question	Assessment method/measure	Additional information specific to models	Assumptions	Outcomes/interpretation
				and efficiency increases cost per QALY (less cost-effective). The seasonal vaccination strategy resulted in favorable ICER values. *Exchange rate: USD 1 = € 0.78; Currency year: 2012; Source: World Bank* R1 [124,143]
Policy question	**Assessment method/measure**	**Additional information specific to models**	**Assumptions**	**Outcomes/interpretation**
Economic burden /cost of illness				
1. Review articles				
What is the economic burden (cost of managing) of RSV ALRI among children <5 years, at global level and by geography?	Systematic review of evidence on costs of RSV management among across all countries. **Measure:** Average cost per episode of RSV management by severity (inpatient and outpatient), with and without follow-up.	Includes 41 studies published between 2000 and 2017. Most studies are from the US and other HICs and UMICs. Includes only 1 study from an LMIC in the South Asia Region and none from Africa.	Qualitative synthesis of evidence and *meta*-analysis of studies to generate global and regional estimates of economic burden. Study-specific key findings are listed in a table in the review paper.	The global cost of RSV ALRI management in young children in 2017 was estimated to be approximately €4.82 billion (95% CI, 3.47–7.93) or USD 5.45 billion (95% CI, 3.92–8.96), 65% of these in developing countries and 55% of global costs accounted for by hospitalization. At global level, the average cost per episode was estimated to be €3,452 (95% CI: 3,265–3,639) or USD 3,900 (95% CI: 3,689–4,112) for inpatient and €299 (95% CI, 295–303) or USD 338 (95% CI, 333–342) for outpatient management without follow-up. The costs of management per episode increased to €8,591 (95% CI, 8,489–8,692) and €2,191 (95% CI, 2,190–2,192) or USD 9,707 (95% CI, 9,592–9,821) and USD 2,476 (95% CI, 2,475–2,477), respectively, with follow-up to 2 years after the initial event. RSV imposes a high economic burden among health systems and society. There is geographic imbalance in data representation for RSV economic burden. *Exchange rate: USD 1 = € 0.885; Currency year: 2017; Source: World Bank* R3 [50]
2. Individual articles not included in the review articles				
What is the cost of managing RSV ALRI and other acute respiratory infections among infants in Malawi?	**Method:** Cost of RSV treatment (inpatient and outpatient) among patients in a tertiary care hospital, using patient survey, patient chart review, and hospital expenditure review. **Measure:** Average cost per episode of illness for inpatient and outpatient care, direct and indirect cost of treatment, and cost to the patient.	**Model type:** Cost of illness. **Data:** Uses data from 429 infants enrolled in a respiratory disease surveillance platform in a tertiary hospital in Malawi. **Time period:** 2015–2016 **Granularity:** Malawi.	Makes comparison of cost of treatment among confirmed RSV cases, cases without confirmed RSV, and cases with other respiratory infections.	The mean costs per RSV episode were USD* 62.26 (95% CI: USD 50.87–73.66) and USD 12.51 (95% CI: USD 8.24–16.79) for inpatient and outpatient cases, respectively. The cost per episode among confirmed RSV-positive cases were comparable to that of other episodes of respiratory illnesses. Household costs accounted for roughly 20% of the total cost per episode. For the lowest-income families, household cost per inpatient RSV episode was about 32% of total monthly household income. RSV causes substantial economic burden to health systems and society. *USD in 2018 units. [144]

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Table 7 (*continued*)

Policy question	Assessment method/measure	Additional information specific to models	Assumptions	Outcomes/interpretation
3. Individual articles from LMICs included in the review articles				
What is the cost of managing RSV ALRI among hospitalized children and infants in Bangladesh?	**Method:** Cost of RSV treatment among hospitalized patients in a tertiary care hospital, using patient survey and expenditure review. **Measure:** Average cost per episode of illness for inpatient care, direct and indirect costs of treatment, and cost to the patient.	**Model type:** Cost of illness. **Data:** Uses data from 39 children (<5 years) identified from a sentinel influenza program database at four tertiary hospitals in Bangladesh. **Time period:** 2010 **Granularity:** Bangladesh.		The total cost per hospitalized case of RSV was USD* 94 IQR: USD 67–127), direct cost: USD 62 (IQR: USD 43–101); indirect cost: USD 19. Out-of-pocket cost of RSV hospitalization constitute considerable proportion (∼24%) of monthly income. Cost of RSV hospitalization at the national level was estimated to be USD 10 million (IQR: USD 7–16) per year (direct cost) and USD 3 million (IQR: USD 2–58) indirect cost. RSV-associated hospitalizations among children represent a substantial economic burden in Bangladesh. *USD in 2010 units. R3 [50]
4. Individual articles from UMICs not included in the review articles				
What are the costs of viral respiratory infections management among children aged ≤5 years in Argentina?	**Method:** Prospective cohort study that followed up with children to identify cases and used administrative hospital records to determine costs of in-hospital care. **Measure:** Cost per hospitalization, cost per hospitalization avoided, cost of outpatient care.	**Model type:** Cost of illness. **Data:** Followed 1,800 children <5 to identify children hospitalized or who sought care at emergency room, with any sign of acute respiratory infections in Argentina. **Time period:** 2008–2010 **Granularity:** Argentina.		The total cost of hospitalization was a median of USD* 529 (IQR, USD 362–789).^ Respiratory viruses, including RSV, that are associated with severe illness cause substantial economic burden. ^*Estimated costs for all ALRI cases, 37% of which were RSV.* *USD in 2009 units. [145]
What are the medical costs associated with bronchiolitis hospitalizations caused by RSV infection among infants aged <2 years in Colombia?	**Method:** Prevalence-based cost-of-illness study from societal perspective. **Measure:** Average cost per hospitalization.	**Model type:** Cost of illness. **Data:** Uses data from 193 RSV patients admitted to tertiary hospitals in Colombia. Data collected from medical invoice and health records. **Time period:** 2015–2016 **Granularity**: Columbia.	Costs are reported as proportions or as average per patient per day. The estimate is inferred from the paper by multiplying item-specific cost (unit cost per service) by median length of stay (5.88 days).	Total direct medical cost per hospitalization of RSV episode was ∼USD* 580. The major contributors to hospitalization costs were room costs (31.5%), drugs (21.8%), and indirect costs (14.9%). RSV infection among children in Colombia places a high economic burden on the health system. *USD in 2020 units. [146]
What are the direct medical costs of RSV-related bronchiolitis hospitalizations in Columbia?	**Method:** Retrospective costing study of hospitalized children with diagnosis of RSV bronchiolitis. **Measure:** Direct medical cost of RSV bronchiolitis.	**Model type:** Cost of illness. **Data:** Uses data from 89 RSV patients admitted <2 years old. Data collected using electronic medical record review of patients discharged from hospital. **Time period**: 2016–2017 **Granularity**: Columbia.		The median (IQR) cost of infants treated in the pediatric ward was *USD 518.0 (IQR: 217.0–768.9). Pediatric intermediate care unit was USD 1,305.2 (IQR: 1,051.4–1,492.2). Pediatric intensive care unit was USD 2,749.7 (IQR: 1,372.7–4,159.9). Significant difference in cost by severity was observed. Substantial economic burden of RSV hospitalization care in Colombia. *USD in 2017 units. [147]
What are the socioeconomic costs associated with children with acute respiratory infection in Malaysia?	**Method:** Costing study among children <5 years old admitted with acute respiratory infection in a teaching hospital in Malaysia.	**Model type:** Cost of illness. **Data:** Uses data from 200 patients of which 74 (37%) had respiratory virus detected, of which 50 were RSV-positive cases. Data collected via interview of ALRI patient		Study compared the costs of managing RSV-positive cases with other ALRI cases. Median direct costs for RSV-positive cases were higher than that for RSV-negative cases (USD 803 versus 729, p = 0.03).

Table 7 (*continued*)

Policy question	Assessment method/measure	Additional information specific to models	Assumptions	Outcomes/interpretation
	Measure: Direct medical cost of RSV bronchiolitis.	caretakers and medical record review. **Time period:** 2013–2015 **Granularity:** Malaysia.		The average out-of-pocket cost due to ALRI hospitalization was USD 189 (IQR: 140–258), representing a median 16.4% (10.4%–22.3%) of reported monthly household income. The median societal cost (combining direct and indirect costs) was USD 871 (653–1,183), which is 1.8 times the Malaysian health expenditure per capita in 2014. Costs were higher with younger age, presence of comorbidity, prematurity, and detection of a respiratory virus. RSV and other ALRI cause substantial economic burden to households and health systems in Malaysia. [148]
5. Individual articles from UMICs included in the review articles				
What are the direct medical costs of RSV infection in children hospitalized in Suzhou, China?	**Method:** Retrospective costing study among children confirmed RSV positive at Suzhou University Children's Hospital in China. **Measure:** Average cost per episode of hospitalization.	**Model type:** Cost of illness. **Data:** Uses data from 2,721 hospitalized children who tested positive for RSV; 87% of the children were <2 years age. Data collection entail medical records review from one tertiary public hospital using structured chart review. **Time period:** 2005–2009 **Granularity:** China.		The mean cost of RSV-related hospitalization was USD 571.8 (USD 909.6 for children referred to intensive care unit and USD 565.4 for those cared for in other wards. Older children >6 months had higher hospitalization cost compared to those <6 months. Children with respiratory distress or chronic lung diseases tended to have higher hospitalization costs than others. The cost of RSV care is relatively high and imposes substantial economic burden among patients and the health system. R3 [50,149]
What are the costs of hospitalization for RSV chest infection in Malaysia?	**Method:** Costing analysis. **Measure:** Direct medical cost per bed-day of hospitalization.	**Model type:** Cost of illness. **Data:** Uses data from 216 children <24 months of age admitted to hospital with RSV chest infection. Data include resource use and unit cost data from the hospital. **Time period:** 1995–1997 **Granularity:** Malaysia.		The median cost per episode of RSV hospitalization was 169.99 (IQR: 128.08–248.47). Children who were ex-premature or with an underlying illness were more likely to have a longer hospital stay, higher treatment costs, and need for intensive care. RSV causes substantial economic burden to health systems in Malaysia. R3 [50,150]

Notes on reading Table 7***:***

– The studies listed in the table are organized in the following order: 1. Review articles, 2. Individual articles not included in the review articles, 3. Individual articles from LMICs included in the review articles, and 4. Individual articles from upper-middle-income countries (UMICs) or HICs (not exhaustive) included in the review articles. Review articles are numbered R1 [124], R2 [125], and R3 [50]. Individual studies included in the review are referenced.

– The column "Policy question" states the main question that each article in the literature is addressing, which may not necessarily address the general policy question in the field.

– Model transparency in the "Additional information specific to models" column is qualitatively rated as high, medium, or low based on availability of parameter values in the article, supplemental files available, and level of detail provided by authors.

ALRI: acute lower respiratory infection; ANC: antenatal care; BCG: Bacille Calmette-Guérin; CFR: case-fatality rate; CI: confidence interval; DALY: disability-adjusted life year; DTP: diphtheria-tetanus-pertussis; EPI: Expanded Program on Immunization; GDP: gross domestic product; GP: general practitioner; HICs: high-income countries; ICER: incremental cost-effectiveness ratio; IQR: interquartile range; LMICs: low- and middle-income countries; mAb: monoclonal antibody; MI: maternal immunization; N/A: not applicable; PI: pediatric immunization; PVZ: palivizumab; QALY: quality-adjusted life year; RSV: respiratory syncytial virus; TL: Turkish lira; TSC: threshold strategy cost; UI: uncertainty interval; UK: United Kingdom; UMICs: upper-middle-income countries; US: United States; USD: United States dollar, WTP: willingness to pay.

- Robust surveillance systems in LMICs to identify and respond to RSV activity.
- Additional data on the broader benefits of RSV immunization such as averting all-cause LRTI, wheezing, and impact on antimicrobial resistance, particularly from LMICs.
- Data on intervention acceptability and delivery strategy preferences from LMICs to inform the full impact of RSV interventions.
- Information on cost and feasibility of identifying and reaching high-risk children in LMICs.

7. Social and/or economic impact of a vaccine

This section summarizes available evidence on the economic impact of using maternal RSV vaccine or mAbs to prevent RSV in infants. The evidence is presented in two main categories: cost-effectiveness and economic burden/cost of illness. The policy questions addressed by individual studies along with the methods used for assessment of costs and cost-effectiveness, key assumptions used to inform the analyses, and the key findings and interpretation from the source paper are listed in Table 7. Apart from the individual country-focused studies, two relevant review articles were identified and are summarized in the table for completeness.

7.1. Summary of knowledge and research gaps in modeling studies that measure anticipated socio-economic impact of the vaccine

Cost-effectiveness of RSV interventions

Priority knowledge

- Maternal RSV vaccines and infant mAbs are potentially cost-effective in LMICs, though dependent upon disease burden, intervention characteristics, and countries' willingness to pay (WTP) thresholds.
- Disease burden (e.g., age-specific RSV hospitalization, incidence rate, and case fatality rate), intervention effectiveness, and duration of protection are important factors in determining cost-effectiveness of RSV interventions.
- At comparable prices, mAbs will likely be more cost-effective than maternal RSV vaccines due to higher expected efficacy and longer duration of protection.
- Seasonal vaccination is likely to be more cost-effective than year-round vaccination in settings with distinct seasonality.

Research gaps

- Additional data on disease burden, intervention effectiveness, and duration of protection from LMICs are needed to improve understanding of cost-effectiveness in these settings.
- Information on the broader benefits of RSV interventions beyond immediate RSV outcomes (such as impact on all-cause ALRI or potentially averting wheezing); including these impacts is likely to improve the value of the interventions.
- Information on intervention costs and optimal delivery strategies in LMICs for a comprehensive understanding of the value of RSV interventions, including seasonal versus year-round vaccination.

Cost of illness (economic burden) of RSV

Priority knowledge

Table 8
Overview of expectations of evidence that are likely to be required to support a global/regional/national policy recommendation or financing.

Parameter for policy/financing consideration	Assumptions	Guidance/reports available
Product efficacy and safety	Vaccines and mAbs are shown to be safe and efficacious in clinical trials.	WHO preferred product characteristics for maternal vaccines and mAbs [89,90].
Evidence for vaccine/mAb effectiveness in LMICs is available	Clinical trials and/or bridging studies or a pharmacokinetics study provide evidence for LMIC effectiveness.	This may be required by SAGE for a policy recommendation (has been required for some other vaccines).
WHO policy recommendation through SAGE	SAGE recommends the wide use of maternal vaccines and/or mAbs.	[151]
PQ of maternal vaccines by WHO	Manufacturers choose to submit package to WHO for PQ. Vaccines receive PQ.	Guidelines on the quality, safety, and efficacy of respiratory syncytial virus vaccines, Annex 2, TRS No 1024 [94,115].
PQ of mAb by WHO	Supporting regulatory guidance for RSV mAbs is adopted by the WHO ECBS. Manufacturers choose to submit package to WHO for PQ. mAbs receive PQ.	Guidance on RSV mAbs expected to be presented to ECBS in late 2022 or 2023.
National (or at least regional) RSV disease burden data	National policy for RSV preventive product use will be based on evidence of disease burden (including health care utilization).	[2,73,152]
National (or at least regional) RSV seasonality data	National policy for how RSV preventive products will be used will be based on evidence of seasonality.	[73,153,128]
Favorable cost-effectiveness	Countries will more likely take up products if cost effectiveness analyses show favorable value for money.	
Product price acceptable to Gavi investment case for use in Gavi-eligible countries	LMICs that are Gavi eligible will apply for use of RSV prevention products only if Gavi support is available.	WHO preferred product characteristics for maternal vaccines and mAbs [89,90]. Gavi vaccine investment strategy – decision on RSV [54,71].
Feasibility of integration into existing delivery platforms (i.e., antenatal care, postnatal check-ups, routine EPI visits)	Integration into existing platforms will favor uptake of products.	[55,58,73]
Impact of the vaccine on antibiotic use and AMR	Vaccine impact on reduction in antibiotic prescribing is demonstrated in phase 3 clinical trials and post introduction observational studies.	[34,36,38]

AMR: antimicrobial resistance; ECBS: Executive Committee on Biological Standardization; EPI: Expanded Program on Immunization; Gavi: Gavi, the Vaccine Alliance; LMICs: low- and middle-income countries; mAb: monoclonal antibody; PQ: prequalification; RSV: respiratory syncytial virus; SAGE: Strategic Advisory Group of Experts on Immunization; WHO: World Health Organization.

- The economic burden of RSV in HICs settings is substantial.
- Available data suggest childhood RSV incurs a substantial economic burden on health systems and households in LMICs.
- Cost-of-illness estimates available for other respiratory infections may be informative for RSV.

Research gaps

- Additional evidence on the economic burden of RSV from LMICs.
- Additional data on the cost of RSV disease treatment and sequelae, particularly in regions where there is currently no available data.
- Further exploration of using cost of illness for other respiratory infections to estimate cost of illness for RSV.

8. Policy considerations and financing

Given the burden on health systems and the economic cost in HICs, national policy recommendations on RSV immunization products for reduction of RSV disease in infants are likely in HICs. While the biggest burden of RSV lies in LMICs, given their limited resources, it is likely that Gavi-eligible countries will require Gavi financing to support the introduction of RSV immunization. For LMICs that are not Gavi-eligible, policymakers will need to make decisions on the introduction of RSV immunization based on their local context and potential impact and cost-effectiveness.

In November 2018, the Gavi board approved the inclusion of RSV immunization products in the Vaccine Investment Strategy 2021–2025 contingent on the availability of a licensed product, outcomes of regulatory and technical review processes (including WHO prequalification and a SAGE recommendation), and if the products meet the financial assumptions used as the basis for the RSV investment case [54,71]. Procurement by United Nations agencies to support Gavi financing is contingent on WHO prequalification.

With regard to a WHO policy recommendation, RSV was first formally presented to SAGE in 2016. At this meeting, SAGE recommended that efforts be made to identify and fill gaps in evidence required for regulatory, prequalification, and policy guidance for RSV preventive interventions, including maternal and pediatric immunization with RSV vaccines, and passive infant immunization with long-acting RSV mAbs [73]. Since then, two informal updates have been given, in 2019 and in 2021. Another formal RSV session at SAGE is being planned for October 2022. At the time of writing, a formal SAGE working group on RSV has yet to be formed.

See Table 8 for an overview of policy and financing considerations, assumptions, and available guidance.

9. Access and implementation feasibility

Due to the high disease burden of ALRI, and occasional death caused by RSV in infants, infants in all countries are the target of RSV maternal vaccines and infant mAbs [6,154,155]. As discussed in Section 2, maternal vaccines will most likely be delivered

Table 9
Access and implementation feasibility of RSV interventions.

	Intervention **Maternal RSV vaccine delivered via ANC services**	**mAbs delivered via the EPI program**
Possibility of implementation within existing delivery systems	Moderate Amendments and improvements to existing vaccine delivery systems will be needed for the delivery of maternal RSV vaccines, as they are intended to be given during ANC services and delivered with each pregnancy; gestational age and seasonality may also impact administration. Maternal immunization in many LMICs is limited to tetanus toxoid-containing vaccination, which has flexible administration timing during pregnancy, making it difficult to pair with a maternal RSV vaccine that may have a fixed administration window during gestation. Disease seasonality may affect ease of implementation.	High The delivery of mAbs could be integrated into the EPI schedule, coinciding with birth-dose vaccines or at other scheduled visits in early infancy. Crowded EPI schedules with multiple injectable vaccines at the same visit may affect acceptance and uptake. Disease seasonality may affect ease of implementation.
Commercial attractiveness	Moderate There is a large target population of pregnant women, distributed predominantly in LMICs, coinciding with the highest RSV disease morbidity and mortality in infants. Vaccine introduction in these areas will require support.	Moderate There are large target populations in many countries, with highest disease burden in LMICs. MAb introduction in LMICs will require support.
Clarity of licensure and policy decision pathway	High There is a clear licensure pathway. The policy decisions may differ in HICs and LMICs depending on availability of other prevention strategies.	Moderate The pathway to licensure is expected to follow a pathway similar to that used for PVZ. The pathway for policy decisions is less clear, particularly in LMICs given the potential cost and prioritization of other infant vaccines.
Expected financing mechanism	Moderate There is interest from global funders, including Gavi. There is limited country-level data on the RSV epidemiology and disease burden to inform decision-making by national procurement agencies once the vaccines are available.	Moderate There is interest from global funders, including Gavi. There is very limited data available on country-level disease burden and epidemiology, which will be required for decision-making by national procurement agencies.
Ease of uptake	Moderate There is a well-defined target population of pregnant women and the acceptability of current maternal vaccines is generally high in LMICs. However, awareness of RSV must be increased, and vaccine delivery will require close coordination between EPI and ANC services.	High There is a well-defined target population with likelihood of high acceptability, though RSV awareness must be increased. Vaccine infrastructure improvements may be needed, especially for seasonal dosing.

ANC: antenatal care; EPI: Expanded Program on Immunization; Gavi: Gavi, the Vaccine Alliance; LMICs: low- and middle-income countries; mAb: monoclonal antibody; PVZ: palivizumab; RSV: respiratory syncytial virus.

through the ANC platform, while mAbs could be administered to infants at birth or soon after through the EPI program, or at other health care visits in early infancy [156]. Vaccine and mAb product development is expected to include licensure by a stringent regulatory authority followed by WHO prequalification and Gavi-supported implementation in eligible LMICs [157]. Both products are prioritized in the Gavi vaccine investment strategy for the 2021–2025 funding period [54,71]. However, there are scarce data available on RSV epidemiology, disease burden, hospital admissions, deaths, and case-fatality rates in many LMICs to inform decision-making once the products are available [129]. While not expected in HICs, LMICs may encounter issues related to access and implementation feasibility for both maternal vaccines and mAbs, as summarized in Table 9.

10. Conclusion

RSV is the predominant cause of ALRI in young children [1], with more than 33.0 million episodes of RSV ALRI, 3.6 million hospital admissions, and up to 101,400 deaths globally occurring in children under five years of age each year [2]. Most morbidity and nearly all mortality occurs in LMICs [2] and there is high unmeasured burden of RSV deaths outside hospitals in LMICs [3]. Given the substantial morbidity and mortality burden of RSV, preventive interventions are needed for young children, especially among infants under six months who have the highest incidence and the most severe disease burden.

Both maternal RSV vaccines and mAbs provided to infants have the potential to substantially reduce disease burden and severe outcomes of RSV among young infants, though model estimates vary and limited data in LMICs contributes to uncertainty in impact. For mAbs, targeting interventions to high-risk infants appears to be more efficient, though costs and feasibility of identifying target populations may pose significant challenges. In areas with distinct and predictable RSV seasons, seasonal interventions are likely to be most efficient in reducing infections per dose administered compared to year-round delivery, though programmatic challenges of this delivery approach may be substantial. Recent data demonstrate RSV immunization may decrease RSV-related hospitalization and all-cause pneumonia hospitalizations, though these broader benefits have not been adequately captured by health impact studies.

Evidence is limited on the economic burden of RSV in LMICs, but available data suggest childhood RSV incurs a substantial economic burden on health systems and households. Based on current models, both maternal RSV vaccines and mAbs are expected to be cost-effective in many countries, though it is highly dependent on parameters such as disease burden, vaccine effectiveness, duration of protection, intervention characteristics, and WTP thresholds. Reducing uncertainty around these parameters, as well as costs of treatment and sequelae, will improve understanding of the potential value of the interventions in these areas. Including broader benefits of the interventions, such as the impact on all-cause ALRI, could further increase their value.

Assuming a comparable price between interventions, mAbs are likely to be more cost-effective due to their expected higher efficacy and longer duration of protection. While there are limited data, seasonal vaccination is likely to be more cost-effective than year-round vaccination in settings with distinct seasonality, though a better understanding of delivery strategies and costs of RSV interventions in LMICs is needed for a comprehensive understanding of the value of RSV interventions.

The probability of technical and regulatory success of RSV vaccine and mAb development for products appropriate for LMICs is high. While cost-prohibitive and unfeasible to deliver in LMIC settings, a licensed mAb already exists and is used in some high-income settings in very high-risk children. For a maternal vaccine, several observations support the biological feasibility for development. RSV-specific functional antibodies have been shown to neutralize virus in vitro, and protection has been shown in numerous preclinical models [99]. RSV antibodies delivered prophylactically to children reduce the incidence of severe RSV disease, and serum neutralizing antibody protects against RSV-associated ALRI [100,158,159]. Data from several late-stage clinical trials provide proof of concept for RSV maternal vaccines and mAbs, and studies have shown good safety profiles for candidates [104,121,160,161].

A robust pipeline with multiple clinical-stage candidates to prevent RSV disease in infant and pediatric populations has developed over the last several years, leveraging a variety of vaccine platforms. Candidates for infants target passive protection via maternal immunization or immunoprophylaxis with mAbs. There are currently-four Phase 3 trials underway evaluating the efficacy of two protein-based maternal RSV vaccine candidates and two mAb candidates. Licensure of one or more of these candidates is feasible over the next one to three years.

Product development of both maternal vaccines and mAbs is expected to include licensure by a stringent regulatory authority followed by WHO prequalification and Gavi-supported implementation in eligible LMICs. Several companies with candidates have received fast-track designations by the US Food and Drug Administration and/or European Medicines Agency for other products, which could accelerate approval. Efficacy trials are expected to be required for licensure/registration; however, if a correlate of protection is identified, subsequent similar products could potentially be registered based on safety and immunogenicity data. Both maternal RSV vaccine and birth-dose mAbs are prioritized in the Gavi vaccine investment strategy for the 2021–2025 funding period [54,71]. Access and implementation of both products are expected to be feasible in LMICs, but likely to require additional programmatic coordination and infrastructure support.

Author agreement

The authors declare that this is original work which has not been published before, and that all authors have agreed to the submitted paper.

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Appendix A. Supplementary material

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