



Assessment of the Effects of Active Immunisation against Respiratory Syncytial Virus (RSV) using Decision-Analytic Models: A Systematic Review with a Focus on Vaccination Strategies, Modelling Methods and Input Data

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Accepted: 20 December 2020 / Published online: 19 January 2021
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Abstract

Background Several vaccine and antibody candidates are currently in development for the prevention of lower respiratory tract infections caused by the respiratory syncytial virus (RSV).

Methods We searched MEDLINE, Embase, and SCOPUS and included model-based evaluations of RSV vaccinations. Two reviewers performed the selection, data extraction, and quality evaluation with EVIDEM. Cost-effectiveness (CE) estimates were converted to \$US purchasing power parity (PPP), year 2018 values. Potential economic and epidemiological outcomes were summarised for maternal, infant, children, and elderly vaccinations. The PROSPERO identifier is CRD42019122570.

Results In total, 22 model-based studies were reviewed. On average, a potential 27% reduction in RSV hospitalisations in infants was projected for maternal vaccination and 50% for direct infant immunisation. The CE of maternal vaccination was \$US1766–5857 PPP 2018/disability-adjusted life-years (DALYs) for Global Alliance for Vaccines and Immunisation (Gavi)-eligible countries. For England, the maximum cost-effective price of maternal vaccination was estimated at \$US81.5 PPP 2018. Infant vaccination was associated with higher CE ratios in low- and high-income settings. Vaccination of neonates born before the RSV season was the most cost effective in high-income settings. Higher values for vaccine effectiveness, duration of protection, and vaccine uptake increased the benefits. Due to indirect effects, the vaccination of school-age children and a cocooning strategy were effective alternatives to protect infants, and the vaccination of children aged < 5 years had a beneficial impact on the elderly.

Conclusion RSV vaccines with anticipated characteristics may reduce a sizeable proportion of the RSV burden. The results are subject to uncertainty because of the limited epidemiological and clinical data. Data on RSV incidence and hospitalisation risk for granular age strata should be prioritised to facilitate the evaluation of RSV interventions and decision making.

1 Introduction

Respiratory syncytial virus (RSV) is the most common cause of acute lower respiratory infection (ALRI), mainly in children aged < 2 years [1–3]. The incidence of RSV infection is lower in the first weeks of life, possibly because of protection from transferred maternal antibodies in newborns, and peaks

in infants up to 3 months of age [4]. By the end of the second year of life, most children have had an RSV infection [1]. A recent review of the global RSV burden estimated 1.4 million (uncertainty range [UR] 1.2–1.7) RSV hospitalisations and 27,300 (UR 20,700–36,200) in-hospital deaths occurred in infants aged < 6 months in 2015. Hospital admissions in this group constituted 45% of global RSV hospitalisations in young children (aged 0–4 years), which were estimated at 3.2 million (UR 2.7–3.8) in 2015. The estimates showed that the incidence of RSV-ALRI in those aged 0–5 months was higher in low-income (117.2 per 1000) than in high-income (66.1 per 1000) regions. In turn, hospital admission rates were reported to be much higher for high-income than for low-income countries. However, the small number of available studies limited the evidence on hospitalisations in low-income countries. The highest hospital admission rates

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40273-020-00991-7>.

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Key Points

Given the absence of clinical evidence on the efficacy of the respiratory syncytial virus (RSV) vaccine and the duration of vaccine-induced immunity, the potential effects of vaccination are subject to uncertainty.

The current decision-analytic models suggest that maternal, infant, and cocooning vaccinations with anticipated vaccine candidates may reduce a considerable proportion of RSV infections and hospitalisations in infants; the evidence for vaccination of the elderly is scarce.

Further economic evaluation of vaccination strategies is needed in the elderly and older children using dynamic-transmission models.

were reported in infants aged < 6 months compared with other age groups across all geographies [5]. The influential factors of acquisition of RSV in children include birth before and shortly after the onset of RSV season and attendance of childcare facilities [4]. Severe RSV illness and complications requiring hospitalisation occur mainly in high-risk children. Premature infants and children with severe respiratory disease, congenital heart disease, cancer, cystic fibrosis, immune deficiency, or Down syndrome have been reported to be at increased risk for severe RSV infection [6, 7]. Moreover, severe RSV disease during infancy presents a considerable risk for the development of recurrent wheezing and asthma later in life [8, 9]. Asymptomatic or mild RSV reinfections are common in adult life [10], with more severe manifestation in immunocompromised individuals [11], patients with cardiopulmonary diseases, and the elderly [12]. The increasing evidence on RSV in the elderly suggests that the impact of the disease is non-negligible, particularly in people with underlying comorbidities, and is comparable to that of non-pandemic influenza [12–14].

Overall, RSV infection has been recognised as a disease with a considerable impact in the community and on hospital services that requires prevention in young children and older adults [14]. Currently, the only preventive strategy is passive immunisation since active immunisation is not yet available. Passive immunisation is attained by transferring antibodies to an unprotected individual [15]. In contrast, active immunisation or vaccination leads the individual's immune system to produce antibodies and build up cellular immunity [16]. While vaccination can induce a long-lasting immunity, passively induced immunity lasts for several weeks or months [15, 16]. The monoclonal antibody (mAb) palivizumab is used for RSV prevention but is usually restricted to infants with an underlying risk of severe RSV infection [1, 17]. No RSV vaccine has yet been licensed, but several vaccine

candidates and mAbs are currently being tested in clinical trials [18]. Although vaccine effectiveness (VE) estimates are not yet available, decision-analytic models exploring the epidemiological and economic outcomes of potential RSV vaccination have been emerging. In this study, we summarised and critically appraised current evidence on the effectiveness and cost effectiveness of potential active vaccination strategies against RSV.

2 Methods

We performed a systematic review of decision-analytic models on active vaccination against RSV. The protocol of the review is published on PROSPERO (CRD42019122570).

The selection criteria were as follows: (1) model-based analyses; (2) original research or a systematic review; (3) focus on RSV vaccination; (4) reported additional costs and/or additional health effects in terms of life-years gained, quality-adjusted life-years (QALYs), disability-adjusted life-years (DALYs), life expectancy, reduction in RSV disease morbidity, reduction in RSV disease mortality; (5) either single- or multi-country study; (6) any language; and (7) publication since 2000.

Studies were excluded if they (1) investigated the epidemiology, transmission, and natural history of RSV without modelling the impacts of vaccination; (2) estimated health-care resource usage and costs of RSV infection only; (3) examined the effects of immunoprophylaxis (passive immunisation) without consideration of any active immunisation.

We searched MEDLINE, Embase, and SCOPUS from 2000 to the present (date of last search 22 October 2020), without restrictions. Two reviewers (MT, FPM) independently performed screening, selection, data extraction, and quality evaluation of selected studies. In case of any disagreement, the third reviewer (STS) arbitrated to reach a consensus. The search syntax and data extraction are described in the electronic supplementary material (ESM 1).

All studies included in the analysis underwent a quality assessment using the 'Evidence and Value: Impact on DEcisionMaking' (EVIDEM) instrument—'Assessment of quality of economic evaluations' [19]. The EVIDEM instrument evaluates (1) the quality of reporting in terms of completeness and consistency with cited sources and (2) the relevance and validity of evidence for decision making. We considered the EVIDEM instrument beneficial for the aims of this review because it provides an adaptable framework and allows a thorough assessment with the scoring of both the relevance of evidence and the completeness of the reporting of the model-based evaluations. We adopted the 'parameters and estimates' domain of EVIDEM to explore and evaluate the essential assumptions that directly govern the outcomes of the modelling of RSV transmission, the

effects and the costs of the interventions, and that are therefore critical for comparing the studies and interpreting the results. Studies that estimated only epidemiological effects of RSV vaccination (hereinafter epidemiological evaluation studies) were also subjected to the quality assessment of the applied methods. For these studies, we considered the absence of cost estimates as a limiting factor but not something that affected their relevance for decision making. Two evaluators (MT, FPM) independently completed the quality assessment across the 11 dimensions and assigned a score for each study, providing a rationale for the given score (1, 2 for low and 3, 4 for high completeness of reporting and relevance/validity).

For the assessed economic evaluations, the results reported were time adjusted to the year 2018 by applying the country-specific consumer price indices and standardised to \$US, year 2018 values using the purchasing power parity (PPP) index and exchange rates for 2018 obtained from Organisation for Economic Co-operation and Development published data.

3 Results

The initial search identified 2491 records after removing duplicates across the databases. Repeated searches added 514 records. Overall, 72 records were selected for abstract screening and eligibility assessment for full-text reading. After the full-text reading of 24 eligible studies, 22 were included in this review (Fig. 1) and subjected to data extraction and quality assessment.

3.1 Methodological Characteristics

Table 1 and Fig. 2 provide an overview of the methodological characteristics of the reviewed studies.

3.1.1 Settings and Target Population

Most studies considered RSV vaccination in high-income countries: five in the USA [20–24], three in Spain [25–27], four in the Netherlands [28–31], two in England [32, 33], and one each in Australia [34], and Turkey [35]. Four studies used data from Kenya [3, 36–38]. Two studies explored RSV interventions in the countries supported by the Global Alliance for Vaccines and Immunisation (Gavi) [39, 40]. Eleven studies evaluated both economic and epidemiological impacts [20, 23, 25–30, 32, 35, 40], and 11 studies provided an evaluation of only epidemiological effects [3, 21, 22, 24, 31, 33, 34, 36–39]. Nineteen studies evaluated interventions that target the reduction of RSV infections in infants and children aged < 5 years, and three studies examined vaccination impact on morbidity and mortality in the elderly [20,

24, 29]. The target population groups for vaccination strategies covered in the review included (1) pregnant women, (2) newborns and infants, (3) young children, and (4) adults and the elderly.

3.1.2 Structure of Models

3.1.2.1 Dynamic and Static Modelling of Respiratory Syncytial Virus (RSV) Epidemiology

Twelve studies used dynamic models (11 compartment models [21, 24–27, 31, 33, 34, 36–38] and one individual-based model [3]), the remaining ten studies used static models. The dynamic models simulated the natural course of RSV infection, the transmission of the virus between the population groups, and, in some studies, healthcare utilisation. The static models concentrated mainly on the medically attended RSV cases.

3.1.2.2 The Natural History of RSV

In the dynamic models, the natural history of RSV infection was approximated by the susceptible-infected-recovered-susceptible (SIRS) model, including the protection of newborns by maternal antibodies as described by Weber et al. [41]. Extensions of the model included a latent period (exposed compartment) of infection [21, 34], subsequent (milder) illness with reduced duration of infectiousness [24, 36], reduction of susceptibility [3, 36, 37] and infectivity in previously infected individuals [36, 37] or children aged > 10 years [34] and adults [24]. Pan-Ngum et al. [37] and Kinyanjui et al. [33] addressed in detail the uncertainty around the acquisition and duration of immunity after primary RSV infection and explored the impact of lifelong and short-term partial immunity after a primary RSV infection.

Most studies used either infections [3, 21, 24–27, 31] or hospitalisations [20, 23, 28, 33, 34, 36, 38–40] as epidemiological ends. Eight studies distinguished between an asymptomatic and symptomatic course of infection and modelled different severity of RSV disease within either a dynamic [33, 37] or static [22, 29, 30, 32, 35, 39, 40] framework. Pan-Ngum et al. [37] and Kinyanjui et al. [33] modelled hospitalised and non-hospitalised upper- and lower respiratory tract infections (URTI, LRTI) and severe LRTIs. Seven studies [22, 29, 30, 32, 35, 39, 40] used healthcare services to classify RSV infections into cases attended in outpatient care, hospital care, and emergency departments.

3.1.2.3 RSV Transmission and Seasonality

RSV transmission was simulated only in the dynamic models [3, 21, 24–27, 31, 33, 34, 36–38], which used mixing between individuals (individual-based model [3]) or age-stratified compartments (compartment models) [21, 24–27, 31, 33, 34, 36–38]. The dynamic models applied age-related mixing, and three studies [3, 36, 38] also simulated household- and community-related contacts.

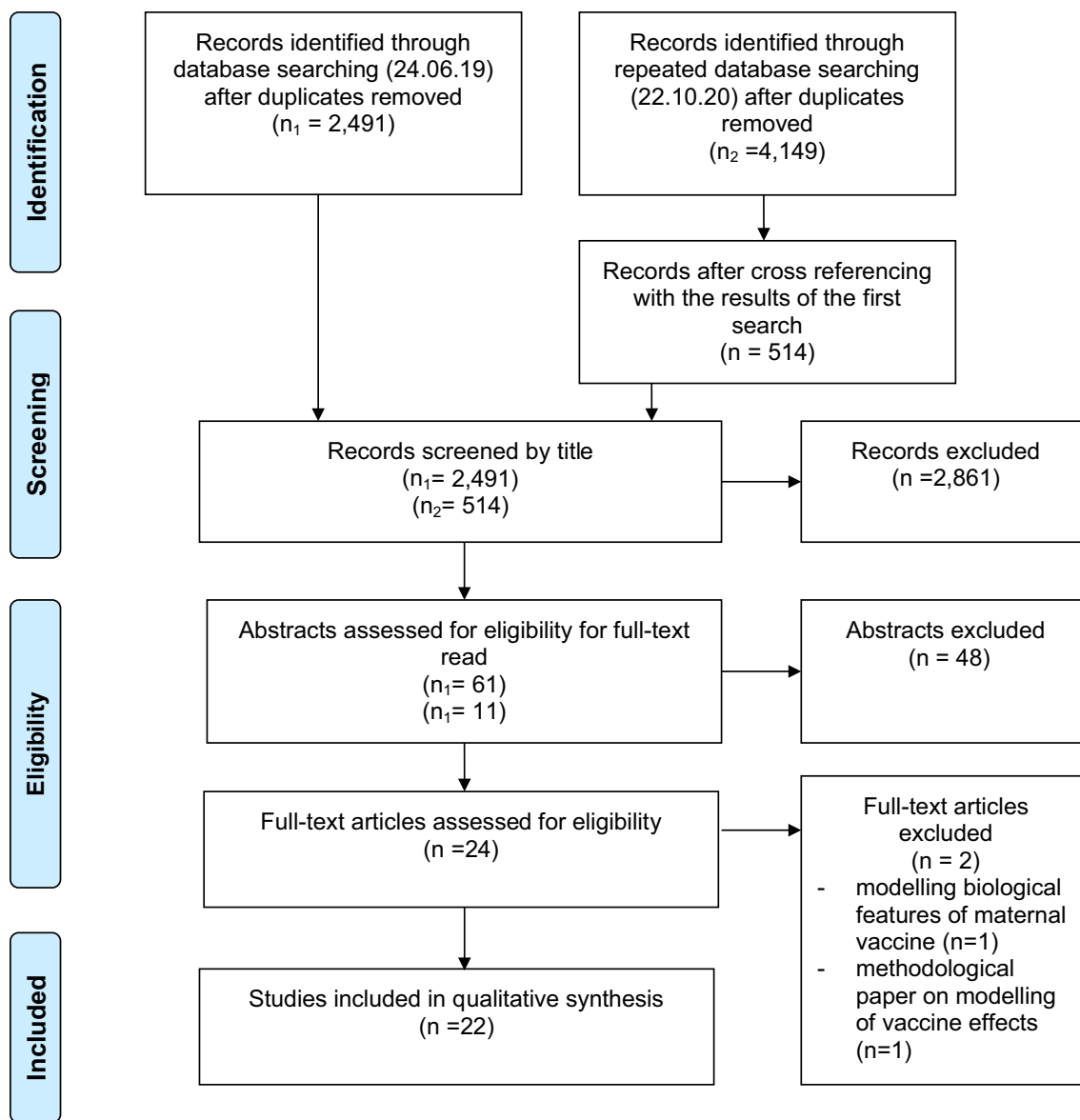


Fig. 1 Flowchart of selection of studies for inclusion in the review. Excluded records are listed in ESM 3

Within the dynamic models, seasonality of RSV epidemiology was implemented mostly as a cosine function. The forced seasonal transmission was supplemented by demography so that RSV incidence varied over the modelled years. Several static models [22, 28, 30, 32, 35] included calendar month-dependent RSV disease risk, and others did not represent seasonality.

The dynamic models, which included a wide range of age groups, simulated indirect protection of non-vaccinated groups provided by the direct vaccination. Static models either considered a birth cohort or an age-structured section of the population, e.g. children aged < 5 years and adults aged ≥ 50 years.

3.2 Vaccine Effects and Vaccination Strategies

3.2.1 Vaccine Uptake

Data on the interventions and assumptions about the vaccine effects are presented in Table 2. In 12 studies that evaluated vaccination of newborns or infants, vaccine uptake was assumed to be higher than 60%, with four assuming more than 90%. Vaccine uptake varied between 25 and 85%, with base-case values around 50% for pregnant women, and from 50 to 87% for the elderly. Meijboom et al. [29] set different values of vaccine coverage for the elderly, depending on the age and health risk

Table 1 Overview of characteristics and applied methods of the included studies (*n* = 22)

Study, country, year	Vaccinated population	Type	Perspective/comparator	Model type/event pathway/age structure/mixing patterns	Time horizon	Seasonality/antigenic diversity	Health outcomes	Economic outcomes/units/year	Discount rate	Industry funding
Acedo et al. [25, 26], Spain, 2010	Newborns	CA	NR/no vaccination	Dynamic/SIRS/two AGs/ARMP	5 years	Cosine FOI/none	Proportion of newborns protected	Total costs/€/NA	NR	NR
Acedo et al. [25, 26], Spain, 2010	Newborns	CA	NR/no vaccination	Dynamic/SIRS/social network model	5 years	Cosine FOI/none	Proportion of newborns protected	Total costs/€/NA	NR	NR
Baral et al. [39], Gavi countries, 2020	Pregnant women	EEA	Not relevant/no vaccination	Two static/RSV-ALRI, severity, healthcare utilisation/cohorts/none	2023–2035	NR/none	Cases by severity, hospitalisations, deaths, DALY averted	Not relevant	Not relevant	None
Bos et al. [28], The Netherlands, 2007	Infants	CEA	Healthcare provider/societal/no vaccination	Cohort/hospitalisation/month increment/none	24 months after birth	Variable in regression/none	Hospitalisations prevented	Cost per prevented hospitalisation, break-even costs/€/2003	C—4% B—NA	NR
Brand et al. [38], Kenya, 2020	Pregnant women, household members cohabiting with infants	EEA	Not relevant/no vaccination	Dynamic/SIRS/21 AGs/age-based household and community mixing	10 years	Seasonal variation in transmission rate/none	Hospitalisations, infections prevented	Not relevant	Not relevant	None
Cromer et al. [32], England (UK), 2017	Infants, pregnant women, neonates	CEA	Healthcare provider/no vaccination	Decision tree/SI healthcare utilisation/two AGs/none	5 years	Variable in regression/none	GP visits, hospitalisations prevented, QALY gained	Maximum cost-effective price per fully protected person/€/2014	C—3.5% B—3.5%	None
Gessner [20], USA, 2000	Elderly	CEA	Healthcare/no vaccination	Decision tree/65-year-old cohort/none	1 year	NR/none	Hospitalisations (incl. due COPD), deaths prevented, LY and QALY gained	Cost per health outcome/\$US/1996	C—3% B—3%	None
Hogan et al. [34], Australia, 2017	Pregnant women	EEA	Not relevant/no vaccination	Dynamic/MSIRS/75 AGs/ARMP	2 years	Cosine FOI/none	Hospitalisations prevented	Not relevant	Not relevant	None
Jornet-Sanz et al. [27], Spain, 2017	Newborns	CEA	NR/no vaccination	Bayesian stochastic/SIRS/NA/none	NR	Cosine function/none	Proportion of newborns protected	Total costs/€/NA	NR	None

Table 1 (continued)

Study, country, year	Vaccinated population	Type	Perspective/comparator	Model type/event pathway/age structure/mixing patterns	Time horizon	Seasonality/antigenic diversity	Health outcomes	Economic outcomes/units/year	Discount rate	Industry funding
Kinyanjui et al. [36], Kenya, 2015	Infants	EEA	Not relevant/no vaccination	Dynamic/MSIRS/99 AGs/two ARMPs	10 years	Cosine FOI/none	Hospitalisations prevented	Not relevant	Not relevant	None
Kinyanjui et al. [33], England and Wales, 2020	Infants	EEA	Not relevant/no vaccination	As in Pan-Ngum et al. [37], two dynamic models: SAI: SIRS/99 AGs ^a /ARMP BWI: MSI (URTI, LRTI, SLRTT) S/15 AGs ^a /ARMP	10 years	Cosine FOI/none	Hospitalisations prevented in age < 1 and < 5 years	Not relevant	Not relevant	GlaxoSmithKline Biologicals SA
Li et al. [40], Gavi countries, 2020	Newborns, pregnant women	CEA	Healthcare/no vaccination	Decision tree/SI healthcare utilisation, death/60 monthly classes/none	Results reported for 2022	Not included/none	Cases, hospitalisations, deaths, DALY averted	Direct costs, ACER cost per DALY/\$US/2016	C—3% B—3% (only DALY)	None
Meijboom et al. [30], The Netherlands, 2012	Newborns	CEA	Societal/no vaccination	Cohort/SI healthcare utilization/birth cohort/none	12 months	Probability of infection depends on the season	Hospitalisations, deaths prevented QALY gained	Cost per QALY gained/€/2009	C—4% B—1.5%	NR
Meijboom et al. [29], The Netherlands, 2013	Elderly	CEA	Healthcare provider/standard medical care	Cohort ^a /NA/ four AGs/none	NR	NR	Hospitalisations, GP visits, antibiotic prescriptions prevented, QALY gained	Cost per QALY gained, maximum total vaccination costs per individual/€/2009	C—4% B—1.5%	NR
Nugraha et al. [21], Indonesia (data from USA), 2017	Young children	EEA	Not relevant/no vaccination	Dynamic/SIRS/≥ 2.5 years/as one parameter	10 years	Cosine FOI/none	Infections prevented	Not relevant	Not relevant	None

Table 1 (continued)

Study, country, year	Vaccinated population	Type	Perspective/comparator	Model type/event pathway/age structure/mixing patterns	Time horizon	Seasonality/antigenic diversity	Health outcomes	Economic outcomes/units/year	Discount rate	Industry funding
Pan-Ngum et al. [37], Kenya, 2017	Newborns, pregnant women	EEA ^b	Not relevant/no vaccination	Two dynamic models: SAI: SIRS/99 AGs/ARMP BWI: MSI (URTI, LRTI, SLRTI) S/15 AGs/ARMP	10 years	Cosine FOI/none	Hospitalisations prevented in age < 1 and < 5 years	Not relevant	Not relevant	GlaxoSmithKline Biologicals SA
Poletti et al. [3], Kenya, 2015	Infants, school-age children, pregnant women	EEA	Not relevant/no vaccination	IBM/MSIRS/NA/ARMP, including households and schools	10 years	FOI/none	Infections prevented	Not relevant	Not relevant	None
Pouwels et al. [35], Turkey, 2016	Infants, pregnant women	CEA	Societal/no vaccination	Cohort/SI healthcare utilization/12 monthly birth cohorts/none	2 years after birth	Transition probabilities are calendar month-specific/none	GP visits, hospitalisations, deaths prevented, QALY gained	Cost per QALY gained/Turkish Lira/2013	C—3% B—3%	None
Rainisch et al. [22], USA, 2020	Infants, pregnant women	EEA	Not relevant/no vaccination	Decision tree/SIR/monthly increment/none Given as a spreadsheet-based tool	1 year	As percentage of cases in month of season/none	Outpatient clinic visits, ED visits, hospitalisations prevented	Not relevant	Not relevant	None
Régnier et al. [23], USA, 2013	Newborns	CEA	Healthcare provider, societal/PAL prophylaxis for children at high risk	Decision tree/vaccination, healthcare utilization, survival, sequelae/seven AGs/none	5 years; 10 years for sequelae	NA/none	Hospitalisations prevented, LY and QALY gained	Cost per health outcome/\$US/2011	C—3% B—3%	Novartis vaccines and diagnostics AG
Van Boven et al. [31], The Netherlands, 2020	Infants, pregnant women	EEA	Not relevant/no vaccination	Dynamic/SIRS/seven AGs/ARMP	20 years	Included/none	Reduction in infection attack rate	Not relevant	Not relevant	None

Table 1 (continued)

Study, country, year	Vaccinated population	Type	Perspective/comparator	Model type/event pathway/age structure/mixing patterns	Time horizon	Seasonality/antigenic diversity	Health outcomes	Economic outcomes/units/year	Discount rate	Industry funding
Yamin et al. [24], USA, 2016	Children, elderly	EEA	Not relevant	Dynamic/MSIRS/eight5 AGs/ARMP. Includes four geographical states	10 years	Cosine FOI/none	Reduction of RSV incidence per dose	Not relevant	Not relevant	None

ACER average cost-effectiveness ratio, AG age group, ALRI acute lower respiratory infections, ARMP age-related mixing pattern, B benefits, BWI boosting and waning of immunity, C costs, CA cost analysis, CEA cost-effectiveness analysis, COPD chronic obstructive pulmonary disease, DALY disability-adjusted life year, ED emergency department, EEA epidemiological effects analysis, FOI force of infection, Gavi the Global Alliance for Vaccines and Immunisation, GP general practitioner, IBM individual-based model, LRTI lower respiratory tract infections, LY life-years, MSIRS maternally protected-susceptible-infectious-recovered-susceptible, NA not available, NR not reported, PAL palivizumab, QALY quality-adjusted life-years, RSV respiratory syncytial virus, SAI sequential acquisition of immunity, SI susceptible-infectious-recovered-susceptible, SIRS susceptible-infectious-recovered-susceptible, SLRTI severe lower respiratory tract infections, URTI upper respiratory tract infections

^a Assumed by the reviewers

^b Optimal target product profile

group. Most of the studies defined the vaccine uptake based on an assumption. Alternatively, the studies used observed influenza vaccine coverages for infants, children [22, 24, 30], and the elderly [20, 24], Bacillus Calmette-Guérin vaccination for infant immunisation [40], and uptake estimates for maternal pertussis and influenza vaccines for the vaccination of pregnant women [22, 34]. For newborns and infants, the dosing schedule varied from one to three doses. One-dose schedules were assessed for vaccinations of pregnant women and the elderly.

3.2.2 Vaccine Effectiveness and Duration of Vaccine-induced Immunity

Given the absence of clinical data on VE and duration of vaccine-induced immunity, the authors made various assumptions about vaccine characteristics. VE was implemented as reduced susceptibility to RSV infection in the dynamic models and as a reduced proportion of hospitalisations or medically attended infections in the static models. Pan-Ngum et al. [37] and Kinyanjui et al. [33] considered a wide range of vaccine characteristics and modelled clinical endpoints in infants as a reduction in the risk of primary infection, the duration of infectivity, infectiousness, the risk of URTI, the risk of LRTI, and the risk of severe LRTI. Gessner [20] also explored possible VE against chronic obstructive pulmonary disease (COPD) in the elderly. VE varied from 25 to 100% among the studies and vaccine types. The baseline parameter ranged from 60 to 80% for the maternal vaccine, from 70 to 80% for the elderly, and from 50 to 100% for infants and children. Uncertainty meant that most studies reported results over a wide range of possible VE values.

For infant vaccination, 11 of 14 studies assumed 3–12 months of vaccine-induced immunity. Cromer et al. [32] set no waning over 5 years, van Boven et al. [31] assumed full protection until the age of 5 years, and Meijboom et al. [30] evaluated no waning, plateau, and linear waning over 10 years. Three studies [20, 24, 29] that evaluated vaccination in the elderly assumed that immunity lasted for one RSV season. Immunity in newborns due to maternal vaccination varied between 3 and 8 months. Additionally, Pan-Ngum et al. [37] and Kinyanjui et al. [33] considered potential interactions between vaccine-induced immunity and natural immunity due to maternal antibodies and modelled the effects of infant vaccine given in the presence of maternal antibodies that wane over time.

3.3 Epidemiological Estimates

Most incidence estimates represent infected individuals who seek healthcare. Eleven studies graphically illustrated monthly or weekly series of RSV cases (hospitalisations)

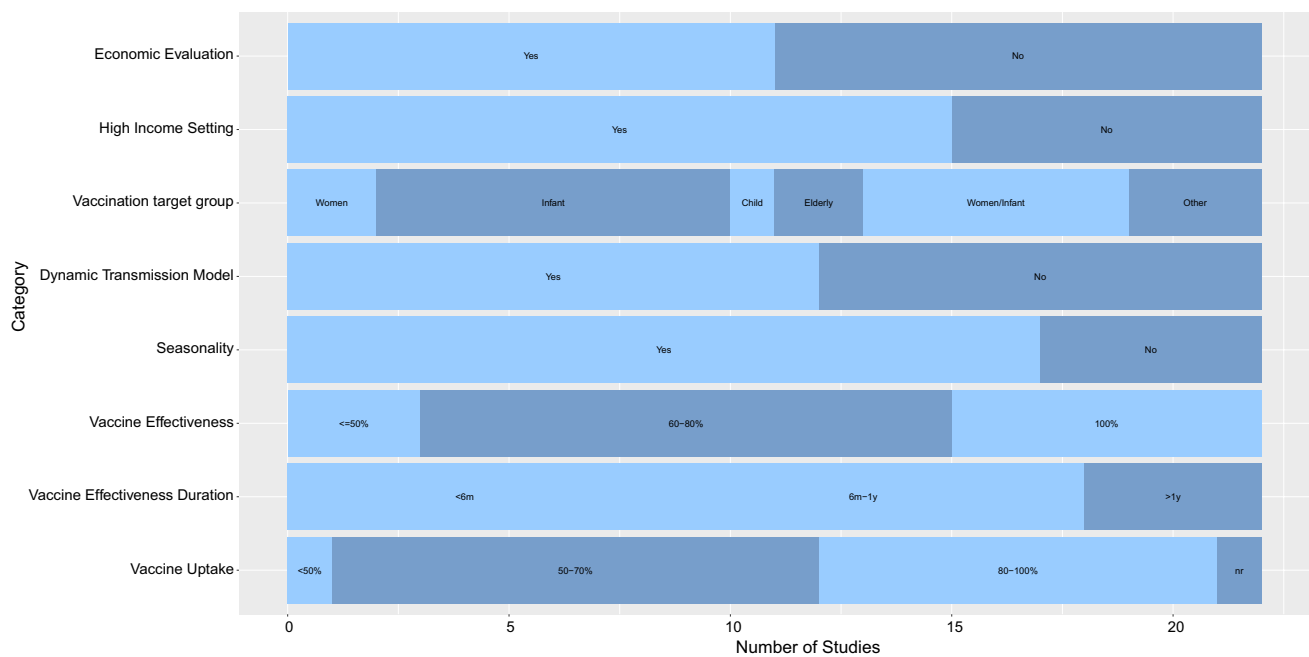


Fig. 2 Overview of selected methodological characteristics of the reviewed studies ($n = 22$). *nr* not reported, *y* year, “Other” group includes: Women/Infant/Children, Elderly/Children, Women/household

over the studied years in the modelled population. The approaches to estimating incidence among children were based on linkage of laboratory data to available administrative data [31, 32, 34], data from the hospital reporting system [3, 27, 33, 36–38], and observational studies [20, 21, 23, 28–30, 35]. Two studies that evaluated the intervention in Gavi-eligible countries obtained the data from a recent review [5], estimated the total burden of the disease for each of the countries, and used statistical modelling to address the lack of granularity in the data [39, 40]. Additionally, the dynamic models used a scaling factor that translated medically attended RSV infection identified in the surveillance systems to the infections in the model.

Table 3 presents the reported RSV incidence estimates without intervention and the resulting incidence reduction. The differences in reporting and the modelled age groups made it challenging to compare the incidence estimates across the studies. The studies that evaluated the protection of infants showed that RSV incidence was high in the first 5 months of life and peaked in infants from 1 to 3 months of age. The studies that included medically attended RSV infections reported that the proportion of cases treated in outpatient care was substantial. Three studies that considered vaccination in the elderly did not represent the age-specific incidence of RSV sufficiently to provide a summary. Meijboom et al. [29] reported that the hospitalisation numbers increased with age and health risk and were highest in the elderly aged ≥ 85 years.

3.4 Economic Evaluation

This review included 11 economic assessments. Six evaluated infant vaccination: (1) three Spanish studies estimated total costs based on dynamic models [25–27] and (2) three cost-effectiveness analyses based on static models (two from the Netherlands [28, 30] and one from the USA [23]).

Three studies (one from England [32], one from Turkey [35], and one including 72 Gavi-eligible countries), conducted cost-effectiveness analyses of passive immunisation of infants and pregnant women separately and in combination, using static models. Two studies provided cost-effectiveness analyses of elderly vaccination based on static models: one from The Netherlands [29] and one from the USA [20]. In the majority of studies, the comparator was no vaccination. Régnier et al. [23], Cromer et al. [32], and Rainisch et al. [22] also included passive immunisation with the mAb palivizumab in the analyses. Other studies did not include current immunoprophylaxis in the analysis, although four described it as an existing prevention [24, 28, 30, 35]. Six studies used the perspective of a healthcare provider [20, 23, 28, 29, 32, 40], two of which also considered the societal perspective [23, 28], and two studies [30, 35] reported only the societal perspective. Three studies did not report the perspective [25–27].

Three studies evaluated economic outcomes other than the incremental cost-effectiveness ratio (ICER). Cromer et al. [32] compared strategies using maximum cost-effective price per fully protected person, Bos et al. [28] calculated

Table 2 Assumed characteristics of vaccines and vaccination programmes in the modelling studies ($n=22$)

Study, country, year	Vaccinated group/ doses	Combined strategies	Administration	Vaccine uptake	Vaccine effectiveness against	Vaccine effectiveness	Duration of vaccine- induced immunity	Herd protection
Acedo et al. [25, 26], Spain, 2010	Newborns/1+2 boosters	No	1st year of life	85%	Infections	100% ^a	365/200 days (as recovered from primary infection)	Yes
Acedo et al. [25, 26], Spain, 2010	Newborns/1+2 boosters	No	Age 2 mo, 4 mo, 1 y	85%, 90%, 95%	Infections	100% ^a	365/200 days (as recovered from primary infection)	Yes
Baral et al. [39], Gavi countries, 2020	Pregnant women/one dose	No	24–36 weeks' gestation	Country-specific, (21–96%), projected to increase to 95%	RSV-ALRI ^a	60% (30%, 90%)	5 mo (3 mo, 6 mo)	No
Bos et al. [28], The Netherlands, 2007	Infants/one dose	No	Not specified, depends on birth month	100% ^a of birth cohort	Hospitalisations	50–100% (by 10% increment)	Over the time horizon (24 mo), starting month of vaccine protection varies: 1–6 mo of life	No
Brand et al. [38], Kenya, 2020	Pregnant women and their household members including adults/one dose	Yes	Pregnant women during prenatal contact; cohabitants at the birth of the baby	Effective coverage: Maternal: 50%, 100% Household: 0%, 25%, 50%, 75%, 100%	Infection	Included in effective coverage	Maternal: 75 additional days to natural protection of 21.6 days (15–90, by 1.5 d increment) Household: mean 6 mo	Yes
Cromer et al. [32], England (UK), 2017	Infants, pregnant women/one dose; newborns with mAb	Yes	3 mo (2 mo, 4 mo)	NR	Symptomatic infection	70% (50–100%, by 10% increment)	Infant: from 3 mo of life, no waning over 5 y Maternal ^b : from birth till 3 mo of life mAb: 6 mo	No
Gessner [20], USA, 2000	Elderly/one dose	No	65 y	50%	Hospitalisation, death, URI, COPD hospitalisation	80%, 50% ag URI, 10% ag COPD hospitalisation	One season	No
Hogan et al. [34], Australia, 2017	Pregnant women/one dose	No	3rd trimester	50% (30–70%)	Infection	80% (60–90%)	6 mo (3 mo, 4 mo)	Yes
Jornet-Sanz et al. [27], Spain, 2017	Newborns/1+2 boosters	No	NR	20%, 80%	Infections	100% ^{a,c}	365/200 days (as recovered from primary infection)	Yes
Kinyanjui et al. [36], Kenya, 2015	Infants/one dose	No	6 mo	70%	Infections	10–100% ^c	6 mo (2–17 mo) (equivalent to primary infection)	Yes

Table 2 (continued)

Study, country, year	Vaccinated group/ doses	Combined strategies	Administration	Vaccine uptake	Vaccine effectiveness against	Vaccine effectiveness	Duration of vaccine- induced immunity	Herd protection
Kinyanjui et al. [33], England and Wales, 2020	Infants/two or three doses	No	0 mo and 2 mo 2 mo and 4 mo 0 mo, 1 mo, and 2 mo 2 mo, 4 mo, and 6 mo	Coverage: 50%, 70% and 90% (baseline)	(a) Risk of primary infection (b) Duration of infectivity (c) Infectiousness (d) Risk of URTI (e) Risk of LRTI (f) Risk of severe LRTI	w.r.t. clinical end- points (see previous column) (a) 0% (25%, 50%) (b) 0% (50%, 75%) (c) 0% (50%, 75%) (d) 0% (50%, 75%) (e) 50% (70%, 90%) (f) 50% (70%, 90%) Compliance: 90%, 100%	1 year (2 years)	Yes
Li et al. [40], Gavi countries, 2020	Pregnant women/one dose Newborns/one dose of mAb	No	Pregnant women: 2nd–3rd trimester Newborns: at birth	Country-specific, based on BCG coverage of 2016	Infection ^a	70% (50–90%)	Maternal: 5 mo (3 mo, 6 mo) mAb: 6 mo (4mo, 8 mo)	No
Meijboom et al. [30], Netherlands, 2012	Newborns/three doses, two doses, seasonal	No	Scenario dependent: < 3 mo all year 3–6 mo October 3–9 mo November 3–12 mo November	96%	Symptomatic infec- tion	As a proportion of infections covered, scenario dependent: 0.620 0.176 0.207 0.270 0.301	No waning	No
Meijboom et al. [29], The Netherlands, 2013	Elderly (low and high health risk groups)/ one dose	No	At the same time as the influenza vac- cine/age \geq 60 y, \geq 65 y, \geq 65 y, \geq 85 y	55–87% depending on age and health risk	As prevention of morbidity and mortality	70% (30–100%)	One season	No
Nugraha et al. [21], Indonesia, 2017	Young children/one dose	No	RSV season, decrease of RSV, RSV out- break, and before season until the peak of the RSV season	Given as proportion: 0.01, 0.02, and 0.03	Infection	100% ^a	No waning	Yes

Table 2 (continued)

Study, country, year	Vaccinated group/ doses	Combined strategies	Administration	Vaccine uptake	Vaccine effectiveness against	Vaccine effectiveness	Duration of vaccine- induced immunity	Herd protection
Pan-Ngum et al. [37], Kenya, 2017	Infants/two or three doses, pregnant women/one dose	No	Age 0 mo and 2 mo 2 mo and 4 mo 0 mo, 1 mo, and 2 mo 2 mo, 4 mo, and 6 mo	Infants: 50%, 70%, 90% Pregnant women: 25%, 50%, 75%	(a) Risk of primary infection (b) Duration of infectivity (c) Infectiousness (d) Risk of URTI (e) Risk of LRTI (f) Risk of severe LRTI	w.r.t. clinical end- points (see previous column) (a) 0% (25%, 50%) (b) 0% (50%, 75%) (c) 0% (50%, 75%) (d) 0% (50%, 75%) (e) 50% (70%, 90%) (f) 50% (70%, 90%) Compliance: 90%, 100%	Infant: 1 year Maternal: 3 mo, 6 mo	Yes
Poletti et al. [3], Kenya, 2015	Infants/one dose School-age children/ one dose Pregnant women/one dose	Yes	3 mo At first school enrol- ment Catch-up campaigns	100%	Infection	60%, 80%, 100%	Infant: 4, 6, and 12 mo Maternal: 5, 6 and 8 mo	Yes
Pouwels et al. [35], Turkey, 2016	Infants/two doses Pregnant women/one dose	Yes	Age 2 mo and 4 mo 2–6 mo December– February	85%	Symptomatic infec- tion	Infant 2 mo: 60% Infant 4 mo: 75% Maternal: 60%	Infant: till age 2 y Seasonal: 5 mo Maternal: 60%	No
Rainisch et al. [22], USA, 2020	Infants/mAb candi- date one dose or PAL monthly Pregnant women/one dose	Yes	PAL and mAb can- didate: during RSV season	PAL: 38% mAb candidate: low risk – 71% high risk – 80% Maternal: 56% (51–61%)	MA-RSV-associated LRTIs	PAL: 51% mAb candidate: 80% (73–85%) Maternal: 80% (73–85%)	PAL and mAb candidate: 150 days (120–180 days) Maternal: 90 days (60–120 days)	No
Régnier et al. [23], USA, 2013	Infants/two doses	No	During regular infant vaccination	69%	MA events	50%	Exponential with half-life 12 mo	No
Van Boven et al. [3], The Nether- lands, 2020	Pregnant women/one dose ^a Infants/one dose ^a	Yes ^a	Infants: during the first half year of life	Maternal: 50% Infant: 100%	Infection	Maternal: 50% Infant: 50%	Maternal: 6 mo Infant: from 6 mo to 4 y	Yes
Yamin et al. [24], USA, 2016	Children and adults/ one dose	Yes	Across modelled age groups Annually	60–70% for both children and adults (Pennsylvania – 75%)	Infection	40–80%	One season	Yes

ALRI acute lower respiratory infection, *BCG* Bacillus Calmette-Guérin, *COPD* chronic obstructive pulmonary disease, *d* days, *Gavi* the Global Alliance for Vaccines and Immunisation, *LRTI* lower respiratory tract infection, *MA* medically attended, *mAb* monoclonal antibody, *mo* months, *NR* not reported, *PAL* palivizumab, *RSV* respiratory syncytial virus, *URI* upper respiratory infection, *URTI* upper respiratory tract infection, *w.r.t.* with respect to, *y* years

^aAssumed by reviewer

^bDuration of immunity due to maternal population implies protection of the newborns

^cVaccine effects are modelled as a proportion of newborns protected from being infected. The parameter combines vaccine effectiveness and vaccine uptake

Table 3 Overview of model input and results: incidence reduction, intervention effects, and conclusions ($n=22$)

Study, country, year	Reported RSV incidence estimates/source of data	Vaccination programmes	Intervention health outcomes (prevented)	Conclusion	EVIDEM quality score ^s ^a
Acedo et al. [25, 26], Spain, 2010	Graphically shown weekly hospitalisations in children aged 1 y, January 2001 to December 2004 (around 160 in week 100)/NA	Vaccination of newborns with two booster doses	NR	Vaccination brings "a positive balance"	2/2
Acedo et al. [25, 26], Spain, 2010	As in Acedo et al. [25, 26]	Vaccination of children at ages 2 mo, 4 mo, and 1 y	As in Acedo et al. [25, 26]	As in Acedo et al. [25, 26]	2/2
Baral et al. [39], Gavi countries, 2020	Total disease burden (cases, hospitalisations, deaths, DALYs) for 73 countries/obtained from systematic review [5] or estimated	Single-dose year-round vaccination of pregnant women between 24 and 35 weeks of gestation during antenatal visits	Reported for 14 scenarios for each of 73 countries aggregated and by year. Across 2023–2035 overall reduction of 3.4 million hospitalisations, 150,000 deaths, 10.3 million DALYs is projected Prevented 41–42% of annual deaths in infants aged < 6 mo	Maternal vaccination in Gavi-supported countries is projected to substantially reduce mortality and morbidity in infants aged < 6 mo	4/3
Bos et al. [28], The Netherlands, 2007	Estimated 3670 hospitalisations annually in children/population-based study by Rietveld et al. [45]	Vaccination of a birth cohort	620–3520 hospitalisations prevented in the birth cohort	Outcomes of the RSV vaccination depend on time of birth of infant in relation to RSV season: vaccination of infants born in or just prior to RSV season would yield optimal benefits. Cost per vaccination should not be above €50	4/2
Brand et al. [38], Kenya, 2020	Graphically shown age-stratified weekly hospitalisations, 2002–2016/Kilifi District Hospital [46]	Vaccination of pregnant women as part of their prenatal contact. Vaccination of the household cohabitants at the birth of a baby in this household	> 50% reduction in hospitalisations (for the scenario of 75 days additional duration of maternal vaccine protection [100% effective coverage] and 75% coverage of the pregnant women's households)	A 50% reduction in RSV hospitalisations is possible if the maternal vaccine effectiveness can achieve 75 days of additional protection for newborns combined with a 75% coverage of their birth household co-inhabitants	4/4
Cromer et al. [32], England (UK), 2017	GP visits: < 6 mo – 21.42/100 > 6 mo – < 5 y – 10.92/100 Hospitalisations: < 6 mo – 4.4/100 > 6 mo – < 5 y – 0.5/100 Deaths in hospital: < 6 mo – 0.00248/100 > 6 mo – < 5 y – 0.00066/100 Estimated	(a) Infant strategy (b) Maternal strategy (c) Newborn strategy: one dose of a long-lasting mAb	Hospitalisations averted: (a) 62% (b) and (c) 86–88% GP visits averted: (a) 95% (b) 80% (c) 83% QALYs gained: (a) 73% (b) 43% (c) 47%	RSV vaccine and antibody strategies are likely to be cost effective if they can be priced below around £200 per fully protected person. A seasonal vaccination strategy is likely to provide the most direct benefits	4/3

Table 3 (continued)

Study, country, year	Reported RSV incidence estimates/source of data	Vaccination programmes	Intervention health outcomes (prevented)	Conclusion	EVIDEM quality score ^a
Gressner [20], USA, 2000	Based on RSV ARI: 13,000/100,000 per year (9750–16,250). Data of 1997/ population studies [47–50]	Vaccination of a cohort of 65-year-olds	Without VE ag COPD (with VE ag COPD): Deaths prevented ^b : 81 (212) LY gained ^b : 1376 (3689) QALY gained ^b : 1879 (4200)	RSV vaccine would be cost effective for elderly population, with cost-effectiveness ratios similar to those for influenza vaccine	3/2
Hogan et al. [34], Australia, 2017	RSV hospitalisations over 2000–2013 monthly for age groups 0–2 mo, 3–5 mo, 6–11 mo, 12–23 mo. Data are graphically represented in supplement/estimated based on national data	Vaccination of pregnant women	Prevented hospitalisations in children aged < 1 y: 0–2 mo: 3–25 per 1000 3–5 mo: 0–17 per 1000	Provided a vaccine is demonstrated to extend protection against RSV disease beyond the first 3 mo of life, a policy using a maternal RSV vaccine could be effective in reducing RSV hospitalisations in children up to 6 mo	4/4
Jornet-Sanz et al. [27], Spain, 2017	Weekly hospitalisations for RSV-related illnesses among children aged ≤ 2 y in the Spanish region of Valencia, 2001–2004. Data are graphically represented/regional hospital admission data	Vaccination of a proportion of newborns with booster doses	NR, but graphically presented	Conclusion of study focused on modeling methods and is not informative for evaluation of vaccination programmes	3/2
Kinyanjui et al. [36], Kenya, 2015	Monthly hospitalisations of age < 5 y, 2004–2010. Data are graphically represented/obtained from Kilifi District Hospital [46]	Infant vaccination: Age: 5–10 mo	Hospitalisations prevented: 10–90% (the best median values are > 60%)	Immunisation of young children (5–10 mo) is likely to be a highly effective method of protection of infants (< 6 mo) against hospitalisation. The majority benefit is derived from indirect protection	4/4
Kinyanjui et al. [33], England and Wales, 2020	Weekly RSV hospitalisations for age 0–5 y, 2000–2013. Graphically represented/Public Health England	Infant vaccination: (a) 2-dose schedule: 0 and 2 mo (b) 2-dose schedule: 2 and 4 mo (baseline) (c) 3-dose: 0 mo, 1 mo, and 2 mo (d) 3-dose: 2 mo, 4 mo, and 6 mo	A potential rapid reduction in hospitalisations during the first 2 years post-vaccination and reaching an equilibrium at 50% of the pre-vaccination level	Vaccine properties that confer indirect protection have the greatest effect in reducing the burden of disease in children age < 5 y	3/4
Li et al. [40], Gavi countries, 2020	Cases, hospitalisations, deaths, DALYs for 72 countries/obtained from systematic review [5] or estimated	Universal single-dose vaccination of pregnant women Universal immunisation newborns at birth with mAb	Maternal: prevention of 1.2 million cases, 104,000 hospitalisations, 3000 deaths, 98,000 DALYs in 2022 mAb strategy can potentially prevent more cases	RSV interventions could prevent substantial RSV-associated cases, hospital admission and deaths, DALYs, and treatment costs. Both the maternal and mAb strategies need to be comparatively priced to be judged as relatively cost effective	4/4

Table 3 (continued)

Study, country, year	Reported RSV incidence estimates/source of data	Vaccination programmes	Intervention health outcomes (prevented)	Conclusion	EVIDEM quality score ^a
Meijboom et al. [30], The Netherlands, 2012	Primary healthcare utilisation as 16,000 GP visits/100,000 children < 12 mo per year (900 hospitalisations/100,000 children < 12 mo per year)/estimated based on published studies	(a) 3-dose schedule: at 0 mo, 1 mo, and 3 mo (b) 3-dose schedule: at 0 mo, 2 mo, and 4 mo (c) 2-dose schedule: at 0 mo and 3 mo (d) Seasonal strategy: vaccination only in the winter months	Prevented hospitalisations ^b : (a) 783–1079 (b) 12–1550 (c) and (d) NR QALY gained ^b : (a) 288–397 (b) 263–352 (c) and (d) NR	Vaccination of infants against RSV might be cost effective. Most health gains are obtained when the vaccine is offered as early as possible	4/3
Meijboom et al. [29], Netherlands, 2013	Primary healthcare utilisation as 929 GP visits/100,000/obtained from a retrospective study in the Netherlands over 1997–2003 [51]	Vaccination all: age ≥ 60 y, ≥ 65 y, ≥ 75 y, ≥ 85 y Vaccination high-risk elderly: age ≥ 60 y, ≥ 65 y, ≥ 75 y, ≥ 85 y	All ≥ 60 y strategy (VE 40%): 1881 GP visits, 1650 antibiotic prescriptions, 300 hospitalisations, 139 deaths prevented High-risk ≥ 60 y (VE 40%): 1128 GP visits, 1107 antibiotic prescriptions, 100 hospitalisations, 117 deaths prevented	Vaccination with a hypothetical RSV vaccine was found cost effective for several scenarios	3/2
Nugraha et al. [21], Indonesia, 2017	Incidence data come from North Carolina, USA, for 2003–2006 given in percentage monthly, maximal numbers in January 28.6%, 32%, and 33.7%/prospective study, USA [52]	Vaccination of a proportion of newborns	Reported as epidemic peak Maximum decrease of 56.13% if vaccinated proportion is 0.03 Vaccination before season until the peak of the RSV season: decreases to 43.87%	Increasing proportion of vaccination decreases infected compartment. Appropriate time for vaccination is at the time interval before the RSV season to the peak of the outbreak	2/2
Pan-Ngum et al. [37], Kenya, 2017	Monthly time series 2004–2011 of hospitalisations in age < 5 yo. Data are graphically represented. 50–70 cases in January/Kenya RSV hospital surveillance	Maternal vaccination Infant vaccination: (a) 2-dose schedule: 0 and 2 mo (b) 2-dose schedule: 2 and 4 mo (c) 3-dose: 0 mo, 1 mo, and 2 mo (d) 3-dose: 2 mo, 4 mo, and 6 mo	Vaccine characteristics with the highest impact: 70% reduction in hospitalisations each 1 unit (i.e. 1%) increase in vaccine effect on risk of infection leads to a 0.062% and 0.134% reduction in hospitalisations in < 5 y	Vaccine properties leading to reduced virus circulation by lessening the duration and infectiousness of infection upon challenge have the major impact on hospitalised RSV and should be a focus for vaccine development. The key elements are longer duration of protection, higher coverage, reductions in infection duration, and degree of infectiousness	4/4
Poletti et al. [3], Kenya, 2015	Primary and consecutive RSV infections in < 30 m (five age groups). Data are graphically represented. Incidence ranges 200–500 per 1000 child years/cohort study, 2002–2005 in the Kilifi district [53]	(a) Routine immunisation at 3 mo (b) Annual repeated vaccination of all school-age children (c) Vaccination of pregnant women (8 mo of immunity)	Reduction of primary infections: (a) by 41.5% in infants over 10 y (b) by 35.6% in infants and 48.0% in general population over 10 y (c) by 31.5% in infants	School-age children should be considered for alternative effective vaccination programmes in case direct immunisation of high-risk infants is not achievable. Vaccination of pregnant women has the potential of being an effective strategy	4/4

Table 3 (continued)

Study, country, year	Reported RSV incidence estimates/source of data	Vaccination programmes	Intervention health outcomes (prevented)	Conclusion	EVIDEM quality score ^a
Pouwels et al. [35], Turkey, 2016	Reported as rates of medically attended RSV in the birth cohort < 2 y (111,459) of 2014 followed over 2 y: GP visits: 343,711 Hospitalisations: 19,334 Deaths: 118/a multicentre prospective study from Bursa, Turkey [54]	(a) Infant vaccination: 2 and 4 mo (b) Vaccination of pregnant women (c) Combined infant and maternal vaccination	Prevented GP visits ^b : (a) 145,802 (b) 58,018 (c) 186,363 Prevented hospitalisations ^b : (a) 8202 (b) 3264 (c) 10,483 Prevented deaths ^b : (a) 48 (b) 23 (c) 64	RSV vaccination of infants and/or pregnant women has the potential to be cost effective in Turkey. The combined strategy has the highest potential	4/3
Rainisch et al. [22], USA, 2020	Reported as rates of medically attended RSV (per 1000 births): Hospitalisations: 8.4 (1.5–30.8) ED visits: 66.2 (16.8–132.7) outpatient clinic visits: 230.9 (71.0–337.2)/estimated	(a) Passive immunisation with PAL (b) Passive immunisation new mAb candidate (c) Vaccination of pregnant women + PAL	Prevented outpatient LRTIs: (a) 2% (b) 48% (c) 14% Prevented LRTIs attended in ED: (a) 2% (b) 51% (c) 13% Prevented hospitalisations: (a) 2% (b) 55% (c) 25%	The anticipated products have a potential to reduce serious RSV illness	4/3
Régnier et al. [23], USA, 2013	Reported as rates of medically attended RSV per 1000, age group-specific: Hospitalisations: 0.2–32.0 ED visits: 13–57 Hospital outpatient: 0.5–88.6 Outpatient clinic visits: 27–132 Mortality rate: 0.9 and 5.4/100,000/retrospective cross-sectional study [55]	Vaccination of children at low and high risk of respiratory sequelae	Impact of vaccinating one cohort (4.2 million live births): Hospitalisations avoided: 23,069 (22,501–23,593) Deaths avoided: 66 (59–75) LY gained: 2047 (1817–2302) QALY gained: 4735 (3698–6037)	RSV vaccine would substantially reduce inpatient hospitalisations and outpatient visits. It would also have an impact on infant mortality	4/2

Table 3 (continued)

Study, country, year	Reported RSV incidence estimates/source of data	Vaccination programmes	Intervention health outcomes (prevented)	Conclusion	EVIDEM quality score ^a
Van Boven et al. [31], Netherlands, 2020	Graphically presented weekly age-stratified number of GP consultations, hospitalisations, fractions of RSV-positive virological samples. 2012–2016/national data, three datasets, the Dutch Hospitalisation Data organisation, the Nivel Primary Care Database, RIVM/Nivel sentinel surveillance	Maternal vaccination Infant vaccination: administration in the first half year of life DTaP-IPV-like programme	20 y after the introduction, Maternal vaccination: 27% reduction of the infection attack rate in infants and a 10% increase in 1–4 y Paediatric vaccination: 30% reduction in infants, 24% in 1–4 y, 8% in 5–9 y, negligible impact in adults	Paediatric vaccination is expected to reduce the incidence of infection in infants and young children (0–5 y), slightly increased incidence in 5–9 y, and have minor indirect benefits	4/3
Yamin et al. [24], USA, 2016	Weekly RSV cases, four states (CA, TX, CO, PA), 2008–2013. Data are graphically represented/NREVSS by CDC	Two vaccine candidates ^c : replicating and nonreplicating. Vaccination of different age groups of children and adults: 0–4 y, 5–24 y, 25–49 y, and ≥ 50 y	Prevented cases per dose: (a) Vaccination of 6 mo–5 y: 0.12–0.35 in children 0.03–0.07 in adults (b) Vaccination of ≥ 50 y: 0.12–0.35 in children 0.03–0.07 in adults There is geographic variability of vaccine effects due to seasonality, demographic, and vaccine uptake differences	Allocating vaccine doses to children age ≤ 5 y is more effective for both children and older adults, due to reduced transmission. Indirect protection can avert even more infections than direct protection of adults ≥ 50 y	4/4

ARI acute respiratory infection, CDC Centers for Disease Control and Prevention, COPD chronic obstructive pulmonary disease, DALY disability-adjust life-year, DTaP-IPV diphtheria tetanus and pertussis, ED emergency department, Gavi the Global Alliance for Vaccines and Immunisation, GP general practitioner, LRTI lower respiratory tract infection, LY life-years, mAb monoclonal antibody, mo months, NA not applicable, NR not reported, NREVSS National Respiratory and Enteric Virus Surveillance System, PAL palivizumab, QALY quality-adjusted life-years, RSV respiratory syncytial virus, VE vaccine effectiveness, y years

^aCompleteness of reporting and relevance for decision making was assessed using EVIDEM: (i) scores 1 and 2 indicate lower completeness and consistency of reporting/relevance and 4 indicate higher completeness and consistency of reporting/relevance

^bCalculated by reviewer based on the reported values

^cReplicating, elicit a mucosal and a systemic response; nonreplicating, elicit only a systemic response

break-even costs, and Meijboom et al. [30] reported maximum total vaccination costs per individual. Li et al. [40] performed a comprehensive comparative analysis of the cost effectiveness of maternal and infant interventions for 72 Gavi-eligible countries, defining an optimal strategy for a range of willingness-to-pay (WTP) values for each country.

Six cost-effectiveness analyses used QALYs gained due to intervention: two in the elderly [20, 29] and four in children [23, 29, 32, 35]. In children, Cromer et al. [32] and Meijboom et al. [30] set QALY loss for an RSV disease based on healthcare services: general practitioner (GP)-treated RSV (0.01), hospitalisation (0.04), and admission to an intensive care unit or chronic respiratory morbidity (0.08). Meijboom et al. [30] obtained these values from the study by The Dutch National Institute for Public Health and the Environment, which assigned QALY decrements of 0.01 to bronchi(oli)tis, 0.04 to pneumonia, and 0.08 to asthma. Pouwels et al. [35] set the disutility for a GP-treated RSV infection at 0.16 and for a hospital-treated RSV infection at 0.43 per day, with an average duration of infection of 14 days. The authors referred to a Canadian study that derived health states for RSV in children and adults using time trade-off and best–worst scales [42]. Régnier et al. [23] estimated a QALY loss per RSV hospitalisation of 0.01 and a QALY loss of 0.005 and 0.008 for mild and severe cough (duration 10 days), respectively. The authors obtained the values from a study that estimated health states for pertussis infections [43]. For the elderly, Gessner [20] and Meijboom et al. [29] reported utilities that the patients experience during RSV treated in outpatient care (0.46 per day for 1 week) and inpatient care (0.35 per day for 3 weeks).

3.5 Quality Assessment

Using the EVIDEM score of 3 or 4 as an indicator, we considered 18 of 22 studies as complete in reporting and 14 studies as relevant for decision making. Four studies [21, 25–27], which were more methodological papers than evaluations, were given a lower score for relevancy for decision making. Overall, the studies that included a dynamic-transmission model, examined uncertainty surrounding VE, and evaluated a wide range of vaccination scenarios were scored more highly. The final EVIDEM forms with comments and scores are available in ESM 2. Figure 3 presents the studies evaluated, categorising them by target group, type of analysis, and relevance for decision making.

3.6 Results of the Epidemiological and Economic Evaluations

Table 3 presents the estimated reduction of RSV burden and the study conclusions. No clinical evaluation of VE and duration of vaccine-induced immunity is yet available, so

all reported estimates of reduction of the RSV disease burden should be considered as potential and theoretical. The absolute and relative potential reductions in the number of hospitalisations were the most frequently used epidemiological outcomes reported in the selected studies. Figure 4 illustrates the reported percentage reduction in the outcomes relative to the ‘no vaccination’ scenario. Table 4 presents the results of economic analyses. In the following sections, we summarise the results of the studies with EVIDEM scores of 3 or 4, indicating higher relevance for decision making.

3.6.1 Vaccination of Pregnant Women (Maternal Vaccination)

In a high-income country setting (Australia), and using a dynamic model, Hogan et al. [34] simulated the potential effects of a wide range of scenarios of maternal vaccination, varying the VE and duration of vaccine-induced immunity on RSV hospitalisations in infants aged 0–2 and 3–5 months. The percentage reduction in hospitalisations ranged from 6 to 51% and was higher for infants aged 3–5 months. The authors reported a 26% reduction in those aged 0–2 months and a 40% reduction in those aged 3–5 months for the scenario defined by 80% VE, 50% vaccine uptake, and 6-months of vaccine-induced immunity. The scenario with higher effectiveness (90%) and coverage (70%) resulted in the most substantial estimated reduction in hospitalisations, of 51% in children aged < 3 months and 63% in those aged 3–5 months. Lower VE and coverage resulted in 10 and 21% reductions in hospitalisations in these groups, respectively. A reduced duration of vaccine-induced immunity of 3 months did not bring additional beneficial health outcomes in infants aged > 3 months. Additionally, the authors pointed out that the impact of maternal vaccination in children aged > 6 months (given that the maximum duration of vaccine-induced immunity was 6 months) was negligible, indicating a small herd effect.

The results of van Boven et al. [31] from The Netherlands support the inference of Hogan et al. [34] about the negligible indirect benefits of maternal vaccination in groups other than infants. The study reported a potential 27% decrease in the infection attack rate as a result of vaccinating 50% of pregnant women with a 50% effective vaccine and assumed duration of protection of 6 months.

In contrast, Brand et al. [38] showed possible indirect protection of newborns and infants via a cocooning vaccination strategy, that is via vaccinating pregnant women and their household members. The study was based on a dynamic-transmission model that captured the transmission within households and in the community in a low-income country setting of Kenya. For 75% household coverage, the authors reported a potential 50% reduction in RSV hospitalisation in infants even if the maternal vaccine fully protected newborns

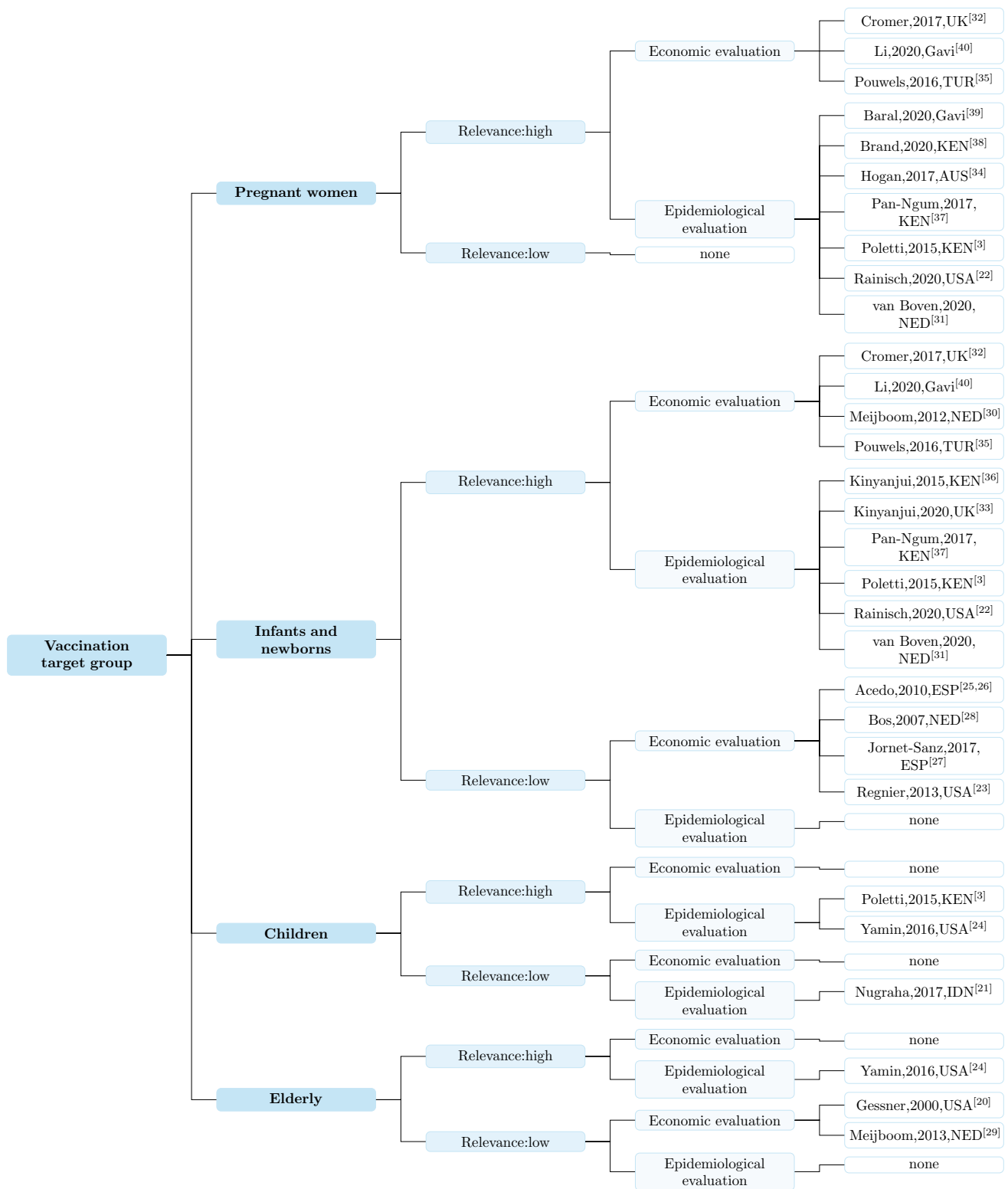


Fig. 3 Overview of included studies by vaccination target, relevance for decision making, and type of evaluation. Economic evaluations reported monetary outcomes of the intervention. Epidemiological evaluations estimated epidemiological effects of vaccination without evaluation of costs. Completeness of reporting and relevance for deci-

sion making was assessed using EVIDEM: (1) scores 3 and 4 indicate higher relevance and (2) scores 1 and 2 indicate lower relevance. The studies are represented as the name of the first author, year of publication and country (as three-letter country code). *Gavi* Global Alliance for Vaccines and Immunisation

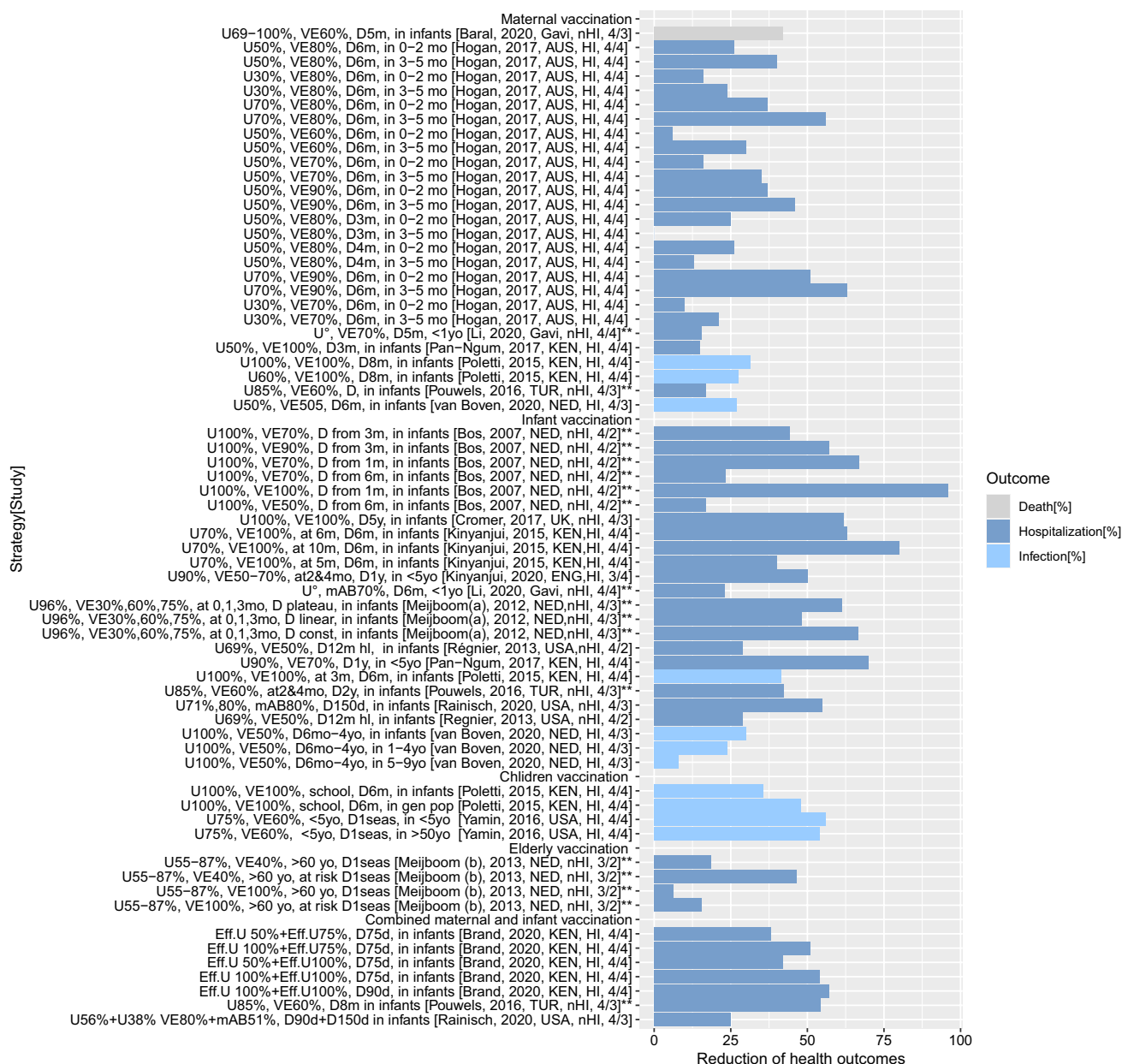


Fig. 4 The estimated relative reduction in respiratory syncytial virus (RSV) infections and RSV-caused hospitalisations. Each strategy is defined by vaccine uptake, U vaccine effectiveness, VE vaccine-induced duration of immunity, D (hl , half-life, $seas$ season), and a group of the population where the reported effect is observed (e.g. in infants). The study is denoted by the first author, year, three-letter country abbreviation, inclusion of herd immunity (HI herd immunity included, nHI herd immunity not included), and EVIDEM scores for completeness of reporting and relevance for decision making. Note: Baral et al. [39] summed the results over 73 Gavi-supported countries, reported for the year 2035, the vaccine uptake is country specific, on average 69% but projected to increase to 95%. Bos et al. [28] varied the month of start of the vaccine-induced immunity. Brand et al. [38]: the vaccination strategy is to vaccinate the pregnant women as part of their prenatal contact and the household cohabitants at the birth of a baby. Kinyanjui et al. [36] reported the results of vaccinating at different ages. Li et al. [40] summed the results over

72 Gavi-supported countries for the year 2022, U° country-specific coverage of Bacillus Calmette-Guérin vaccination in 2016. Meijboom et al. [30] reported the results of three-dose vaccination policy with VE given for the first, second, and third dose. The vaccine waning period was 10 years. Régnier et al. [23] was set in the base-case vaccine-induced duration with a half-life of 12 months. Poletti et al. [3] reported the outcomes for annual vaccination over 10 years. Only results are included that were reported or could be calculated. The studies by Acedo et al. [25, 26], Jornet-Sanz et al. [27], and Nugraha et al. [21] could not be included. Not all results that were reported in the study are presented in the figure. The values that are graphically presented are not included because of the absence of an actual number, and this refers to the studies by Cromer et al. [32], Kinyanjui et al. [36], Pan-Ngum et al. [37], Poletti et al. [3], and Yamin et al. [24]. “Double asterisk” calculated in the review. Gavi Global Alliance for Vaccines and Immunisation

Table 4 Economic estimates reported in the included economic evaluations (in \$US PPP 2018) ($n = 11$)

Study, country, year	Evaluation	Economic outcome	\$US PPP 2018
Acedo et al. [25, 26], Spain, 2010	Vaccination of newborns with two booster doses	Cost saved	3,816,392.93
Acedo et al. [25, 26], Spain, 2010	Vaccination of newborns with two booster doses	Cost saved	3,816,392.93
Bos et al. [28], The Netherlands, 2007	Vaccination of infants born in January; VE 70%, protection from 3 mo onwards	Cost per hospitalisation averted	5353.15
	Vaccination of infants born in January; VE 70%, protection from 3 mo onwards	Break-even costs	45.66
Cromer et al. [32], England (UK), 2017	Infant (base case without seasonal restrictions)	Maximum cost-effective price per fully protected person	289.65
	Newborn (base case without seasonal restrictions)		122.20
	Maternal (base case without seasonal restrictions)		81.46
	Combined a newborn and infant programme		371.11
	Protect only neonates born in November (the most cost-effective strategy)		331.89
Gessner [20], USA, 2000	Elderly ≥ 65 y; without a 10% VE against COPD	Cost per death prevented	207,270.95
	Elderly ≥ 65 y; without a 10% VE against COPD	Cost per year of life gained	11,726.49
	Elderly ≥ 65 y; without a 10% VE against COPD	Cost per QALY gained	8592.99
	Elderly ≥ 65 y; with a 10% VE against COPD	Cost per death prevented	136,440.70
	Elderly ≥ 65 y; with a 10% VE against COPD	Cost per year of life gained	7841.79
	Elderly ≥ 65 y; with a 10% VE against COPD	Cost per QALY gained	6886.30
Jornet-Sanz et al. [27], Spain, 2017	Vaccination of 80% newborns, VE 100%	Cost saved (calculated by reviewer)	18,076,645.59
	Vaccination of 20% newborns, VE 100%		7,952,622.57
Li et al. [40], 72 Gavi-eligible countries, 2020	Maternal vaccination: VE 70%, duration 5 mo	Average cost per DALY averted	1766 (Angola) – 5857 (Vietnam)
	Infant immunisation with mAb: effectiveness 70%, duration 6 mo	Average cost per DALY averted	3260 (Angola) – 8198 (Vietnam)
Meijboom et al. [30], The Netherlands, 2012	Infant vaccination: 3 doses, 0, 1, 3 m., no waning VE	Cost per QALY gained	48,566.79
	Infant vaccination: 3 doses, 0, 1, 3 mo, plateau waning VE	Cost per QALY gained	55,131.41
	Infant vaccination: 3 doses, 0, 1, 3 mo, linear waning VE	Cost per QALY gained	73,407.08
	Infant vaccination: 3 doses, 0, 2, 4 mo, no waning VE	Cost per QALY gained	58,178.30
	Infant vaccination: 3 doses, 0, 2, 4 mo, plateau waning VE	Cost per QALY gained	62,469.84
	Infant vaccination: 3 doses, 0, 2, 4 mo, linear waning VE	Cost per QALY gained	83,357.13

Table 4 (continued)

Study, country, year	Evaluation	Economic outcome	\$US PPP 2018
Meijboom et al. [29], The Netherlands, 2013	Vaccination of elderly ≥ 60 y cohort; VE 40%	Cost per QALY gained	189,282.90
	Vaccination of elderly ≥ 60 y cohort; VE 100%	Cost per QALY gained	72,700.12
	Vaccination of elderly ≥ 60 y cohort; VE of 40%; vs. WTP of €50,000/QALY	Maximum total vaccination costs per individual	20.68
	Vaccination of elderly ≥ 60 y cohort; VE 100%; vs. WTP of €50,000/QALY		52.25
Pouwels et al. [35], Turkey, 2016	2+4 mo infant vaccination	Cost per QALY gained	49,018.00
	Maternal vaccination	Cost per QALY gained	57,194.74
	Combined 2+4 mo infant and maternal programme	Cost per QALY gained	58,152.10
Régnier et al. [23], USA, 2013	Vaccination of one cohort (4.2 million live births)/healthcare system perspective	Cost per hospitalisation averted	21,551.54
	Vaccination of one cohort (4.2 million live births)/healthcare system perspective	Cost per year of life gained	242,943.86
	Vaccination of one cohort (4.2 million live births)/healthcare system perspective	Cost per QALY gained	104,993.52
	Vaccination of one cohort (4.2 million live births)/societal perspective	Cost per QALY gained	73,196.79

The outcomes are vs. no intervention

COPD chronic obstructive pulmonary disease, *DALY* disability-adjusted life-year, *Gavi* Global Alliance for Vaccines and Immunisation, *mAb* monoclonal antibody, *mo* month old, *PPP* purchasing power parity, *QALY* quality-adjusted life-year, *VE* vaccine effectiveness, *WTP* willingness-to-pay, *y* year

for a short period of 3 months. Increasing the household coverage up to 100% would induce an additional reduction of 5% in RSV hospitalisations.

Among the other two studies based on the data from Kenya, Pan-Ngum et al. [37] showed that the majority of modelled vaccination profiles with a maximum duration of protection of 6 months resulted in a 7–15% reduction in hospitalisations in children aged < 5 years. Poletti et al. [3] modelled the effect of maternal vaccination as an increase of duration of natural immunity in newborns derived from maternal antibodies. Vaccination was assumed to prolong the 4 months of natural maternal protection up to 5, 6, and 8 months. Assuming 8 months of immunity in 100% of protected newborns in the modelled cohort, the authors predicted a 31.5% potential reduction in RSV infant infections.

Using a static model without herd effects in the USA, Rainisch et al. [22] evaluated the introduction of maternal vaccination in addition to within-season passive immunisation of high-risk infants with palivizumab as one of three strategies. The base-case scenario was defined as 80% VE, 56% vaccine uptake, and 90 days of vaccine-induced immunity for

maternal vaccination and 51% effectiveness, 38% coverage, and 150 days of protection for palivizumab. Compared with no intervention, this scenario resulted in a 14% reduction in RSV-associated LRTIs attended in outpatient clinics, a 13% reduction in emergency department visits, and a 25% reduction in hospital admissions.

Two further studies [32, 35] estimated the epidemiological and economic outcomes of maternal vaccination using static models. In the study by Pouwels et al. [35] in Turkey, a 17% reduction in infant hospitalisations was estimated due to maternal vaccination assuming 60% VE, 85% vaccine coverage, and 8 months of protection. The estimated cost effectiveness of this strategy was \$US57,195 PPP 2018 per QALY gained. Cromer et al. [32] estimated an 80% potential reduction in outpatient-attended RSV infections in England, averting around 1.5 RSV-attributable hospital admissions per 100 births and implying a 43% QALY gain. They showed that maternal vaccination with 70% effectiveness and 3 months of protection could be cost effective if the price of the vaccine was set at \$US81.5 PPP 2018 or lower.

Two static-model-based evaluations explored the effects of maternal vaccination in Gavi-eligible countries. The structure of the models, underlying incidence data, and assumed vaccine-related parameters were similar between the studies. Li et al. [40] reported the results for 2022 for 72 countries and projected the potential prevention of 1.2 million RSV cases, 104,000 RSV hospitalisations, 3000 deaths, and 98,000 DALYs (3% discounted) for maternal vaccination (VE of 70% and 5 months of protection). Further, between 2023 and 2035, Baral et al. [39] projected a potential reduction of, on average, 11.3 million cases, more than 3.4 million RSV hospitalisations, 150,000 deaths, and 10.3 DALYs (not discounted) reached through maternal vaccination (VE of 60% and 5 months of protection) with increased coverage in 73 Gavi-supported countries. The economic evaluation by Li et al. [40] provided an estimation of cost-effectiveness ratios (\$US/DALY averted) compared with no intervention for each country. For a vaccine price of \$US3.10 PPP 2018, the reported estimates vary from \$US1766 PPP 2018 per DALY for Angola to \$US5857 PPP 2018 per DALY for Vietnam. The study shows that, if the WTP value is more than \$US1000 per DALY averted, a change from the current situation to the introduction of maternal vaccination could be optimal.

3.6.2 Infant Vaccination

Most of the studies included in this review evaluated active vaccination of children aged < 1 year. Ten studies [3, 22, 30–33, 35–37, 40] were considered relevant for decision making (see Table 3 and Fig. 3) and are presented in this section. Three [3, 36, 37] of them conducted dynamic modelling of routine infant immunisation based on Kenyan hospital data and, as such, incorporated herd immunity. Poletti et al. [3] estimated that routine vaccination of all infants aged 3 months with a vaccine providing full protection over 6 months led to a 41.5% decrease in RSV primary infections in infants (see Fig. 4). Pan-Ngum et al. [37] reported a median reduction of $\geq 50\%$ RSV-associated hospitalisations within a year if 90% of infants were vaccinated at 2 and 4 months of age. Kinyanjui et al. [36] investigated the optimal age to vaccinate children aged < 1 year, aiming to increase reductions in RSV hospitalisations. Over 60% of hospitalisations were averted with 70% vaccination coverage at 6 months of age. The most considerable reduction (80%) was achieved when infants were vaccinated at 10 months, and the smallest effect (40% reduction) was obtained with a vaccine administered at 5 months.

Poletti et al. [3] noticed that infant vaccination had little impact on infections in other age groups. However, Pan-Ngum et al. [37], who considered a more extensive array of vaccine characteristics, proposed that a substantial reduction of hospitalisations was due to the vaccine-induced

shortening of the duration of infection and decreasing infectiousness. They pointed out the importance of herd protection with the decrease of RSV transmission in the age group at risk. Kinyanjui et al. [36] confirmed the essential benefits of the indirect effects of vaccination and proposed that thorough consideration of vaccine-induced herd immunisation influenced the optimal allocation of the vaccine.

Kinyanjui et al. [33] applied two dynamic models described in Pan-Ngum et al. [37] in England and Wales. They explored the effects on RSV hospitalisations of children aged < 1 and < 5 years associated with vaccinating infants at different ages and using different dose regimens. The authors projected a potential rapid reduction (within a year) and further stabilisation of incidence at 50% of the pre-vaccination level. The projected estimates were similar to those reported by Pan-Ngum et al. [37] for Kenya.

Van Boven et al. [31] evaluated the vaccination of infants in The Netherlands, but, in contrast, applied lower VE with a more extended period of protection (up to the age of 4 years). The study showed a potential 30% reduction of the infection attack rate in infants. It also projected a 28% decrease in infections in those aged 1–4 years and an 8% reduction in those aged 5–9 years. These potential effects in older children could stem from the assumption of a long-lasting vaccine-induced immunity coupled with the indirect effects of the vaccination. The authors did not further investigate possible changes in the potential effects under varying assumptions for the vaccine-related parameters.

Rainisch et al. [22] compared the currently licensed mAb (palivizumab) with a hypothetical and more effective antibody for passive immunisation of infants in the USA. Using a static model, the authors assessed the effects of passive immunisation, applying different effectiveness and uptake parameters. Targeting all infants with an antibody candidate that was 80% effective against LRTIs and provided 150 days of induced immunity led to reductions of cases attending outpatient clinics by 48%, hospitalisations by 55%, and emergency care by 51%.

Similarly, using a cohort model, Li et al. [40] evaluated the immunisation of infants with a mAb candidate in 72 Gavi-supported countries and compared it with the maternal strategy. For 70% effective mAb with 6 months of induced immunity, they showed an average of a 23% reduction in RSV hospitalisations in those countries, though the estimates of the averted burden of the disease varied considerably between the countries. The results indicated that the assumed additional month of mAb-induced protection led to prevention of more cases, hospitalisation, and deaths than the maternal vaccine. The economic evaluation resulted in potential cost-effectiveness ratios ranging from \$US3260 (for Angola) to \$US8198 (for Vietnam) PPP 2018 per DALY averted compared with no intervention. Passive immunisation (\$US6.2 PPP 2018/dose) will potentially be an optimal

strategy if the WTP value is higher than \$US6000 (\$US6205 PPP 2018) per DALY. The price difference between the maternal vaccine and the mAb influences the choice of optimal intervention. The study indicated that, if an additional month of protection were worth more than \$US1, the potential optimal strategy would be passive immunisation for all countries.

Three other studies [30, 32, 35] reported health economic estimates of infant vaccination strategies (see Table 4). The cost per QALY gained ranged from \$US48,566 to 83,357 PPP 2018, and the maximum cost-effective price per fully protected person was estimated as \$US290 PPP 2018 (relative to the UK National Institute for Care and Excellence cost-effectiveness threshold). These studies reported health economic estimates of a large set of infant strategies, varying age at vaccination, efficacy, and uptake parameters.

The lowest cost per QALY gained was estimated by Meijboom et al. [30] for vaccinating infants at 0, 1, and 3 months of age with a vaccine with long-lasting protection (10 years). The authors assumed increasing VE for each subsequent dose, i.e. 30%, 60%, and 75%, respectively. A 66.5% reduction in hospitalisations was estimated for this scenario. The study showed that vaccination at the earliest possible age brought more health benefits. Delay in the administration of succeeding doses increased the ICER. Waning vaccine-induced immunity decreased health outcomes and increased the cost-effectiveness estimates.

Pouwels et al. [35] considered vaccination at ages 2 and 4 months assuming increased effectiveness of the second dose (60 and 75%, respectively). A strategy with 85% coverage and an 8-month duration of vaccine-induced immunity resulted in a 42% reduction in hospitalisations and a gain of 2172 discounted QALYs for a cost of \$US49,018 PPP 2018/QALY.

Cromer et al. [32] reported that infant vaccination at 3 months of age resulted in 62% averted hospitalisations and 95% prevented outpatient visits. Most of the 73% QALY gain associated with this strategy was achieved via the reduction of cases in primary care. The assumptions included 70% (50–100%) VE and immunity lasting for 5 years. Seasonal immunisation strategies to protect newborns and infants were shown to be potentially cost effective. In particular, restricting passive prophylaxis to infants born before the peak of the RSV season (in November in England) was the most cost-effective strategy.

3.7 Vaccination of Young Children

Vaccination of children aged < 5 years [24] and vaccination of school-aged children [3] are proposed alternatives to protect younger age groups. Yamin et al. [24] characterised the vaccination of children aged 6 months to 5 years as highly effective. For VE of 80% with a duration of protection over

one season, they predicted the reduction of 0.1–0.5 RSV cases per dose in children and 0.1–0.4 cases per dose in adults aged ≥ 50 years. Poletti et al. [3] found that, over 10 years, vaccination at school enrolment could reduce RSV incidence by 35.6% in infants and, additionally, by 40% in the general population because of herd effects. Under the assumption of 6-month vaccine-induced immunity, repeated vaccination of students was shown to be an effective alternative, although it would require a larger number of vaccine doses. There was no economic evaluation of vaccination of children in this review.

3.8 Vaccination of the Elderly

Yamin et al. [24] evaluated the epidemiological impact of targeting adults aged ≥ 50 years. One dose of RSV vaccine with VE of 80% given to adults aged ≥ 50 years was predicted to prevent 0.0036–0.0086 cases in the elderly and 0.0001–0.0014 cases in children aged ≤ 5 years. The study showed that the direct effects of elderly vaccination were lower than the indirect effects of vaccinating children, even when VE was assumed to be the same in all age groups. Two economic evaluations [20, 29] suggested that vaccination in the elderly could be potentially cost effective depending on the vaccine characteristics and target population (ICER range \$US6886.30–189,282.90 PPP 2018/QALY gained). However, the quality assessment demonstrated methodological limitations in these studies.

3.9 Combined Vaccination Strategies

Cromer et al. [32] estimated that a combination of active infant vaccination at 3 months of age and passive newborn immunisation prevented around eight RSV cases per 100 births with the maximum cost-effective price of \$US371 PPP 2018. Pouwels et al. [35] showed that vaccinating infants at 2 and 4 months of age as well as pregnant women prevented 54.2% of hospitalisations in infants and estimated an ICER of \$US58,152 PPP 2018. Both studies indicated that the combination of maternal and infant strategies had a higher potential impact on RSV incidence in infants and children aged < 5 years but was less attractive from the cost-effectiveness point of view.

4 Discussion

This systematic review summarises the current research activity in the assessment of the effectiveness and cost effectiveness of RSV vaccination strategies in the absence of clinical evidence. Although all studies demonstrated a considerable impact from vaccinating different sections of the population, the estimates varied considerably. The

review shows that the potential epidemiological impact largely depends on the modelling approaches, assumptions surrounding the epidemiology of RSV, and definition of vaccination scenarios. The economic outcomes were additionally driven by the economic inputs (e.g. assumed vaccine price, costs per RSV case, QALY decrements) and the choice of epidemiological endpoints. For example, the economic evaluations showed the importance of including outpatient care into the analysis. Careful consideration of adopted approaches to represent RSV epidemiology, health-care utilisation, and vaccination impact at the population level is critical for the facilitation of decision making.

4.1 Model Structures and RSV Epidemiology

The static models can be a helpful initial estimation of the direct impact of vaccination on epidemiological outcomes for economic evaluations. This is particularly the case for maternal vaccination, which produces passive protection of newborns. However, they do not include potential protective effects in the unvaccinated groups of the population. The dynamic models in this review differed in the assumptions surrounding the natural history of disease and vaccine effects, which influenced the epidemiological outcomes. All of them assumed the SIRS structure but varied in the description of immunity due to maternal antibodies, the transmission of RSV by asymptomatic and reinfected groups, and the acquisition and duration of natural immunity. These differences show the remaining gaps in knowledge surrounding the age-dependent risk of RSV infection and its epidemiology in different population groups, which limits the modelling efforts.

In both high- and low-middle-income settings, the studies illustrate a critical lack of data on RSV incidence in children. For Gavi-eligible countries, Li et al. [40] and Baral et al. [39] highlighted the essential gaps in data on RSV-attributable hospitalisation and mortality rates and called for better evidence on RSV incidence and on the disease burden for fine age strata. Other modelling studies that explore interventions in low-income settings used only the data from surveillance of children admitted to the Kilifi district hospital. In high-income settings, the researchers addressed the lack of data either by obtaining the data from observational studies or inferring the incidence and hospitalisation rates using data from different sources, such as administrative and laboratory data. It is important to note that only three studies in our review, all conducted in high-income settings, considered targeting the elderly for vaccination. Given the changing demographic structure in high-income countries and increasing evidence of the substantial impact of RSV in the elderly, further projections of the potential direct and indirect effects of prevention strategies are necessary. To facilitate model-based evaluations of prevention strategies,

further estimates of the disease burden in the elderly, including quality-of-life impairment, are needed, especially across health risk groups and in both nursing homes and the community. Overall, there is a need for epidemiological research on RSV transmission, especially within households, age- and period-stratified RSV incidence, hospitalisation rates, in-hospital mortality, and reinfection rates in different settings. With regard to the latter, the dynamic-transmission models assume decreasing susceptibility with increasing age and levels of exposure. However, the current state of knowledge does not allow separation of the two effects within a model, and further epidemiological evidence is needed.

Additionally, the clinical context was not fully represented in the models, which reported mostly hospitalisations and infections. Clinical stages determined costs and health outcomes and constituted crucial inputs into the economic evaluations. Cromer et al. [32], for example, showed a non-negligible contribution of primary care into resource utilisation attributable to RSV.

Further, only one study [23] in our selection considered asthma as a long-term complication of a severe RSV infection in infancy. Díez-Domingo et al. [44] presented evidence on the frequent occurrence of RSV-associated respiratory (and other) complications, such as asthma and COPD, later in life. Inclusion of the respective quality-of-life impairment and costs into models and evaluations of preventive strategies will be informative.

4.2 RSV Vaccination

Estimation of vaccination impact strongly depended on the age at administration (and the health risk group), and the assumptions about VE, duration of vaccine-induced immunity, and vaccine uptake. Although most of the studies presented the results across a wide range of VE parameters, the duration of vaccine-induced immunity varied between vaccine types. The most commonly used assumption was that immunity lasted over one season or for the same period as natural immunity. Other assumptions included long-lasting immunity with or without waning. These assumptions influence the effects of maternal vaccination and the optimal age of infant vaccination. The optimal age of vaccination could not be determined in this review. Most studies evaluated vaccination of infants aged 0–4 months, probably targeting the group with the highest numbers of RSV (severe) disease.

As most studies considered medically attended RSV infections as epidemiological outcomes, they applied VE as a reduction in primary infections and healthcare utilisation. However, because clinical evidence is currently not available, studying different vaccine characteristics can decrease uncertainty and provide better evidence for decision making. Pan-Ngum et al. [37], for example, showed that consideration of VE against infectiousness and duration of infection

affected the clinical endpoints. The dynamic models also showed that assumptions about effective age-dependent contact rates influenced the magnitude of the vaccination effects, and the inclusion of households and schools into the models could facilitate a more targeted approach to developing vaccination strategies.

The vaccine uptake parameter influenced the effectiveness and cost-effectiveness estimates. Some studies might have overestimated vaccine uptake, reaching over 90%, which contributed to the high impact of the vaccination. The values of vaccine uptake based on the observed rates for similar vaccinations were lower. Additionally, the number of vaccine doses influenced the cost of vaccination programmes and was important for the economic evaluations.

4.3 Epidemiological Outcomes

Most studies focused on the protection of newborns, neonates, infants, and young children. Vaccination of the elderly is currently not well-examined as a strategy in models, although RSV impact in the elderly has been well-documented. The studies reviewed here predicted a considerable potential direct impact on RSV disease in infants associated with maternal vaccination and high-coverage active and passive immunisation of infants aged < 6 months in both high- and low-middle-income settings. Compared with maternal vaccination, infant strategies were considered more effective possibly because of the assumption of a longer-lasting immunity.

The dynamic models suggested beneficial indirect effects of vaccination of young children and school-aged children on RSV infections in infants and the elderly, but the indirect effects of maternal vaccination in children aged ≥ 6 months might be small. Yamin et al. [24] showed that infected children aged < 5 years transmitted the infection to more than one individual. Infected older individuals, on the other hand, were less responsible for transmission than any other age group. Therefore, the models that applied restricted age structures likely underestimated the potential vaccination impact at the population level. In contrast, given the suggested small herd effect of maternal vaccination, the application of a limited age structure in modelling this intervention could be sufficient to estimate the vaccination impact. A more detailed social structure allowed modelling of more targeted vaccination scenarios. In Kenya, Poletti et al. [3] found that infant infections were caused by transmission within a household when infants cohabitated with one or more older siblings aged < 13 years. In these households, the school-age children were mainly responsible for introducing the infection and causing about half of the household outbreaks. Overall, vaccination of school-aged children and maternal vaccination, which can induce passive protection for 8 months, represented effective strategies when direct

vaccination of newborns and infants was not achievable. Compared with the maternal vaccination in Poletti et al. [3] and using the data from the same source, Brand et al. [38] illustrated that additional reductions in hospitalisation of infants could be potentially achieved through a cocooning strategy, i.e. vaccinating pregnant women and the members of their households. None of the studies in our review explored RSV transmission within households in high-income settings.

Combining vaccination groups can increase the potential benefits, but it may be less cost effective. Current evidence on possible combinations of vaccination programmes is scarce. The combination of maternal vaccination and passive immunisation of infants can be considered as an alternative to direct vaccination of infants. Three studies [22, 32, 40] evaluated the potential impact of passive immunisation with novel mAbs, indicating a further need in assessing the antibody candidates currently under development.

Further, the results suggest that consideration of RSV seasonality is important for the development of a vaccination policy. The dynamic models incorporated increased transmission during the RSV season. Therefore, restricting vaccination to children born before the beginning and peak of the RSV season can be more effective. The seasonal peaks differed between the studies, supporting the statement that RSV seasonality is related to climate. Therefore, the development of an optimal vaccination strategy needs careful consideration of country-specific RSV epidemiology.

4.4 Economic Outcomes

Half of the reviewed studies analysed the economic outcomes of RSV vaccination. Most studies used static models to investigate cost effectiveness. The reported estimates included cost per gained health outcome such as QALY and cost per averted healthcare service. Other estimates, such as the maximum cost-effective price per fully protected person and the break-even costs calculated for a wide range of vaccination scenarios, can guide decision making and vaccine development. Overall, the results indicate that RSV vaccination of different groups would be cost effective; however, the epidemiological analyses suggest that infant and childhood vaccinations contribute more health benefits than maternal vaccination in protecting children. That might be because of the assumption of longer-lasting vaccine-induced immunity in infants.

For high-, middle-, and low-income countries, the cost effectiveness of maternal vaccination depends on WTP. In Gavi-supported countries, when WTP is lower than \$US1000/DALY, no intervention is optimal. For WTP above \$US1000, maternal vaccination becomes cost effective, and passive infant immunisation is cost effective only when WTP is above \$US3500. Although WTP values differ

considerably between high- and low-income countries, a similar pattern can be seen in the results by Cromer et al. [32] for England. The study reported a lower maximum cost-effective price for maternal vaccination than for passive or active infant immunisation. These evaluations pointed out that maternal and infant strategies should be competitively priced to be considered good value for money. Cocooning strategies have not been economically evaluated and need to be looked at in further research.

The effectiveness and cost effectiveness of potential elderly vaccination need further exploration, preferably using dynamic-transmission models in the settings of childhood immunisation. The indirect protection of the elderly might reduce the economic suitability of vaccination in the elderly. Additionally, the review shows a need for further measurement and analysis of health-related quality of life of patients with RSV across the age and disease severity groups. Also, the possible impact of vaccination on RSV-induced long-term conditions, such as asthma, requires further investigation and inclusion in economic evaluations. Further, the chosen comparator in most of the studies reviewed was no vaccination, whereas if passive immunisation with palivizumab were in place, it would reduce the RSV incidence and hence the beneficial impact of vaccination [32] in infants. Therefore, the consideration and inclusion of current practice in economic analysis is necessary.

Lastly, a thorough examination of uncertainty is beneficial for decision making. Current studies demonstrate the influence of the following inputs on the performance of vaccination: RSV incidence and distribution of RSV burden over the age groups, vaccine characteristics, vaccine uptake and vaccination age, duration of natural maternally derived protection and natural immunity, cost-related parameters (including vaccine price), and QALY losses. These elements require careful analysis to interpret the findings of economic evaluations.

4.5 Limitations of This Review

The review was restricted to peer-reviewed publications exploring active immunisation against RSV. Therefore, it does not provide any new evidence on the evaluation of passive immunisation of infants with palivizumab, which might have been published after publication of the review on its cost effectiveness [17]. Regarding the quality assessment, the appraisal was performed using the EVIDEM instrument, which was not initially intended for the evaluation of methods used for the simulation of infectious diseases. Nonetheless, EVIDEM enabled a transparent and thorough appraisal of the methodological approaches and assumptions, which was performed by two reviewers independently and described in the EVIDEM forms available in ESM 2. Overall, the synthesis of evidence presented in this review

posed more difficulties than usually expected in this type of study because of the vast range of studied vaccination strategies and considerable methodological differences in modelling RSV epidemiology and vaccine effects.

5 Conclusion

This review indicates that, if clinical estimates of effectiveness and vaccine-induced protection, as well as actual vaccination uptake rates, are close to the values assumed in the modelling studies, maternal and infant RSV interventions will prevent a sizeable number of RSV-related severe and non-severe LRTIs in children. Maternal vaccination can be considered a feasible and less expensive strategy to protect infants in the first months of life. If the vaccine-induced immunity is short lasting, infant immunisation or a combination of infant and maternal vaccination might be examined for implementation. In the case of infant vaccination, in countries where surges in RSV cases follow seasonal patterns, immunisation before and during an RSV season might be preferred. Further modelling-based evaluations of a wider range of scenarios, including maternal, seasonal, cocooning, and elderly strategies for varying coverage rates will be beneficial for decision making.

Currently, studies investigating the epidemiological and economic impacts of vaccinating different population groups against RSV based on a dynamic-transmission model are lacking. The availability of age-specific epidemiological, clinical, and health economic data restricts the development of the mathematical models and limits model-based health economic analyses. To reduce decision uncertainty and facilitate more conclusive evaluations, epidemiological research and the estimation of RSV cases and hospitalisations for fine age strata is required. Additionally, natural immunity, reinfections, and household contacts in the transmission of RSV infections needs further investigation.

Declarations

Funding Open Access funding enabled and organized by Projekt DEAL. This research was supported by the Innovation Fund of the Joint Federal Committee (grant number 01VSF18015).

Conflict of Interest Marina Treskova, Francisco Pozo-Martin, Stefan Scholz, Viktoria Schönfeld, Ole Wichmann, and Thomas Harder have no conflicts of interest that are directly relevant to the content of this article.

Ethics approval Not applicable.

Availability of Data and Material The data presented in this review were obtained from the included studies, which are cited in the main and supplemental text. All other data generated during the review are presented in the tables in the review.

Consent to participate Not applicable.

Consent for publication Not applicable.

Code Availability Not applicable.

Author Contributions All authors contributed to the conception of the study, the search and selection strategies, and the interpretation of the results. MT, FPM, STS, and VS conducted the searches, selected the studies, extracted the data and evaluated the quality. MT and FPM drafted the manuscript, with input from VS, TH, and OW. STS, VS, TH, and OW critically revised the manuscript and contributed to the final draft. All authors read and approved the final manuscript.

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