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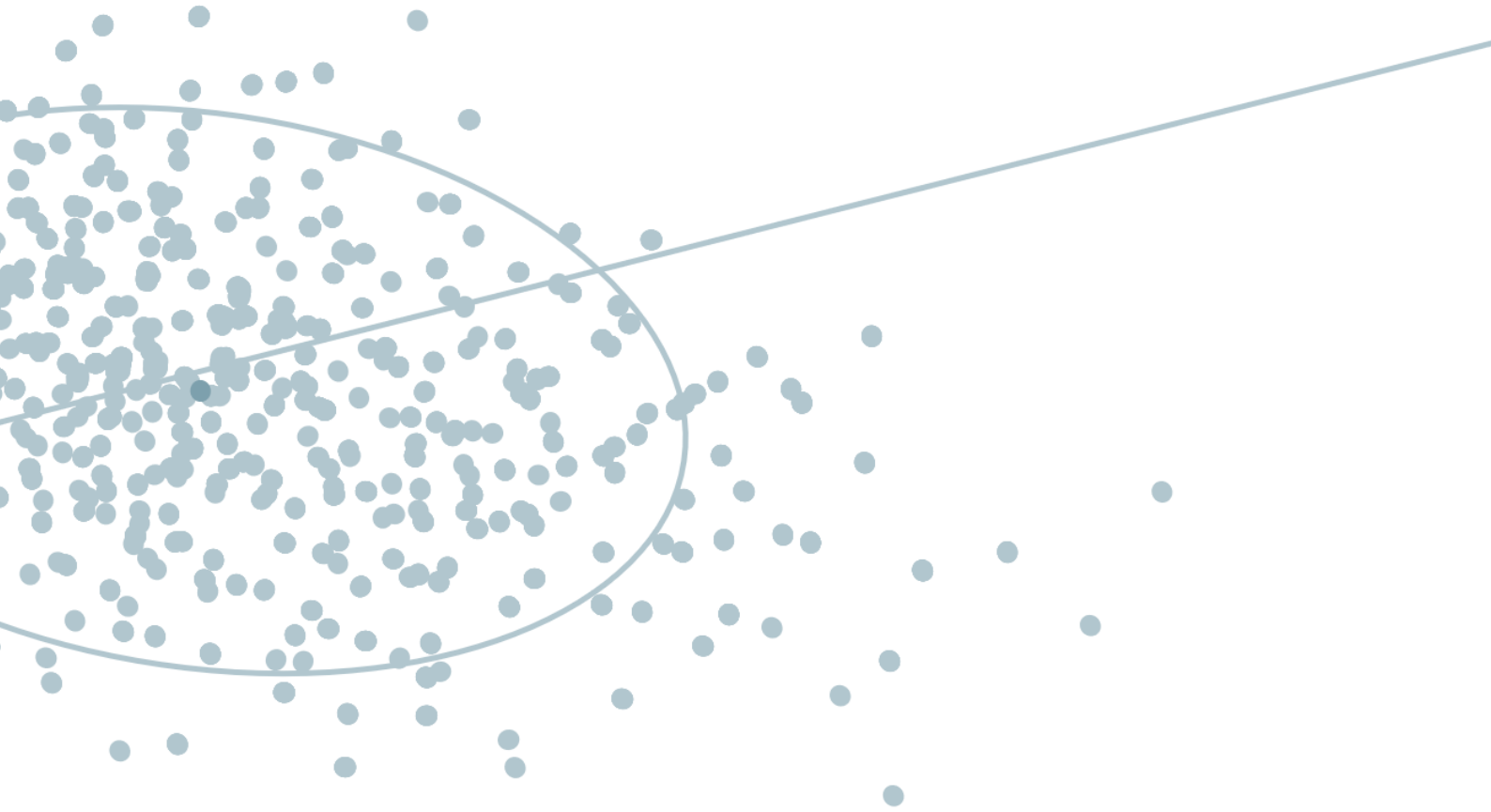
Health Technology Assessment (HTA)

Health Economic Evaluation

RSVpreF for maternal vaccination against RSV during pregnancy

Version 24.01.2025



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Technology	Abrysvo® (RSVpreF)
Type of Technology	Immunization
Date	24 January 2025

Conflict of Interest:

The authors have no individual financial, academic, personal or any other conflicts of interest to declare in relation to this project.

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Cover image: Simplified representation of a fictional probabilistic sensitivity analysis on a cost-effectiveness plane with the diagonal willingness-to-pay line.

Executive Summary

Introduction

Respiratory syncytial virus (RSV) is a common virus that causes mild, cold-like symptoms. Infants, young children, and older adults are susceptible to more severe RSV infection; this can lead to potentially life-threatening lower respiratory tract infections (LRTIs).[1, 2]

RSVpreF (Abrysvo®) is intended to vaccinate against RSV. In Switzerland, the vaccine is indicated for two populations:

1. The passive protection of infants from birth to 6 months of age against LRTIs caused by RSV after immunization of pregnant women between the 32nd and 36th week of pregnancy.
2. The active immunization of persons aged 60+ years to prevent LRTI caused by RSV.

This report evaluates the cost effectiveness and budget impact of maternal RSVpreF vaccination during pregnancy compared with nirsevimab/no RSV prophylaxis for preventing RSV infections that result in healthcare-seeking behavior in newborns and infants.

Methods

Two rapid systematic reviews of nirsevimab and RSVpreF were conducted: one of clinical outcomes and one of economic outcomes. A single set of searches informed both reviews and double independent record screening was used. Data extraction and quality appraisal of included studies was conducted by a single reviewer with a second reviewer checking a sample. Data were tabulated and explored in narrative synthesis.

A Markov model with a one-year time horizon was constructed. The modelled cohort corresponded to the annual number of live births in Switzerland between October and March. The model health states corresponded to RSV infections requiring a primary care visit, emergency department visit, or hospitalization.

The budget impact of adopting RSVpreF into the existing treatment landscape in Switzerland was estimated over 5 years. This assessment compared 2 scenarios: one where individuals received either RSVpreF, nirsevimab, or no RSV prophylaxis and one where individuals could not receive RSVpreF.

Review of clinical evidence

Six RCTs were included; 4 of nirsevimab and 2 of RSVpreF. Two studies (both nirsevimab) were considered to be at high risk of bias, and 4 studies were at moderate risk of bias.

The trials appeared to report favorable efficacy outcomes for both drugs. However, statistical significance was not reported by any trial for all but 2 outcomes, making it difficult to determine

whether reported differences are true effects. Favorable safety profiles were reported for both drugs, but no trials assessed the statistical significance of safety outcomes.

Review of economic evidence

Ten high quality economic evaluations were included: 5 of nirsevimab, one of RSVpreF, and 4 of both. No Swiss-based models were identified. Within the parameters of the willingness-to-pay thresholds reported, RSVpreF dominated (more effective and less costly) no prophylaxis, nirsevimab was cost effective compared with no prophylaxis, and nirsevimab was cost effective against maternal immunization.

Cost-effectiveness of RSVpreF compared with nirsevimab

For an annual cohort of live births in Switzerland, RSVpreF decreases costs and QALYs by CHF 9'781'506 and 18.2, respectively (an ICER of CHF 538'075 per QALY lost). The percentage of cost-effective iterations for RSVpreF is 100.0% at CHF 50’000 and 99% at CHF 200’000. The deterministic sensitivity analyses (DSA) and scenario analyses align with the probabilistic sensitivity analysis (PSA) and indicate these results are robust.

Cost-effectiveness of RSVpreF compared with no RSV prophylaxis

For an annual cohort of live births in Switzerland, RSVpreF increases costs and QALYs by CHF 430'224 and 27.8, respectively (an ICER of CHF 15'497 per QALY gained). The percentage of cost-effective iterations for RSVpreF is 80.0% at CHF 50’000 and 100.0% at CHF 200’000. The DSA and scenario analyses align with the PSA and indicate these results are robust.

Budget impact

The analysis estimates that adopting RSVpreF in each annual cohort of live births in Switzerland over a 5-year time horizon would reduce cumulative total costs by CHF 14’832’734. This conclusion is robust in all scenarios considered.

Conclusion

The 6 trials in the clinical review suggest that nirsevimab and RSVpreF are safe and effective in preventing RSV-related outcomes in infants. The certainty of this evidence and confidence in subsequent conclusions is limited by several factors, including trial quality and the lack of statistical significance reporting. However, the consistency of numerically improved outcomes across the 6 included trials would indicate the plausibility of a beneficial effect.

When RSVpreF is compared with nirsevimab, the reduction in QALYs is compensated by a reduction in healthcare expenditure and RSVpreF is likely to be cost-effective. When RSVpreF is compared with no RSV prophylaxis, the increase in QALYs compensates for an increase in healthcare expenditure and RSVpreF is likely to be cost-effective. Therefore, adopting RSVpreF into the existing RSV prophylaxis treatment landscape is predicted to reduce total healthcare expenditure.

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Abbreviations and acronyms

AE	Adverse event
BIA	Budget impact analysis
BPD	Bronchopulmonary dysplasia
CADTH	Canadian Agency for Drugs and Technologies in Health
CCPA	Cost of purchasing and administration
CDA-AMC	Canada's Drug Agency
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CHD	Congenital heart disease
CI	Confidence interval
CIHR	Canadian Institutes of Health Research
CIRN	Canadian Immunisation Research Network
CLD	Chronic lung disease
CRD	Centre for Reviews and Dissemination
CRI	Credible interval
DSA	Deterministic sensitivity analysis

ED	Emergency department
ERG	Evidence Review Group
EU	European Union
EU-CTR	EU Clinical Trials Register
FDHA	Federal Department of Home Affairs
FOPH	Federal Office of Public Health
FSO	Federal Statistical Office
GA	Gestational age
GP	General Practitioner
GW	General ward
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICD	International classification of diseases
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
ITT	Intention to treat
KM	Kaplan Meier
LMI	Combined nirsevimab and RSVpreF immunization program

LOCF	Last observation carried forward
LRTI	Lower respiratory tract infection
LY	Life years
MV	Mechanical ventilation
NA	Not applicable
NMB	Net monetary benefit
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NR	Not reported
PC	Primary care
PICU	Pediatric intensive care unit
PPD	Price per dose
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year

RCT	Randomized controlled trial
RSV	Respiratory syncytial virus
SD	Standard deviation
SE	Standard error
SoC	Standard of care
STA	Single technology appraisal
TRAE	Treatment-related adverse event
UK	United Kingdom
US	United States
VAT	Value added tax
wGA	Weeks gestational age
WHO	World Health Organization
WTP	Willingness to pay

Objective of the health economic evaluation

The objective of a health economic evaluation is to generate a focused assessment in terms of costs and consequences of a health technology. The analytic methods applied to assess the value of using a health technology, their execution and the results are described. The analytical process is comparative and systematic. The domains covered in a health economic evaluation report include cost-effectiveness and budget impact. The purpose is to inform health policy and decision-making to promote an efficient, sustainable, equitable and high-quality health system.

1. Policy Question and Context

Respiratory syncytial virus (RSV) is a common virus that most frequently causes mild, cold-like symptoms. However, infants, young children and older adults are susceptible to more severe RSV infection. This can lead to potentially life-threatening lower respiratory tract infections (LRTIs), such as pneumonia, bronchitis and bronchiolitis.[1, 2] In 2019, it was estimated that RSV was responsible for 3.6 million LRTIs in children aged <60 months around the world.[3]

RSVpreF (Abrysvo®) is a vaccine intended to vaccinate against RSV. While RSVpreF is the first RSV vaccination to receive marketing authorization in Switzerland, a long-acting monoclonal antibody (nirsevimab [Beyfortus®]) is currently recommended for routine RSV prophylaxis in specific populations.[4] The marketing authorization for RSVpreF was granted by Swissmedic on 23 August 2024 for two indications:

1. The passive protection of infants from birth to 6 months of age against LRTIs caused by RSV after immunization of pregnant women between the 32nd and 36th week of pregnancy.
2. The active immunization of persons aged 60+ years to prevent LRTI caused by RSV.

To inform policy decision making, the Federal Office of Public Health (FOPH) engaged a third party to analyze the cost effectiveness and budget impact of RSV vaccination with RSVpreF during pregnancy in Switzerland. This submission is supported by rapid systematic literature reviews of clinical and economic evidence. The insights reported in the submission will be used by the FOPH and the Federal Department of Home Affairs (FDHA) to consider whether RSVpreF should be reimbursed via the Swiss mandatory health insurance. Investigations of the value of RSVpreF vaccination for any other indication will be subject to another evaluation. The decision problem for the outlined policy question is described in Table 1.

Table 1: The decision problem

Model element	Description
Population	Newborns born between October and March whose mothers did, or did not, receive RSV vaccination during pregnancy
Perspective	Swiss healthcare payer
Intervention	RSV vaccination with RSVpreF administered between October and February in pregnant women who are between 32 and 36 weeks of gestation and have a due date before the end of March
Comparator(s)	– RSV prophylaxis in newborns with nirsevimab – No RSV prophylaxis
Model design	Markov model
Time horizon	One year
Cycle length	Monthly
Discount rate	– 3% per annum for costs – 3% per annum for health outcomes
Key outcomes of the model	– Incremental and total QALYs – Incremental and total costs – Incremental and total life years – RSV-related events (hospitalizations, emergency visits, primary care visits and deaths) – ICER
Sensitivity analysis	– Deterministic sensitivity analysis – Probabilistic sensitivity analysis

Abbreviations

ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life year, RSV = respiratory syncytial virus.

2. Medical Background

2.1 Overview and Clinical Presentation of RSV

RSV is a contagious virus that is primarily transmitted via direct contact with contaminated surfaces or from inhalation of airborne droplets released from an infected person.[1, 5, 6] The virus belongs to the *Paramyxoviridae* family and possesses a single-stranded negative-sense ribonucleic acid (RNA) genome.[7] It was first isolated from chimpanzees in 1956 and subsequently isolated from infants in 1957.[8, 9] Following this, RSV was quickly identified to be a major respiratory pathogen, capable of causing infection of the lungs and respiratory tract, especially in infants, young children, and older adults.

Symptoms of RSV infection typically include a cough, sore throat, sneezing, and a runny or blocked nose. In infants, RSV infection can also lead to irritability, decreased activity, apnea, and reduced eating and drinking.[10] The pooled incidence of mild RSV clinical manifestations is 51%, compared with 37% for moderate clinical manifestations and 7% for severe clinical manifestations.[11] Severe RSV infections can lead to potentially life-threatening LRTIs, such as pneumonia, bronchitis and bronchiolitis.[1, 2] Involvement of the lower respiratory tract occurs in 15% to 50% of infants and young children with primary RSV infection.[1] Reinfections with RSV are observed in 30% to 75% of children <2 years of age who have experienced RSV infection during the first 12 months of life and usually occur during the following season.[12, 13] In the long-term, RSV infection in early life can increase the risk of developing asthma, worsen the symptoms of asthma, and increase the risk of recurrent wheezing in childhood.[14-16]

Older adults are an additional population that are susceptible to RSV infection. Among older adults, RSV is responsible for almost 8% of symptomatic respiratory infections in seasonal studies – as reported by a systematic review and meta-analysis.[17] It has also been reported that the rate of hospitalization and mortality associated with RSV infection in older adults is not statistically different to those associated with influenza.[18]

2.2 Risk Factors for Severe RSV Infection

Populations that are at a higher risk of severe RSV infection include people living with underlying chronic medical conditions and people living with weakened immune systems.[1, 11] Both younger and older populations are also at a higher risk of severe RSV infection, with RSV-associated hospitalization and mortality following a U-shaped age pattern.[19] A systematic review conducted in 2023 identified that the mortality of RSV-associated acute respiratory infection (ARI) in upper- and middle-income countries is highest in children <one year of age. In comparison, the mortality of RSV-associated ARI in high-income countries is highest in adults ≥75 years of age.[19] Prematurity has also been demonstrated as a risk factor that impacts the severity of RSV infection.[20]

2.3 Burden of RSV Infection

Transplacental transfer of maternal antibodies can protect newborns against severe RSV infection. RSV is a leading cause of ARIs in infants and young children[1] and infects almost 90% of children by age 2.[21, 22] A global systematic review estimated that RSV accounted for 33 million acute LRTI episodes and 3.6 million LRTI hospitalizations in young children (≤60 months of age) in 2019; 20% of the LRTI episodes and 38% of the LRTI hospitalizations occurred in children aged 0 to 6 months.[3] The review also reported that RSV was associated with 101'400 deaths worldwide in children aged ≤60 months.[3]

In Italy, a retrospective study from 2011 to 2023 reported that RSV caused 48.9% of ARIs among children <one year.[23] In Germany, the incidence of RSV-related hospitalizations was 1'117 per 100'000 children in 2004; when extrapolated, this was equivalent to 26,524 hospitalizations in children throughout the whole country. [24, 25] Across seven European countries (not including Switzerland), the average length of stay in hospital due to RSV infection ranged from 2 to 4 days, and it is believed that RSV hospitalization accounted for between 9.9 and 21.2 bed days per 1'000 children aged <5 years annually.[26] In 2023, it was also estimated that 75% of annual RSV hospital admissions across the EU occur in children aged under one year.[27] In adults aged ≥60 years, the hospitalization rate of RSV in industrialized countries is 157 per 100'000, with the fatality rate as high as 7.1%.[28] This demonstrates that RSV imposes a substantial global burden – even though it is believed that RSV infection is underreported and underdiagnosed in both children and adults.[5, 29-31] In younger populations, this underdiagnosis may be because some countries do not recommended RSV testing in children presenting with bronchiolitis.[32]

In Switzerland, RSV is a leading cause of hospitalization in infants, with approximately 1% to 2% of each annual birth cohort admitted to intermediate (IMCs) or intensive care units (ICUs).[33] It has been reported that deaths due to RSV infection are rare in previously healthy infants born in industrialized countries.[34] However, 70% of hospitalizations due to RSV in Switzerland occur in children who were previously healthy.[35]

In 2024, an analysis was published that used administrative data to estimate the inpatient burden of RSV in Switzerland.[36] The article identified 902 hospitalizations due to RSV in 2020/21, which was substantially lower than previous years (3'575 in 2018/19 and 2'487 in 2019/20). Around two-thirds of all RSV hospitalizations occurred in infants between 2003 and 2021, with the mean age of hospitalized infants being 118 days. Lower birth weight, gestational age, and congenital disorders were associated with a higher risk of hospitalization. Despite this, the majority of hospitalized infants <12 months of age with RSV (90.8%) were born after 35 weeks of gestation without bronchopulmonary dysplasia or congenital health disease. This proportion reduced to between 60% and 75% in infants aged 12 to 24 months.[36] In a smaller prospective study (n=577) conducted in Switzerland between 2001 and 2005, only 11% of children were aged >12 months at the time of

hospital admission. Of the remaining children who were aged ≤12 months, 77% were near-term or full-term infants without additional risk factors.[33]

2.4 Epidemiology of RSV in Switzerland

RSV causes annual winter epidemics, with the RSV season in Switzerland typically lasting from November to April each year, with a peak in January.[4] Despite this, the pattern of hospitalizations in Switzerland was characterized by a biannual variation between 2003 and 2019 (

Figure 1).[36, 37] This pattern was likely interrupted by the onset of the COVID-19 pandemic in early 2020. There has also been a gradual increase in the incidence of RSV hospitalizations between the early-2000s and 2019 – reported both in Switzerland[36] and several other countries.[38]

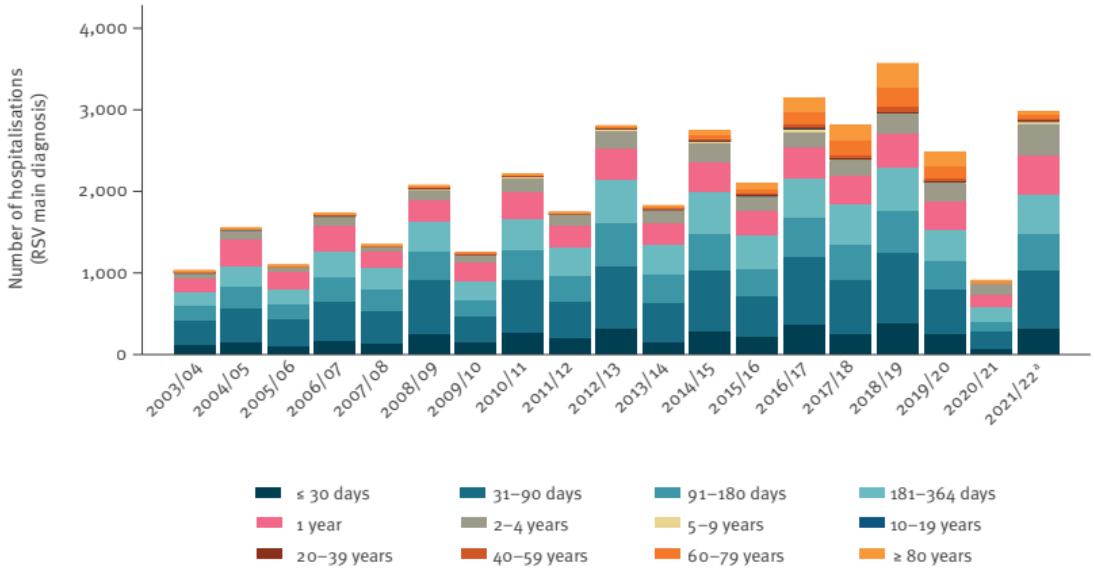

Figure 1: The number of RSV main diagnosis hospitalizations in pediatric and adult populations by age group in Switzerland from 2003 to 2022 (n = 39'382), which follows a biannual variation until 2019. This figure has been reproduced from Stucki et al. (2024).[36]

Switzerland has recently introduced a national real-time surveillance system for RSV in children called the 'RSV EpiCH', which represents >90% of available pediatric beds in Switzerland.[39] Using this system, the incidence of RSV infection in the 2023/24 winter season was estimated to be 3.1 per 1'000 children years.[39] However, it should be noted that this system only collects data on a voluntary basis and only covers 21 of 29 pediatric acute care hospitals in Switzerland.[39, 40]

2.5 Diagnostic and Treatment Pathways for RSV

Discussions with an expert clinician revealed that there are no RSV-specific guidelines used in Switzerland, but individuals presenting to hospital with acute bronchiolitis (a potential consequent of RSV infection) are typically treated with supportive care.[1] Between 38% and 53% of pediatricians in Switzerland prescribe bronchodilators to children with bronchiolitis and between 44% and 53% of pediatricians prescribe physiotherapy.[42] Corticosteroids are less commonly prescribed (by between 23% and 37% pediatricians).[42] Despite this, it should be noted that the clinical value of bronchodilators to treat RSV is debated,[6] and there is evidence that systemic corticosteroid treatment is not advisable.[1]

Until 2024, the Swiss standard of care for RSV infection in newborns and infants was no RSV prophylaxis. This was updated in September 2024, when RSV prophylaxis with nirsevimab became the standard of care in Switzerland, reimbursed by mandatory health insurance.[4] More information about the comparators for RSVpreF are reported in Section 3.2.

3. Technology

3.1 Technology Description

RSVpreF is a bivalent, recombinant vaccine developed by Pfizer. It is indicated for maternal immunization during pregnancy to provide passive protection in infants from birth to 6 months of age against LRTI caused by RSV, and for active immunization of individuals ≥60 years of age for the prevention of LRTI caused by RSV.[43] The recommended dose of RSVpreF is one single 0.5mL intramuscular injection into the deltoid region of the upper arm, to be administered by healthcare providers (doctors, nurses and pharmacists). It can also be administered concurrently with a seasonal influenza vaccine,[43, 44] reducing the possible number of visits to the healthcare provider. In comparison, a minimum interval of 2 weeks is recommended between administration of RSVpreF and a tetanus, diphtheria and acellular pertussis vaccine (Tdap).[43] However, it is noted that RSVpreF should not be mixed with any other vaccines or medicinal products.

Contraindications of RSVpreF include a history of severe allergic reaction (e.g. anaphylaxis) and hypersensitivity to any component of RSVpreF.[43] This includes powder, trometamol, trometamol hydrochloride, sucrose, mannitol (E421), polysorbate 80 (E433), sodium chloride, hydrochloride acid, solvent, or water.[43]

In order to provide protection for infants, the European Medicines Agency (EMA) recommends that RSVpreF should be administered to the mother between weeks 28 and 36 of gestation. In older adults, the EMA has approved RSVpreF administration in any individual aged ≥60 years. The EMA does note that the safety and efficacy of administering Abrysvo in children (from birth to <18 years) has not yet been established, with limited data available in pregnant adolescents and their infants. The EMA also notes that RSVpreF should not be studied in individuals who are less than 24 weeks pregnant in clinical trials and should not be used in pregnant individuals less than 28 weeks of gestation.[43]

Prefusion F is a key part of the RSV virus and is a primary target of neutralizing antibodies that block RSV infection. Following intramuscular administration of the RSVpreF vaccine, the prefusion F antigens elicit an immune response that protects against RSV-associated LRTI. Individuals who are vaccinated with RSVpreF during pregnancy will transfer RSV-neutralizing antibodies through the placenta, providing protection for their infant until 6 months of age. In adults aged ≥60 years, RSVpreF provides protection via active immunization.[43]

RSVpreF contains two recombinant RSV prefusion F antigens, representing RSV-A and RSV-B (RSV subgroup A stabilized prefusion F protein and RSV subgroup B stabilized prefusion F protein, respectively). In one dose (0.5mL) of RSVpreF, there are 60µg of each of these active substances. The RSV-A prefusion F antigen is a glycoprotein F that is stabilized in the prefusion confirmation; the RSV-B prefusion F antigen is produced in Chinese hamster ovary cells by recombinant DNA technology. RSVpreF should be stored between 2°C and 8°C and should not be frozen.[43]

3.2 Alternative Technologies

In addition to RSVpreF, there are two other technologies authorized in Switzerland that are intended to prevent severe disease caused by RSV infections in newborns and infants: nirsevimab and palivizumab. As of September 2024, nirsevimab became the standard of care to prevent RSV infection.[4] As palivizumab is not recommended for routine administration to children, it remains out of scope for the rest of this submission. Descriptions of the alternative technologies available in Switzerland and their recommendations for use are described in Table 2.

Table 2: Technologies available in Switzerland that are intended to prevent RSV infections in newborns and infants

Technology	Description of the technology	The regulatory and policy status of the technology in Switzerland
Beyfortus® (nirsevimab)[4]	– Nirsevimab is a human recombinant monoclonal antibody against RSV developed by AstraZeneca and Sanofi. – Nirsevimab is administered via a single intramuscular injection. The dose depends on body weight (<5 kg: 50 mg purple syringe; ≥5 kg: 100 mg blue syringe). – Nirsevimab can be given concurrently with other childhood vaccines in a separate area of the body (at least 2.5 cm apart).	– As of September 2024, the routine administration of a single dose of nirsevimab for children aged ≤12 months **is recommended.** In children born from April to September, nirsevimab should be administered in October (or as soon as possible thereafter). In children born from October to March, nirsevimab should be administered in the first post-natal week, ideally at a maternity ward. If hospitalized after birth, preferentially before discharge or earlier at the discretion of the treating healthcare provider. – The administration of nirsevimab for children aged ≤24 months entering their second RSV season with chronic congenital or acquired medical conditions associated with a persistent high risk of severe RSV disease **is recommended**. These include, but are not limited to prematurity, heart disease, pulmonary arterial hypertension, chronic lung disease, immune deficiency, and Down syndrome. – The costs associated with nirsevimab are covered by compulsory health insurance in Switzerland.
Synagis® (palivizumab)[a] [45]	– Palivizumab is a monoclonal antibody against RSV developed by AstraZeneca. – Palivizumab is administered via an intramuscular injection at a dose of 15 mg/kg body weight in intervals. It must be administered monthly during the RSV season.	– Palivizumab was first authorized for use in Switzerland in 1999. – The routine administration of palivizumab for children **is not recommended** (including children with congenital heart disease). – The administration of palivizumab for children aged <12 months at the start of the RSV season **and** severe BPD is recommended. – Palivizumab is not registered nor covered by insurance for infants with other RSV risk factors, including cystic fibrosis, immune deficiencies, Down syndrome, anatomical lung malformations, and neuromuscular diseases.

Abbreviations

BPD = bronchopulmonary dysplasia, RSV = respiratory syncytial virus.

[a] As palivizumab is not recommended for routine administration to children, it remains out of scope for the rest of this report.

3.3 Regulatory Status / Provider

RSVpreF received marketing authorization from Swissmedic on 23 August 2024[46] for the passive protection of infants from birth to six months of age against RSV-associated LRTI following maternal immunization between 32 and 36 weeks of pregnancy and for active immunization of people aged ≥60 years from RSV-associated LRTI. RSVpreF has not yet been recommended for routine administration through Swiss mandatory health insurance. The current national policy in Switzerland is to provide one dose of RSVpreF to pregnant women aged 18 years and older; this should be offered and administered between the 32nd and 36th week of pregnancy. RSVpreF should be planned and administered at least 14 days before birth and administered from October to February, if the due date is before the end of March.[47] This is similar to a selection of other countries worldwide, recorded in Table 3.

Table 3: Countries where RSVpreF is approved for immunization against RSV-associated LRTI in individuals between weeks 32 and 36 of pregnancy and in people aged ≥60 years

Country or region	Date that RSVpreF received regulatory approval	Details of RSVpreF reimbursement and roll-out
US[48]	August 2023	RSVpreF is reimbursed via the Medicaid federal/state program and private insurance.
EU[49]	August 2023	Decisions regarding the reimbursement and the availability of RSVpreF is the responsibility of individual member states. There is currently no reimbursement for RSVpreF in Belgium, Sweden, Austria or Denmark [50-53]
France[54]	August 2023	As of August 2024, RSVpreF is listed among the pharmaceutical specialties reimbursable under the French social security system.
Argentina[55]	September 2023	N/A
UK[56]	November 2023	As of September 2024, RSVpreF is included in a nationwide RSV vaccination program for adults aged ≥75 and individuals ≥28 weeks pregnant. [56]
Canada[57, 58]	December 2023	N/A
Japan[59]	January 2024	N/A
Australia[60, 61]	March 2024	N/A

Abbreviations

EU = European Union, LRTI = lower respiratory tract infection, N/A = not applicable, RSV = respiratory syncytial virus, UK = United Kingdom, US = United States.

4. Population, Intervention, Comparator, Outcome, Study Design (PICOS)

Table 4: PICOS scheme

P:	Pregnant women, neonates (up to 28 days) and infants (up to 12 months)
I:	– RSV vaccination with RSVpreF during pregnancy. – RSV prophylaxis with nirsevimab (any dose) for newborns and infants.*
C:	– RSV vaccination with RSVpreF during pregnancy. – RSV prophylaxis with nirsevimab (any dose) for newborns and infants. – Placebo or standard of care.
O:	**Efficacy and safety:** – Treatment coverage. – Hospitalization due to RSV LRTIs. – Emergency room visit associated with RSV. – Primary care visit related to RSV. – All cause LRTI hospitalization. – Rates of medically attended RSV LRTI. – Rates of very severe ICU medically attended RSV LRTI. – Rates of mechanical ventilation related to RSV. – Adverse events. – Mortality. **Economic:** – Effectiveness outcomes (such as QALYs, life years): incremental and total. – Costs: incremental and total. – Incremental analyses and other summary economic outcomes (e.g. ICERs, budget-impact per year). – Costs and healthcare resource use data used as modelling inputs in eligible economic evaluations.
S:	– Randomized controlled trials and economic evaluations (including economic evaluations reported in health technology assessments).

Abbreviations

ICER = incremental cost-effectiveness ratio, ICU = intensive care unit, LRTI = lower respiratory tract infection, QALY = quality-adjusted life year, RSV = respiratory syncytial virus.

Notes

* The aim of this report is to compare RSVpreF to placebo, standard or care, or nirsevimab. However, nirsevimab is also listed as an ‘intervention’ in order to identify studies that compare nirsevimab to placebo or standard of care. This allows the literature search to identify data on nirsevimab in the scenario that there are no head-to-head trials of RSVpreF and nirsevimab.

5. HTA Research Questions

5.1 Research Questions

For the evaluation of the technology the following research questions are addressed:

1. What is the cost effectiveness and budget impact of maternal RSVpreF vaccination during pregnancy compared with RSV prophylaxis with nirsevimab for newborns and infants?
2. What is the cost effectiveness and budget impact of maternal RSVpreF vaccination during pregnancy compared with no RSV prophylaxis for newborns and infants?

5.2 Additional Question(s)

No additional questions were investigated within this report.

6. Methodology Literature Review

This rapid systematic review was undertaken according to the principles of systematic reviewing embodied in the Cochrane handbook[62] and guidance published by the Centre for Reviews and Dissemination (CRD).[63]

To identify relevant clinical and economic evidence, a review protocol was developed with the FOPH that outlined the proposed methods of the rapid systematic review, defined by Cochrane as a "systematic review…accelerated through streamlining or omitting specific methods".[64] The review methods reflected the rapid systematic review context.

6.1 Systematic Literature Review of Clinical Evidence

6.1.1 Databases and search strategy

One set of searches was conducted to inform the review of clinical and economic evidence.

6.1.1.1 Search strategy

A MEDLINE (OvidSP) search strategy was developed to identify eligible studies. The final MEDLINE strategy is presented in Figure 2, and searches translated for other information sources are reported in Appendix A. The strategy was designed to identify randomized controlled trials (RCTs) or economic evaluations on either:

– RSV vaccination with RSVpreF during pregnancy.

– RSV prophylaxis with nirsevimab (any dose) for newborns and infants.

The main structure of the strategy comprised six concepts:

– RSV (search lines 1 to 10).

– Vaccination (search lines 11 to 20).

– Pregnancy (search lines 26 to 36).

– Nirsevimab (search lines 37 to 40).

– RCTs (search lines 45 to 52).

– Economic evaluations (search lines 53 to 69).

The concepts were combined as follows: (RSV AND ((vaccination AND pregnancy) OR nirsevimab) AND (RCTs OR economic evaluations)).

In addition, the pre-combined MeSH term for RSV vaccines and brand name terms for RSVpreF (Abrysvo®) (search lines 21 to 25) were combined with the pregnancy concept terms and the RCT / economic evaluation concept terms using Boolean AND.

The strategy was devised using a combination of subject indexing terms and free text search terms in the Title, Abstract, Keyword Heading Word, Registry Number, Name of Substance, Original Title, and Subject Heading Word fields. The search terms for the population and intervention concepts were identified through discussion within the research team, scanning background literature, and browsing database thesauri.

The search terms for the RCT concept (search lines 45 to 52) were based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE (sensitivity- and precision-maximizing version (2008 revision); Ovid format).[65] Two changes were made to the Cochrane filter to enhance potential sensitivity: in line 47 randomized.ab. (as found in the original filter) was changed to (randomiz* or randomis*).ti,ab.; in line 50 randomly.ab. (as found in the original filter) was changed to randomly.ti,ab.

The search terms for the economic evaluations concept (search lines 53 to 69) were based on the filter developed by the University of York CRD for identification of economic evaluations to include in NHS Economic Evaluation Database (NHS EED).[66]

The strategy excluded animal studies from MEDLINE using a standard algorithm (search line 73). The strategy also excluded some ineligible publication types that were unlikely to yield relevant study reports (editorials, news items and case reports) and records with the phrase ‘case report’ in the title (search line 74). Reflecting the eligibility criteria, the strategy was not restricted by date or language.

During strategy development, the performance of the strategy was tested using records for the studies included in 4 recent relevant systematic reviews.[67-70] Across the 4 reviews, 11 RCTs were included for which records were available to be found in Ovid MEDLINE. The scoping strategy successfully retrieved records for all 11 RCTs.

The final Ovid MEDLINE strategy was peer-reviewed before execution by a second Information Specialist. Peer review considered the appropriateness of the strategy for the review scope and eligibility criteria, inclusion of key search terms, errors in spelling, syntax and line combinations, and application of exclusions.

1 Respiratory Syncytial Virus Infections/ (9552)
2 respiratory syncytial viruses/ or respiratory syncytial virus, human/ (10968)
3 (respiratory adj1 (syncytial or syncitial)).ti,ab,kf. (18506)
4 (respirosyncytial or respirosyncitial or respiro syncytial or respiro syncitial).ti,ab,kf. (0)
5 ((syncytial or syncitial) adj virus*).ti,ab,kf. (18321)
6 ((syncytial or syncitial) adj (pneumovirus* or viral)).ti,ab,kf. (142)
7 (chimpanzee coryza agent* or orthopneumovirus* or txid11250 or txid 11250 or txid1868215 or txid 868215).ti,ab,kf. (63)
8 rs virus*.ti,ab,kf. (455)
9 (hrsv or hrsvs or rsv or rsvs).ti,ab,kf. (17337)
10 or/1-9 (25716)
11 vaccines/ or vaccines, attenuated/ or vaccines, combined/ or vaccines, inactivated/ or vaccines, marker/ or exp vaccines, subunit/ or exp vaccines, synthetic/ or vaccines, live, unattenuated/ or viral vaccines/ (110482)
12 exp Immunization Programs/ (16627)
13 exp Immunization/ (219103)
14 vaccin*.ti,ab,kf,hw. (517353)
15 revaccin*.ti,ab,kf,hw. (2547)
16 (immunis* or immuniz*).ti,ab,kf,hw. (221876)
17 (reimmunis* or reimmuniz*).ti,ab,kf,hw. (331)
18 (jab or jabs or shot or shots).ti,ab,kf,hw. (28259)
19 inoculat*.ti,ab,kf,hw. (146363)
20 or/11-19 (794585)
21 Respiratory Syncytial Virus Vaccines/ (1105)
22 ((respiratory syncytial virus or rsv) adj2 (prefusion* or pref*3 or pre f*3)).ti,ab,kf,rn,nm,ot. (142)
23 (abrysvo* or pf6928316*2 or pf 6928316*2 or pf06928316*2 or pf 06928316*2 or RSVpreF*3 or rsvpre f*3).ti,ab,kf,rn,nm,ot. (89)
24 (4pdl43y9mr or 34fs5xsd5q).ti,ab,kf,rn,nm,ot. (0)
25 or/21-24 (1185)
26 exp Pregnancy/ (1041771)
27 Prenatal Care/ (33843)
28 exp Pregnancy Complications/ (489812)
29 Obstetrics/ (25248)
30 maternal health services/ or perinatal care/ (22309)
31 Immunity, Maternally-Acquired/ (5902)
32 pregnan*.ti,ab,kf,hw. (1181553)
33 (gestation* or gravid* or trimester*).ti,ab,kf,hw. (367295)
34 (antenatal* or ante natal* or antepart* or ante part* or obstetric* or perinatal* or peri natal* or peripart* or peri part* or prenatal* or pre natal* or prepart* or pre part*).ti,ab,kf,hw. (505594)
35 (maternal* or maternit* or mother*).ti,ab,kf,hw. (600246)
36 or/26-35 (1642526)
37 nirsevimab*.ti,ab,kf,rn,nm,ot. (179)
38 (beyfortus*2 or nirsevumab or medi8897*2 or medi 8897*2 or med 18897*2 or med18897*2 or sp 0232*2 or sp 232*2 or sp0232*2 or sp232*2).ti,ab,kf,rn,nm,ot. (37)
39 (1989556-22-0 or vrn8s9cw5v).ti,ab,kf,rn,nm,ot. (56)
40 or/37-39 (198)
41 10 and 20 and 36 (753)
42 25 and 36 (263)
43 10 and 40 (177)
44 or/41-43 (894)
45 randomized controlled trial.pt. (622411)
46 controlled clinical trial.pt. (95610)
47 (randomiz* or randomis*).ti,ab. (884647)
48 placebo.ab. (252168)
49 clinical trials as topic.sh. (203378)
50 randomly.ti,ab. (443878)
51 trial.ti. (318934)
52 or/45-51 (1712461)
53 economics/ (27539)
54 exp "costs and cost analysis"/ (273336)
55 economics, dental/ (1922)
56 exp economics, hospital/ (25988)
57 economics, medical/ (9291)
58 economics, nursing/ (4013)
59 economics, pharmaceutical/ (3149)
60 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic*).ti,ab. (1149712)

61 (expenditure* not energy).ti,ab. (39692)
62 value for money.ti,ab. (2289)
63 budget*.ti,ab. (38192)
64 or/53-63 (1318939)
65 ((energy or oxygen) adj cost).ti,ab. (5011)
66 (metabolic adj cost).ti,ab. (1823)
67 ((energy or oxygen) adj expenditure).ti,ab. (30577)
68 or/65-67 (36310)
69 64 not 68 (1310517)
70 44 and 52 (131)
71 44 and 69 (140)
72 70 or 71 (259)
73 exp animals/ not humans/ (5261402)
74 (news or editorial or case reports).pt. or case report.ti. (3416630)
75 72 not (73 or 74) (236)

Key to Ovid symbols and commands:

*	Unlimited right-hand truncation symbol
*N	Limited right-hand truncation - restricts the number of characters following the word to N
ti,ab,kf,ot,rn,nm,hw	Searches are restricted to the Title (ti), Abstract (ab), Keyword Heading Word (kf), Original Title (ot), Registry Number/Name of Substance (rn), Name of Substance Word (nm) and Subject Heading Word (hw) fields.
adj	Retrieves records that contain terms next to each other (in the shown order)
adjN	Retrieves records that contain terms (in any order) within a specified number (N) of words of each other
/	Searches are restricted to the Subject Heading field
exp	The subject heading is exploded
pt.	Search is restricted to the publication type field
or/1-9	Combines sets 1 to 9 using OR

Figure 2: Search strategy for MEDLINE ALL

6.1.1.2 Resources searched

The literature search was conducted in the databases and information resources shown Table 5.

Table 5: Databases and information sources searched

Resource	Interface / URL
Databases	
MEDLINE(R) ALL	OvidSP
Embase	OvidSP
Cochrane Database of Systematic Reviews (CDSR)	Cochrane Library/Wiley
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane Library/Wiley
HTA Database	https://database.inahta.org/
NHS Economic Evaluation Database (NHS EED)	https://www.crd.york.ac.uk/CRDWeb/HomePage.asp
EconLit	OvidSP
Trials Registers	
ClinicalTrials.gov	https://clinicaltrials.gov/
WHO International Clinical Trials Registry Platform (ICTRP)	https://trialsearch.who.int/
Other	
National Institute for Health and Care Excellence (NICE) webpages	https://www.nice.org.uk/
Canada's Drug Agency (CDA-AMC) webpages (formerly Canadian Agency for Drugs and Technologies in Health (CADTH))	https://www.cadth.ca/
Reference list checking	N/A

Abbreviations

HTA = health technology assessment, N/A = not applicable.

The trials register sources listed in Table 5 (ClinicalTrials.gov and ICTRP) were searched to identify information on studies in progress. A number of data providers provide data to WHO for inclusion in ICTRP, including the EU Clinical Trials Register (EU-CTR).

In addition to searching the HTA database, targeted searches of the listed technology assessment and regulatory agency websites were conducted as follows:

– NICE webpages were searched for company submissions to NICE, Final Appraisal Determination documents, Evidence Review Group (ERG) reports (for single technology assessments only), and assessment reports (for multiple technology appraisals only).

– CDA-AMC webpages were searched for Health Technology Reviews and Clinical Guidance, Economic Guidance and Final Recommendations associated with Reimbursement Reviews.

Reflecting the eligibility criteria, records indexed as preprints or conference abstracts were excluded from Embase search results.

The included studies list of any retrieved relevant systematic reviews published in the last 3 years was also checked to identify any eligible studies that may have been missed by the database searches.

For each paper that was selected for inclusion in the review, a check was made to establish if any of the following notices were associated with the included paper: retraction notice, erratum notice, corrected and republished paper notice, expression of concern notice. The check was conducted via the PubMed record for the paper or (if no PubMed record was found) via the journal webpage for the paper. If a relevant notice was associated with an included paper, the notice was assessed by the review team.

6.1.1.3 Running the search strategies and downloading results

The searches were conducted using each database or resource listed in Table 5, translating the agreed Ovid MEDLINE strategy appropriately. Translation included consideration of differences in database interfaces and functionality, in addition to variation in indexing languages and thesauri. The final translated database strategies were peer-reviewed by a second Information Specialist. Peer review considered the appropriateness of the translation for the database being searched, errors in syntax and line combinations, and application of exclusions. Appendix A contains the full strategies (including search dates) for all sources searched.

Where possible, the results of searches were downloaded in a tagged format and loaded them into bibliographic software (EndNote).[71] The results were deduplicated using several algorithms and the duplicate references held in a separate EndNote database for checking if required. Results from resources that did not allow export in a format compatible with EndNote were saved in Word or Excel documents as appropriate and manually deduplicated.

6.1.2 Eligibility criteria

The eligibility criteria for the clinical evidence review reflects the PICO presented in Section 5 of this report and are summarized in Table 6.

Table 6: Eligibility criteria for the clinical efficacy review

	Inclusion criteria	Exclusion criteria
Population	Pregnant women, neonates (up to 28 days) and infants (up to 12 months)	– Older children. – Non-pregnant adults. – Infants not in their first RSV season.
Intervention	– RSV vaccination with RSVpreF during pregnancy. – RSV prophylaxis with nirsevimab (any dose) for newborns and infants.	Any other intervention
Comparators	– RSV vaccination with RSVpreF during pregnancy. – RSV prophylaxis with nirsevimab (any dose) for newborns and infants. – Placebo or standard of care.	Any other intervention
Outcomes	– Treatment coverage. – Hospitalization due to RSV LRTIs. – Emergency room visit associated with RSV. – Primary care visit related to RSV. – All-cause LRTI hospitalization. – Rates of medically attended RSV LRTI. – Rates of very severe ICU medically attended RSV LRTI. – Rates of mechanical ventilation related to RSV. – All cause medically attended LRTI. – Adverse events. – Mortality.	Any other outcomes
Study design	RCTs	Any other study design Relevant identified systematic reviews (published from 2021 to 2024) were referenced checked for eligible primary studies but were not included in the review.
Limits	No date or language limits.	– Conference abstracts. – News articles, editorials, and preprints.

Abbreviations

HTA = health technology appraisal, ICER = incremental cost-effectiveness ratio, ICU = intensive care unit, LRTI = lower respiratory tract infection, QALY = quality-adjusted life year, RSV = respiratory syncytial virus.

6.1.3 Study selection

Record assessment was undertaken as follows:

– A single reviewer assessed the search results according to their relevance to the review and removed obviously irrelevant records, such as those about ineligible diseases or in animals.
– The titles and abstracts of remaining records were assessed for relevance against the protocol criteria by double independent reviewer selection, with disagreements adjudicated by a third reviewer.
– The full text of potentially relevant studies was obtained, and these were assessed for relevance against the protocol criteria by double independent reviewer selection with disagreements adjudicated by a third reviewer.

When selecting publications for inclusion, relevant systematic reviews published in the past 3 years (published 2021 to 2024) and meeting the eligibility criteria were checked for additional references only. Data were not extracted from the reviews. Any potentially relevant non-duplicate publications included in any of these reviews were assessed for their eligibility.

Where results for one trial / patient population were reported in more than one paper, all related papers were identified and grouped together to ensure that participants in individual trials were only included once.

The number of records included and removed at each stage are detailed in the PRISMA flow diagram (Figure 3).

6.1.4 Data extraction, analysis and synthesis

One reviewer extracted data from the eligible trials and a second reviewer checked a 20% sample of the data points.

A data extraction sheet was developed in Excel and piloted on a trial before progressing to full data extraction.

The following elements were extracted from the eligible trials:

– Trial details (bibliographic details).
– Trial funding and affiliation(s), where reported.
– Study characteristics (where relevant to clinical evaluations):
    - Trial characteristics:
    - Trial design.
    - Trial objective.
    - Number of participating centers and countries.
    - Eligibility criteria.
    - Number of patients randomized/analyzed.

- Treatment duration.
- Follow up duration.
- Data collection time points.

– Patient baseline characteristics:
  - Age (of both mother and baby, if applicable).
  - Sex of baby.
  - Gestational age of baby.
  - Co-morbidities (of both mother and baby, if applicable).
  - Month/season of illness.
  - Any other disease specific characteristics of interest in either the mother or child.

– Details of intervention:
  - Treatment.
  - Dose.
  - Timing of the intervention (e.g. week of pregnancy, age of baby, month/season).

– Details of statistical analyses.

– For each of the outcomes specified extracted the following:
  - Outcome definition.
  - The unit of measurement.
  - The number of patients included in the analysis.
  - The size of the effect:
    – For dichotomous outcomes: absolute and relative risks (or odds ratios) and risk (or rate) differences.
    – For continuous outcomes: the mean change and measure of variance from baseline (or at both baseline and final visit), or mean difference between treatments.
    – For time-to-event analysis: the number of events in each arm, median time to event and a hazard ratio and p-value.
    – Where possible, absolute and relative data will be extracted.
  - A measure of precision for each estimate of effect (95% confidence intervals, standard error, or standard deviation).

– For each outcome, data at all available time points was collected.

6.1.5 Quality appraisal of clinical studies

One reviewer assessed the risk of bias of each included trial using the Cochrane Risk of Bias 1 tool.[72] A second reviewer checked the risk of bias assessment. Results of the clinical risk of bias assessment are reported in Section 7.2.3.

6.1.6 Statistical analysis

The results of the review are provided in Section 7. Data are tabulated and a narrative synthesis is provided. To ensure compliance with systematic review guidance, the report content was shaped by the PRISMA reporting guidance for systematic reviews and meta-analyses.[73]

6.2 Review of Economic Evidence

6.2.1 Search methods

One set of searches was conducted to inform the review of clinical and economic evidence. The details of the search methods are described in Section 6.1.1.

6.2.2 Eligibility criteria

The eligibility criteria for the economic evidence review reflects the PICO presented in Section *5* of this report and are summarized in Table 7.

Table 7: Eligibility criteria for the economic evidence review

	Inclusion criteria	Exclusion criteria
Population	Pregnant women, neonates (up to 28 days) and infants (up to 12 months)	– Older children. – Non-pregnant adults. – Infants not in their first RSV season.
Intervention	– RSV vaccination with RSVpreF during pregnancy. – RSV prophylaxis with nirsevimab (any dose) for newborns and infants.	Any other intervention
Comparators	– RSV vaccination with RSVpreF during pregnancy. – RSV prophylaxis with nirsevimab (any dose) for newborns and infants. – Placebo or standard of care.	Any other intervention
Outcomes	– Effectiveness outcomes (such as QALYs, life years); incremental and total. – Total costs; incremental and total. – Incremental analyses and other summary economic outcomes (for example ICERs, budget-impact per year). – Costs and healthcare resource use data used as modelling inputs in eligible economic evaluations.	Any other outcomes
Study design	Economic evaluations (including economic evaluations reported in HTAs)	– Any other study design – Relevant identified systematic reviews (published from 2021 to 2024) were referenced checked for eligible primary studies but were not included in the review.
Limits	– No date or language limits. – Studies in Europe, the US or Canada.	– Conference abstracts. – News articles, editorials, and preprints. – Studies in any other country than those that are eligible.

Abbreviations:

HTA = health technology appraisal, ICER = incremental cost-effectiveness ratio, ICU = intensive care unit, LRTI = lower respiratory tract infection, QALY = quality-adjusted life year, RSV = respiratory syncytial virus.

6.2.3 Study selection

Record assessment was undertaken for the using the same methods as for the clinical evidence review, as described in Section 6.1.3.

6.2.4 Data extraction, analysis and synthesis

One reviewer extracted data from the eligible studies and a second reviewer checked a 20% sample of the data points.

A data extraction sheet was developed in Excel and piloted on a study before progressing to full data extraction. The following elements were extracted from eligible studies:

- Study details (bibliographic details).
- Study funding and affiliation(s), where reported.
- Study characteristics (where relevant to economic evaluations):
    - Study design.
    - Study objective.
    - Number of participating centers and countries.
    - Eligibility criteria.
    - Number of patients randomized/analyzed.
    - Treatment duration.
    - Follow up duration.
    - Data collection time points.
- Modelled population characteristics:
    - Age (of both mother and baby, if applicable).
    - Sex of baby.
    - Gestational age of baby.
    - Co-morbidities (of both mother and baby, if applicable).
    - Month/season of illness.
    - Any other disease specific characteristics of interest in either the mother or child.
- Details of intervention:
    - Treatment.
    - Dose.
    - Timing of the intervention (e.g. week of pregnancy, age of baby, month/season).
- Modelling methods:
    - Type of economic evaluation – author definition.
    - Type of economic evaluation – reviewer definition (i.e. as determined by the reviewer).

- Analytic approach (trial based, model based).
- Model setting (including country).
- Perspective.
- Time horizon.
- Discounting (costs and effects).
- Reference year of the analysis.
- Currency.
- Model type (e.g. Markov, Decision Tree, Discrete Event Simulation).
- Model cycle lengths.
- Model health states used.
- Model assumptions (briefly described).
- Main input sources:
  - Utilities / disutilities / health-related quality of life (HRQoL) data:
    - Source of these data (e.g. from the literature, study elicited).
    - Mean or median data used (standard error and confidence intervals, if reported).
    - Mapping – i.e. how any mapping was conducted.
  - Effectiveness data – a summary of the source(s) of these data.
  - Resource use and costs data – a summary of the source(s) of these data.
- Sensitivity analyses methodology, brief description.

- Methods for non-models:
  - Cost calculation method brief description.
- Key results:
  - Costs outcomes, e.g. total costs (incremental and total).
  - Effectiveness outcomes, e.g. quality-adjusted life years (QALYs), life-year (incremental and total).
  - Base case incremental analyses outcomes, e.g. ICERs, budget-impact per year.
  - Base case outcomes for other economic evaluation types.
  - Sensitivity analyses:
    - Was this conducted (yes/no)? If ‘yes’, answer the following items too:

    - For any deterministic sensitivity analysis, what were the key drivers of cost-effectiveness?
    - For any probabilistic sensitivity analysis, what percentage were cost-effective?
  - Scenario analysis:
    - Was this conducted (yes/no)? If ‘yes’, answer the following items too:
    - Describe any scenarios analyzed.
    - Describe the effect on the economic evaluation outcome.
- Author-reported strengths and limitations of the approach.
- For HTAs, summary of any critique/strengths/limitations of the approach by, for example, an evidence review group or HTA committee.

6.2.5 Quality appraisal of economic studies

One reviewer assessed the risk of bias of each included study using the Checklist specified in NICE single technology appraisal guidance, adapted from Drummond (1996).[74] A second reviewer checked the risk of bias assessment. Full results of the risk of bias assessment of clinical studies are reported in Appendix A with a summary in Section 7.3.1.7. Results of the risk of bias assessment of economic studies are reported in Section 7.3.1.6.

7. Results of the Rapid Systematic Review

Summary statement of the rapid literature review

A single set of searches informed both the clinical and economic evaluation reviews. 1'133 records were identified, with 6 RCTs (reported in 18 publications) included in the clinical review and 10 studies included in the economic evaluations review.

Four RCTs assessed nirsevimab and two assessed RSVpreF. Regardless of whether the study drug was administered to infants or pregnant women, efficacy was assessed in infants. Outcomes were typically reported at 150 or 180 days. Two trials were considered at high risk of bias due to unclear randomization processes, unbalanced groups at baseline, and an open label design. The remaining trials were at moderate risk of bias due to unclear randomization processes, unclear concealment of allocation, and inadequate addressing of incomplete outcome data. Both nirsevimab and RSVpreF appeared to result in favorable efficacy outcomes compared with placebo or control. However, few trials conducted statistical significance testing to assess whether these findings were due to chance.

The 4 nirsevimab RCTs reported safety outcomes for infants, and the 2 RSVpreF RCTs reported safety outcomes for both infant and maternal participants. Timepoint of assessment varied from one to 12 months after birth/injection. All RCTs reported a favorable safety profile for nirsevimab and RSVpreF. However, none of the 6 RCTs assessed the statistical significance of safety outcomes.

The 10 economic evaluation studies were all identified from primary publications and were of high quality. No additional eligible economic evaluations were identified from HTA reports. No Swiss-based models were identified. The most applicable study estimated the cost effectiveness of maternal vaccination with RSVpreF compared with no prophylaxis from a Spanish healthcare payer and societal perspective. Within the parameters of the willingness-to-pay thresholds used in the studies: maternal vaccination with RSVpreF dominated no prophylaxis (i.e. it was more effective and less costly); nirsevimab was reported to be cost-effective when compared with no prophylaxis; and nirsevimab was reported to be cost-effective against maternal immunization.

7.1 Results of the Searches

The searches were undertaken between 25 September 2024 and 26 September 2024 and identified 1'133 records (Table 8). Following deduplication, 749 records remained for assessment. 610 records were excluded after an assessment of the information in the title and abstract. 139 full text documents were assessed for relevance, and 16 studies (reported in 28 documents) were eligible for inclusion. 6 RCTs (reported in 18 documents) were eligible for the clinical review, and 10 economic evaluations were included in the economic review. HTA reports identified by the searches

were assessed for inclusion in the economic review. However, none contained eligible de novo economic evaluations. In accordance with the protocol, the included studies list of relevant systematic reviews (including those conducted as part of an HTA) were checked for eligible primary trials or economic evaluations, but no further included studies were identified in this way.

Figure 3 summarizes the numbers of records included and excluded at each stage of the process. Table 9 presents a list of the included studies and their associated publications. Appendix A Table 1 presents a list of documents excluded following full-text review along with the reason for exclusion.

Table 8: Literature search results

Resource	Records identified
Databases	
MEDLINE(R) ALL	236
Embase	459
Cochrane Database of Systematic Reviews (CDSR)	1
Cochrane Central Register of Controlled Trials (CENTRAL)	178
HTA Database	25
NHS Economic Evaluation Database (NHS EED)	56
EconLit	0
Trials Registers	
ClinicalTrials.gov	95
WHO International Clinical Trials Registry Platform (ICTRP)	80
Other	
National Institute for Health and Care Excellence (NICE) webpages	0
Canada's Drug Agency (CDA-AMC) webpages (formerly Canadian Agency for Drugs and Technologies in Health (CADTH))	3
Reference list checking	0
Total	**1’133**

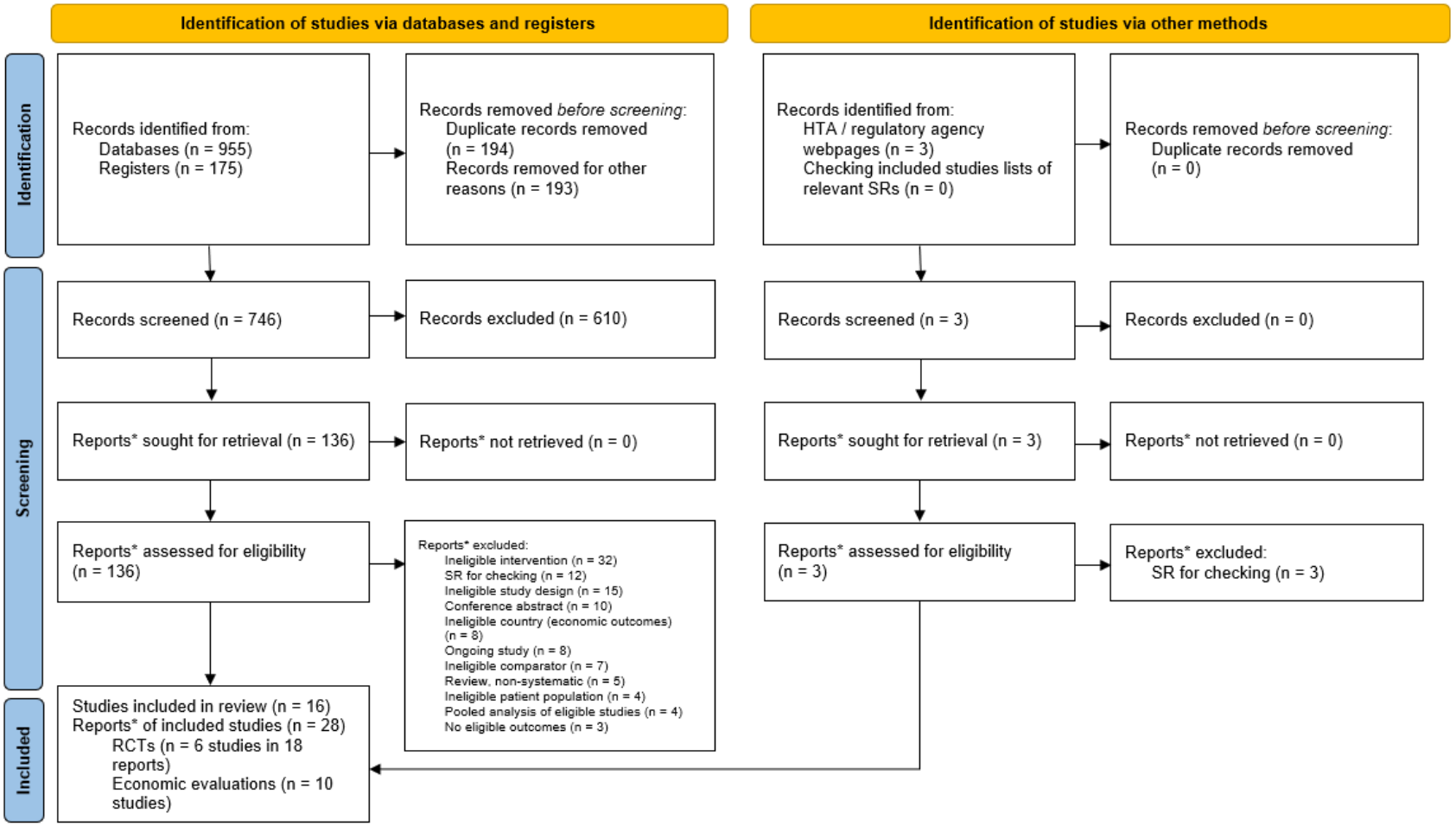

Figure 3: PRISMA flow diagram for reviews of clinical and economic evidence

*"Note that a "report" could be a journal article, preprint, conference abstract, study register entry, clinical study report, dissertation, unpublished manuscript, government report or any other document providing relevant information": https://www.bmj.com/content/372/bmj.n71.

Adapted from: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Table 9: Summary of included studies (n = 16 in 28 records, primary records in bold)

Study	References
Clinical outcomes (n = 6)	
Domachowske 2018[75]	**Domachowske JB, Khan AA, Esser MT, Jensen K, Takas T, Villafana T, et al. Safety, tolerability and pharmacokinetics of MEDI8897, an extended half-life single-dose respiratory syncytial virus prefusion F-targeting monoclonal antibody administered as a single dose to healthy preterm infants. Pediatr Infect Dis J. 2018.37(9):886-92. doi: 10.1097/INF.0000000000001916** MedImmune LLC. A phase 1b/2a randomized, double-blind, placebo-controlled, dose-escalation study to evaluate the safety, tolerability, and pharmacokinetics of MEDI8897, a monoclonal antibody with an extended half-life against respiratory syncytial virus, in healthy preterm infants. Identifier: NCT02290340. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2014. Available from https://clinicaltrials.gov/show/NCT02290340.
HARMONIE[76]	**Drysdale SB, Cathie K, Flamein F, Knuf M, Collins AM, Hill HC, et al. Nirsevimab for prevention of hospitalizations due to RSV in infants. N Engl J Med. 2023.389(26):2425-35. doi: 10.1056/NEJMoa2309189** Sanofi. Study of a single intramuscular dose of nirsevimab in the prevention of hospitalizations due to respiratory syncytial virus (RSV) infection in healthy term and preterm infants during the first year of life. Identifier: NCT05437510. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2022. Available from https://clinicaltrials.gov/study/NCT05437510.
Griffin 2020[77]	**Griffin MP, Yuan Y, Takas T, Domachowske JB, Madhi SA, Manzoni P, et al. Single-dose nirsevimab for prevention of RSV in preterm infants. N Engl J Med. 2020.383(5):415-25. doi: 10.1056/NEJMoa1913556** MedImmune LLC. A study to evaluate the safety and efficacy of MEDI8897 for the prevention of medically attended RSV LRTI in healthy preterm infants. Identifier: NCT02878330. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2016. Available from https://clinicaltrials.gov/show/NCT02878330. MedImmune LLC. Clinical study to evaluate the safety and efficacy of MEDI8897, an experimental drug, for preventing serious respiratory syncytial virus disease in healthy preterm infants. Identifier: 2016-001677-33. In: EU Clinical Trials Register [internet]. Amsterdam: European Medicines Agency: 2016. Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-001677-33/HU.
MATISSE[78]	**Kampmann B, Madhi SA, Munjal I, Simões EAF, Pahud BA, Llapur C, et al. Bivalent prefusion F vaccine in pregnancy to prevent RSV Illness in infants. N Engl J Med. 2023.388(16):1451-64. doi: 10.1056/NEJMoa2216480** Otsuki T, Akada S, Anami A, Kosaka K, Munjal I, Baber J, et al. Efficacy and safety of bivalent RSVpreF maternal vaccination to prevent RSV illness in Japanese infants: subset analysis from the pivotal randomized phase 3 MATISSE trial. Vaccine. 2024.42(22):126041. doi: 10.1016/j.vaccine.2024.06.009 Pfizer. A phase 3, randomized, double-blinded, placebo-controlled trial to evaluate the efficacy and safety of a respiratory syncytial virus (RSV) prefusion f subunit vaccine in infants born to women vaccinated during pregnancy. Identifier: NL-OMON52627. In: The Central Committee on Research Involving Human Subjects [internet]. The Hague: Ministry of Health: 2020. Available from https://onderzoekmetmensen.nl/en/trial/52627. Pfizer. A trial to evaluate the efficacy and safety of RSVpreF in infants born to women vaccinated during pregnancy. Identifier: NCT04424316. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2020. Available from https://clinicaltrials.gov/ct2/show/NCT04424316. Pfizer. A trial to evaluate the efficacy and safety of a respiratory syncytial virus (rsv) prefusion f subunit vaccine in infants born to women vaccinated during pregnancy. Identifier: EUCTR2019-002943-85. In: EU Clinical Trials Register [internet]. Amsterdam: European Medicines Agency: 2020. Available from https://clinicaltrialsregister.eu/ctr-search/trial/2019-002943-85/DK.
MELODY[79]	**Hammitt LL, Dagan R, Yuan Y, Baca Cots M, Bosheva M, Madhi SA, et al. Nirsevimab for prevention of RSV in healthy late-preterm and term infants. N Engl J Med. 2022.386(9):837-46. doi: 10.1056/NEJMoa2110275**

Study	References
	AstraZeneca. A study to evaluate the safety and efficacy of MEDI8897 for the prevention of medically attended lower respiratory tract infection due to respiratory syncytial virus in healthy late preterm and term infants (MELODY). Identifier: NCT03979313. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2019. Available from https://clinicaltrials.gov/study/NCT03979313. MedImmune LLC. Clinical study to evaluate the safety and efficacy of MEDI8897, an experimental drug, for preventing serious respiratory syncytial virus disease in healthy late preterm and term infants. Identifier: 2019-000114-11. In: EU Clinical Trials Register [internet]. Amsterdam: European Medicines Agency: 2019. Available from https://www.clinicaltrialsregister.eu/ctr-search/trial/2019-000114-11/PL. MedImmune LLC. MELODY study. Identifier: jRCT2080224798. In: Japan Registry of Clinical Trials (JRCT) [internet]. Tokyo: Ministry of Health, Labor and Welfare (MHLW): 2019. Available from https://jrct.niph.go.jp/latest-detail/jRCT2080224798.
Simões 2022[80]	**Simões EAF, Tita ATN, Swanson KA, Radley D, Houghton J, McGrory SB, et al. Prefusion F protein-based respiratory syncytial virus immunization in pregnancy. N Engl J Med. 2022.386(17):1615-26. doi: 10.1056/NEJMoa2106062** Pfizer. A phase 2b placebo-controlled, randomized study of a respiratory syncytial virus (RSV) vaccine in pregnant women. Identifier: NCT04032093. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2019. Available from https://clinicaltrials.gov/study/NCT04032093.
Economic outcomes (n = 10)	
Alvarez Aldean 2024[81]	Alvarez Aldean J, Rivero Calle I, Rodriguez Fernandez R, Aceituno Mata S, Bellmunt A, Prades M, et al. Cost-effectiveness analysis of maternal immunization with RSVpreF vaccine for the prevention of respiratory syncytial virus among infants in Spain. Infectious Diseases and Therapy. 2024.13(6):1315-31. doi: 10.1007/s40121-024-00975-6
Gebretekle 2024[82]	Gebretekle GB, Yeung MW, Ximenes R, Cernat A, Simmons AE, Killikelly A, et al. Cost-effectiveness of RSVpreF vaccine and nirsevimab for the prevention of respiratory syncytial virus disease in Canadian infants. Vaccine. 2024.42(21):126164. doi: 10.1016/j.vaccine.2024.126164
Getaneh 2023[83]	Getaneh AM, Li X, Mao Z, Johannesen CK, Barbieri E, van Summeren J, et al. Cost-effectiveness of monoclonal antibody and maternal immunization against respiratory syncytial virus (RSV) in infants: evaluation for six European countries. Vaccine. 2023.41(9):1623-31. doi: 10.1016/j.vaccine.2023.01.058
Gil-Prieto 2024[84]	Gil-Prieto R, Perez JJ, Drago G, Kieffer A, Roiz J, Kazmierska P, et al. Modelling the potential clinical and economic impact of universal immunisation with nirsevimab versus standard of practice for protecting all neonates and infants in their first respiratory syncytial virus season in Spain. BMC Infect Dis. 2024.24(1):924. doi: 10.1186/s12879-024-09642-0
Hodgson 2024[85]	Hodgson D, Wilkins N, van Leeuwen E, Watson CH, Crofts J, Flasche S, et al. Protecting infants against RSV disease: an impact and cost-effectiveness comparison of long-acting monoclonal antibodies and maternal vaccination. Lancet Reg Health Eur. 2024.38:100829. doi: 10.1016/j.lanepe.2023.100829
Kieffer 2022[86]	Kieffer A, Beuvelet M, Sardesai A, Musci R, Milev S, Roiz J, et al. Expected impact of universal immunization with nirsevimab against RSV-related outcomes and costs among all us infants in their first RSV season: a static model. J Infect Dis. 2022.226(Suppl 2):S282-92. doi: 10.1093/infdis/jiac216
Li 2022[87]	Li X, Bilcke J, Fernandez LV, Bont L, Willem L, Wisloff T, et al. Cost-effectiveness of respiratory syncytial virus disease prevention strategies: maternal vaccine versus seasonal or year-round monoclonal antibody program in Norwegian children. J Infect Dis. 2022.226(Suppl 1):S95-S101. doi: 10.1093/infdis/jiac064
Nourbakhsh 2021[88]	Nourbakhsh S, Shoukat A, Zhang K, Poliquin G, Halperin D, Sheffield H, et al. Effectiveness and cost-effectiveness of RSV infant and maternal immunization programs: a case study of Nunavik, Canada. EClinicalMedicine. 2021.41:101141. doi: 10.1016/j.eclinm.2021.101141
Shoukat 2023[89]	Shoukat A, Abdollahi E, Galvani AP, Halperin SA, Langley JM, Moghadas SM. Cost-effectiveness analysis of nirsevimab and maternal RSVpreF vaccine strategies for prevention of respiratory syncytial virus disease among infants in Canada: a simulation study. Lancet Reg Health Am. 2023.28:100629. doi: 10.1016/j.lana.2023.100629
Yu 2024[90]	Yu T, Padula WV, Yieh L, Gong CL. Cost-effectiveness of nirsevimab and palivizumab for respiratory syncytial virus prophylaxis in preterm infants 29-34 6/7 weeks' gestation in the United States. Pediatr Neonatol. 2024.65(2):152-58. doi: 10.1016/j.pedneo.2023.04.015

7.2 Review of Clinical Evidence

7.2.1 Study characteristics

4 trials assessed nirsevimab, 3 comparing to placebo,[75, 77, 79] and one comparing to no intervention.[76] 2 trials compared maternal vaccination with RSVpreF to placebo.[78, 80] All 6 trials were multinational and reported both safety and efficacy outcomes. Nirsevimab trials used Phase 1b to Phase 3b designs: one was Phase 1b/2a trial,[75] one was a Phase 2b trial,[77] one was a Phase 3 trial,[79] and one was Phase 3b.[76] Of the 2 RSVpreF trials, one was a Phase 2b trial[80] and one was a Phase 3 trial.[78] All trials were funded by pharmaceutical companies. The 4 nirsevimab trials were funded by MedImmune (AstraZeneca)[75] or MedImmune (AstraZeneca) in conjunction with Sanofi.[76, 77, 79] Both RSVpreF trials were funded by Pfizer.[78, 80] Key trial characteristics of nirsevimab and RSVpreF studies are summarized in Table 10 and Table 12, respectively. The interventions assessed by the 4 nirsevimab trials and 2 RSVpreF trials, including details of doses and timing, are summarized in Table 12 and Table 13, respectively.

Three nirsevimab RCTs[76, 77, 79] and one RSVpreF RCT[78] randomized more than 1'000 participants. Griffin 2020 and MELODY both randomized participants (1'453 in Griffin 2020 and 3'012 in MELODY) 2:1 to nirsevimab and placebo, respectively. HARMONIE randomized 8'058 participants 1:1 to either nirsevimab or placebo.[76] MATISSE randomized 7'357 participants 1:1 to either RSVpreF or placebo.[78]

The 2 remaining RCTs recruited fewer participants. The remaining nirsevimab study, Domachowske 2018, randomized 89 participants to either placebo (18 participants) or to one of 3 doses of nirsevimab (8 participants to 10 mg, 31 participants to 25 mg, and 32 participants to 50 mg).[75] The authors reported that participants were randomized 4:1 to nirsevimab or placebo but it is not clear how the nirsevimab participants were then assigned to each dose group.[75] The remaining RSVpreF RCT, Simões 2022, randomized 572 maternal participants equally to placebo, 120 µg RSVpreF, 120 µg RSVpreF with aluminum hydroxide, 240 µg RSVpreF, or 240 µg with aluminum hydroxide.[80] However, outcomes for the whole cohort were only reported in the clinical trial record, which reported safety outcomes only. The efficacy data (and some safety data) were derived from the US cohort of 406 participants.[80] Simões 2022 also reported efficacy data for all 508 US infants analyzed through to the end of the 2019/20 season.[80]

Of the 4 nirsevimab trials, 2 assessed a dose of 50 mg for infants weighing <5 kg and 100 mg for those weighing ≥5 kg.[76, 79] All nirsevimab patients in Griffin 2020 received 50 mg.[77] The fourth trial, Domachowske 2018, compared 3 doses of nirsevimab (10 mg, 25 mg, and 50 mg) against placebo.[75] Both trials of RSVpreF assessed a dose of 120 µg.[78, 80] One[80] also assessed a dose of 240 µg, with doses assessed with and without aluminum hydroxide.[80] Both nirsevimab and RSVpreF (and placebo, where relevant) were given as a single intramuscular injection in all included trials.

All 6 trials reported efficacy and safety outcomes. Efficacy was assessed in infants, regardless of whether the study drug was administered to infants or pregnant women. In all 4 nirsevimab trials, the injection was administered to infants entering their first RSV season.[75-77, 79] In both RSVpreF trials, the injection was given to pregnant women between 24 and 36 weeks gestation.[78, 80]

The most commonly reported efficacy outcomes were hospitalization due to RSV LRTI (reported by 5 RCTs)[76-80] and medically attended RSV LRTI (reported by 4 RCTs).[77-80] Two RCTs also reported severe RSV LRTI.[76, 78] Two reported medically attended LRTI from any cause[75, 78] and one reported hospitalization for any cause LRTI.[76] Three nirsevimab trials reported efficacy outcomes for up to 151 days after injection.[75, 77, 79] The remaining nirsevimab trial[76] and the RSVpreF trials reported efficacy outcomes up to 181 days after injection or birth.[78, 80]

For safety outcomes, all 6 RCTs reported adverse events (AEs). The RSVpreF trials reported AEs in both maternal and infant participants, including any AEs, serious AEs, severe AEs, AEs due to study drug, injection site reactions, and AEs of special interest. Safety outcomes were collected for up to 361,[75, 77] 366[76] or 510[79] days after injection in the nirsevimab trials. In MATISSE,[78] infants were followed up to 12 or 24 months of age depending on when they were recruited. Simões 2022[80] was an interim analysis so any safety events before the data cutoff were reported.

Some trials also reported outcomes such as serum concentrations of antibodies, which were not eligible outcomes for this review.

Table 10: Trial characteristics for RCTs reporting clinical evidence of nirsevimab

Trial	Objective	Funding	Location of trial (n)/countries	Date of trial	Outcomes and outcome measures	Data collection timepoints/length of follow up
Griffin 2020[77] **NCT02878330/2016-001677-33** **Phase 2b RCT**	To assess the efficacy of MEDI8897 when administered as a single 50 mg intramuscular dose to healthy preterm infants born between 29 weeks 0 days and 34 weeks 6 days GA and entering their first RSV season for the reduction of medically attended LRTI due to RT-PCR-confirmed RSV, compared with placebo	MedImmune (a subsidiary of AstraZeneca) and Sanofi Pasteur	164 (161 reported in NCT record) sites in 23 countries[77]	August 2016 (ethics approval) to June 2018	**Primary outcome(s) and measure(s):** – Incidence of medically attended LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV over the duration of the 5-month RSV season. **Secondary outcome(s) and measure(s):** – Incidence of hospitalizations due to RT-PCR-confirmed RSV over the duration of the 5-month RSV season. – Safety and tolerability of MEDI8897 as assessed by the occurrence of all treatment-emergent AEs, treatment-emergent serious AEs, AEs of special interest, and new onset chronic diseases. – Single-dose MEDI8897 serum concentrations. – Incidence of Anti-drug Antibodies to MEDI8897 in serum.	Up to day 151 for efficacy outcomes, up to day 361 for safety outcomes: by telephone every 2 weeks and in person during trial site visits on days 8, 31, 91, and 151, as well as on day 361 after administration of the dose.
Domachowske 2018[75] **NCT02290340** **Phase 1b/2a RCT**	To report results from the first infant study to evaluate the safety and pharmacokinetics of MEDI8897 when administered to healthy preterm infants as a single 10, 25 or 50 mg intramuscular dose	MedImmune (a subsidiary of AstraZeneca)	10 sites in 3 countries according to the full text publication, but the NCT record reports 13 sites	October 2014 to September 2018	**Primary outcome(s) and measure(s):** – Number of patients with AEs, serious AEs, AEs of special interest, number of participants with clinical laboratory abnormalities reported as AEs. **Secondary outcome(s) and measure(s):** 1. Medically attended LRTI (up to day 151). 2. Time to reach maximum observed serum concentration (Tmax) of MEDI8897. 3. Maximum observed serum concentration (Cmax) of MEDI8897. 4. Area under the concentration-time curve from Day 1 to Day 151 of MEDI8897. 5. Area under the concentration-time curve from zero to infinity of MEDI8897. 6. Terminal elimination half-life (t1/2) of MEDI8897, extravascular clearance (CL/F) of MEDI8897.	Up to day 361

Trial	Objective	Funding	Location of trial (n)/countries	Date of trial	Outcomes and outcome measures	Data collection timepoints/length of follow up
					7. Extravascular volume of distribution (Vz/F) of MEDI8897. **8.** Number of participants positive for anti-drug antibodies to MEDI8897.	
HARMONIE[76] **NCT05437510** **Phase 3b RCT**	To determine the efficacy and safety of a single intramuscular injection of nirsevimab as compared with standard care in preventing RSV-associated hospitalizations in infants 12 months of age or younger	Sanofi and AstraZeneca	235 sites (240 in clinical trial record) in 3 countries[76]	NR (patients followed for 366 days after randomization and administration)	**Primary outcome(s) and measure(s):** – Hospitalization for RSV-associated LRTI, defined as admission to the hospital on the basis of the treating physician's decision and confirmation of RSV by means of a positive result of a test performed in accordance with routine practice, during the RSV season in France, Germany, and the United Kingdom. **Secondary outcome(s) and measure(s):** – Very severe RSV-associated LRTI (defined as hospitalization for RSV-associated LRTI with an oxygen saturation <90% [in accordance with the World Health Organization case definition] at any time during hospitalization and the need for supplemental oxygen). – Hospitalization for RSV-associated LRTI in each country. – Hospitalization for LRTI from any cause – AEs	Efficacy up to day 181. Safety up to day 366, but the trial is ongoing.
MELODY[79] **NCT03979313/2019-000114-11/jRCT2080224798** **Phase 3 RCT**	To evaluate the efficacy and safety of nirsevimab in healthy late-preterm and term infants entering their first RSV season	MedImmune (a subsidiary of AstraZeneca) and Sanofi	150 sites in 21 countries[79], although NCT record reports 199 sites in 31 countries	May 2019 to February 2024	**Primary outcome(s) and measure(s):** – Medically attended RSV-associated LRTI. **Secondary outcome(s) and measure(s):** – Hospitalization due to medically attended RSV-associated LRTI. – AEs (any AE, AE related to study drug, serious AE, AE of special interest, AE related to Covid-19, all-cause mortality).	150 days (follow-up planned for up to 510 days)

Abbreviations

AE = adverse event, LRTI = lower respiratory tract infection, RT-PCR = reverse transcription polymerase chain reaction, RSV = respiratory syncytial virus.

Notes

Grey text indicates outcomes that were not eligible for this review.

[1] Belgium, Bulgaria, Canada, Czech Republic, Estonia, Finland, France, Hungary, Italy, Latvia, Lithuania, Poland, Spain, Sweden, Turkey, United Kingdom, United States, Argentina, Australia, Brazil, Chile, New Zealand, South Africa.

[2] 4 sites each in the US and South Africa and 2 in Chile according to the full text, but the NCT record reports 13 sites (7 in the US, 4 in South Africa and 2 in Chile).

[3] France, Germany, UK.

[4] 20 in the northern hemisphere (Austria, Belgium, Bulgaria, Canada, Czech Republic, Estonia, Finland, France, Germany, Israel, Japan, Republic of Korea, Latvia, Lithuania, Poland, Russia, Spain, Sweden, UK, US] and South Africa). The NCT record reports 199 sites in 31 countries: US, Argentina, Australia, Austria, Belgium, Bulgaria, Canada, Chile, Colombia, Czechia, Estonia, Finland, France, Germany, Israel, Italy, Japan, Republic of Korea, Latvia, Lithuania, Mexico, New Zealand, Panama, Poland, Russia, South Africa, Spain, Sweden, Turkey, Ukraine, UK.

Table 11: Trial characteristics for RCTs reporting clinical evidence of RSVpreF

Trial	Objective	Funding	Location of trial (n)/countries	Date of trial	Outcomes and outcome measures	Data collection timepoints/length of follow up
MATISSE[78] **NCT04424316** **Phase 3 RCT**	To report the results of MATISSE, evaluating the efficacy and safety of maternal RSVpreF vaccination in preventing RSV-associated LRTI in infants	Pfizer	499 sites in 18 countries[1]	June 2020 to October 2023	**Primary outcome(s) and measure(s):** – Medically attended severe RSV-associated LRTI in infants within 90, 120, 150 and 180 days after birth. – Medically attended RSV-associated LRTI in infants within 90, 120, 150, and 180 days after birth. – Reactogenicity and AEs in the maternal participants. – AEs and newly diagnosed chronic medical conditions in the infants. **Secondary outcome(s) and measure(s):** – RSV-associated hospitalization. – Medically attended LRTI of any cause. – Serious AEs and newly diagnosed chronic medical conditions from birth through 12 months of age (birth through 24 months of age in infants enrolled during the first trial year).	90, 120, 150 and 180 days after birth. Follow-up of 1 year (2 years in participants recruited in first year of study).
Simões 2022[80] **NCT04032093** **Phase 2b RCT**	To report on a planned interim analysis of the safety and immunogenicity of RSVpreF vaccine and of the transplacental transfer of RSV neutralizing antibodies	Pfizer	Clinical trial record reports 159 sites in 4 countries,[2] but the Simões 2022 paper is an interim analysis of data from the US only	2019 to 2020	**Primary outcome(s) and measure(s):** – Solicited local and systemic reactions recorded with the use of an electronic diary kept by the participants for 7 days after vaccination. – Unsolicited AEs that occurred during the month after vaccination (in maternal participants) or during the first month of life (in infant participants). – Serious AEs, medically attended AEs, and AEs of special interest that occurred throughout the observation period from the first participant's vaccination through 31 January 2020.	Weekly electronic diaries and planned visits 2 and 4 weeks later, at delivery, and at 1, 6 and 12 months after birth. Infants were enrolled at birth and were evaluated 1, 2, 4, 6 and 12 months later. In the Simões 2022 interim analysis, participants were followed from the participant's vaccination through January 2020.

Trial	Objective	Funding	Location of trial (n)/countries	Date of trial	Outcomes and outcome measures	Data collection timepoints/length of follow up
					Secondary outcome(s) and measure(s): – 50% titers of RSV A, B, and combined A/B neutralizing antibodies in maternal serum at delivery and in umbilical-cord blood. – Transplacental transfer ratios. – Any medically attended RSV-associated LRTI. – Participants with RSV who required hospitalization.	

Abbreviations

AE = adverse event, LRTI = lower respiratory tract infection, RSV = respiratory syncytial virus.

Notes

Grey text indicates outcomes that were not eligible for this review.

[1] US, Argentina, Australia, Brazil, Canada, Chile, Denmark, Finland, Gambia, Japan, Republic of Korea, Mexico, Netherlands, New Zealand, Philippines, South Africa, Spain, Taiwan.

[2] Wider trial conducted in United States, Chile, Argentina, and South Africa.

Table 12: Intervention details for RCTs reporting clinical evidence of nirsevimab

Trial	Number of participants analyzed	Intervention	Timing
Domachowske 2018[75]	18	Placebo	Day 1 of study (infants entering their first full RSV season)
	8	Nirsevimab 10 mg	
	31	Nirsevimab 25 mg	
	32	Nirsevimab 50 mg	
Griffin 2020[77]	969	Nirsevimab 50 mg	Day 1 of study (infants ≤8 months of age entering their first full RSV season)
	484	Placebo	
HARMONIE[76]	4’037	Nirsevimab 50 mg for infants weighing <5 kg and 100 mg for those weighing ≥5 kg	Nearly all the infants who received nirsevimab (3’998 [99.6%]) received it during the RSV season
	4’021	Standard care (no intervention)	NA
MELODY*[79]	994	Nirsevimab 50 mg if they weighed <5 kg or 100 mg if they weighed ≥5 kg	Infants were 1 year of age or younger and were entering their first RSV season
	496	Placebo	
	2’009	Nirsevimab 50 mg if they weighed <5 kg or 100 mg if they weighed ≥5 kg	
	1’003	Placebo, dose NA	

Abbreviations

NA = not applicable, RCTs = randomized controlled trials, RSV = respiratory syncytial virus, SD = standard deviation.

Notes

* 1’490 (994 to nirsevimab and 496 placebo) in primary analysis (full text). Some outcomes reported in trials records from a later data cutoff: 3’012 (2’009 to nirsevimab and 1’003 to placebo).

Table 13: Intervention details for RCTs reporting clinical evidence of RSVpreF

Trial	Number of participants analyzed	Intervention	Timing
MATISSE[78]	3'695 expectant mothers randomized 3'570 infants analyzed	RSVpreF 120 µg (intramuscularly)	Week 24 to 36 of pregnancy Mean (SD) week of pregnancy at vaccination: 30.8 (3.5) Median (range) week of pregnancy at vaccination: 31.3 (24.0 to 36.6)
	3'697 expectant mothers randomized 3'558 infants analyzed	Placebo, dose NA	Week 24 to 36 of pregnancy Mean (SD) week of pregnancy at vaccination: 30.8 (3.6) Median (range) week of pregnancy at vaccination: 31.3 (24.0 to 36.9)
Simões 2022†[80]	Maternal participants: 79 Infant participants: 79	RSVpreF 120 µg (without aluminum hydroxide)	24 through 36 weeks' gestation Mean (SD) gestational age at vaccination: 31.1 (3.3) Median (range) gestational age at vaccination: 31.6 (24.1 to 36.1)
	Maternal participants: 84 Infant participants: 84	RSVpreF 120 µg (with aluminum hydroxide)	24 through 36 weeks' gestation Mean (SD) gestational age at vaccination: 30.8 (3.1) Median (range) gestational age at vaccination: 30.6 (24.0 to 36.0)
	Maternal participants: 78 Infant participants: 78	RSVpreF 240 µg (without aluminum hydroxide)	24 through 36 weeks' gestation Mean (SD) gestational age at vaccination: 31.3 (3.1) Median (range) gestational age at vaccination: 31.5 (24.3 to 35.9)
	Maternal participants: 86 Infant participants: 85	RSVpreF 240 µg (with aluminum hydroxide)	24 through 36 weeks' gestation Mean (SD) gestational age at vaccination: 31.4 (3.0) Median (range) gestational age at vaccination: 31.4 (24.3 to 36.9)
	Maternal participants: 79 Infant participants: 78	Placebo, dose NA	24 through 36 weeks' gestation Mean (SD) gestational age at vaccination: 31.1 (2.9) Median (range) gestational age at vaccination: 31.4 (24.1 to 35.9)
	Maternal participants: 115 Infant participants: 114	RSVpreF 120 µg (without aluminum hydroxide)	24 through 36 weeks' gestation
	Maternal participants: 117 Infant participants: 117	RSVpreF 120 µg (with aluminum hydroxide)	24 through 36 weeks' gestation
	Maternal participants: 116 Infant participants: 113	RSVpreF 240 µg (without aluminum hydroxide)	24 through 36 weeks' gestation
	Maternal participants: 114 Infant participants: 112	RSVpreF 240 µg (with aluminum hydroxide)	24 through 36 weeks' gestation
	Maternal participants: 117 Infant participants: 116	Placebo, dose NA	24 through 36 weeks' gestation

Abbreviations

NA = not applicable, RCTs = randomized controlled trials, SD = standard deviation.

Notes

† Simões 2022 is an article reporting the US cohort of NCT04032093. As NCT04032093 does not report any efficacy data, both Simões 2022[80] and the clinical trial record for NCT04032093[91] are reported.

7.2.2 Patient characteristics

Key patient characteristics for clinical studies of nirsevimab and RSVpreF are summarized in Table 14 and Table 15, respectively.

The participants in all 4 nirsevimab trials were ≤12 months of age (mean age ranged from 2.92[79] to 6.95[75] months) entering their first RSV season at the time of injection. All participants in the nirsevimab trials were born, at least, at 29 weeks gestation, but the eligibility requirements for gestational age at birth varied across the nirsevimab trials.[75-77, 79] Griffin 2020 included participants born between 29 and 35 weeks gestational age,[77] while Domachowske 2018 included patients born between 32 and 35 weeks gestational age.[75] HARMONIE and MELODY included both preterm and term infants – born at ≥29 weeks gestational age[76] and ≥35 weeks gestational age,[79] respectively.

Maternal participants in the RSVpreF trials were ≤49 years of age (mean age between 26.4 and 29.1 years old)[78] and between 24 and 36 weeks pregnant at the time of vaccination.[78, 80]

Both the highest and lowest proportion of male infants in a study group were in Domachowske 2018: 38.9% (7/18) in the placebo group and 61.3% (19/31) in the nirsevimab 25 mg group.[75] This is likely due to the smaller size of the study and study groups compared with other included studies. Across the other 3 nirsevimab studies, the proportion of male participants ranged from 48.2%[79] to 53.7%.[77] The authors of Domachowske 2018 also noted that participants in the 10 mg group were younger and weighed less than other trial participants.[75]

All 6 studies recruited healthy participants, and none conducted subgroup analyses on participants at higher risk.

For the 2 RSVpreF studies (MATISSE[78] and Simões 2022),[80] papers were available reporting on a geographic subgroup of patients. Otsuki 2024[92] reported the Japanese cohort from MATISSE, while Simões 2022[80] reported only US patients from NCT04032093. Otsuki 2024 has not been discussed in this report because Kampmann 2023[78] reported the full global cohort of patients in MATISSE and has, therefore, been used as the primary data source for this trial. Since no other papers were identified reporting on NCT04032093, and the trial record does not report all the eligible outcomes, Simões 2022[80] has been used as the primary data source for this trial – despite only reporting the US cohort of patients.

Of the 4 nirsevimab trials, 3 reported data on participant race and HARMONIE did not. Griffin 2020 and the primary cohort of MELODY recruited mainly white participants. Black/African American participants representing 13.8% and 19.5% (placebo and nirsevimab arms, respectively) of the population of Griffin 2020, and 27.4% and 28.8% (placebo and nirsevimab arms, respectively) of the population of MELODY. Domachowske 2018 recruited a higher proportion of black/African American participants, although they did not appear to be evenly distributed across arms (12.5% in nirsevimab 10 mg, 61.3% in nirsevimab 25 mg, 65.5% in nirsevimab 50 mg, and 55.6% placebo).[75] The majority of other patients in Griffin 2020 and MELODY were white, while Domachowske 2018 contained up to 35% participants per arm identifying as "other". One trial of

nirsevimab (Griffin 2020) reported participant ethnicity, with 23.2% and 18.8% Hispanic/Latino participants in the nirsevimab and placebo arms, respectively.

In the 2 RSVpreF trials, the proportion of black/African American maternal participants ranged from 17.4% (RSVpreF 240 µg with aluminium hydroxide, Simões 2022) to 19.7% (placebo, MATISSE). The exception was the placebo arm of Simões 2022, which contained 6.3% black/African American maternal participants, meaning that this trial was imbalanced at baseline in terms of participants' race. In both trials, the majority of the remaining participants were white. Both trials reported patient ethnicity, with the proportion of Hispanic/Latino maternal participants ranging from 21.8% (RSVpreF 240 µg, Simões 2022) to 31.6% (placebo, Simões 2022) across arms.

Table 14: Patient characteristics for RCTs reporting clinical evidence of nirsevimab

Study	Key inclusion criteria	Intervention	N of participants analyzed	Age Mean (SD) months (infants) or years (mothers)	Sex of baby n (%) male	Gestational age of baby Mean (SD) weeks	Race or ethnic group n (%)
Griffin 2020[77]	Healthy infants born between 29 weeks 0 days and 34 weeks 6 days gestational age and ≤12 months of age (≤8 months for EU participants) and entering their first full RSV season at the time of screening.	Nirsevimab (50 mg)	969	3.29 (2.22)	501 (51.7*)	32.7 (1.4)	**Race:** American Indian or Alaska Native: 0 Asian: 5 (0.5*) Native Hawaiian or Other Pacific Islander: 8 (0.8*) Black or African American: 189 (19.5*) White: 693 (71.5*) More than one race: 12 (1.2*) Other: 61 (6.3*) Unknown or NR: 1 (0.1*) **Ethnicity:** Hispanic or Latino: 225 (23.2*) Not Hispanic or Latino: 743 (76.7*) Unknown or NR: 1 (0.1*)
		Placebo	484	3.28 (2.31)	260 (53.7*)	32.7 (1.5)	**Race:** American Indian or Alaska Native: 1 (0.2*) Asian: 10 (2.1*) Native Hawaiian or Other Pacific Islander: 3 (0.6*) Black or African American: 67 (13.8*) White: 355 (73.3*) More than one race: 5 (1.0*) Other: 43 (8.9*) Unknown or NR: 0 **Ethnicity:** Hispanic or Latino: 91 (18.8*) Not Hispanic or Latino: 393 (81.2*) Unknown or NR: 0
Domachowske 2018[75]	Healthy infants, born between 32 weeks 0 days and 34 weeks 6 days gestational age, who are entering their first RSV season at the time of screening.	Nirsevimab (10 mg)	8	4.18 (2.05)	4 (50.0)	33.1 (0.8)	Black: 1 (12.5) White: 6 (75.0) American Indian/Alaskan Native: 0 (0.0) Asian: 0 (0.0) Other: 0 (0.0) Multiracial: 1 (12.5)
		Nirsevimab (25 mg)	31	6.65 (2.69)	19 (61.3)	33.0 (0.8)	Black: 19 (61.3) White: 0 (0.0) American Indian/Alaskan Native: 0 (0.0) Asian:1 (3.2) Other: 11 (35.5) Multiracial: 0 (0.0)

Study	Key inclusion criteria	Intervention	N of participants analyzed	Age Mean (SD) months (infants) or years (mothers)	Sex of baby n (%) male	Gestational age of baby Mean (SD) weeks	Race or ethnic group n (%)
		Nirsevimab (50 mg)	32	6.94 (2.49)	19 (59.4)	33.2 (0.8)	Black: 21 (65.6) White: 2 (6.3) American Indian/Alaskan Native: 1 (3.1) Asian: 0 (0.0) Other: 7 (21.9) Multiracial: 1 (3.1)
		Placebo	18	6.95 (2.63)	7 (38.9)	33.1 (0.6)	Black: 10 (55.6) White: 4 (22.2) American Indian/Alaskan Native: 0 (0.0) Asian: 0 (0.0) Other: 4 (22.2) Multiracial: 0 (0.0)
HARMONIE[76]	Born at ≥29 weeks gestational age and aged 0 to 12 months entering their first RSV season on the day of randomization.	Nirsevimab (50 mg for infants weighing <5 kg and 100 mg for those weighing ≥5 kg)	4'037	4.53 (3.34)	2'087 (51.7)	38.84 (2.28)	NR
		No intervention	4'021	4.48 (3.30)	2'108 (52.4)	38.93 (5.35)	NR
MELODY[79]	Healthy infants in their first year of life and born at or after 35 weeks 0 days gestational age and are entering their first RSV season at the time of screening.	Nirsevimab (50 mg if they weighed <5 kg or 100 mg if they weighed ≥5 kg)	Primary cohort: 994	2.912 (2.2099)	530 (53.3)	n (%): ≥35 to <37 weeks: 132/993 (13.3) ≥37 weeks: 861/993 (86.7)	American Indian or Alaska Native: 57 (5.7) Asian: 36 (3.6) Black or African American: 286 (28.8) Native Hawaiian or other Pacific Islander: 6 (0.6) White: 524 (52.7) Multiple categories checked: 12 (1.2) Other: 70 (7.0) Missing: 3 (0.3)
		Placebo	Primary cohort: 496	3.012 (2.2520)	239 (48.2)	n (%): ≥35 to <37 weeks: 76/495 (15.4) ≥37 weeks: 419/495 (84.6)	American Indian or Alaska Native: 26 (5.2) Asian: 18 (3.6) Black or African American: 136 (27.4) Native Hawaiian or other Pacific Islander: 5 (1.0) White: 272 (54.8) Multiple categories checked: 1 (0.2) Other: 38 (7.7) Missing: 0 (0.0)
		Nirsevimab (50 mg if they weighed <5 kg or 100 mg if they weighed ≥5 kg)	All subjects: 2'009	2.905 (2.220)	1'071 (53.3)	NR	American Indian or Alaska Native: 92 (4.6) Asian: 109 (5.4) Black or African American: 299 (14.9) Native Hawaiian or other Pacific Islander: 15 (0.7) White: 1'052 (52.4) Multiple categories checked: 19 (0.9) Other: 420 (20.9) Missing: 3 (0.1)

Study	Key inclusion criteria	Intervention	N of participants analyzed	Age Mean (SD) months (infants) or years (mothers)	Sex of baby n (%) male	Gestational age of baby Mean (SD) weeks	Race or ethnic group n (%)
		Placebo	All subjects: 1’003	2.918 (2.2740)	503 (50.1)	NR	American Indian or Alaska Native: 52 (5.2) Asian: 50 (5.0) Black or African American: 138 (13.8) Native Hawaiian or other Pacific Islander: 8 (0.8) White: 541 (53.9) Multiple categories checked: 8 (0.8) Other: 206 (20.5) Missing: 0 (0.0)

Abbreviations

EU = European Union, NR = not reported, RSV = respiratory syncytial virus, SD = standard deviation.

Table 15: Patient characteristics for RCTs reporting clinical evidence of RSVpreF

Study	Key inclusion criteria	Intervention	N of participants analyzed	Age Mean (SD) months (infants) or years (mothers)	Sex of baby n (%) male	Gestational age of baby Mean (SD) weeks	Race or ethnic group n (%)
MATISSE[78]	Healthy women ≤49 years of age between 24 0/7 and 36 0/7 weeks of gestation with an uncomplicated, singleton pregnancy, who are at no known increased risk for complications.	RSVpreF (120 µg)	Maternal participants: 3'682 Infant participants: 3'568	29.1 (5.6)	1'816 (50.9)	24 to <28 weeks: 1/3'568 (<0.1) 28 to <34 weeks: 20/3'568 (0.6) 34 to <37 weeks: 180/3'568 (5.0) 37 to <42 weeks: 3'343/3'568 (93.7) ≥42 weeks: 21/3'568 (0.6)	**Race:** White: 2'383 (64.7) Black: 720 (19.6) Asian: 454 (12.3) Multiracial: 30 (0.8) Race NR: 41 (1.1) Race unknown: 7 (0.2) **Ethnicity:** Hispanic or Latinx: 1'049 (28.5) Not Hispanic or Latinx: 2'603 (70.7) American Indian or Alaska Native: 38 (1.0) Native Hawaiian or other Pacific Islander: 9 (0.2) Ethnic group NR or unknown: 30 (0.8)
		Placebo	Maternal participants: 3'675 Infant participants: 3'558	29.0 (5.7)	1'793 (50.4)	24 to <28 weeks: 1/3'558 (<0.1) 28 to <34 weeks: 11/3'558 (0.3) 34 to <37 weeks: 157/3'558 (4.4) 37 to <42 weeks: 3'356/3'558 (94.3) ≥42 weeks: 30/3'558 (0.8)	**Race:** White: 2'365 (64.4) Black: 723 (19.7) Asian: 464 (12.6) Multiracial: 21 (0.6) Race NR: 45 (1.2) Race unknown: 8 (0.2) **Ethnicity:** Hispanic or Latinx: 1'075 (29.3) Not Hispanic or Latinx: 2'567 (69.8) American Indian or Alaska Native: 37 (1.0) Native Hawaiian or other Pacific Islander: 12 (0.3) Ethnic group NR or unknown: 33 (0.9)
Simões 2022[80]	Healthy women 18 to 49 years of age between 24 and 36 weeks of gestation on the day of planned vaccination, with an uncomplicated pregnancy, who are at no known increased risk for complications, and whose fetus has no significant abnormalities observed on ultrasound.	RSVpreF (120 µg)	Maternal participants: 79, infant participants: 79	26.9 (4.7)	34 (43.0)	39.17 (1.040)	**Race:** White: 62 (78.5) Black or African American: 14 (17.7) Asian: 1 (1.3) American Indian or Alaskan native: 0 Multiracial: 0 NR: 2 (2.5) **Ethnicity:** Hispanic/Latina: 21 (26.6) Non-Hispanic/non-Latina: 58 (73.4)
		RSVpreF (120 µg with	Maternal participants: 84,	27.2 (5.4)	45 (53.6)	38.91 (1.431)	**Race:** White: 63 (75.0) Black or African American: 16 (19.0)

Study	Key inclusion criteria	Intervention	N of participants analyzed	Age Mean (SD) months (infants) or years (mothers)	Sex of baby n (%) male	Gestational age of baby Mean (SD) weeks	Race or ethnic group n (%)
		aluminum hydroxide)	infant participants: 84				Asian: 1 (1.2) American Indian or Alaskan native: 1 (1.2) Multiracial: 0 NR: 3 (3.6) **Ethnicity:** Hispanic/Latina: 25 (29.8) Non-Hispanic/non-Latina: 59 (70.2)
		RSVpreF (240 µg)	Maternal participants: 78, infant participants: 78	27.3 (5.1)	45 (53.6)	38.90 (1.284)	**Race:** White: 62 (79.5) Black or African American: 15 (19.2) Asian: 0 American Indian or Alaskan native: 0 Multiracial: 0 NR1 (1.3) **Ethnicity:** Hispanic/Latina: 17 (21.8) Non-Hispanic/non-Latina: 61 (78.2)
		RSVpreF (240 µg with aluminum hydroxide)	Maternal participants: 86, infant participants: 85	27.1 (5.3)	41 (48.2)	39.01 (1.068)	**Race:** White: 67 (77.9) Black or African American: 15 (17.4) Asian: 3 (3.5) American Indian or Alaskan native: 0 Multiracial: 0 NR: 1 (1.2) **Ethnicity:** Hispanic/Latina: 24 (27.9) Non-Hispanic/non-Latina: 62 (72.1)
		Placebo	Maternal participants: 79, infant participants: 78	26.4 (5.0)	41 (52.6)	39.18 (0.914)	**Race:** White: 71 (89.9) Black or African American: 5 (6.3) Asian: 0 American Indian or Alaskan native: 1 (1.3) Multiracial: 2 (2.5) NR: 0 **Ethnicity:** Hispanic/Latina: 25 (31.6) Non-Hispanic/non-Latina: 54 (68.4)

Abbreviations

EU = European Union, NR = not reported, RSV = respiratory syncytial virus, SD = standard deviation.

7.2.3 Study quality appraisal

Section 1.3 of Appendix A summarizes the risk of bias assessments for the 6 trials providing clinical evidence. Section 1.3 of Appendix A also contains full risk of bias assessments for each trial. Overall judgements were arrived at by qualitatively weighting the individual fields. Unless evidence to suggest the contrary was identified (e.g. for Domachowske 2018), allocation sequences were assumed likely to be adequately generated. As such, a trial's risk of bias was not automatically raised if it failed to report this information. Any unclear ratings for all other domains were considered to introduce a risk of bias; trials with unclear ratings (but no 'No' ratings) were judged at moderate risk of bias. An intentionally open-label design, failure to adequately address incomplete outcome data selective reporting of outcomes or baseline imbalances were all considered to introduce a high risk of bias.

Overall, 4 of the 6 trials were at moderate risk of bias, while 2 had a high risk of bias. The most common issues were failure to report how randomization was performed or whether concealment of treatment allocation was adequate, creating the risk of selection bias. All but one of the trials were placebo controlled and blinded; HARMONIE[76] compared nirsevimab to no intervention using unblinded methods.

Two trials of nirsevimab (Griffin 2020[77] and MELODY[79]) and both trials of RSVpreF (Simões 2022[80] and MATISSE[78]) were judged to be at a moderate risk of bias. These 4 trials did not report details of the methods used for conducting randomization or concealing treatment allocation, and MATISSE[78] also failed to report adequate methods for addressing incomplete outcome data.

Two trials of nirsevimab (HARMONIE[76] and Domachowske 2018[75]) were judged to be at a high risk of bias. HARMONIE[76] did not mask patients, caregivers or outcome assessors, although investigators attempted to mitigate the risk of outcome measurement bias by strictly defining endpoints and standardizing questions in electronic diaries. However, trialists did not report how incomplete data were addressed. Domachowske 2018[75] was a small trial across 4 doses. Participant numbers were not balanced across arms, with 18 participants in the placebo arm, 8 in the nirsevimab 10 mg arm, and 31 and 32 in the nirsevimab 25 mg and 50 mg arms, respectively. Although the trial was described as a dose escalation study, the reported methods did not appear consistent with this statement: participants were randomized to arms. The authors also noted that the baseline demographics of the 10 mg group were slightly different to the other participants, with both a lower age and mean body weight at randomization.

Participant flow diagrams were reported by all 6 trials, including reasons for participant withdrawal or exclusion. 3 of the 4 nirsevimab trials and both RSVpreF trials showed similar rates of discontinuation across intervention and placebo arms. Specific reasons for discontinuing were not well reported, but where these data were reported, they also appeared to be balanced across arms.

HARMONIE, Griffin 2020, and MELODY all showed similar rates of discontinuations across arms. The fourth nirsevimab trial, Domachowske 2018, reported that the proportion of participants who withdrew consent or were lost to follow up for other reasons was higher in the placebo arm: 11% versus 2.3% across nirsevimab arms. However, the small size of this trial and imbalance in patient numbers across arms may have contributed to this finding.

The 2 RSVpreF trials showed similar rates of discontinuation across arms. Maternal withdrawals across arms in MATISSE were proportionally similar. Of the maternal participants in Simões 2022, only 2 out of 406 withdrew or were lost to follow up.

7.2.4 Trial outcomes and results

Both nirsevimab and RSVpreF reported numerically favorable efficacy outcomes compared with control arms for most outcomes. Given that statistical significance was NR by any included trial for all but 2 outcomes, it is not possible to determine with certainty whether reported differences are true effects. However, the consistency of numerically improved outcomes across the 6 included trials would indicate the plausibility of a beneficial effect. The trials were generally large, with 4 of the 6 trials including between 1'000 and 4'000 participants.[76-79]

Statistical significance was reported by 3 trials of nirsevimab, which found significantly better outcomes for nirsevimab than placebo patients in hospitalization for RSV-related LRTI,[76, 77, 79] and for rates of medically attended RSV LRTI.[77, 79]

No data were identified for treatment coverage, or primary care (PC) and emergency department (ED) visits associated with RSV.

7.2.4.1 Treatment coverage

No eligible trials reported this outcome.

7.2.4.2 Hospitalization due to RSV LRTIs

Three trials of nirsevimab and one RSVpreF trial reported the number of patients hospitalized due to RSV.

In the nirsevimab trials, these ranged from 0.3%[76] to 2%[79] for nirsevimab-treated patients, and 1.5%[76] to 4.1%[77] for placebo-treated patients. Across trials, rates of hospitalization were consistently higher for placebo- than nirsevimab-treated patients. Of the 3 RSVpreF participants with medically attended RSV-associated LRTI in the US cohort in Simões 2022[80], none required hospitalization, compared with 2/5 (40%) placebo patients with medically attended RSV-associated LRTI.

Of the 25/969 nirsevimab patients reported by Griffin 2020[77] to have had medically attended, RSV-related LRTI, 8/25 (32%) were hospitalized, compared with 20/46 (43.5%) of those receiving placebo. These figures comprise 0.8% and 4.1% of the nirsevimab- and placebo-treated arms, respectively. Griffin 2020 reported a relative risk reduction of 78.4 (95% CI: 51.9 to 90.3, p=0.0002)

for the number of nirsevimab participants hospitalized due to RSV LRTI compared with placebo, along with a hazard ratio of 0.19 (95% CI: 0.08 to 0.44).[77]

HARMONIE[76] and MELODY[79] reported that hospitalization for RSV-related LRTI was experienced by 11/4’037 (0.3%)[76] at 181 days, and 40/2’009 (2%) at 150 days[79] following nirsevimab. This compared with 60/4’021 (1.5%)[76] and 38/1’003 (3.8%)[79] patients receiving placebo or no intervention (neither reported statistical significance). HARMONIE also reported efficacy as 83.2% (95% CI: 67.8 to 92.0, p<0.001) for hospitalization due to RSV LRTI.[76] MELODY reported a relative risk reduction of 76.84 (95% CI: 49.36 to 89.41, p=0.0002).[79]

Additionally, one nirsevimab study[79] and one RSVpreF study[78] reported hospitalization due to any RSV-related illness, and another nirsevimab study reported hospitalization due to any respiratory illness[77] (neither reported statistical significance) (Table 16).

Table 16: Hospitalization due to RSV-related LRTI

Study	Outcome definition and measure	Timepoint of assessment	Month/season of assessment or outcome	Analysis population	Intervention	Number of patients analyzed	Number (%) experiencing event
Griffin 2020[77]	Hospitalized participants with medically attended RSV-confirmed LRTI	Up to day 151	Any point during 5-month RSV season	ITT patients with RSV LRTI	Nirsevimab 50 mg	25	8 (32)
					Placebo	46	20 (43.5)
	Participants hospitalized due to any respiratory illness	Up to day 151	Any point during 5-month RSV season	ITT	Nirsevimab 50 mg	969	53 (5.5)
					Placebo	484	46 (9.5)
HARMONIE[76]	Hospitalization for RSV-associated LRTI	Up to day 181	Before or during first RSV season	ITT	Nirsevimab 50 mg for infants <5 kg or 100 mg over ≥5 kg	4'037	11 (0.3)
					No intervention	4'021	60 (1.5)
MELODY[79]	Hospitalization for RSV-associated LRTI	Up to 150 days after injection	NR	ITT	Nirsevimab 50 mg for infants <5 kg or 100 mg over ≥5 kg	2'009	40 (2.0*)
					Placebo	1'003	38 (3.8)
	Hospitalization for any RSV-related illness	Up to 150 days after injection	NR	ITT	Nirsevimab 50 mg for infants <5 kg or 100 mg over ≥5 kg	994	9 (0.9)
					Placebo	496	11 (2.2)
MATISSE[78]	Hospitalizations due to RSV	150 days after birth	NR	As treated (infant participants)	RSVpreF	3'495	17 (0.5)
					Placebo	3'480	39 (1.1)
		180 days after birth	NR	As treated (infant participants)	RSVpreF	3'495	19 (0.5)
					Placebo	3'480	44 (1.3)
Simões 2022[80]	Participants with medically attended RSV-associated LRTI who required hospitalization	NR	NR	Participants from the US cohort with RSV	RSVpreF (any dose)	3	0
					Placebo	5	2 (40*)

Abbreviations

ITT = intention to treat, LRTI = lower respiratory tract infection, NR = not reported, RSV = respiratory syncytial virus.

7.2.4.3 Emergency room visit associated with RSV

No eligible trials specifically reported ED visits associated with RSV.

7.2.4.4 Primary care visit related to RSV

No eligible trials specifically reported PC visits related to RSV.

7.2.4.5 All-cause LRTI hospitalization

Only one trial reported hospitalization for all-cause LRTI. HARMONIE[76] reported that up to day 181, 45/4'037 (1.1%) infants receiving nirsevimab were hospitalized for all-cause LRTI, compared with 98/4'021 (2.4%) in the placebo arm (p value NR). HARMONIE also reported a efficacy for preventing all-cause LRTI hospitalization of 58.0% (95% CI: 39.7 to 71.2, p value NR) for all-cause LRTI hospitalization.[76]

7.2.4.6 Rates of medically attended, RSV-associated LRTI

Two nirsevimab trials and both RSVpreF trials reported the number of patients receiving medical attendance due to an RSV-related LRTI (Table 17), ranging from 0.7%[80] to 1.6%[78] after RSVpreF, from 2.6%[77] to 2.7%[79] 150 days after nirsevimab, and from 3.4%[78] to 9.5%[77] after placebo. Two trials of nirsevimab reported statistical significance, with better outcomes for nirsevimab than placebo ($p<0.001$[77] and $p<0.0001$).[79]

At 150/151 days after injection, medically attended, RSV-related LRTI was experienced by 25 patients (2.6%)[77] and 55 patients (2.7%)[79] receiving nirsevimab, compared with 9.5%[77] and 7.1%[79] of patients receiving placebo. Griffin 2020 reported a relative risk reduction of 70.1 (95% CI: 52.3 to 81.2, $p<0.0001$) for nirsevimab compared with placebo from medically attended RSV-related LRTI, as well as a hazard ratio of 0.26 (95% CI: 0.16 to 0.43).[77] MELODY reports a relative risk reduction of 76.36% (95% CI: 62.27 to 85.18, $p<0.0001$) for nirsevimab compared with placebo.[79]

The 2 RSVpreF trials reported at 150 and 180 days after birth[78] and at an unspecified timepoint.[80] In these trials, 57/3'495 (1.6%) (180 days)[78] and 3/405 (0.7%)[80] infants receiving RSVpreF experienced medically attended, RSV-associated LRTI. In comparison, 117/3'480 (3.4%)[78] and 5/103 (4.9%) infants receiving placebo[80] (p value NR) experienced medically attended, RSV-associated LRTI. MATISSE reported a vaccine efficacy of 52.5% (p value NR) at 150 days and 51.3% (p value NR) at 180 days.[78] In the US cohort reported in Simões 2022, vaccine efficacy was reported as 84.7% (95% CI: 21.6 to 97.6, p value NR, timepoint NR).[80]

Table 17: Medically attended, RSV-related LRTI

Study	Outcome definition and measure	Timepoint of assessment	Month/season of assessment or outcome	Analysis population	Intervention	Number of patients analyzed	Number (%) experiencing event
Nirsevimab							
Griffin 2020[77]	Participants with medically attended, RSV confirmed LRTI	Up to day 151	Any point during 5-month RSV season	ITT	Nirsevimab 50 mg	969	25 (2.6)
					Placebo	484	46 (9.5)
MELODY[79]	Medically attended, RSV-associated LRTI	Up to 150 days after injection	NR	ITT	Nirsevimab 50 mg for infants <5 kg or 100 mg over ≥5 kg	2'009	55 (2.7)
		Up to 150 days after injection	NR	ITT	Placebo	1'003	71 (7.1)
RSVpreF							
MATISSE[78]	Medically attended, RSV-associated LRTI	150 days after birth	NR	As treated (infant participants)	RSVpreF 120 µg	3'495	47 (1.3)
			NR		Placebo	3'480	99 (2.8)
		180 days after birth	NR	As treated (infant participants)	RSVpreF 120 µg	3'495	57 (1.6)
			NR		Placebo	3'480	117 (3.4)
	Medically attended, severe RSV-associated LRTI	150 days after birth	NR	As treated (infant participants)	RSVpreF 120 µg	3'495	16 (0.5)
			NR		Placebo	3'480	55 (1.6)
		180 days after birth	NR	As treated (infant participants)	RSVpreF 120 µg	3'495	19 (0.5)
			NR		Placebo	3'480	62 (1.8)
Simões 2022[80]	Any medically attended, RSV-associated LRTI	NR	NR	Subgroup: US cohort	RSVpreF 120 µg	405	3 (0.7*)
					Placebo	103	5 (4.9*)
	Medically attended, severe RSV-associated LRTI	NR	NR	Subgroup: US cohort	RSVpreF 120 µg	405	1 (0.2*)
					Placebo	103	3 (2.9*)

Abbreviations

ITT = intention to treaty, LRTI = lower respiratory tract infection, NR = not reported, RSV = respiratory syncytial virus, US = United States.

7.2.4.7 Rates of ICU admission for medically attended, RSV-associated LRTI

Two trials of nirsevimab reported data on ICU admission for medically attended, RSV-LRTI, but neither reported statistical significance. No trials of RSVpreF reported this outcome.

Griffin 2020[77] reported ICU admission for people with medically attended, RSV-confirmed LRTI, whereas HARMONIE[76] reported ICU admission for people with very severe RSV-associated LRTI. This means it may not be possible to directly compare data for these outcomes between the two trials.

Griffin 2020[77] reported that 8/969 patients in the nirsevimab arm and 20/484 patients in the placebo arm were hospitalized with medically attended, RSV-confirmed LRTI in the first 151 days. No patients in the nirsevimab arm and 5 patients in the placebo arm required ICU admission (equating to 0% and 1% of patients in each arm, respectively).

HARMONIE[76] reported that 5/4'037 patients in the nirsevimab arm and 19/4'021 patients in the placebo arm experienced very severe RSV-associated LRTI in the first 181 days. Two patients in the nirsevimab arm and five patients in the placebo arm required ICU admission (equating to 0.05% and 0.12% in each arm, respectively). Although these numbers are relatively small, ICU admission for very severe RSV-associated LRTI was more than twice as high in the placebo arm than the nirsevimab arm.

7.2.4.8 Rates of mechanical ventilation related to RSV

Two of the nirsevimab trials reported rates of mechanical or assisted ventilation related to RSV, but neither reported statistical significance. No RSVpreF trials reported this outcome.

25/969 patients receiving nirsevimab in the Griffin 2020 trial[77] had medically attended, RSV-confirmed LRTI; 8 of whom required assisted ventilation. 46/484 patients receiving placebo had medically attended, RSV-confirmed LRTI; 4 of whom required assisted ventilation. These figures equate to 0.8% of the ITT population in both arms. 4/25 nirsevimab patients and 15/46 placebo patients with medically attended, RSV-confirmed LRTI received supplemental oxygen. This equated to 0.4% of the ITT population of the nirsevimab arm and 3.1% of the ITT population of the placebo arm.

In the HARMONIE trial,[76] 2 patients in the nirsevimab arm and 5 patients in the placebo arm were admitted to ICU with very severe RSV-associated LRTI. None of these patients in the nirsevimab arm required mechanical ventilation; one in the placebo arm required mechanical ventilation.

7.2.4.9 All-cause, medically attended LRTI

Four trials reported rates of medically attended LRTI from any cause, though none reported statistical significance (Table 18).

Three nirsevimab trials reported medically attended LRTI from any cause, ranging from 7%[75] to 19.7%[77] for nirsevimab-treated patients and 0%[75] to 25.8%[77] for placebo-treated patients. Griffin 2020[77] and MELODY[79] both observed lower rates of medically attended LRTI in the nirsevimab group than the placebo group (19.7% versus 25.8%[77], and 8.7% versus 18.1%).[79]

We note that Domachowske 2018[75] recruited 18 patients to the placebo group compared with 71 patients recruited to the nirsevimab groups; this may account for the lower rates observed in the placebo arm of this trial (0%, compared with an average of 7% across nirsevimab arms). See Section 7.2.3 for more details regarding imbalances in this trial.

The third nirsevimab trial, Domachowske 2018[75], recorded zero medically attended all-cause LRTIs in the placebo group. However, rates in the 10 mg group were higher than in the 25 mg or 50 mg groups; 12.5% compared with 6.5% and 6.3%. The small sample size and baseline imbalances in patient characteristics (patients in the 10 mg group had a lower age and a lower mean body weight at randomization than other participants) may have impacted these results.

One trial of RSVpreF (MATISSE)[78] reported that at 150 days after birth, 9.5% of patients receiving RSVpreF had a medically attended LRTI, compared with 10% in the placebo group. These figures increased to 11.2% and 11.6% at 180 days but remained similar between arms. They reported vaccine efficacy for all-cause, medically attended LRTI of 5.2% (99.17% CI: -16.5 to 19.4, p value NR) at 150 days and 2.5 % (99.17 CI: -17.9 to 19.4, p value NR) at day 180.

Table 18: All-cause, medically attended LRTI

Study	Outcome definition and measure	Timepoint of assessment	Month/season of assessment or outcome	Population	Intervention	Number of participants analyzed	Number (%) experiencing event
Nirsevimab							
Domachowske 2018[75]	Medically attended LRTI	Up to day 151	Participants' first RSV season	ITT	Nirsevimab (any dose: 10, 25 or 50 mg)	71	5 (7.0*)
					Nirsevimab 10 mg	8	1 (12.5*)
					Nirsevimab 25 mg	31	2 (6.5*)
					Nirsevimab 50 mg	32	2 (6.3*)
					Placebo	18	0
Griffin 2020[77]	Participants experiencing medically attended LRTI from any cause	Up to day 151	Any point during 5-month RSV season	ITT	Nirsevimab 50 mg	969	191 (19.7)
					Placebo	484	125 (25.8)
MELODY[79]	Medically attended LRTI of any cause	Up to 150 days after injection	NR	Subgroup: Northern hemisphere patients	Nirsevimab 50 mg for infants <5 kg or 100 mg over ≥5 kg	686	60 (8.7)
					Placebo	342	62 (18.1)
RSVpreF							
MATISSE[78]	All-cause, medically attended LRTI	150 days after birth	NR	As treated (infant participants)	RSVpreF 120 µg	3'495	331 (9.5)
					Placebo	3'480	349 (10)
		180 days after birth	NR		RSVpreF 120 µg	3'495	392 (11.2)
					Placebo	3'480	402 (11.6)

Abbreviations

ITT = intention to treat, LRTI = lower respiratory tract infection, NR = not reported, RSV = respiratory syncytial virus.

7.2.4.10 Adverse events

AEs were reported using different metrics across the included trials, including overall AEs, treatment-emergent and treatment-related AEs, severe AEs, serious AEs, local reactions, specific named AEs, and AEs of special interest. None of the studies assessed the statistical significance of any differences between arms.

All 6 studies reported treatment-related AEs (TRAEs), serious AEs and serious TRAEs. The AEs for the nirsevimab studies are reported in Table 19, and the AEs for the RSVpreF studies are reported in Table 20.

7.2.4.10.1 Overall TRAEs

TRAEs were generally uncommon. Rates reported by the RSVpreF trials were lower than those reported by the nirsevimab trials, although a lack of statistical testing and differences between study populations mean that comparative conclusions cannot be drawn.

Of the 4 nirsevimab trials, TRAE rates were similar between arms in the Griffin 2020 trial (2.3% nirsevimab arm, 2.1% placebo)[77] and the primary cohort of the MELODY trial (1% nirsevimab, 1.4% placebo)[79]. Rates in Domachowske 2018 were variable; 6.5% in the nirsevimab 25 mg arm, 9.4% in the nirsevimab 50 mg, and zero in the nirsevimab 10 mg and placebo arms [75]. However, this trial was small, and the 2 arms recording zero TRAEs were numerically the smallest of the trial (8 and 18 participants, respectively).[75] The HARMONIE trial reported higher TRAE rates in the nirsevimab (2.1%) than placebo (0%) arms.[76] As this trial contained more than 4'000 participants per arm, this equates to a difference of 86 participants.[76]

In the RSVpreF trials, TRAEs in the maternal participants in MATISSE were 0.4% and 0.2% in the RSVpreF and placebo arms, respectively, while rates in infants were 0% in both arms.[78] Simões 2022 reported no TRAEs in either the maternal or infant populations.[80]

7.2.4.10.2 Overall serious adverse events

Rates of serious adverse events varied across trials.

Of the nirsevimab trials, rates of serious AEs in Domachowske 2018 increased with the dose of nirsevimab, with none in the placebo and 10 mg arms, 3.2% in the 25 mg arm, and 6.3% in the 50 mg arm. However, we note that this may reflect the numerically smaller size of the placebo and 10mg arms. Rates in HARMONIE and MELODY were similar across arms, each respectively reporting 2.2% and 6.8% in the nirsevimab arms and 1.7% and 7.3% in the placebo arms. Finally, Griffin 2020 reported more serious AEs in the placebo than nirsevimab arm: 16.9% and 11.1%, respectively.

Three of the four nirsevimab studies reported that no serious AEs in either the nirsevimab or placebo groups were related to the injection.[75, 77, 79] HARMONIE reported that one serious AE in the nirsevimab group (an infant experiencing infantile spasms [West syndrome] 23 days after injection) was potentially related to nirsevimab, compared with none in the placebo group.[76]

Both trials of RSVpreF reported higher rates of serious AEs in infants than maternal participants. At one month after injection, MATISSE reported maternal serious AE rates of 4.2% and 3.7%, respectively, in the RSVpreF and placebo arms, while rates in infants were higher: 15.2% and 15.5% per arm.[78] In the US cohort of the Simões 2022 trial, maternal serious AE rates were between 1% and 5% in the RSVpreF arms one month after vaccination, compared with 3% in the placebo arm.[80] Like MATISSE, AE rates in the infant population of Simões 2022 were higher (20% to 22% in the RSVpreF arms and 15.4% in the placebo arm) than in the maternal population.

Table 19: Treatment-related and serious AEs for nirsevimab studies

Study	Outcome definition and measure	Timepoint of assessment	Population	Intervention	Number of participants analyzed	Number (%) experiencing event
Griffin 2020[77]	TRAEs	Up to day 361	As-treated population	Nirsevimab (50 mg)	968	22 (2.3)
				Placebo	479	10 (2.1)
	Serious AEs	Up to day 361	As-treated population	Nirsevimab (50 mg)	968	108 (11.12*)
				Placebo	479	81 (16.91*)
	Serious TRAEs	Up to day 361	As-treated population	Nirsevimab (50 mg)	968	0
				Placebo	479	0
Domachowske 2018[75]	TRAEs	Up to day 361	ITT	Nirsevimab (any dose)	71	5 (7.0)
				Nirsevimab (10 mg)	8	0
				Nirsevimab (25 mg)	31	2 (6.5)
				Nirsevimab (50 mg)	32	3 (9.4)
				Placebo	18	0
	Serious AEs	Up to day 361	ITT	Nirsevimab (any dose)	71	3 (4.2)
				Nirsevimab (10 mg)	8	0
				Nirsevimab (25 mg)	31	1 (3.2)
				Nirsevimab (50 mg)	32	2 (6.3)
				Placebo	18	0
	Serious TRAEs	Up to day 361	ITT	Nirsevimab (any dose)	71	0
				Nirsevimab (10 mg)	8	0
				Nirsevimab (25 mg)	31	0
				Nirsevimab (50 mg)	32	0
				Placebo	18	0

Study	Outcome definition and measure	Timepoint of assessment	Population	Intervention	Number of participants analyzed	Number (%) experiencing event
HARMONIE[76]	TRAEs	Up to data cutoff date	Safety analysis population	Nirsevimab (50 mg if they weighed <5 kg or 100 mg if they weighed ≥5 kg)	4’015	86 (2.1)
				No intervention	4’020	0 (0)
	Serious AEs	Up to data cutoff date	Safety analysis population	Nirsevimab (50 mg if they weighed <5 kg or 100 mg if they weighed ≥5 kg)	4’015	89 (2.2)
				No intervention	4’020	67 (1.7)
	Serious TRAEs	Up to data cutoff date	Safety analysis population	Nirsevimab (50 mg if they weighed <5 kg or 100 mg if they weighed ≥5 kg)	4’015	1 (<0.1)
				No intervention	4’020	0 (0)
MELODY[79]	TRAEs	Up to 360 days after injection	As-treated population (primary cohort)[79]	Nirsevimab (50 mg if they weighed <5 kg or 100 mg if they weighed ≥5 kg)	987	10 (1)
				Placebo	491	7 (1.4)
	Serious AEs	Up to 360 days after injection	As-treated population (primary cohort)[79]	Nirsevimab (50 mg if they weighed <5 kg or 100 mg if they weighed ≥5 kg)	987	67 (6.8)
				Placebo	491	36 (7.3)
	Serious TRAEs	Up to 360 days after injection	As-treated population (primary cohort)[79]	Nirsevimab (50 mg if they weighed <5 kg or 100 mg if they weighed ≥5 kg)	987	0 (0)
				Placebo	491	0 (0)
	Serious AEs	Up to 360 days after injection	As-treated population (all subjects)[93]	Nirsevimab (50 mg if they weighed <5 kg or 100 mg if they weighed ≥5 kg)	1’997	149 (7.46)
				Placebo	997	83 (8.32)

Abbreviations

AE = adverse event, LRTI = lower respiratory tract infection, ITT = intention to treat, NR = not reported, TRAE = treatment-related adverse events.

Notes

* Reviewer calculated

Table 20: Treatment-related and serious AEs for RSVpreF studies

Study	Outcome definition and measure	Timepoint of assessment	Population	Intervention	Number of participants analyzed	Number (%) experiencing event
MATISSE[78]	TRAEs	Within 1 month after injection	Maternal participants who received the injection	RSVpreF (120 µg)	3'682	NR (0.4)
				Placebo	3'675	NR (0.2)
	Serious AEs	Within 1 month after injection	Maternal participants who received the injection	RSVpreF (120 µg)	3'682	NR (4.2)
				Placebo	3'675	NR (3.7)
		Up to 6 months	Maternal participants who received the injection (in clinical trial record)[94]	RSVpreF (120 µg)	3'698	NR (16.6)
				Placebo	3'687	NR (15.8)
	TRAEs	Within 1 month after injection	Infants born to vaccinated maternal participants	RSVpreF (120 µg)	3'558	0
				Placebo	3'568	0
	Serious AEs	Within 1 month after injection	Infants born to vaccinated maternal participants	RSVpreF (120 µg)	3'558	NR (15.2)
				Placebo	3'568	NR (15.5)
		From birth to 6 months	Infants born to vaccinated maternal participants	RSVpreF (120 µg)	3'558	NR (16.4)
				Placebo	3'568	NR (16.7)
		From birth to 24 months	Infants born to vaccinated maternal participants	RSVpreF (120 µg)	3'646	NR (18.9)
				Placebo	3'659	NR (19)
	Serious TRAEs	Within 1 month after injection	Infants born to vaccinated maternal participants	RSVpreF (120 µg)	3'558	0
				Placebo	3'568	0
Simões 2022[80]	TRAEs	Up to 1 month after vaccination	Maternal participants in US ITT cohort	RSVpreF (120 µg)	79	0
				RSVpreF (120 µg with aluminum hydroxide)	84	0
				RSVpreF (240 µg)	78	0
				RSVpreF (240 µg with aluminum hydroxide)	86	0
				Placebo	79	0

Study	Outcome definition and measure	Timepoint of assessment	Population	Intervention	Number of participants analyzed	Number (%) experiencing event
	Serious AEs	Up to 1 month after vaccination	Maternal participants in US ITT cohort	RSVpreF (120 µg)	79	1 (1)
				RSVpreF (120 µg with aluminum hydroxide)	84	3 (4)
				RSVpreF (240 µg)	78	2 (3)
				RSVpreF (240 µg with aluminum hydroxide)	86	4 (5)
				Placebo	79	2 (3)
			Maternal participants, as administered, clinical trial cohort[91]	RSVpreF (120 µg)	114	7* (6.1)
				RSVpreF (120 µg with aluminum hydroxide)	115	15* (12.8)
				RSVpreF (240 µg)	116	15* (12.9)
				RSVpreF (240 µg with aluminum hydroxide)	114	19* (16.7)
				Placebo	117	14* (12)
	Serious TRAEs	Up to 1 month after vaccination	Maternal participants in US ITT cohort	RSVpreF (120 µg)	79	0
				RSVpreF (120 µg with aluminum hydroxide)	84	0
				RSVpreF (240 µg)	78	0
				RSVpreF (240 µg with aluminum hydroxide)	86	0
				Placebo	79	0
	TRAEs	During the trial period	Infant participants in US ITT cohort	RSVpreF (120 µg)	79	0
				RSVpreF (120 µg with aluminum hydroxide)	84	0
				RSVpreF (240 µg)	77	0
				RSVpreF (240 µg with aluminum hydroxide)	85	0
				Placebo	78	0
	Serious AEs	Up to 1 month after birth	Infant participants in US ITT cohort	RSVpreF (120 µg)	79	18 (22.8*)
				RSVpreF (120 µg with aluminum hydroxide)	84	17 (20.2*)
				RSVpreF (240 µg)	77	17 (22.1*)

Study	Outcome definition and measure	Timepoint of assessment	Population	Intervention	Number of participants analyzed	Number (%) experiencing event
				RSVpreF (240 µg with aluminum hydroxide)	85	17 (20.0*)
				Placebo	78	12 (15.4*)
		Within 12 months of birth	Infant participants, as administered, clinical trial cohort[91]	RSVpreF (120 µg)	114	41* (36)
				RSVpreF (120 µg with aluminum hydroxide)	117	38* (33.3)
				RSVpreF (240 µg)	113	36* (31)
				RSVpreF (240 µg with aluminum hydroxide)	112	45* (39.3)
				Placebo	116	38* (32.8)

Abbreviations

AE = adverse event, LRTI = lower respiratory tract infection, ITT = intention to treat, NR = not reported, TRAE = treatment-related adverse events.

Notes

* Reviewer calculated

7.2.4.10.3 Overall severe adverse events

Only the 2 RSVpreF studies reported the incidence of severe AEs.[78, 80] Both reported them for both maternal and infant participants,[78, 80] as summarized in Table 21.

In the MATISSE trial, 1.7% of maternal participants receiving RSVpreF and 1.3% receiving placebo,[78] experienced severe AE. Simões 2022 reported that 1%, 4%, 3% and 5% of maternal participants in the RSVpreF arms (120 µg, 120 µg with aluminum hydroxide, 240 µg, and 240 µg with aluminum hydroxide) experienced severe AEs, compared with 3% of the placebo group.[80]

Of the infant participants in MATISSE, 3.8% in the RSVpreF group experienced severe AEs compared with 4.5% in the placebo group.[78] Simões 2022 reported that 4%, 5%, 2%, 3% of infant participants in the RSVpreF arms (120 µg, 120 µg with aluminum hydroxide, 240 µg, and 240 µg with aluminum hydroxide) experienced severe AEs, compared with 3% in the placebo arm.[80]

Table 21: Overall incidence of severe AEs

Study	Timepoint of assessment	Population	Intervention	Number of participants analyzed	Number (%) experiencing event
MATISSE[78]	Within 1 month after injection	Maternal participants	RSVpreF (120 µg)	3’675	NR (1.3)
			Placebo	3’682	NR (1.7)
		Infant participants	RSVpreF (120 µg)	3’558	NR (3.8)
			Placebo	3’568	NR (4.5)
Simões 2022[80]	Up to 1 month after vaccination	Maternal participants in US ITT cohort	RSVpreF (120 µg)	79	1 (1)
			RSVpreF (120 µg with aluminum hydroxide)	84	3 (4)
			RSVpreF (240 µg)	77	2 (3)
			RSVpreF (240 µg with aluminum hydroxide)	85	4 (5)
			Placebo	78	2 (3)
	Up to 1 month after birth	Infant participants in US ITT cohort	RSVpreF (120 µg)	79	3 (4)
			RSVpreF (120 µg with aluminum hydroxide)	84	5 (5)
			RSVpreF (240 µg)	77	2 (2)
			RSVpreF (240 µg with aluminum hydroxide)	85	3 (3)
			Placebo	78	3 (3)

Abbreviations

AEs = adverse events, ITT = intention to treat, NR = not reported, US = United States.

7.2.4.10.4 Overall life-threatening adverse events

Only the 2 RSVpreF studies reported the incidence of life-threatening AEs.[78, 80] Both reported them for both maternal and infant participants,[78, 80] as summarized in Table 22.

MATISSE reported that 0.5% of maternal participants receiving RSVpreF compared with 0.3% in the placebo group experienced life-threatening AEs.[78] Simões 2022 reported that 1%, 0%, 1%, 0% of maternal participants in the RSVpreF arms (120 µg, 120 µg with aluminum hydroxide, 240 µg, and 240 µg with aluminum hydroxide) experienced life-threatening AEs, compared with 0% in the placebo arm.[80] MATISSE reported that 1% of infant participants in both the RSVpreF group and the placebo group experienced life-threatening AEs.[78] Simões 2022 reported that 0%, 5%, 3%, 0% of infant participants in the RSVpreF arms (120 µg, 120 µg with aluminum hydroxide, 240 µg, and 240 µg with aluminum hydroxide) experienced life-threatening AEs, compared with 0% in the placebo group.[80]

Table 22: Overall incidence of life-threatening AEs

Study	Timepoint of assessment	Population	Intervention	Number of participants analyzed	Number (%) experiencing event
MATISSE[78]	Within 1 month after vaccination	Maternal participants	RSVpreF (120 µg)	3'682	NR (0.5)
			Placebo	3'675	NR (0.3)
	Within 1 month after birth	Infant participants	RSVpreF (120 µg)	3'568	NR (1)
			Placebo	3'558	NR (1)
Simões 2022[80]	Within 1 month after vaccination	Maternal participants in US ITT cohort	RSVpreF (120 µg)	79	1 (1)
			RSVpreF (120 µg with aluminum hydroxide)	84	0
			RSVpreF (240 µg)	78	1 (1)
			RSVpreF (240 µg with aluminum hydroxide)	86	0
			Placebo	79	0
	Within 1 month after birth	Infant participants in US ITT cohort	RSVpreF (120 µg)	79	0
			RSVpreF (120 µg with aluminum hydroxide)	84	4 (5)
			RSVpreF (240 µg)	77	2 (3)
			RSVpreF (240 µg with aluminum hydroxide)	85	0
			Placebo	78	0

Abbreviations

AEs = adverse events, ITT = intention to treat, NR = not reported, US = United States.

7.2.4.10.5 Medically attended adverse events

Two studies (one of nirsevimab[76] and one of RSVpreF)[80] reported the incidence of medically attended AEs, as reported in Table 23. However, definitions of medically attended varied. Simões 2022 specified that medically attended AEs were "non-serious AEs that resulted in evaluation at a medical facility",[80] whereas HARMONIE defined medically attended AEs as "any event prompting unplanned in-person medical advice in any clinical setting".[76] These discrepancies in definitions likely explain the large differences in figures reported by both studies.

HARMONIE reported that similar proportions of patients in either arm experienced medically attended AEs (29.5% of participants in the nirsevimab group, 27.4% in the placebo group).[76]

For Simões 2022, medically attended AEs were reported by both the journal article (US cohort) and the clinical trial record (all participants) and appears to differ between these two sources.[80] The global cohort reports that a much higher proportion of both maternal and infant participants appeared to experience medically attended AEs than the US subgroup, as shown in Table 23. It is not clear why the geographic differences appear so pronounced (although the sample size in this study was relatively small), and it is not discussed by the authors. The statistical significance of any difference between intervention and placebo arms was not assessed within either cohort.

Table 23: Overall incidence of medically attended AEs

Study	Timepoint of assessment	Population	Intervention	Number of participants analyzed	Number (%) experiencing event
Nirsevimab					
HARMONIE[76]	Up to data cut-off date	Safety analysis population	Nirsevimab (50 mg if they weighed <5 kg or 100 mg if they weighed ≥5 kg)	4’015	1’185 (29.5)
			No intervention	4’020	1’102 (27.4)
RSVpreF					
Simões 2022[80]	During the trial period*	Maternal participants in US ITT cohort	RSVpreF (120 µg)	79	5 (6)
			RSVpreF (120 µg with aluminum hydroxide)	84	6 (7)
			RSVpreF (240 µg)	78	3 (4)
			RSVpreF (240 µg with aluminum hydroxide)	86	9 (10)
			Placebo	79	2 (3)
	Up to 12 months after birth	Maternal participants, as administered, clinical trial cohort[91]	RSVpreF (120 µg)	114	23* (20)
			RSVpreF (120 µg with aluminum hydroxide)	115	22* (18.8)
			RSVpreF (240 µg)	116	18* (15.5)
			RSVpreF (240 µg with aluminum hydroxide)	114	24* (21.1)
			Placebo	117	20* (17.1)
	During the trial period*	Infant participants in US ITT cohort	RSVpreF (120 µg)	79	3 (4)
			RSVpreF (120 µg with aluminum hydroxide)	84	5 (6)
			RSVpreF (240 µg)	77	4 (5)
			RSVpreF (240 µg with aluminum hydroxide)	85	5 (6)
			Placebo	78	2 (3)
	Up to 12 months of age	Infant participants, as administered, clinical trial cohort[91]	RSVpreF (120 µg)	114	26* (22.8)
			RSVpreF (120 µg with aluminum hydroxide)	117	34* (29.9)

	RSVpreF (240 µg)	113	35* (30.1)
	RSVpreF (240 µg with aluminum hydroxide)	112	44* (38.4)
	Placebo	116	37* (31.9)

Abbreviations

AEs = adverse events, ITT = intention to treat, US = United States.

Notes

* While most AEs for the US cohort (reported in Table 1 of Simões 2022 [80]) are reported at a specific timepoint (e.g. within one month of vaccination), medically attended AEs are only reported for "during the trial period". However, the duration of the study at the cut-off point for inclusion of data in this paper is not reported.

7.2.4.10.6 Specific adverse events

All included trials reported specific AEs, but it was beyond the scope of this rapid review to report every individual AE. Discussions with clinicians suggested that critical adverse events would be those impacting the safety and viability of pregnancy. The following sections, therefore, summarize the available data relating to premature labor (Table 24), delivery or birth (Table 25 and Table 26), and pregnancy loss or stillbirth (Table 27) following the administration of a maternal vaccine.

Both RSVpreF trials (Simões 2022[80] and MATISSE)[78] reported these safety outcomes (and a number of other pregnancy- and birth-related outcomes). However, in both trials there were a number of inconsistencies and inaccuracies in the relevant data tables, while the peer-reviewed publications relating to these trials included minimal discussion or explanation of pregnancy-related outcome data.

A lack of explicit outcome definitions made it difficult to interpret the reported data. For example, it was unclear what the differences were between the outcomes “premature labor”, “premature delivery”, and “premature baby” (all three reported by both studies). The number of premature babies plus fetal deaths did not always sum to the total number of reported premature deliveries. There were also inconsistencies in the timepoints at which these events were reported, making interpretation challenging. Despite prematurity being a birth outcome, “premature baby” was reported in MATISSE as being much higher at one month of age (5.7% in the RSVpreF group and 4.7% in the placebo group) than at 24 months of age (1.4% in the RSVpreF group and 1.2% in the placebo group). Similarly, “spontaneous abortion” was reported in both the maternal population and the infant population in MATISSE, with reported numbers differing for each population.

Explanation of what constituted a serious AE was also lacking; Simões 2022[80] reported both overall and serious incidences of premature labor, but the difference between the two outcomes was not defined.

Due to the apparent inconsistencies in the reported data and the lack of outcome definition or explanation, we were not able to draw any overall conclusions from these data. No within-trial comparisons between arms were available as neither trial undertook testing for statistical significance for any of these outcomes.

Premature labor:

While no testing for statistical significance was undertaken by the authors of MATISSE, rates of premature labor appear to be numerically similar between RSVpreF and placebo groups. Four cases (0.1%) in the RSVpreF group and none in the placebo group were reported to be “severe or life-threatening”, but the authors did not report what constituted “severe or life-threatening” premature labor. As premature labor is a birth-related outcome, it is unclear why 11 cases of premature labor were reported within one month of vaccination in the placebo group, but only 10 cases in the 6 months after delivery.

Overall, 4 serious AEs in the RSVpreF group of MATISSE and one in the placebo group were considered by the investigator to be related to vaccination, including one case of premature labor in the RSVpreF arm and one case of premature placental separation in the placebo arm.

In the US cohort of maternal participants in Simões 2022, there were no differences in the frequency of premature labor between RSVpreF and placebo: 3 participants were reported as experiencing premature labor within one month of vaccination (one each in the RSVpreF 120 µg with aluminum hydroxide, RSVpreF 240 µg with aluminum hydroxide, and placebo groups).

When reported as a serious AE in the same cohort 'throughout the study' (i.e. a longer timepoint), only 2 cases were reported (one each in the RSVpreF 120 µg with aluminum hydroxide and RSVpreF 240 µg with aluminum hydroxide groups). It is not clear why these data appear to be internally inconsistent.

For the global cohort of Simões 2022, rates of premature labor as a serious AE appear to be numerically similar to the rates reported for the US cohort.

Simões 2022 did not report when premature labor was considered to be a "serious" AE, but they did state that no serious AEs were considered to be related to the vaccination.

Table 24: AEs relating to premature labor

Study	Outcome definition	Timepoint of assessment	Analysis population	Intervention	Number of participants analyzed	Number (%) experiencing event
Simões 2022[80]	Adverse event: premature labor	Within 1 month after vaccination	US cohort safety population (maternal participants)	RSVpreF 120 µg	79	0 (0)
				RSVpreF 120 µg with aluminum hydroxide	84	1 (1.2)
				RSVpreF 240 µg	78	0 (0)
				RSVpreF 240 µg with aluminum hydroxide	86	1 (1.2)
				Placebo	79	1 (1.3)
	Serious adverse event: premature labor	Throughout study	US cohort safety population (maternal participants)	RSVpreF 120 µg	79	0 (0)
				RSVpreF 120 µg with aluminum hydroxide	84	1 (1.2)
				RSVpreF 240 µg	78	0 (0)
				RSVpreF 240 µg with aluminum hydroxide	86	1 (1.2)
				Placebo	79	1 (1.3)
		NR	All maternal patients	RSVpreF 120 µg	115	0 (0)
				RSVpreF 120 µg with aluminum hydroxide	117	1 (0.85)
				RSVpreF 240 µg	116	0 (0)
				RSVpreF 240 µg with aluminum hydroxide	114	2 (1.75)
				Placebo	117	0 (0)
MATISSE[78]	Adverse event: premature labor	Within 1 month after vaccination	Maternal participants	RSVpreF 120 µg	3’682	13 (0.4)
				Placebo	3’675	11 (0.3)
		Up to 6 months after delivery		RSVpreF 120 µg	3’682	16 (0.4)
				Placebo	3’675	10 (0.3)
	Severe or life-threatening AE: premature labor	Within 1 months of vaccination	Maternal participants	RSVpreF 120 µg	3’682	4 (0.1)
				Placebo	3’675	0 (0)

Abbreviations

AE = adverse event, US = United States.

Premature delivery:

Similar to premature labor, the rates of premature delivery in MATISSE appear to be similar between groups (Table 25). Eight cases (0.2%) in the RSVpreF group and four cases (0.1%) in the placebo group were reported to be a “severe or life-threatening”, but definitions of what was considered to be a “severe or life-threatening” premature delivery were not provided.

In the US cohort of maternal participants in Simões 2022, rates of premature delivery appear to be similar across groups, with a total of 6 cases reported: 2 in the RSVpreF 120 µg with aluminum hydroxide group and one in each of the other groups. In this cohort, 3 cases of premature delivery constituting a “serious AE” were reported: 2 in the RSVpreF 120 µg with aluminum hydroxide group and one in placebo. The authors reported that these were not considered to be related to vaccination.

Premature delivery is also reported in the global cohort for this study but is split into “serious AEs: premature delivery” and “non-serious AEs: premature delivery”. However, the authors did not report how premature deliveries were determined to be serious or non-serious.

Rates of premature delivery appear to be numerically higher in the global cohort than the US cohort of Simões 2022, but this is not discussed by the authors, and no statistical testing was conducted.

Table 25: AEs relating to premature delivery

Study	Outcome definition	Timepoint of assessment	Analysis population	Intervention	Number of patients analyzed	Number (%) experiencing event
Simões 2022[80]	Adverse event: premature delivery	Within 1 month after vaccination	US cohort safety population (maternal participants)	RSVpreF 120 µg	79	1 (1.3)
				RSVpreF 120 µg with aluminum hydroxide	84	2 (2.4)
				RSVpreF 240 µg	78	1 (1.3)
				RSVpreF 240 µg with aluminum hydroxide	86	1 (1.2)
				Placebo	79	1 (1.3)
	Serious event: premature delivery	Throughout study	US cohort safety population (maternal participants)	RSVpreF 120 µg	79	0 (0)
				RSVpreF 120 µg with aluminum hydroxide	84	2 (2.4)
				RSVpreF 240 µg	78	0 (0)
				RSVpreF 24 0µg with aluminum hydroxide	86	0 (0)
				Placebo	79	1 (1.3)
		NR	All maternal participants	RSVpreF 120 µg	115	2 (1.71)
				RSVpreF 120 µg with aluminum hydroxide	117	0 (0)
				RSVpreF 240 µg	116	0 (0)
				RSVpreF 240 µg with aluminum hydroxide	114	1 (0.85)
				Placebo	117	0 (0)
	Non serious adverse event: premature delivery	NR	All maternal participants	RSVpreF 120 µg	115	6 (5.22)
				RSVpreF 120 µg with aluminum hydroxide	117	2 (1.71)
				RSVpreF 240 µg	116	7 (6.03)
				RSVpreF 240 µg with aluminum hydroxide	114	4 (3.51)
				Placebo	117	2 (1.71)
MATISSE[78]	AE: premature delivery	Within 1 month after vaccination	Maternal participants	RSVpreF 120 µg	3’682	79 (2.1)
				Placebo	3’675	70 (1.9)
		Up to 6 months after delivery		RSVpreF 120 µg	3’682	28 (0.8)
				Placebo	3’675	23 (0.6)
	Severe or life-threatening AE: premature delivery	Within 1 months of vaccination	Maternal participants	RSVpreF 120 µg	3’682	8 (0.2)
				Placebo	3’675	4 (0.1)

Abbreviations

AE = adverse event, NR = not reported, US = United States.

Premature baby:

In the infant population of MATISSE, incidences of “premature baby” (Table 26), were reported to be higher at one month of age (5.7% in the RSVpreF group and 4.7% in the placebo group) than at 24 months of age (1.4% in the RSVpreF group and 1.2% in the placebo group), despite being a birth-related outcome. No further outcome definitions or explanation of these apparent differences were reported by the authors. The rate of “severe or life-threatening” prematurity was the same (0.4%) in the RSVpreF and placebo groups.

In the global cohort of Simões 2022, “premature baby” was reported as both a serious and non-serious AE. Both these outcomes were zero in all groups (i.e. it appears that no premature births occurred).

Table 26: AEs relating to premature baby

Study	Outcome definition	Timepoint of assessment	Analysis population	Intervention	Number of participants analyzed	Number (%) experiencing event
Simões 2022[80]	Serious AE: premature baby	NR	All maternal participants	RSVpreF 120 µg	115	0 (0)
				RSVpreF 120 µg with aluminum hydroxide	117	0 (0)
				RSVpreF 240 µg	116	0 (0)
				RSVpreF 240 µg with aluminum hydroxide	114	0 (0)
				Placebo	117	0 (0)
	Non-serious AE: premature baby	NR	All maternal participants	RSVpreF 120 µg	115	0 (0)
				RSVpreF 120 µg with aluminum hydroxide	117	0 (0)
				RSVpreF 240 µg	116	0 (0)
				RSVpreF 240 µg with aluminum hydroxide	114	0 (0)
				Placebo	117	0 (0)
MATISSE[78]	AE: premature baby	Within 24 months of age	Infant participants	RSVpreF 120 µg	3’568	49 (1.4)
				Placebo	3’558	42 (1.2)
		Within 1 month of age		RSVpreF 120 µg	3’568	202 (5.7)
				Placebo	3’558	169 (4.7)
	Severe or life-threatening AE: premature baby	Birth to 1 month of age		RSVpreF 120 µg	3’568	16 (0.4)
				Placebo	3’558	14 (0.4)

Abbreviations

AE = adverse event, NR = not reported.

Fetal death, stillbirth and spontaneous abortion:

For the maternal population in MATISSE, “fetal death/stillborn baby” (Table 27) was reported as an AE (0.3% and 0.2% in the RSVpreF and placebo groups, respectively) and as a severe or life-threatening AE (2 participants, <0.1%, in each group).[78] However, these figures for the number of fetal deaths/stillborn babies do not appear consistent with the author-reported data for prematurity as a cause of infant death (only one infant in each arm). It is unclear what the distinctions and overlap between these 3 reported outcomes are.

Furthermore, MATISSE also reported “spontaneous abortion” in both the maternal population and the infant population, with reported numbers differing for each. One maternal participant in the RSVpreF group and no maternal participants in the placebo group were reported as having a spontaneous abortion. However, the infant population were reported to have no spontaneous abortions in the RSVpreF group and 2 in the placebo group.

The peer-reviewed publication for MATISSE reports that “spontaneous abortion during a subsequent pregnancy occurred in one participant in the vaccine group and 2 participants in the placebo group”, suggesting that this outcome related to subsequent pregnancies. In contrast, the timepoint in the clinical trial record is reported as up to 28 days after vaccination for maternal participants and up to 28 days of age for infant participants. No further explanation for these apparent discrepancies was reported.

In both the US and the global cohort of Simões 2022, only one fetal death is reported. This was in the placebo group and was not considered to be related to the vaccine.

Table 27: AEs relating to fetal death

Study	Outcome definition	Timepoint of assessment	Analysis population	Intervention	Number of participants analyzed	Number (%) experiencing event
Simões 2022[80]	Serious AE: fetal death	Throughout study	US cohort safety population (Maternal participants)	RSVpreF 120 µg	79	0 (0)
				RSVpreF 120 µg with aluminum hydroxide	84	0 (0)
				RSVpreF 240 µg	78	0 (0)
				RSVpreF 240 µg with aluminum hydroxide	86	0 (0)
				Placebo	79	1 (1.3)
		NR	All maternal participants	RSVpreF 120 µg	115	0 (0)
				RSVpreF 120 µg with aluminum hydroxide	117	0 (0)
				RSVpreF 240 µg	116	0 (0)
				RSVpreF 240 µg with aluminum hydroxide	114	0 (0)
				Placebo	117	1 (0.85)
MATISSE[78]	AE: fetal death/stillborn baby	Up to 6 months after delivery	Maternal participants	RSVpreF 120 µg	3'682	10 (0.3)
				Placebo	3'675	8 (0.2)
	Severe or life-threatening AE: fetal death	Within 1 months of vaccination	Maternal participants	RSVpreF 120 µg	3'682	2 (<0.1)
				Placebo	3'675	2 (<0.1)
	Spontaneous abortion	Consent to 28 days after vaccination	Maternal participants	RSVpreF 120 µg	3'698	1 (0.03)
				Placebo	3'659	0 (0)
		Birth to 28 days old	Infant participants	RSVpreF 120 µg	3'646	0 (0)
			Infant participants	Placebo	3'687	2 (0.05)

Abbreviations

AE = adverse event, NR = not reported.

7.2.4.11 Mortality

Three trials of nirsevimab and both trials of RSVpreF reported mortality among participants, though none reported statistical significance (Table 28). Mortality was low across both active interventions and placebo, ranging from 0% to 0.3% in intervention arms and 0% to 0.6% in placebo arms.[77]

All 5 of these trials reported all-cause mortality. For nirsevimab, the small trial reported no mortality in the ITT population, while rates in the nirsevimab and placebo arms were 0.2% versus 0.6% (as-treated population),[77] and 0.25% versus 0% (all subjects) respectively.[79] In the 2 trials of RSVpreF, infant mortality in the RSVpreF and placebo arms, respectively, were 0.1% versus 0.3% within 24 months of birth,[78] and 0% in both arms within 12 months of birth.[80] Simões 2022 also reported mortality in maternal participants which was also 0% in all arms at 12 months after vaccination.[80]

Two trials of nirsevimab also reported treatment-related mortality[77] or deaths from adverse events caused by the study drug.[79] At 360 and 361 days after injection, none of the as-treated population in either the nirsevimab or placebo groups had died for reasons related to treatment.

Table 28: Mortality

Study	Outcome definition and measure	Timepoint of assessment	Month/season of assessment or outcome	Population	Intervention	Number of participants analyzed	Number (%) experiencing event
Nirsevimab							
Griffin 2020[77]	Mortality	Up to day 361	Any point during 5-month RSV season	As-treated population	Nirsevimab 50 mg	968	2 (0.2*)
					Placebo	479	3 (0.6*)
	Treatment-related mortality	Up to day 361	Any point during 5-month RSV season	As-treated population	Nirsevimab 50 mg	968	0
					Placebo	479	0
Domachowske 2018[75]	Death	Up to day 361	Participants entering first RSV season followed for 361 days	ITT	Nirsevimab (any dose: 10, 25 or 50 mg)	71	0
					Nirsevimab 10 mg	8	0
					Nirsevimab 25 mg	31	0
					Nirsevimab 50 mg	32	0
					Placebo	18	0
MELODY[79]	Adverse event that resulted in death	Up to 360 days after injection	NR	As-treated population	Nirsevimab: 50 mg for infants <5 kg or 100 mg ≥5 kg	987	3 (0.3)
					Placebo	491	0
	Adverse event that resulted in death considered to be related to the study drug	Up to 360 days after injection	NR	As-treated population	Nirsevimab: 50 mg for infants <5 kg or 100 mg ≥5 kg	987	0
					Placebo	491	0
	All-cause mortality	Up to 360 days after injection	NR	All subjects as-treated population. Wider population as reported by the ClinicalTrials.gov record.	Nirsevimab: 50 mg for infants <5 kg or 100 mg ≥5 kg	1’997	5 (0.25)
					Placebo	997	0
RSVpreF							
MATISSE[78]	Infant death	Birth to 24 months of age	NR	NR (infant participants)	RSVpreF 120 µg	3’568	5 (0.1)
					Placebo	3’558	12 (0.3)

Study	Outcome definition and measure	Timepoint of assessment	Month/season of assessment or outcome	Population	Intervention	Number of participants analyzed	Number (%) experiencing event
Simões 2022[80]	Infant participants: all-cause mortality	Within 12 months of birth and up to 12 months after vaccination (outcomes for both time points were 0)	NR	As administered (infant participants)	RSVpreF 120 µg	114	0* (0)
					RSVpreF 120 µg with aluminum hydroxide	117	0* (0)
					RSVpreF 240 µg	113	0* (0)
					RSVpreF 240 µg with aluminum hydroxide	112	0* (0)
					Placebo	116	0* (0)

Abbreviations

ITT = intention to treat, NR = not reported, RSV = respiratory syncytial virus.

Notes

* Reviewer calculated.

7.2.5 Summary of key findings from the clinical efficacy and safety review

Four trials (two assessing nirsevimab[77, 79] and both trials assessing RSVpreF)[78, 80] were judged to be at a moderate risk of bias. Two trials assessing nirsevimab[75, 76] were judged to be at a high risk of bias: HARMONIE[76] was an unblinded trial that did not report adequate methods for addressing incomplete outcome data, and Domachowske 2018[75] was smaller than the other trials, with unbalanced patient numbers and baseline characteristics across arms. Although Domachowske 2018[75] was described as a dose escalation study, the reported methods did not appear consistent with this statement.

No outcomes of interest were reported by all 6 included trials and some outcomes of interest were NR by any trials. Not all studies calculated or reported the statistical significance of findings, and this was NR by any study for safety outcomes. Included studies of nirsevimab were heterogeneous in study populations, specifically in terms of the gestational age at birth of the participants. For these reasons, it was difficult to collate the results of the included studies. However, all trials reported favorable results for both nirsevimab and RSVpreF, compared with placebo or no treatment, in terms of both safety and efficacy.

Hospitalization rates for RSV LRTIs were lower with nirsevimab or RSVpreF than placebo, ranging from 0.3%[76] to 2%[79] for nirsevimab-treated patients, and 1.5%[76] to 4.1%[77] for placebo-treated patients. The 3 nirsevimab trials reported statistically significantly better outcomes for nirsevimab than placebo patients, with p values = 0.0002 (RR reduction)[77, 79] and <0.001.[76] One trial of RSVpreF reported that 0/3 RSVpreF patients and 2/5 (40%, statistical significance NR) placebo patients with a medically attended, RSV-related LRTI required hospitalization.[80]

Only one trial[76] reported **hospitalization for all-cause LRTI**, with lower rates in the intervention arm; 1.1% of infants receiving nirsevimab were hospitalized for all-cause LRTI, compared with 2.4% in the placebo arm (statistical significance NR).

Two trials of nirsevimab and both trials of RSVpreF reported the number of patients receiving **medical attendance due to an RSV-related LRTI**, with better outcomes after intervention than placebo. Rates ranged from 0.7%[80] to 1.6%[78] after RSVpreF, from 2.6%[77] to 2.7%[79] after nirsevimab, and from 3.4%[78] to 9.5%[77] after placebo. Only the nirsevimab trials calculated statistical significance, with significantly better outcomes for nirsevimab than placebo (p<0.001[77] and <0.0001[79]).

Two trials of nirsevimab reported data on **ICU admission for medically attended RSV LRTI.** Outcomes were better after nirsevimab than placebo, but neither trial reported the statistical significance of this difference. While Griffin 2020[77] reported ICU admission for medically attended, RSV-confirmed LRTI (0% in the nirsevimab arm and 1% in the placebo arm), HARMONIE[76] reported ICU admission for very severe RSV-associated LRTI (0.05% in the nirsevimab arm and 0.12% in the placebo arm). This means it is not possible to directly compare data for these outcomes across the two trials. No trials of RSVpreF reported this outcome.

Two trials of nirsevimab reported rates of **mechanical or assisted ventilation related to RSV**. Although outcomes appeared better after nirsevimab than placebo, neither reported statistical significance. Griffin 2020[77] reported that 0.8% of patients in both nirsevimab and placebo arms required assisted ventilation, while 0.4% of the nirsevimab arm and 3.1% of the placebo arm required supplemental oxygen. In the HARMONIE trial,[76] no patients in the nirsevimab arm and one patient (0.02%) in the placebo arm required mechanical ventilation following admission to ICU with very severe, RSV-associated LRTI. No trials of RSVpreF reported this outcome.

Four trials reported rates of **medically attended LRTI** from any cause, though none reported statistical significance. Rates appeared better after nirsevimab than placebo, and similar between RSVpreF and placebo. Two of three trials of nirsevimab[77, 79] found lower rates of medically attended LRTI in the nirsevimab group than the placebo group (19.7% versus 25.8%,[77] and 8.7% versus 18.1%[79]). One trial of RSVpreF (MATISSE)[78] reported that at 150 days after birth, 9.5% of patients receiving RSVpreF had a medically attended LRTI, compared with 10% in the placebo group. These figures rose to 11.2% and 11.6% at 180 days but remained similar between arms.

No studies reported a calculation of the statistical significance of any differences in safety outcomes between arms. However, rates of **TRAEs** were generally low, between 0% and 2.3% across arms (except Domachowske 2018, which has already been discussed in Sections 7.2.2 to 7.2.4).

Fear of AEs impacting the fetus/baby has been reported as a barrier to maternal vaccination uptake during pregnancy. Therefore, AEs relating to **premature labor, premature delivery, premature baby or fetal death** following maternal vaccination were extracted. Due to apparent inconsistencies in the reported data and the lack of outcome definition or explanation by the trial authors, it was not possible to draw any overall conclusions from these data. No within-trial comparisons between arms were available because neither trial of RSVpreF undertook testing for statistical significance for any of these outcomes.

7.3 Review of Economic Evidence

Ten eligible studies were identified that reported economic evaluation evidence for RSVpreF vaccination during pregnancy and/or RSV prophylaxis with nirsevimab for newborns and infants.[81-90] .

Three of these studies assessed both monoclonal antibody and maternal vaccination programs but were not explicit about which maternal vaccination was under assessment.[83 87, 88] Two studies stated that the monoclonal antibody data was sourced from nirsevimab trials, but they did not state which maternal vaccination data source was used.[87, 88] Therefore, only the nirsevimab outcomes were extracted from these studies.[87, 88] In the third study, the maternal vaccination under assessment was not explicitly named as RSVpreF, but the data used were sourced from RSVpreF trials; the study clearly stated that the monoclonal antibody was nirsevimab.[83] Both the nirsevimab and RSVpreF outcomes were extracted from this study.[83]

7.3.1 Study characteristics

7.3.1.1 General characteristics

Key study characteristics for studies of nirsevimab, RSVpreF and both nirsevimab and RSVpreF are summarized in Table 29, Table 30 and Table 31, respectively. The identified economic evaluations were performed for Canada (n=3),[82, 88, 89] Spain (n=2),[81, 84] the US (n=2),[86, 90] Norway (n=1),[87] and England and Wales (n=1).[85] One economic evaluation was performed across 6 European countries.[83] No Swiss-based models were identified.

Eight studies performed a cost-utility analysis (assessing cost per QALY).[81-83, 85, 87-90] The remaining 2 studies performed a cost-consequence analysis and applied a cost to clinical events (such as RSV-related hospitalizations and PC visits).[84, 86]

The base case analyses were performed from the healthcare perspective in all studies. A societal perspective was considered in a scenario analysis in 5 evaluations.[82-84, 89, 90]

Table 29: Objectives and general characteristics of studies reporting economic evaluations of nirsevimab (only)

Study	Country setting	Objective	Study design	Perspective	Funding
Gil-Prieto, 2024[84]	Spain	To assess the potential public health and economic impact of a universal passive immunization strategy with nirsevimab versus the current SoC (palivizumab) for all neonates and infants experiencing their first RSV season.	Cost consequence analysis	Healthcare payer and societal	AstraZeneca and Sanofi
Kieffer, 2022[86]	US	To evaluate the health and cost outcomes associated with the use of nirsevimab against SoC (palivizumab) in the prevention of RSV, medically attended LRTIs in all infants in their first RSV season.	Cost consequence analysis	NR – however, it appears to be the US healthcare system	AstraZeneca and Sanofi
Li, 2022[87]	Norway	To evaluate the health and economic burden of RSV and the cost effectiveness of RSV disease prevention strategies using maternal vaccination (product not stated) and monoclonal antibody (nirsevimab), including both seasonal and year-round programs in children under 5.	Cost-effectiveness analysis	Healthcare payer	Innovative Medicines Initiative 2 Joint Undertaking[1]
Nourbakhsh, 2021[88]	Canada (Nunavik, Quebec)	To evaluate the cost effectiveness of immunization programs with RSV prophylactics long-acting monoclonal antibodies (nirsevimab) and maternal vaccine (ResVax).	Cost-effectiveness analysis	NR – however, it appears to be the healthcare perspective	CIHR and Public Health Agency of Canada[2]
Yu, 2024[90]	US	To analyze the cost effectiveness of palivizumab and nirsevimab compared with SoC (no prophylaxis) for preterm infants without additional risk factors.	Cost-effectiveness analysis	Healthcare payer and societal	No financial support received

Abbreviations

LRTI = lower respiratory tract infection, RSV = respiratory syncytial virus, SoC = standard of care, US = United States.

Notes

[1] With support from the European Union's Horizon 2020 research and innovation program and the European Federation of Pharmaceutical Industries and Associations.

[2] Through the Canadian Immunization Research Network.

Table 30: Objectives and general characteristics of studies reporting economic evaluations of RSVpreF (only)

Study	Country setting	Objective	Study design	Perspective	Funding
Alvarez Aldean, 2024[81]	Spain	To evaluate the cost effectiveness of vaccinating pregnant women with RSVpreF to prevent RSV in infants.	Cost-effectiveness analysis	Spanish National Healthcare System	Pfizer

Abbreviations

RSV = respiratory syncytial virus.

Table 31: Objectives and general characteristics of studies reporting economic evaluations of both nirsevimab and RSVpreF

Study	Country setting	Objective	Study design	Perspective	Funding
Gebretekle, 2024 [82]	Canada	To assess the cost effectiveness of RSVpreF and nirsevimab programs in preventing RSV in infants, compared with a palivizumab program.	Cost-effectiveness analysis	Healthcare and societal	One Society Network[1]
Getaneh, 2023[83]	Denmark, Finland, England, Scotland, Italy, and the Netherlands	To evaluate the cost effectiveness of year-round RSV maternal immunization (RSVpreF) and monoclonal antibody (nirsevimab) programs, as well as seasonal monoclonal antibody program, and a seasonal monoclonal antibody plus catch-up program.	Cost-effectiveness analysis	Healthcare and societal	Innovative Medicines Initiative 2 Joint Undertaking[2]
Hodgson, 2024[85]	England and Wales	Using an existing dynamic transmission model, the authors compared RSVpreF to nirsevimab for RSV by calculating the impact and cost effectiveness.	Cost-effectiveness analysis	National Health Service	NIHR
Shoukat, 2023[89]	Canada (the southern provinces)	To conduct a comprehensive cost-effectiveness analysis of RSV infant and maternal immunization strategies using nirsevimab and RSVpreF, based on local population demographics.	Cost-effectiveness analysis	Healthcare and societal	CIRN and CIHR

Abbreviations

CIHR = Canadian Institutes of Health Research, CIRN = Canadian Immunization Research Network, NIHR = National Institute for Health Research, RSV = respiratory syncytial virus.

Notes

[1] Funded through the Natural Sciences and Engineering Research Council of Canada (NSERC).

[2] With support from the European Union's Horizon 2020. One author also received support from the Research Foundation Flanders and another author from NI

7.3.1.1 Population, intervention and comparator

Key details about the modelled populations, interventions and comparators for studies of nirsevimab, RSVpreF and both nirsevimab and RSVpreF are summarized in Table 32, Table 33 and Table 34, respectively. All 10 studies modelled cohorts of newborns from birth. Strategies were modelled based on the month the infant was born. For example, the injection could be given all-year-round to infants born in the RSV season only or to those born in the RSV season followed by a catch-up at the start of the season (usually October). The licensing for maternal vaccinations was often defined as pregnant women in the last trimester of pregnancy (between 24- and 36-weeks of pregnancy). The models often did not stratify the cohort by sex and sex distributions did not impact the model results significantly.

Nine studies included nirsevimab as a comparator in the analysis.[82-90] The effectiveness of nirsevimab was predominantly informed from the Phase III MELODY trial [93] and a Phase 2b trial (NCT02878330).[77] In 2 studies, the efficacy of nirsevimab was informed from the Phase 2/3 MEDLEY trial in which nirsevimab was compared with palivizumab.[84, 86]

Seven studies[81-83, 85, 87-89] included maternal immunization as a comparator in the analysis. Five of these studies[81-83, 85, 89] explicitly noted this to be RSVpreF, with the efficacy inputs informed from the MATISSE trial. One study[88] modelled the RSV F-nanoparticle vaccine ResVax and, therefore, was not of interest to this review. One study[87] did not specify the maternal vaccine modelled and the World Health Organization's preferred product characteristic was used to inform the efficacy (70% efficacy and 4-month protection).

Table 32: The population and interventions of economic studies that assess nirsevimab (only)

Study	Population		Interventions and comparator
Gil-Prieto, 2024[84]	Newborns and infants Spain	The population was stratified: Palivizumab-eligible infants. Preterm infants not eligible for palivizumab (born at 29 to 34 weeks and 6 days GA). Late preterm and term infants not eligible for palivizumab (born at or after 35 wGA). SoC was five monthly doses of palivizumab to premature infants or those with chronic lung disease or congenital heart disease.	Nirsevimab – Universal immunization (single dose) at the beginning of or during the first RSV season (November to March). SoC – Monthly palivizumab during RSV season (up to five doses) and no prophylaxis for non-eligible preterm and term infants*.
Kieffer, 2022[86]	Newborns and infants US	The entire US birth cohort was stratified: Term and late pre-term infants: born at or after 35 wGA. Preterm infants not eligible for palivizumab: born between 29 wGA and 34 weeks, 6 days GA. Palivizumab-eligible infants: born before 29 wGA or with chronic lung disease of prematurity or congenital heart disease.	Nirsevimab – Passive immunization. SoC – Monthly palivizumab during RSV season (up to five doses) and no prophylaxis for non-eligible preterm and term infants*.
Li, 2022[87]	Newborns and infants Norway	Monthly birth cohorts were used from birth to 5 years old.	Nirsevimab – At birth, throughout the year. – Seasonal programs n=28 (a single-month program or any combination of consecutive months during the RSV season to prevent RSV disease from October to April). – Catch-up program, at birth during RSV season (October to April) plus to infants (<6 months) born May to September. No RSV disease prevention strategy. Maternal immunization (no product specified). – Year round in the third trimester of pregnancy*.
Nourbaksh, 2021[88]	Newborns and infants		Nirsevimab – Preterm infants (3 to 5 months); and chronically ill infants (3 to 11 months old).

Study	Population		Interventions and comparator
	Canada	The model population was based on 2016 Statistics Canada census in Nunavik and included 13'284 individuals stratified by age. The infant population was split into three age-groups: 0 to 2 months, 3 to 5 months, and 6 to 11 months Infants under 1 year of age were categorized as healthy full-term or preterm/chronically ill (high-risk). High-risk included prematurely born infants under a chronological age of 6 months and infants with underlying comorbidities, such as chronic lung disease and hemodynamically significant heart disease and made up approximately 10% of the birth cohort. The children population was split into the following groups: 12 to 33 months, 24 to 25 months, 24 to 35 months, 36 to 47 months, and 5 to 18 years. Adults represented individuals over 18 years of age.	– Preterm infants (3 to 5 months); chronically ill infants (3 to 11 months old); and healthy infants. No intervention Palivizumab – Pilot immunization program: 5 doses for eligible infants during the RSV season (January to June). Eligible infants included: pre-term infants under 6 months of age, chronically ill infants under 2 years of age, and healthy full-term infants aged 0 to 2 months at the start of the RSV season or born during the season. – Pilot immunization program: 5 doses for eligible infants during the RSV season (January to June). Eligible infants included: pre-term infants under 6 months of age, chronically ill infants under 2 years of age, and healthy full-term infants aged 0 to 2 months at the start of the RSV season or born during the season. Plus, palivizumab for healthy infants*. ResVax – Maternal vaccine (ResVax) for pregnant women. – ResVax for pregnant women plus nirsevimab for preterm infants (3 to 5 months) and chronically ill infants (3 to 11 months old)*.
Yu, 2024[90]	Newborns and infants US	Preterm infants 29 0/7 to 34 6/7 wGA with no additional risk factors who were one year of age or younger and entering their first full RSV season.	Nirsevimab NB: This was assessed in a threshold analysis only due to no price estimate being available at the time of analysis. SoC – No prophylaxis. Palivizumab

Abbreviations

RSV = respiratory syncytial virus, SoC = standard of care, US = United States, wGA = weeks gestational age.

Notes

* Descriptions of interventions and comparators in the studies that were not of interest to this review are provided for context.

Table 33: The population and interventions of economic studies that assess RSVpreF (only)

Study	Population		Interventions and comparator
Alvarez Aldean, 2024[81]	Newborns and infants Spain	Live born infants (n=360'633) born to 355'250 women during a 1-year period. Infants were characterized by term status: – Full term: 92.9% were born at ≥37 wGA. – Late preterm: 6.0% were born at 32 to 36 wGA. – Early preterm: 0.8% were born at 28 to 31 wGA. – Extreme preterm: 0.3% were born at ≤27 wGA.	RSVpreF – Maternal immunization year-round. No intervention

Abbreviations

wGA = weeks gestational age.

Table 34: The population and interventions of economic studies that assess both nirsevimab and RSVpreF

Study	Population		Interventions and comparator
Gebretekle, 2024[82]	Newborns and infants Canada	Newborns were stratified into three groups: – High risk: extremely/very preterm, <33 wGA. – Moderate risk: late preterm, 33 to 36 wGA. – Low risk (full-term, ≥37 wGA). Extremely/very preterm infants accounted for 1.2% of all live births and late preterm infants was 6.8%.	Nirsevimab – Year-round program administered at birth for all infants. – Seasonal program without catch-up, administered at birth for all infants born during the RSV season (November to May). – Seasonal program with catch-up, in which all infants born during the RSV season receive their dose at birth and a catch-up dose is administered at the start of the RSV season (November) for all infants born outside of the RSV season (June to October). – Year-round program, administered at birth for infants at moderate- and high-risk.

Study	Population		Interventions and comparator
			– Seasonal program without catch-up, administered at birth for infants at moderate- and high-risk born during the RSV season (November to May). – Seasonal program with catch-up, in which infants at moderate- and high-risk born during the RSV season receive their dose at birth and a catch-up dose is administered at the start of the RSV season (November) for infants at moderate- and high-risk born outside of the RSV season (June to October). RSVpreF – Year-round for all pregnant women. Nirsevimab and RSVpreF – A combined program of year-round RSVpreF offered to all pregnant women plus year-round nirsevimab offered to infants at high-risk (assuming no protection from RSVpreF). SoC – Palivizumab for infants at high risk*.
Getaneh, 2023[83]	Newborns and infants Denmark, Finland, England, Scotland, Italy, and the Netherlands	Monthly birth cohorts of children from birth to 5 years old.	Nirsevimab – Year-round. – Seasonal, October to April ('seasonal'). – Seasonal with catch-up in October ('catch up'). RSVpreF No treatment.
Hodgson, 2024[85]	Newborns and infants	The cohort entered the model as newborns. The population were then split into 25 age groups:	Nirsevimab – Seasonal program (born between September and February).

Study	Population		Interventions and comparator
	England and Wales	– Monthly up to 1 year. – Yearly from 1 to 4 years, then 5 to 9, 10 to 14, 15 to 24, 25 to 34, 35 to 44, 45 to 54, 55 to 64, 65 to 74, 75+ years.	– Seasonal program with a yearly catch up of all infants aged <6 months during September. – Year-round program (at birth). RSVpreF – Seasonal program (pregnant women 24 to 36 wGA between July and December). – Year-round program (pregnant women 24 to 36 wGA).
Shoukat, 2023[89]	Newborns and infants Canada	Twelve monthly birth cohorts were categorized: – Preterm: <29 wGA. 29 to 32 wGA. 33 to 36 wGA. – Term infants: 37+ wGA. Preterm infants comprised about 9% of the cohort (<29 wGA: 7%; 29 to 32 wGA: 17%; 33 to 36 wGA: 76%).	Nirsevimab – Preterm infants ≤32 wGA, and infants with CLD or CHD. Only given if an infant is born in RSV season. Infants born in off-season given top up at the start of the RSV season. – Preterm infants ≤36 wGA, and infants with CLD or CHD. Only given if an infant is born in RSV season. Infants born in off-season given top up at the start of the RSV season. – Preterm infants ≤36 wGA, infants with CLD or CHD, and term infants born during the RSV season (October to March). Only given if an infant is born in RSV season. Infants born in off-season given top up at the start of the RSV season. – Birth cohort. Only given if an infant is born in RSV season. Infants born in off-season given top up at the start of the RSV season. RSVpreF – Year-round program, with vaccination of pregnant women who are in their last trimester before gestation week 33. RSVpreF plus nirsevimab

Study	Population	Interventions and comparator
		– All round vaccination of pregnant women followed by administration of nirsevimab to infants at high risk of severe RSV (preterm infants ≤32 wGA and infants with CLD or CHD condition) during RSV season.

Abbreviations

CHD = congenital heart disease, CLD = chronic lung disease, LMI = combined nirsevimab and RSVpreF immunization program, RSV = respiratory syncytial virus, SoC = standard of care, wGA = weeks gestational age.

Notes

* Descriptions of interventions and comparators in the studies that were not of interest to this review are provided for context in grey text

7.3.1.2 Type of model and model characteristics

Key model characteristics are summarized in Table 35. Seven of the economic evaluations used a static cohort-based approach and three used an individual dynamic transmission approach.

Four evaluations used a time horizon of one year,[81, 82, 88, 89] and one of these evaluations captured health outcomes over a lifetime in a scenario analysis. Three evaluations used a time horizon of 5 years to capture the long-term consequences of RSV-related hospitalizations (such as the impact of sequelae, asthma and wheezing).[83, 87, 90] One dynamic transmission model used a time horizon of 10 years[85] and two evaluations described the time horizon to cover one RSV season.[84, 86]

Discounting was used in 8 evaluations. The authors explained that discounting was not used in one study because the time horizon was one year.[81] Discounting was not mentioned in the other study. Of the 8 evaluations where discounting was used, costs and effects were distributed equally in 6 evaluations.[86] In one evaluation, costs and effects were discounted at 4% and 1.5%, respectively (as per the Netherlands guidelines). In the final evaluation, only benefits were discounted (the costs were estimated for one year but the benefits over a lifetime).

Table 35: Model characteristics

Study	Country setting	Analytic approach	Model description	Time horizon	Discount rate	
					Costs	Effect
Assessments of nirsevimab						
Gil-Prieto, 2024[84]	Spain	Model based	A static decision analytic model was developed to estimate the cost impact of a universal passive immunization strategy with nirsevimab versus the current SoC (palivizumab) for all neonates and infants experiencing their first RSV season.	The first RSV season (except premature deaths which was considered lifetime)	3%	NA
Kieffer, 2022[86]	US	Model based	A static decision tree-based model was developed to estimate the health and cost outcomes associated with the use of nirsevimab against SoC (palivizumab) in the prevention of RSV-MALRTIs in all infants in their first RSV season.	1 to 3 RSV seasons/years for some resource, 'user-defined' for complications and lifetime for RSV deaths	NR	NR
Li, 2022[87]	Norway	Model based	A static cohort model was developed to estimate the health and economic burden of RSV disease and the cost effectiveness of RSV disease prevention strategies using maternal vaccination (product not stated) and monoclonal antibody (nirsevimab), including both seasonal and year-round programs in children under 5.	Not explicitly reported The model tracked monthly birth cohorts of children from birth to 5 years old	4%	4%
Nourbaksh, 2021[88]	Canada (Nunavik, Quebec)	Model based	A discrete-event agent-based simulation model was developed to evaluate the cost effectiveness of immunization programs with the RSV prophylactics long-acting monoclonal antibodies (nirsevimab) and maternal vaccine (ResVax).	1 year	NA	NA
Yu, 2024[90]	US	Model based	A hybrid model (decision tree followed by Markov) was developed to analyze the cost effectiveness of palivizumab and nirsevimab compared with SoC (no prophylaxis) for preterm infants.	5 years	3%	3%
Assessment of RSVpreF						
Alvarez Aldean, 2024[81]	Spain	Model based	A cohort Markov-type model was developed to evaluate the cost effectiveness of vaccinating pregnant women with the RSVpreF vaccine to prevent RSV in infants.	1 year	NA	3%
Assessments of both nirsevimab and RSVpreF						

Study	Country setting	Analytic approach	Model description	Time horizon	Discount rate	
					Costs	Effect
Gebretekle, 2024[82]	Canada	Model based	A hybrid model (Markov and decision tree) was designed to estimate the cost-effectiveness of RSVpreF and nirsevimab programs in preventing RSV disease in infants, compared with a palivizumab program.	1 year	1.50%	1.50%
Getaneh, 2023[83]	Denmark, Finland, England, Scotland, Italy, and the Netherlands	Model based	A static cohort model was developed to evaluate the cost-effectiveness of year-round RSV maternal immunization (RSVpreF) and monoclonal antibody (nirsevimab) programs, as well as a seasonal RSV monoclonal antibody program, and a seasonal monoclonal antibody plus catch-up program for six European countries.	Not explicitly reported The model tracked monthly birth cohorts of children from birth to 5 years old	Denmark: 3.5% England: 3.5% Scotland: 3.5% Finland: 3% Italy: 3% Netherlands: 4%	Denmark: 3.5% England: 3.5% Scotland: 3.5% Finland: 3% Italy: 3% Netherlands: 1.5%
Hodgson, 2024[85]	England and Wales	Model based	A dynamic transmission model designed to estimate the cost-effectiveness of RSVpreF compared with nirsevimab against RSV.	10 years	3.50%	3.50%
Shoukat, 2023[89]	Canada (the southern provinces)	Model based	A dynamic transmission model designed to estimate the cost-effectiveness of RSV infant and maternal immunization strategies using nirsevimab and RSVpreF.	1 year	1.50%	1.50%

Abbreviations

NHS = National Health Service, NR = not reported, RSV = respiratory syncytial virus, US = United States.

7.3.1.3 Model inputs

Key details about the model inputs for studies of nirsevimab, RSVpreF and both nirsevimab and RSVpreF are summarized in Table 36, Table 37 and Table 38, respectively. In general, unit costs were obtained from published literature and were dependent on the perspective of the model. Common cost inputs included the cost of hospitalization, the cost of ICU stays and the cost per PC visit. Separate efficacy inputs were often used to inform each of these inputs. Some studies also included productivity loss costs in a scenario analysis. It was often necessary to vary the cost of the intervention in sensitivity and/or scenario analysis due to a lack of alternative information. No Swiss-specific costs were identified.

Two studies included resource use only and, therefore, did not capture HRQoL. Equations informed by Hodgson (2020)[95] were often used to inform the QALY loss associated with symptomatic RSV and RSV hospitalizations. Other common utility sources included Glaser (2022) and Roy (2013).[96, 97] The most applicable utilities to the Swiss setting were those used in Getaneh (2023);[83] these are considered the most robust because they were estimated using data from 4 European countries.

Table 36: Models input sources for economic studies that assess nirsevimab (only)

Study	Country setting	Healthcare costs and resource use data	Effectiveness data	HRQoL/utilities data
Gil-Prieto, 2024[84]	Spain	Cost inputs were obtained from the BARI study (Martinon-Torres 2022), published literature (Moreno-Perez 2014), and tariffs from the national eSalud database.	Nirsevimab efficacy against RSV medically attended LRTIs in term infants and preterm infants not eligible for palivizumab was determined from pre-specified pooled efficacy data from the pivotal Phase 2b and Phase 3 studies (MELODY, Simeos, 2023). Nirsevimab efficacy was assumed non-inferior to palivizumab for palivizumab-eligible infants based on the results of the MEDLEY trial.	NA
Kieffer, 2022[86]	US	Costs were derived from published sources. The cost of RSV treatment in an inpatient hospitalization requiring an ICU visit or MV was obtained from McLaurin 2016. Costs associated with an ED or PC visit were also derived as a weighted average of Medicaid and commercial costs informed from InHealth Professional Services, Agency for Healthcare Research and Quality 2017 for Commercial and the Centers for Medicare & Medicaid Services Physician Fee Schedule Look-Up Tool for Medicare.	The overall pooled efficacy of nirsevimab in the prevention of medically attended RSV-associated lower respiratory tract infections was utilized for all term and preterm infants, and noninferiority in terms of protection against RSV-MALRTIs versus palivizumab was assumed for the palivizumab-eligible population, according to MEDLEY, head-to-head Phase 2/3 trial of nirsevimab versus palivizumab (Domachowske 2022).	NA
Li, 2022[87]	Norway	The price per dose for both monoclonal antibody (nirsevimab) and maternal immunization (product not specified) were assumed based on a Norwegian rotavirus vaccine evaluation in the absence of pricing information from manufacturers (Eckermann 2008). Hospital costs (inpatient and outpatient) were obtained from the Diagnosis-Related Group based hospital financing system. PC costs were obtained from the Norwegian Health Economics Administration.	Phase 3 efficacy data for the monoclonal antibody (nirsevimab) programs were from MELODY. For maternal immunization, the WHO preferred product characteristic 16 was in the base-case analysis (2017). A scenario analysis using efficacy values from the Phase 3 trial were used in a scenario (Madhi 2020).	The QALY loss associated with each RSV-related outcome was estimated from published literature (Hodgson 2020).
Nourbaksh, 2021[88]	Canada - specifically Nunavik, Quebec	Average costs of outpatient visits, pediatric ward visits and intensive care were informed from published literature (Sharif 2018, Tam 2009, and Banerji 2013, respectively).	Efficacy of nirsevimab to prevent outpatient and pediatric ward use was obtained from NCT02878330 (Griffin 2020). The efficacy of nirsevimab to prevent ICU visits was assumed the same as palivizumab and informed literature (Rainisch 2020).	Obtained from published literature (Tam 2009, Pouwels 2016, Roy 2013, and Roy 2014).
Yu, 2024[90]	US	The costs of outpatient visits and hospitalization were obtained from published literature (Chirikov 2019).	The effectiveness of nirsevimab was based on the nirsevimab Phase 2b trial (Griffin 2020).	The utility for preterm infants with chronic lung disease but no history of RSV illness (no RSV

Study	Country setting	Healthcare costs and resource use data	Effectiveness data	HRQoL/utilities data
		ICU costs were obtained from SENTINEL (Anderson 2017). Sequelae management costs were obtained from published literature (Nurmagambetov 2018).		hospitalization) was informed from published literature (Greenough 2004). The utility associated with RSV hospitalization was obtained from published literature (Glaser 2022).

Abbreviations

HRQoL = health-related quality of life, ICU = intensive care unit, LRTI = lower respiratory tract infection, MV = mechanical ventilation, NA = not applicable, PC = primary care, QALY = quality-adjusted life year, RCT = randomized controlled trial, RSV = respiratory syncytial virus, WHO = World Health Organization.

Table 37: Models input sources for economic studies that assess RSVpreF (only)

Study	Country setting	Healthcare costs and resource use data	Effectiveness data	HRQoL/utilities data
Alvarez Aldean, 2024[81]	Spain	The cost of hospitalizations were extracted from an observational study employing Spanish Minimum Basic Data Set (Law 2023). The cost for both ED and PC events were extracted from the BARI study (Martinón-Torres 2022). The vaccine cost was based on the list price from the Spanish Official College of Pharmacists database.	Effectiveness data were informed from the MATISSE trial (Kampmann 2023). Effectiveness data among late preterm infants was informed from published literature (Atwell 2023).	Utility values during the period of illness for infants treated in hospital and in patient settings were informed from published literature (Roy 2013).

Abbreviations

ED = emergency department, HRQoL = health-related quality of life, PC = primary care, RCT = randomized controlled trial, RSV = respiratory syncytial virus.

Table 38: Models input sources for economic studies that assess both nirsevimab and RSVpreF

Study	Country setting	Healthcare costs and resource use data	Effectiveness data	HRQoL/utilities data
Gebretekle, 2024[82]	Canada	Unit costs for pediatric hospitalizations and ICU costs were obtained from a previous model (Lanctot 2008) and the Canadian Institute for Health Information. Outpatient healthcare provider and ED visit costs were obtained from a population-based matched retrospective case–control study using administrative data from Alberta (Rafferty 2022). Canadian list prices were used for RSVpreF.	Efficacy data were obtained from targeted literature searches. A meta-analysis of 2 RCTs (MELODY and a study reposted by Griffin 2020) estimated the pooled effectiveness of nirsevimab against RSV medially attended LRTI, RSV hospitalization and very severe RSV disease. The MATISSE trial was used to inform the efficacy of RSVpreF.	The disutility weights for hospitalized infants and their caregivers (one per child) were derived from a systematic review (Glaser 2022). There was a 45% increase in utility loss for infants admitted to the ICU and their caregivers, compared with those hospitalized in a pediatric general ward, based on observed utility difference for infants with these different RSV outcomes (Roy 2013). Utility decrements for outpatient healthcare provider or ED visits for RSV were derived from a previous cost-effectiveness study of RSV prophylactic products that estimated QALY loss based on pertussis (Regnier 2013).
Getaneh, 2023[83]	6 European countries: Denmark, Finland, England, Scotland, Italy, and the Netherlands	Intervention cost per dose was €50 for both maternal immunization (RSVpreF) and monoclonal antibody (nirsevimab). Annual implementation costs, which were applied in a scenario analysis only, was assumed to be €300,000. Country-specific costs were obtained for hospitalizations, including ICU admissions, PC visits, and monoclonal antibody and maternal immunization administration costs: Denmark The cost of hospitalization was from published literature (Jepsen 2018). Cost per PC visit was the HONORARTABEL tariff (2020). Finland The cost of hospitalization was from published literature (Maklin 2020). The source of the cost per PC visit was NR. England	The effectiveness of monoclonal antibody (nirsevimab) was estimated from the MELODY trial. The World Health Organization (WHO) preferred product characteristics was used for maternal immunization (RSVpreF).	The QALY loss associated with each RSV-related outcome was estimated from published literature (Mao 2022). Estimates based on QALY loss from published literature (Hodgson 2020) were used in a scenario analysis.

Study	Country setting	Healthcare costs and resource use data	Effectiveness data	HRQoL/utilities data
		The cost of hospitalization and of intensive care was from NHS Reference costs (2019). The cost per PCvisit was from published literature (Curtis and Burns 2020). Italy-Veneto region The cost of hospitalization was from published literature (Bozzola 2010). The cost of a family pediatrician was from published literature (Barbieri 2022). The Netherlands The costs of hospitalization, ICU and per PC visit were taken from published literature (Hakkaart-van Roijen 2016).		
Hodgson, 2024[85]	England and Wales	GP costs were taken from PSSRU. RSV hospital costs and ICU costs taken from NHS Reference Costs. The cost of palivizumab was assumption based.	Efficacy for RSVpreF in newborns was informed from the MATISSE trial. The KM plot for Medically Attended RSV-Associated Lower Respiratory Tract Illness was used to estimate the time-varying efficacy against infection. The protection for mothers was assumed to be equivalent to the GSK product. Efficacy against more severe outcomes, such as Medically Attended Severe RSV-associated Lower Respiratory Tract Illness in infants was informed by published literature (Kampmann 2023). For nirsevimab the KM plot for Medically Attended RSV-LRTI from the MELODY trial was used to estimate the time-varying efficacy against infection. Published literature (Simões 2023) was used to inform efficacy against more severe outcomes, such as very severe LRTI.	All utility data were obtained from the previously published model (Hodgson 2020).
Shoukat, 2023[89]	Canada (specifically the southern provinces)	The single-dose cost of both nirsevimab and RSVpreF was varied to determine the price range within which an immunization program would be cost-effective. Unit costs for other healthcare resources were obtained from a previous model (Lanctot 2008) and the Canadian Institute for Health Information.	Nirsevimab against medically attended RSV-LRTI was informed by the MELODY trial. RSVpreF was informed by MATISSE trial.	Utilities taken from published literature (Greenough 2004). The authors noted that the disutility values were consistent with recent estimates by Hodgson (2020).

Abbreviations

ED = emergency department, GP = General Practitioner, HRQoL = health-related quality of life, ICU = intensive care unit, KM = Kaplan Meier, LRTI = lower respiratory tract infection, PC = primary care,

PSSRU = Personal Social Services Research Unit, QALY = quality-adjusted life year, RCT = randomized controlled trial, RSV = respiratory syncytial virus.

7.3.1.4 Results

Key model outcomes studies of nirsevimab, RSVpreF and both nirsevimab and RSVpreF are summarized in Table 39, Table 40 and Table 41, respectively. RSVpreF and nirsevimab were found to be cost-effective when compared with no prophylaxis. In Spain, the maternal vaccine with RSVpreF dominated (i.e. was more effective and less costly) compared with no prophylaxis.[81] In Canada, RSVpreF was considered cost-effective compared with no prophylaxis where the willingness-to-pay (WTP) threshold was $50'000 per QALY gained with an ICER of $41'321.[89] Nirsevimab was found to be cost-effective when compared with no prophylaxis across Europe and North America.[83, 88, 90]

Seasonable injection with nirsevimab was found to be cost-effective when compared with RSVpreF. In Canada, seasonal nirsevimab for infants at moderate or high risk with a catch-up program was cost-effective compared with RSVpreF (year-round).[82] In Denmark, England, Finland, Italy, the Netherlands and Scotland, seasonal nirsevimab programs were cost saving or cost effective (at different WTP thresholds) versus year-round nirsevimab, RSVpreF and no program.[83] In England and Wales, when nirsevimab was priced above £84, a seasonal maternal vaccine program with RSVpreF was optimal between £36 and £80 per cost of purchasing and administration (CCPA) and a year-round RSVpreF program was optimal up to £35 per CCPA.[85] If RSVpreF was priced above £80, then a seasonal nirsevimab program was optimal for up to £55 to £83 CCPA and a seasonal nirsevimab with a catch-up program was optimal for up to £55 CCPA.[85]

Table 39: Outcomes of the economic studies that assess nirsevimab (only)

Study	Country setting	Currency, cost year	Costs outcomes	Effectiveness outcomes	Base case incremental analyses outcomes
Gil-Prieto, 2024[84]	Spain	Euros (€), 2023	Total healthcare costs Nirsevimab Palivizumab eligible infants PC visits: €161'540 Specialist visits: €44'076 ED visits: €116'984 Inpatient hospitalizations: €1'595'185 PICU admissions: €800'547 Mechanical ventilation: €148'831 Total: €2'867'162 Preterm infants PC visits: €129'586 Specialist visits: €35'842 ED visits: €94'213 Inpatient hospitalizations: €1'256'740 PICU admissions: €660'421 Mechanical ventilation: €118'228 Total: €2'295'030 Term infants PC visits: €3'801'056 Specialist visits: €1'051'338 ED visits: €2'763'482 Inpatient hospitalizations: €9'270'642 PICU admissions: €3'478'321 Mechanical ventilation: €1'475'344 Total: €21'840'184	NA	NA All incremental outcomes were presented against SoC using palivizumab (which was not of relevance for this review)*.
Kieffer, 2022[86]	US	US Dollars ($), 2021	Costs (millions) of health events (range associated with RSV rates) Nirsevimab Hospitalizations: $342.2 ($286.4 to $514.9) ICU: $520.5 ($292.9 to $1,248.8) Mechanical ventilation: $272.8 ($211.8 to $439.2) ED visits: $64.7 ($55.4 to $74.0) PC visits: $41.7 ($34.7 to $48.6) Total: $1'241.8 ($881.1 to $2'325.4)	NA	NA All incremental outcomes were presented against SoC using palivizumab (which was not of relevance for this review)*.

Study	Country setting	Currency, cost year	Costs outcomes	Effectiveness outcomes	Base case incremental analyses outcomes
Li, 2022[87]	Norway	Norwegian Kroner (NOK), 2019	Program costs Nirsevimab Year-round and catch-up programs including delivery: approximately NOK 31 million Seasonal programs: from NOK 5.3 million (single-month programs) to NOK 19.1 million (7-month "October to April" program)	Discounted QALYs Nirsevimab Assuming NOK 500 (€51) per dose, catch-up program estimated to gain: 13 discounted QALYs 6-month monoclonal antibody "October to March" program gained almost the same as the 7-month monoclonal antibody "October to April" program: 7 discounted QALYs	WTP value thresholds Below NOK 0.4 million per QALY gained Seasonal nirsevimab 'October to February' program was preferred Between 0.4 and 0.5 million NOK per QALY gained Nirsevimab 'November to February' program was preferred Greater than 0.5 million NOK per QALY gained Nirsevimab 'October to March' program was preferred
Nourbaksh, 2021[88]	Canada – specifically Nunavik, Quebec	Canadian Dollars ($), 2021	Cost savings (95% credible interval) Mild RSV season No intervention vs nirsevimab: -$71'927 (-$77'598 to $66'406) Nirsevimab vs nirsevimab (inc. healthy infants): $35'084 ($32'603 to $37'447) Moderate RSV season No intervention vs nirsevimab: -$154'831 (-$162'779 to -$147'164) Nirsevimab vs nirsevimab (inc. healthy infants): $9'291 ($7'024 to $11'566) Severe RSV season No intervention vs nirsevimab: -$227'282 (-$237'507 to -$217'361) Nirsevimab vs nirsevimab (inc. healthy infants): -$18'453 (-$32'665 to -$15'274)	QALYs gained (95% credible interval) Mild RSV season No intervention vs nirsevimab: 0.0814 (0.0780 to 0.0898) Nirsevimab vs nirsevimab (inc. healthy infants): 0.8906 (0.8324 to 0.9452) Moderate RSV season No intervention vs nirsevimab: 0.1661 (0.1580 to 0.1734) Nirsevimab vs nirsevimab (inc. healthy infants): 1.7677 (1.6931 o 1.8416) Severe RSV season No intervention vs nirsevimab: 0.2511 (0.2402 to 0.2610) Nirsevimab vs nirsevimab (inc. healthy infants): 2.6195 (2.5281 to 2.7078)	ICER (cost per QALY gained) (95% credible interval) [negative values indicate the second listed strategy was dominant] Mild RSV season No intervention vs nirsevimab: -$883'539 (-$885'162 to -$881'099) Nirsevimab vs nirsevimab (inc. healthy infants): $39'414 ($39'314 to $40'017) Moderate RSV season No intervention vs nirsevimab: -$931'845 (-$932'832 to -$930'793) Nirsevimab vs nirsevimab (inc. healthy infants): -$5'255 ($5'222 to $5'307) Severe RSV season No intervention vs nirsevimab: -$905'256 (-$906'069 to $904'322) Nirsevimab vs nirsevimab (inc. healthy infants): -$7'049 (-$7'072 to -$7'007)
Yu, 2024 [90]	US	US Dollars ($), 2021	Costs No prophylaxis: $1'748	QALYs No prophylaxis: 4.3186	Threshold analysis Nirsevimab could be cost-effective below a price of $1'923 (healthcare perspective) at a WTP threshold of $150'000 per QALY gained

Abbreviations

CCPA = combined cost of purchasing and administration, ED = emergency department, ICER = incremental cost-effectiveness ratio, ICU = intensive care unit, LY = life years, NA = not applicable, PC = primary care, PICU = pediatric ICU, PPD = price per dose, QALY = quality-adjusted life year, RSV = respiratory syncytial virus, US = United States, WTP = willingness to pay.

Notes

* Grey text indicates outcomes that were not eligible for this review.

Table 40: Outcomes of the economic studies that assess RSVpreF (only)

Study	Country setting	Currency, cost year	Costs outcomes	Effectiveness outcomes	Base case incremental analyses outcomes
Alvarez Aldean, 2024[81]	Spain	Euros (€), 2023	Costs (millions) RSVpreF Medical care: €88.63 Hospitalization: €55.38 ED: €13.10 PC : €20.15 Maternal vaccination: €42.32 Total: €130.96 No intervention Medical care: €132.76 Hospitalization: €91.08 ED: €16.69 PC : €24.99 Maternal vaccination: €0 Total: €132.76	QALYs (discounted) RSVpreF: 10’529’537 No intervention: 10’528’986 Life years (LY) (discounted) Maternal vaccine: 10’961’910 No intervention: 10’961’583	ICER (cost per QALY gained) RSVpreF dominated no intervention (it was more effective and less costly). ICER (cost per LY gained) RSVpreF dominated no intervention (it was more effective and less costly).

Abbreviations

ED = emergency department, ICER = incremental cost-effectiveness ratio, LY = life years, PC = primary care, QALY = quality-adjusted life year.

Table 41: Outcomes of the economic studies that assess nirsevimab and RSVpreF

Study	Country setting	Currency, cost year	Costs outcomes	Effectiveness outcomes	Base case incremental analyses outcomes
Gebretekle, 2024[82]	Canada	Canadian Dollars ($), 2023	Costs Seasonal nirsevimab for infants at moderate or high risk, no catch-up: $212'251 Seasonal nirsevimab for infants at moderate or high risk, with catch-up: $220'799 Year-round nirsevimab for infants at moderate or high risk: $231'567 Year-round RSVpreF plus nirsevimab for infants at high-risk: $316'971 Year-round RSVpreF for all pregnant women and pregnant people: $334'187 Seasonal nirsevimab for all infants, no catch-up: $554'487 Seasonal nirsevimab for all infants, with catch-up: $824'113 Year-round nirsevimab for all infants: $855'494	QALYs Seasonal nirsevimab for infants at moderate or high risk, no catch-up: 4.27 Seasonal nirsevimab for infants at moderate or high risk, with catch-up: 3.95 Year-round nirsevimab for infants at moderate or high risk: 4.15 Year-round RSVpreF plus nirsevimab for infants at high-risk: 3.48 Year-round RSVpreF for all pregnant women and pregnant people: 3.91 Seasonal nirsevimab for all infants, no catch-up: 3.58 Seasonal nirsevimab for all infants, with catch-up: 2.49 Year-round nirsevimab for all infants: 3.20	Sequential ICERs (cost per QALY gained) SoC (palivizumab for infants at high risk)*: - Seasonal nirsevimab for infants at moderate or high risk, no catch-up: dominated [more costly and less effective than the intervention immediately above] Seasonal nirsevimab for infants at moderate or high risk, with catch-up: 27'891 Year-round nirsevimab for infants at moderate or high risk: Dominated Year-round RSVpreF plus nirsevimab for infants at high-risk: 204'621 Year-round RSVpreF for all pregnant women and pregnant people: dominated Seasonal nirsevimab for all infants, no catch-up: dominated Seasonal nirsevimab for all infants, with catch-up : 512'265 Year-round nirsevimab for all infants: dominated
Getaneh, 2023[83]	6 European countries: Denmark Finland England Scotland Italy Netherlands	Euros (€), 2021	Treatment costs averted; intervention costs; incremental costs (compared with no program). All costs are for ('000) and the mean [95% confidence interval] Denmark Nirsevimab catch up: €2'301 [501 to 3'602]; €3'045 [3'045 to 3'045]; €743 [-557 to 2'535] Nirsevimab year-round: €1'761 [372 to 2'771]; €3'045 [3'045 to 3'045]; €1'284 [274 to 2'672] Nirsevimab October to April: €1'575 [333 to 2'479]; €1'776 [1'776 to 1'776]; €201 [-703 to 1'443] RSVpreF year-round: €1'695 [1'312 to 2'020]; €3'057 [3'057 to 3'057]; €1'362 [1'037 to 1'745] England Nirsevimab catch up: €28'712 [7'245 to 44'339]; €32'022 [32'022 to 32'022]; €3'310 [-12'317 to 24'777] Nirsevimab year-round: €24'056 [5'482 to 37'501]; €32'022 [32'022 to 32'022]; €7'950 [3'351 to 13'399] Nirsevimab October to April: €24'193 [18'745 to 28'793];	QALYs gained [95% confidence interval] Denmark Nirsevimab catch up: 44 [29 to 58] Nirsevimab year-round: 24 [15 to 34] Nirsevimab October to April: 22 [14 to 370] RSVpreF year-around: 19 [13 to 24] England Nirsevimab catch up: 478 [316 to 636] Nirsevimab year-round: 291 [182 to 400] Nirsevimab October to April: 225 [161 to 292] RSVpreF year-around: 197 [123 to 271] Finland Nirsevimab catch up: 42 [27 to 56] Nirsevimab year-round: 28 [17 to 38] Nirsevimab October to April: 26 [16 to	ICER (cost per QALY gained) Denmark, England, Italy, and the Netherlands The cost-effective programs were either: no treatment, seasonal nirsevimab, or seasonal nirsevimab with catch-up, depending on the WTP threshold value (including versus RSVpreF). Seasonal nirsevimab was preferred for WTP threshold values from €4'444 (England), €9'129 (Denmark), €23'814 (Italy) and €21'187 per QALY gained (the Netherlands), seasonal nirsevimab with catch-up was preferred for WTP values from €8'864 (England), €24'664 (Denmark), €42'245 (Italy) and €130'308 per QALY gained (the Netherlands), and no program was preferred for lower WTP values.

Study	Country setting	Currency, cost year	Costs outcomes	Effectiveness outcomes	Base case incremental analyses outcomes
			€32’144 [32’144 to 32’144]; €7’950 [3’351 to 13’399] RSVpreF year-round: €17’804 [3’979 to 27’816]; €18’679 [18’679 to 18’679]; €876 [-9’137 to 14’700] Finland Nirsevimab catch up: €3’211 [937 to 4’856]; €2’290 [2’290 to 2’290]; -€921 [-2’566 to 1’353] Nirsevimab year-round: €2’724 [721 to 4’184]; €2’290 [2’290 to 2’290]; -€434 [-1’895 to 1’569] Nirsevimab October to April: €2’470 [659 to 3’791]; €1’336 [1’336 to 1’336]; -€1’135 [-2’455 to 676] RSVpreF year-round: €2’662 [2’066 to 3’168]; €2’296 [2’296]; -€366 [-872 to 230] Italy-Veneto region Nirsevimab catch up: €1’113 [256 to 1’733]; €1’731 [1’731 to 1’731]; €618 [-2 to 1’475] Nirsevimab year-round: €965 [208 to 1’512]; €1’682 [1’682 to 1’682]; €717 [169 to 1’474] Nirsevimab October to April: €743 [161 to 1’165]; €981 [981 to 981]; €238 [-183 to 820] RSVpreF year-round: €998 [772 to 1’189]; €1’509 [1’509 to 1’509]; €512 [320 to 737] The Netherlands Nirsevimab catch up: €6’617 [1’462 to 10’352]; €11’243 [11’243 to 11’243]; €4’626 [891 to 9’782] Nirsevimab year-round: €5’682 [1’204 to 8’942]; €10’186 [10’186 to 10’186]; €4’503 [1’244 to 8’982] Nirsevimab October to April: €5’094 [1’080 to 8’016]; €5’942 [5’942 to 5’942]; €848 [-2’074 to 4’862] RSVpreF year-round: €5’843 [4’523 to 6’965]; €12’753 [12’753 to 12’753];€ 6’910 [5’700 to 8’231] Scotland Nirsevimab catch up: €2’591 [650 to 4’004]; €2’561 [2’561 to 2’561]; -€29 [-1’443 to 1’912] Nirsevimab year-round: €2’077 [476 to 3’237]; €2’561 [2’561 to 2’561]; €572 [193 to 1’022] Nirsevimab October to April: €2’000 [1’550 to 2’380]; €2’572 [2’572 to 2’572]; €572 [193 to 1’022] RSVpreF year-round: €1’479 [335 to 2’306]; €1’494 [1’494 to 1’494]; €15 [-812 to 1’160]	35] RSVpreF year-around: 22 [15 to 28] Italy-Veneto region Nirsevimab catch up: 19 [13 to 26] Nirsevimab year-round: 13 [8 to 18] Nirsevimab October to April: 10 [6 to 14] RSVpreF year-around: 10 [8 to 14] The Netherlands Nirsevimab catch up: 69 [46 to 93] Nirsevimab year-round: 45 [28 to 61] Nirsevimab October to April: 40 [25 to 55] RSVpreF year-around: 35 [25 to 46] Scotland Nirsevimab catch up: 42 [28 to 56] Nirsevimab year-round: 26 [16 to 35] Nirsevimab October to April: 20 [14 to 26] RSVpreF year-around: 17 [11 to 24]	Finland Seasonal nirsevimab with catch-up was cost-effective versus other programs from €13’373 per QALY gained, and for lower WTP values seasonal nirsevimab without catch-up was preferred versus other programs. Scotland Seasonal nirsevimab with catch-up was preferred over other programs for the range of WTP values considered. The results for all locations depended strongly on the following: the assumed intervention procurement price; the assumed intervention administration cost; the perspective; the type of data used to inform RSV-related hospitalizations (ICD10-coded counts or estimates based on time series analysis).

Study	Country setting	Currency, cost year	Costs outcomes	Effectiveness outcomes	Base case incremental analyses outcomes
Hodgson, 2024[85]	England and Wales	GBP, 2021/22	Cost savings Nirsevimab seasonal: £118'731'529 Nirsevimab year-round: £167'160'601 RSVpreF seasonal: £73'650'588 RSVpreF year-round: £96'604'729	QALY gains Nirsevimab seasonal: 3'819 Nirsevimab year-round: 5'867 RSVpreF seasonal: 3'042 RSVpreF year-round: 3'819	ICER An ICER WTP threshold of £20'000/QALY gained was used. If nirsevimab is priced above £84, then a seasonal RSVpreF program is optimal between £36 to £80 cost of purchasing and administration (CCPA), and a year-round RSVpreF program is optimal up to £35 CCPA. If RSVpreF is priced above £80, then a seasonal nirsevimab program is optimal up to £55 to £83 CCPA, and a seasonal nirsevimab with a catch-up program is optimal up to £55 CCPA. The year-round nirsevimab program was dominated by the seasonal nirsevimab with an annual catch-up program across all CCPAs. If both nirsevimab and RSVpreF are priced below £30 then the nirsevimab program is optimal. If both products are priced similarly above £30, then both programs are similarly cost effective.
Shoukat, 2023[89]	Canada (specifically the southern provinces)	Canadian Dollars, 2023	Incremental costs versus no intervention Nirsevimab, preterm infants <32 wGA: $1'199 Nirsevimab, preterm infants <36 wGA: $1'648 Nirsevimab, preterm and term infants: $3'235 Nirsevimab, birth cohort: $467 RSVpreF: $4'501	Incremental QALYs gained versus no intervention Nirsevimab, preterm infants <32 wGA: 0.024 Nirsevimab, preterm infants <36 wGA: 0.036 Nirsevimab, preterm and term infants: 0.094 Nirsevimab, birth cohort: 0.111 RSVpreF: 0.109	ICERs An ICER WTP threshold of $50'000/QALY gained was used. Nirsevimab, preterm infants <32 wGA vs no intervention: $49'577 Nirsevimab, preterm infants <36 wGA vs no intervention: $45'924 Nirsevimab, preterm and term infants vs no intervention: $34'331 Nirsevimab, birth cohort vs no intervention: $4'200 RSVpreF vs no intervention: $41'321

Study	Country setting	Currency, cost year	Costs outcomes	Effectiveness outcomes	Base case incremental analyses outcomes
					RSVpreF plus nirsevimab vs no intervention (at a price per dose (PPD) of $615 for nirsevimab) Using sigmoidal efficacy profiles: was cost-effective for a PPD up to $140 for RSVpreF Using constant efficacy profiles: was cost-effective at PPD of $610 for nirsevimab and $165 for RSVpreF. Net monetary benefit Maximum price per dose (PPD) for a positive net monetary benefit Using sigmoidal efficacy profiles Nirsevimab, preterm infants <32 wGA: $615 Nirsevimab, preterm infants <36 wGA: $375 Nirsevimab, preterm and term infants: $300 Nirsevimab, birth cohort: $215 Using constant efficacy Nirsevimab, preterm infants <32 wGA: $610 Nirsevimab, preterm infants <36 wGA: $370 Nirsevimab, preterm and term infants: $295 Nirsevimab, birth cohort: $215

Abbreviations

CCPA = combined cost of purchasing and administration, ED = emergency department, ICER = incremental cost-effectiveness ratio, ICU = intensive care unit, LMI = combined nirsevimab and RSVpreF immunization program, LY = life years, NA = not applicable, PC = primary care, PPD = price per dose, QALY = quality-adjusted life year, RSV = respiratory syncytial virus, WTP = willingness to pay.

7.3.1.5 Uncertainty

Key details about how studies of nirsevimab, RSVpreF and both nirsevimab and RSVpreF addressed uncertainty are summarized in Table 42, Table 43 and Table 44, respectively. All 10 studies presented scenarios and sensitivity analysis. Key drivers of the models were coverage rates, intervention costs, efficacy values and the length of time the treatment effect was applied (i.e. treatment waning assumptions). The results were also sensitive to the month in which the injections were administered.

Table 42: Sensitivity analyses for economic studies of nirsevimab (only)

Trial	Location	Sensitivity analysis	Scenario analyses
Gil-Prieto, 2024[84]	Spain	Deterministic sensitivity analysis: the most significant drivers on healthcare costs were RSV risk by age for term infants, treatment costs in the term infant population and the variance in the distribution of RSV infection by month. Probabilistic sensitivity analysis: NR	Reducing nirsevimab efficacy to 65.9% prevented more than half of hospitalizations and outpatient visits. Narrowing the definition of RSV to specific ICD-10 codes resulted in a slightly higher proportion of nirsevimab-prevented outpatient visits versus those prevented in the base case and healthcare cost savings. Modelling a six-month RSV season (October to March) with a 6-month duration of protection provided by nirsevimab averted 9.4% more health events than in the base case (November to March). The proportion of deaths prevented through universal nirsevimab immunization was moderately sensitive to the variation in RSV mortality rates from available literature, ranging between 49.3% of deaths prevented (when applying a 2.33% in-hospital mortality among palivizumab eligible and preterm infants) and 57.9% (when applying a 0.15% inpatient mortality rate among term infants).
Kieffer, 2022[86]	US	Deterministic sensitivity analysis: The risk of RSV-MALRTI had the largest impact on the total prevented hospitalizations (including ICU admissions and MVs). Application of the lower and upper bounds for hospitalizations, ICU admissions, and mechanical ventilation resulted in a variation of -30% and +93% in prevented hospitalizations (including ICU admissions and mechanical ventilation). The number of ED and PC visits were most sensitive to variations in nirsevimab coverage rate. The lower bound for nirsevimab coverage rate resulted in 3'113 fewer prevented ED visits and 8'516 fewer prevented PC visits. Alternately, the upper bound for nirsevimab coverage resulted in 15'817 additional prevented ED visits and 43'267 additional prevented PC visits. Alternative sources for nirsevimab efficacy showed minimal variability in the total number of prevented hospitalizations compared with the base case. Probabilistic sensitivity analysis: NA	NA
Li, 2022[87]	Norway	Deterministic sensitivity analysis: The results were most sensitive to the assumed severity of the season and to the price of nirsevimab.	Different assumptions for interventions' efficacy, duration of protection, disease burden, and accounting for RSV hospitalization-associated recurrent wheeze and asthma were considered.

Trial	Location	Sensitivity analysis	Scenario analyses
		The 4-month 'November to February' nirsevimab program was cost-effective compared with all other programs evaluated when the WTP value was below NOK 0.3 million per QALY gained, if nirsevimab was priced at NOK 500 and maternal immunization was priced NOK 300 or more. When nirsevimab was priced NOK 100, the catch-up program was the cost-effective program for all WTP threshold values considered, regardless of the price for maternal immunization, and with limited uncertainty.	Recurrent wheezing up to 3 years of age - The seasonal nirsevimab 'November to February' program was the cost-effective strategy if the WTP value was <NOK 145'000 per QALY gained. The nirsevimab 'October to February' program was cost-effective for WTP values between NOK 145'000 and 175'000 per QALY gained. With higher WTP values, the nirsevimab 'October to March' (up to NOK 623'000 per QALY) and the catch-up program became cost-effective. Recurrent wheezing and asthma up to age 13 years - Seasonal nirsevimab 'October to March' program was the cost-effective program if the WTP value was between NOK 130'000 and NOK 536'000 per QALY gained. With higher WTP values, monoclonal antibody 'catch-up' program became the preferred strategy. Nirsevimab using efficacy values from a Phase 2b trial in preterm infant - 6-to-11-month nirsevimab 'October to March' program was cost-effective compared with all other 12 programs evaluated when the WTP value was below NOK 0.9 million per QALY gained, if nirsevimab was priced NOK 500 and maternal immunization was priced NOK 300 or more. When nirsevimab was priced NOK 300 or less, the catch-up program was the cost-effective program for all WTP values considered, regardless of the price for maternal immunization. Monoclonal antibody with six months duration of protection, similar to base case, but when nirsevimab was priced NOK 500, longer seasonal program (e.g. October to February) were cost-effective compared with base case. Higher RSV disease burden - severe RSV season - Nirsevimab seasonal 'catch-up' program became cost-effective at a much lower WTP value (NOK 290'000 per QALY gained) compared with base case. Lower RSV disease burden - mild RSV season - No intervention was the preferred program if the WTP was below NOK 1 million per QALY gained. A higher number of PC visits. Findings were similar to the base case. Higher QALY loss per RSV case. The nirsevimab catch-up program became cost-effective if WTP values were above NOK 550'000 per QALY gained. Including intervention preventable RSV-coded mortality in infants. Similar results as the base case, but the longer programs became cost-effective at slightly lower WTP values.
		Deterministic sensitivity analysis: NA	

Trial	Location	Sensitivity analysis	Scenario analyses
Nourbaksh, 2021[88]	Canada - specifically Nunavik, Quebec	Probabilistic sensitivity analysis: NR	The results were produced using scenarios for mild, moderate and severe RSV seasons.
Yu, 2024[90]	US	Deterministic sensitivity analysis: NA Probabilistic sensitivity analysis: NA Probabilistic sensitivity analysis: The probabilities of nirsevimab program interventions being cost-effective using a sigmoidal vaccine efficacy were 50%, 56%, 79%, and 99%, respectively. For RSVpreF, the maximum PPD was $160, at which the program was cost-effective with the probability of 68%. The probabilities of the nirsevimab program interventions being cost-effective using constant vaccine efficacies were 54%, 69%, 90%, and 86%, respectively. For RSVpreF, the maximum PPD was $185 with cost-effectiveness probability of 81%. At PPD of $615 for nirsevimab with sigmoidal vaccine efficacy profiles, nirsevimab plus RSVpreF was cost-effective (Neuromuscular blockade level>0) for a PPD up to $140 for RSVpreF. Reducing PPD for nirsevimab to $215, nirsevimab plus RSVpreF was cost-effective for a PPD up to $155 for RSVpreF. With constant vaccine efficacy profiles, nirsevimab plus RSVpreF was cost-effective at PPD of $610 for nirsevimab and $165 for RSVpreF. Reducing PPD for nirsevimab to $215, nirsevimab plus RSVpreF was cost-effective at a PPD of $180 for RSVpreF.	NA

Abbreviations

CCPA = Combined cost of purchasing and administration, ED = emergency department, ICER = incremental cost-effectiveness ratio, ICU = intensive care unit, MV = mechanical ventilation, NA = not applicable, NR = not reported, NR = not reported, PC = primary care, PPD = price per dose, QALY = quality-adjusted life year, RSV = respiratory syncytial virus, US = United States, WTP = willingness to pay.

Table 43: Sensitivity analyses for economic studies of RSVpreF (only)

Trial	Location	Sensitivity analysis	Scenario analyses
Alvarez Aldean, 2024[81]	Spain	Deterministic sensitivity analysis: The only variations to the parameters that affected the outcomes were: in the 25% decrease in the effectiveness of RSVpreF, in the incidence of RSV hospitalization and in the cost of hospitalizations; and the 25% increase in the cost of RSVpreF. RSVpreF still remained cost-effective at a WTP threshold of €25'000/QALY in all cases. Probabilistic sensitivity analysis: 1'000 simulations were run. Maternal immunization was cost-effective in 99% of these iterations at a WTP threshold of €25'000/QALY. RSVpreF was dominant 63% of the time.	If vaccine coverage was reduced from 70% to 50%, RSVpreF would still be dominant. When the vaccine administration cost was reduced (to €1.43), the cost savings increased to €2.9 million. When the vaccine price was reduced (to €158.20), the cost savings increased to €3.9 million. At a lower WTP threshold (€21'000/QALY) RSVpreF had a 98.6% probability of being cost-effective. When indirect costs were included in the analysis (taking a societal perspective), savings increased to €2.1 million.
		Probabilistic sensitivity analysis: The probabilities of nirsevimab program interventions being cost-effective using a sigmoidal vaccine efficacy were 50%, 56%, 79%, and 99%, respectively. For RSVpreF, the maximum PPD was $160, at which the program was cost-effective with the probability of 68%. The probabilities of the nirsevimab program interventions being cost-effective using constant vaccine efficacies were 54%, 69%, 90%, and 86%, respectively. For RSVpreF, the maximum PPD was $185 with cost-effectiveness probability of 81%. At PPD of $615 for nirsevimab with sigmoidal vaccine efficacy profiles, nirsevimab plus RSVpreF was cost-effective (Neuromuscular blockade level>0) for a PPD up to $140 for RSVpreF. Reducing PPD for nirsevimab to $215, nirsevimab plus RSVpreF was cost-effective for a PPD up to $155 for RSVpreF. With constant vaccine efficacy profiles, nirsevimab plus RSVpreF was cost-effective at PPD of $610 for nirsevimab and $165 for RSVpreF. Reducing PPD for nirsevimab to $215, nirsevimab plus RSVpreF was cost-effective at a PPD of $180 for RSVpreF.	

Abbreviations

PC = primary care, PPD = price per dose, QALY = quality-adjusted life year, RSV = respiratory syncytial virus, WTP = willingness to pay.

Table 44: Sensitivity analyses for economic studies of nirsevimab and RSVpreF

Trial	Location	Sensitivity analysis	Scenario analyses
Gebretekle, 2024[82]	Canada	Deterministic sensitivity analysis: The following inputs were key drivers of the model: the price of nirsevimab, medical costs for infants at high-risk with RSV managed in the ICU, nirsevimab effectiveness against ICU admission and RSV monthly infection rates. Probabilistic sensitivity analysis: Not conducted	Infants were assumed to have 5-fold higher rates of RSV hospitalization than the rest of Canada. When comparing all strategies sequentially, the nirsevimab program for all infants with catch-up was dominant (less costly and more effective), except when compared with year-round RSVpreF for all pregnant women and pregnant people plus nirsevimab for infants at high-risk, which resulted an ICER of $5'700 per QALY.
Getaneh, 2023[83]	6 European countries: Denmark, Finland, England, Scotland, Italy, the Netherlands	Deterministic sensitivity analysis: The results depended strongly on the following aspects: 1) The assumed intervention procurement price. 2) The assumed intervention administration cost. 3) The perspective. 4) The type of data used to inform RSV-related hospitalizations (ICD10-coded counts or estimates based on time series analysis). Probabilistic sensitivity analysis: NR	Using ICD 10 RSV hospitalizations, recurrent wheezing of up to 3 years of age, recurrent wheezing and Asthma up to 13 years of age, assuming RSV-related mortality if preventable, including implementation costs, higher maternal immunization (RSVpreF) efficacy based on Phase 2b data, using longer duration of protection of maternal immunization based on "top-line" Phase 3 efficacy data. Using ICD 10 RSV hospitalizations: Applying this data generally made the interventions less favorable in all countries. The effect was highest for England and Italy region and the Netherlands where all strategies become dominated by the no intervention strategy for the range of WTP values considered. For Denmark, the WTP value at which the seasonal nirsevimab with or without catch-up was cost-effective shifted from €10'000 to ~€60'000. Recurrent wheezing of up to 3 years of age: In all countries, accounting for the costs and QALY loss due to recurrent wheezing up to 3 years of age generally made the preferred strategy cost-effective at a lower WTP value compared with the base case analysis. Recurrent wheezing and Asthma up to 13 years of age: affected the cost effectiveness in a similar way to wheezing alone, but to a greater extent. Assuming RSV-related mortality if preventable: had limited impact on cost effectiveness. Including implementation costs: minimum WTP increased for the preferred strategy. Higher MI efficacy based on Phase 2b data: for all countries, except the Netherlands, year-round became preferred over any other program at procurement prices equal to that of nirsevimab (€25), but only for low 8 WTP values (i.e. €0 per QALY gained for Denmark, England and Scotland; up to €25'000 per QALY gained for Finland, and up to €50'000 per QALY gained for Veneto Region – Italy. Using longer duration of protection of MI based on "top-line" Phase 3 efficacy data: did not impact results.

Trial	Location	Sensitivity analysis	Scenario analyses
Hodgson, 2024[85]	England and Wales	Deterministic sensitivity analysis: The maximum CCPA for maternal vaccination programs and coverage rates. Probabilistic sensitivity analysis: NA - whole model was probabilistic.	Different coverage rates were used assuming the same CCPA for each product. The nirsevimab program was optimal except if coverage of RSVpreF was 90% versus coverage of 70% for nirsevimab and the CPPA was below £10 a dose.
Shoukat, 2023[89]	Canada (specifically the southern provinces)	Deterministic sensitivity analysis: NA Probabilistic sensitivity analysis: The probabilities of nirsevimab program interventions being cost-effective using a sigmoidal vaccine efficacy were 50%, 56%, 79%, and 99%, respectively. For RSVpreF, the maximum PPD was $160, at which the program was cost-effective with the probability of 68%. The probabilities of the nirsevimab program interventions being cost-effective using constant vaccine efficacies were 54%, 69%, 90%, and 86%, respectively. For RSVpreF, the maximum PPD was $185 with cost-effectiveness probability of 81%. At PPD of $615 for nirsevimab with sigmoidal vaccine efficacy profiles, nirsevimab plus RSVpreF was cost-effective (Neuromuscular blockade level>0) for a PPD up to $140 for RSVpreF. Reducing PPD for nirsevimab to $215, nirsevimab plus RSVpreF was cost-effective for a PPD up to $155 for RSVpreF. With constant vaccine efficacy profiles, nirsevimab plus RSVpreF was cost-effective at PPD of $610 for nirsevimab and $165 for RSVpreF. Reducing PPD for nirsevimab to $215, nirsevimab plus RSVpreF was cost-effective at a PPD of $180 for RSVpreF.	The reduction of RSV-related infant mortality was 18% to 25% higher in the nirsevimab-only program with 80% coverage of the birth cohort compared with the combined program with 60% coverage of RSVpreF vaccination of pregnant women and 80% coverage of infants at high risk with nirsevimab. The results showed that PPD for cost-effective programs with nirsevimab is sensitive to the target groups among the infant population. However, remained relatively robust with respect to the efficacy profiles of nirsevimab and the coverage of immunization.

Abbreviations

CCPA = Combined cost of purchasing and administration, ED = emergency department, ICER = incremental cost-effectiveness ratio, ICU = intensive care unit, LMI = combined nirsevimab and RSVpreF immunization program, NA = not applicable, NR = not reported, PC = primary care, PPD = price per dose, QALY = quality-adjusted life year, RSV = respiratory syncytial virus, WTP = willingness to pay.

7.3.1.6 Conclusions

Within the parameters of the WTP thresholds used in the studies: maternal vaccine with RSVpreF was reported to dominate no prophylaxis (i.e. was more effective and less costly); nirsevimab was reported to be cost-effective when compared with no prophylaxis; and nirsevimab was reported to be cost-effective against maternal immunization. No Swiss-based models were identified.

Five economic evaluations assessed nirsevimab.

Li[87] assessed year-round, seasonal (n=28) and catch-up nirsevimab programs in Norway in a 2019 analysis. Three WTP thresholds from a healthcare perspective were assessed: below NOK 0.4 million per QALY gained (seasonal nirsevimab October to February was preferred), between 0.4 and 0.5 million NOK per QALY gained (seasonal nirsevimab November to February), and greater than 0.5 million NOK per QALY gained (seasonal nirsevimab October to March).

Nourbakhsh[88] assessed nirsevimab against no intervention in Canada in 2021. In a mild RSV season, nirsevimab for preterm infants was considered cost-effective versus the same nirsevimab program that included healthy infants also (CAN $39'414 per QALY gained). In moderate and severe seasons, nirsevimab for preterm infants also including healthy children was highly cost-effective versus nirsevimab for preterm infants only (CAN $5'255 and CAN $7'049, respectively).

Yu[90] conducted a 2021 threshold analysis in the US from a healthcare payer and societal perspective and reported that nirsevimab could be cost-effective versus no prophylaxis below a price of $1'923 at a WTP threshold of $150'000 per QALY gained.

Two cost consequence analyses reported cost outcomes for nirsevimab. Gil-Prieto[84] reported 2023 total healthcare costs in Spain from a healthcare payer and societal perspective for: palivizumab eligible infants (€2'867'162), preterm infants (€2'295'030) and term infants (€21'840'184). Kieffer[86] reported the 2021 total cost of health events in the US as $1'241'000'000 (ranging from $881'100'000 to $2'325'400'000 based on RSV rates).

One economic evaluation assessed RSVpreF.

Alvarez Aldean[81] reported that RSVpreF was dominant (more effective and less costly) compared with no intervention in Spain in 2023 from a National Healthcare System perspective, where pregnant women were vaccinated to prevent RSV in infants.

Four economic evaluations included assessments of both nirsevimab and RSVpreF.

Gebretekle[82] was a 2023 assessment of seasonal and year-round nirsevimab and year-round RSVpreF programs in Canada from a healthcare and societal perspective. Nirsevimab programs for all infants and year-round RSVpreF programs exceeded WTP thresholds. Seasonal nirsevimab with catch-up for infants born outside the RSV season was cost-effective if prioritized for infants at moderate/high-risk (CAN$27'891 per QALY gained).

Getaneh[83] was a 2021 assessment of seasonal and year-round nirsevimab, year-round RSVpreF programs, and no program in 6 European countries, from a healthcare and societal perspective. Seasonal nirsevimab was preferred for WTP threshold values from €4'444 (England), €9'129 (Denmark), €23'814 (Italy) and €21'187 per QALY gained (the Netherlands). Seasonal nirsevimab with catch-up was preferred for WTP values from €8'864 (England), €24'664 (Denmark), €42'245 (Italy) and €130'308 per QALY gained (the Netherlands). No program was preferred for lower WTP values in Denmark, England, Italy and the Netherlands. For Finland, seasonal nirsevimab with catch-up was cost-effective versus other programs from €13'373 per QALY gained, and for lower WTP values seasonal nirsevimab without catch-up was preferred versus other programs. For Scotland, seasonal nirsevimab with catch-up was preferred over other programs for the range of WTP values considered.

Hodgson[85] was a 2021/22 assessment of seasonal and year-round nirsevimab and RSVpreF programs in England and Wales. If nirsevimab was priced above £84, then a seasonal RSVpreF program was optimal between £36 to £80 cost of purchasing and administration (CCPA), and a year-round RSVpreF program was optimal up to £35 CCPA. If RSVpreF is priced above £80, then a seasonal nirsevimab program is optimal up to £55 to £83 CCPA, and a seasonal nirsevimab with a catch-up program is optimal up to £55 CCPA. The year-round nirsevimab program was dominated by the seasonal nirsevimab with an annual catch-up program across all CCPAs. If both nirsevimab and RSVpreF are priced below £30 then the nirsevimab program is optimal. If both products are priced similarly above £30, then both programs are similarly cost-effective.

Shoukat[89] was a 2023 assessment that assessed nirsevimab and RSVpreF at a WTP threshold of $50'000 per QALY gained in Canada, from healthcare and societal perspectives. Nirsevimab and RSVpreF were each cost-effective versus no intervention. RSVpreF plus nirsevimab vs no intervention was cost-effective at a price per dose (PPD) of $615 for nirsevimab, at $140 for RSVpreF (using sigmoidal efficacy profiles), and at $610 for nirsevimab and $165 for RSVpreF (using a constant efficacy profile).

7.3.1.7 Study quality appraisal

Critical appraisal using the adapted Drummond checklist (1996)[74] was used to determine if the conduct of the studies was appropriate and reported in a transparent and comprehensive way. Table 10 and Table 11 in Appendix A report the risk of bias assessments for RSVpreF and nirsevimab studies, respectively.

In general, all studies were well conducted and of high quality. Eight studies[81-83, 85, 87-90] were clearly self-described as cost-effectiveness analyses. Two studies [84, 86] did not state the form of economic evaluation; these were judged to be cost consequence analyses. Two studies did not clearly state the perspective taken for the analysis.[86, 88] The time horizon for two studies[83, 87] was not explicitly reported though they did describe tracking infants from birth to five years old so it was assumed to be 5 years. Author-reported limitations are reported in Table 12 of Appendix A.

8. Methodology Economic Evaluation and Budget Impact Analysis

8.1 Economic Evaluation

8.1.1 Patient population, intervention and comparator

The model generated outcomes for newborns and infants throughout an entire RSV season. The population entering the model was defined as newborns whose mothers did or did not receive RSV vaccination with RSVpreF during pregnancy. To align with the Swiss RSV vaccination recommendations, published in November 2024, the model population included only newborns born between October and March.[98] Therefore, individuals born between April and September were excluded from the model. A one-year time horizon was used to ensure that each individual was exposed to a full RSV season regardless of the timing of their birth between October and March.

The intervention was defined as the administration of RSVpreF in women between 32 and 36 weeks of pregnancy from October to February, provided their due date was before the end of March.[98] The model estimated the cost effectiveness of RSV vaccination with RSVpreF against the following 2 standalone comparators:

1. Newborns receiving RSV prophylaxis with nirsevimab.
2. Newborns receiving no RSV prophylaxis.

No other monoclonal antibodies (e.g. palivizumab) or vaccines (e.g. Arexvy®) were incorporated as comparators in the model.

The administration of nirsevimab was aligned with the schedule outlined in the Swiss expert working group consensus statement published in September 2024.[99] Therefore, individuals born from the beginning of October to the end of March were assumed to be administered nirsevimab in their first post-natal week (equivalent to the model entry), subject to coverage.

Although nirsevimab is also indicated for administration in October for individuals born between April and September, these individuals were excluded from the model population because RSVpreF is not indicated for pregnant women with due dates between these months. This exclusion was necessary to ensure consistency in the model population between model arms.

The mothers of the newborns in the intervention cohort received the RSVpreF vaccine (subject to coverage). In the comparator cohort, the mothers of the newborns did not receive the RSVpreF vaccine during pregnancy, and the cohort either received nirsevimab (subject to coverage) or no RSV prophylaxis instead.

The size of the modelled cohort corresponded to the annual number of live births in Switzerland between October and March. The distribution of live births across calendar months was informed using data from the Federal Statistical Office (FSO) (as presented in Table 45).[100]

Table 45: Model cohort size

Annual number of live births	Value	Source
October	6’823	Live births per month in 2023. FSO[100]
November	6’428	
December	6’319	
January	6’524	
February	6’059	
March	6’691	
Total	**38’844**	

Abbreviations

FSO = Federal Statistical Office.

Newborns who were born with a term status of less than 32 wGA at birth were excluded from the model because RSVpreF is indicated for pregnant mothers between 32 and 36 wGA. Although newborns with a term earlier than 32 wGA at birth could be eligible for either nirsevimab or no RSV prophylaxis, it was necessary to exclude these individuals to ensure the model population was consistent across model arms. Furthermore, the proportion of newborns born at less than 32 wGA at birth in Switzerland was estimated to be 0.679%.[101] Therefore, the exclusion of these individuals was judged not to detract from the usefulness of the model outcomes.

The distribution of wGA at birth in each model cohort was also used to define the population entering the model. This allowed the model to consider the impact of wGA at birth on model components, such as RSV incidence and mortality rates. The distribution of wGA at birth is presented in

Table 46; this distribution was assumed to be equivalent across both arms of the model.

Table 46: Distribution of wGA and weight at birth

wGA at birth	Proportion	Source
Full-term ≥37 wGA	95.3%	Data taken from a Swiss census-based linkage study.[101] Proportions were calculated using data from Table 45, with data excluded for <32 wGA at birth.
Late preterm 32 to 36 wGA	4.7%	

Abbreviations

wGA = weeks of gestational age.

8.1.2 Type of economic evaluation

The clinical data identified in the rapid systematic literature review (Section 7.2) provided consistent high-quality evidence to suggest a difference in effectiveness between RSV vaccination with RSVpreF, RSV prophylaxis with nirsevimab, and no RSV prophylaxis. Utilities were also identified that could be used to inform the HRQoL for each of the health states in the model. Therefore, a cost-utility analysis was considered most applicable.

8.1.3 Perspective

The model was built from a Swiss Healthcare payers' perspective. Costs of healthcare services covered by the Swiss mandatory health insurance were analyzed, irrespective of the actual payer (mandatory health insurer, other social insurer, government [federal government, cantons, communities] out-of-pocket). The analysis did not include indirect costs due to informal care or productivity losses or additional non-medical costs for patients, such as travel costs.

8.1.4 Time horizon

A one-year time horizon was adopted to ensure that the consequences of a full RSV season, regardless of birth month between October and March, were captured.

The use of lifetime horizon, whereby the general population life expectancy would have been applied to all newborns/infants who survived the RSV season, was considered. The rapid systematic literature review identified 2 economic modelling approaches that were commonly used to capture these longer-term outcomes. However, these approaches were both considered to be inappropriate.

Firstly, previous studies applied a QALY loss due to premature death.[81, 85] However, this QALY loss was considered in a scenario analysis only. The authors of these studies noted that infants who die due to RSV commonly have multiple comorbidities and would not be expected to survive beyond childhood in the absence of RSV. As a result, assigning general population life expectancy to all newborns/infants who survive the RSV season may have overestimated the improvement in health outcomes associated with reducing RSV-associated deaths. Therefore, the actual lifetime

QALY loss due to premature death was anticipated to have a negligible impact on model outcomes and did not warrant inclusion in the model.

Secondly, the longer-term impact of chronic wheezing/asthma was considered, as applied in previous models.[83, 87] However, these models cited only a *possible* relationship between RSV hospital admission in infancy and the development of chronic wheezing/asthma in childhood.[83, 87] This was, therefore, associated with considerable uncertainty. Furthermore, it was anticipated that this element of the model would have a negligible impact on overall model outcomes because hospitalizations were relatively low when compared with ED and PC visits (as described further in Section 8.1.7.1).

The time horizon was limited to one year because of the anticipated negligible impact on model outcomes associated with both approaches and the increased uncertainty that would have been introduced.

8.1.5 Discount rate

Future costs and effects were discounted at 3% per annum in the base case scenario. Discount rates of 0% and 5% were applied in scenario analyses.

8.1.6 Modelling

8.1.6.1 Model structure

A static modelling approach was deemed preferable over a dynamic transmission model because it allowed the essential consequences of each vaccination to be captured without additional data requirements, additional complexity, and the potential uncertainty of a transmission model. A decision tree model was also considered during the model conceptualization process. However, this option was discarded because it would have prevented the inclusion of both the impact of seasonality and the change in treatment efficacy through the model time horizon. Therefore, a Markov model was considered the most appropriate structural framework.

A hypothetical cohort of newborns entered the model in the 'No RSV infection' health state immediately after birth. The mothers of the newborns in the intervention arm had received an RSV vaccination with RSVpreF during pregnancy (subject to coverage). The cohort in the comparator arms received either RSV prophylaxis with nirsevimab (subject to coverage) or no RSV prophylaxis (assumed equivalent to the pre-nirsevimab standard of care).

A proportion of the cohort developed an RSV infection that resulted in healthcare-seeking behavior within each monthly cycle. Those who did not develop an RSV infection remained in the 'No RSV infection' health state. Those who developed an RSV infection transitioned to one of the following health states, which were representative of the healthcare setting required to treat the RSV infection, where they remained for one cycle: 'RSV infection: Hospitalization', 'RSV infection: Emergency department', or 'RSV infection: Primary care visit'. Individuals within the 'RSV infection:

Hospitalization' health state could experience either a general ward (GW) or ICU admission. The hospital admission type impacted the mortality, hospitalization costs, and utility input values applied. The use of these RSV health state definitions meant that asymptomatic or mild cases of RSV infections were not considered in the model, due to their anticipated negligible impact on model outcomes. Therefore, the analysis only accounted for RSV infections that resulted in healthcare-seeking behavior in infected individuals.

Individuals transitioned to the 'Post-RSV infection' health state after one cycle in any of the 3 RSV health states and remained in this health state until the end of the time horizon or they died. The cohort could die whilst residing in any health state of the model and an increased risk of death was applied to newborns that were born preterm and those that required an RSV-related hospitalization.

The transition of the cohort through the model health states in the 'no RSV prophylaxis' arm was determined by the incidence of RSV under standard care. The transition of the cohort in the 'RSV vaccination with RSVpreF during pregnancy' and 'RSV prophylaxis with nirsevimab' arms was determined by the incidence of RSV under standard care and the efficacy of RSVpreF and nirsevimab, respectively.

It was assumed that each newborn/infant could only develop one RSV infection over the model time horizon that required contact with the health system. In reality, a newborn/infant may experience multiple RSV infections. However, a paucity of data was available to reliably parameterize the possibility of multiple infections without introducing unnecessary uncertainty into the model. For example, data were not available to inform the incidence of repeat RSV infections or the difference in treatment efficacy between cohorts that had and had not experienced RSV previously. This assumption was similarly made in all the economic evaluations identified in the rapid systematic literature review.[81-88]

It was essential to consider the seasonality of RSV and the timing at which each vaccination was received to accurately estimate the number of newborns that developed an RSV infection. For example, there is an unequal distribution of RSV infections between each calendar month, and over 99% of RSV cases occur between October and April during the RSV season (Table 49). This seasonality of RSV should be accounted for when calculating the number of RSV infections. It was anticipated that RSVpreF and nirsevimab would have a larger absolute impact on the number of infections averted and, therefore, on the economic and HRQoL outcomes when given to pregnant women or newborns in the RSV season (when RSV incidence is higher than outside of the season). A monthly cycle length was used to capture the impact of this seasonality.

Functionality to consider the implications of term status, in terms of wGA at birth, was also included in the model (as displayed in

Table 46). The wGA at birth impacted the following model components: the efficacy of RSVpreF, the proportion of RSV-associated hospitalizations requiring an ICU admission, the background rate of newborn/infant mortality, and the in-hospital GW rate of mortality.

Each health state was associated with different HRQoL and healthcare resource use. The number of months each individual spent in each health state was estimated over a one-year time horizon. The economic costs and HRQoL were aggregated for each cohort to estimate the cost-effectiveness of the RSV vaccination with RSVpreF during pregnancy compared with RSV prophylaxis with nirsevimab and no RSV prophylaxis. A model schematic is presented in Figure 4.

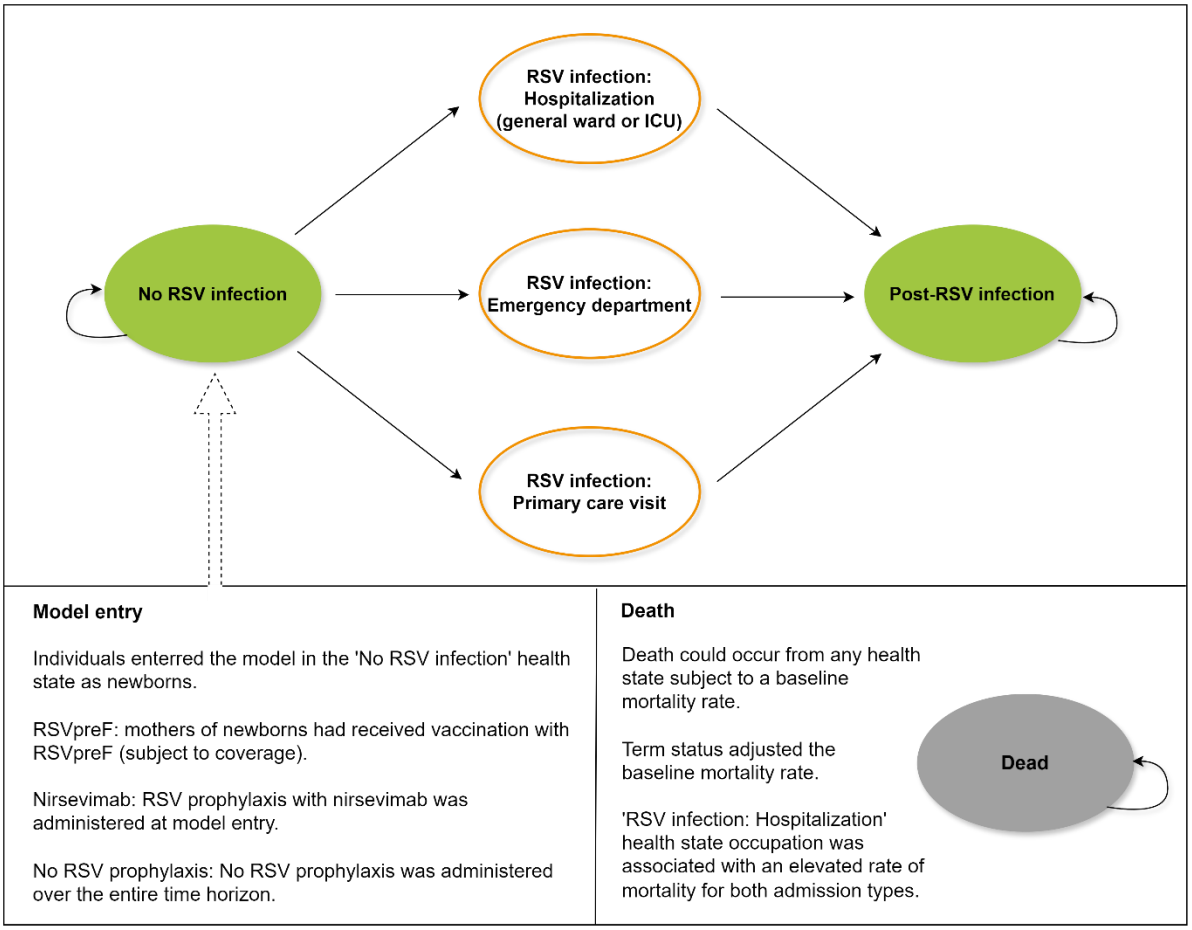

Figure 4: Model schematic

Abbreviations

ICU = intensive care unit, RSV = respiratory syncytial virus.

8.1.6.2 Model software and validity of the model

The model was built in Microsoft Excel and subject to a thorough quality assurance procedure, which included technical validation and cross-validation. The technical validation ensured that there were no functional errors in the model calculations and was completed by a senior analyst who was not involved in developing the model. A standardized ‘model review checklist’ was used for

pressure testing the model. The cross-validation involved comparing the results of the present model with other published models to ensure the results have face validity. This type of validation increases confidence in the results generated by the model.

An interview with a clinical expert – a Switzerland-based Professor specializing in infectious diseases and hospital hygiene – was conducted to ensure that key clinical assumptions and parameters reflected clinical practice. Details are provided throughout this report highlighting which model assumptions and parameters were validated by the clinical expert.

8.1.7 Input parameters

8.1.7.1 RSV incidence

The baseline rate of RSV in the model was stratified by age and care setting (i.e. hospitalization, ED and PC). Previous literature was available that reported the Swiss-specific incidence of RSV infections requiring hospitalization[36] – but not those requiring an ED or PC visit. A retrospective observational study conducted in Spain reported the incidence of RSV infections requiring hospitalization, an ED visit, or a PC visit.[102]

As presented in Table 47, there were notable differences in the incidence rates of RSV infections requiring hospitalization between the Swiss-specific and Spanish-specific estimates, which were primarily due to the different case definitions adopted in each study.[36, 102] Both studies employed International Classification of Diseases (ICD) codes to identify hospitalizations. However, fewer codes were adopted for the Swiss case definition. The rationale for adopting a wider case definition in the Spanish study was that a broader case definition, defined as using RSV-specific and LRTI codes, has been shown to increase sensitivity without sacrificing specificity.[102] The underestimation of hospitalization rates using RSV-specific coded data was also discussed in the previously reviewed cost-effectiveness study by Getaneh et al. (2023).[83] In this study, a broader hospitalization rate defined as RSV-attributable was adopted in the base case analysis, with an additional scenario analysis presented using a narrower definition.

The Swiss-specific incidence rates for RSV-related hospitalization and Spanish-specific incidence rates for RSV-related ED and PC visits were used in the base case analysis. A scenario analysis was run using only data from the Spanish study given the notable differences in the rate of RSV-related hospitalization between each source. This approach was validated by the clinical expert.

Table 47: Annual RSV incidence rates per 1'000 by care setting and age

Age (months)	Spanish data			Swiss data	Source
	Hospitalization	ED	PC	Hospitalization	
<1	137.9	124.1	124.1	43.0	Spanish data: Martinón-Torres et al. (2022)[102] Swiss data: Stucki et al. (2024)[36] Rates for 2016 to 2019 were used, as presented by the nirsevimab expert working group.[99]
1 to <2	164.3	166.3	168.3	51.0	
2 to <3	94.3	101.4	102.9	51.0	
3 to <6	56.9	76.3	98.4	21.0	
6 to <12	34.9	85.5	146.0	11.0	

Abbreviations

ED = emergency department, PC = primary care, RSV = respiratory syncytial virus.

As outlined in Section 8.1.6.1, an RSV-associated hospitalization was defined as either a GW or an ICU admission. When an RSV-associated hospitalization occurred, individuals were exclusively distributed between receiving care in either a GW or an ICU. The proportion of newborns and infants treated in an ICU was estimated using data from Gebretekle et al. (2024).[82] These data were also stratified by term status and are presented in Table 48. Although Gebretekle et al. used a different late preterm definition than that adopted in this economic model (i.e. 33 to 36 wGA versus 32 to 36 wGA, respectively), these data were assumed to apply to individuals defined as late preterm in the present economic model.

Table 48: Proportion of hospital admissions treatment in ICU, by term status

Term status	Proportion treated in ICU	Source
Late preterm: 32 to 36 wGA	31.5%	Gebretekle et al. (2024)[82]
Full-term: ≥37 wGA	15.8%	

Abbreviations

ICU = intensive care unit, wGA = weeks of gestational age.

After calculating the baseline rates of RSV infections that resulted in healthcare-seeking behavior, the seasonality of RSV infections was accounted for by considering the distribution of RSV infections by calendar month. In particular, baseline RSV rates were multiplied by the proportion of RSV infections occurring in each calendar month, in order to calculate baseline rates that were specific

to each month. The corresponding distribution of RSV infections by calendar month is presented in Table 49.

Table 49: Distribution of RSV infections by calendar month

Calendar month	Proportion of RSV infections	Source
January	29.3%	Provided by the FOPH using data from 2016 to 2019[103]
February	25.3%	
March	13.1%	
April	4.0%	
May	1.0%	
June	0.0%	
July	0.0%	
August	0.0%	
September	0.0%	
October	1.0%	
November	4.0%	
December	22.2%	

Abbreviations

FOPH = Federal Office of Public Health, RSV = respiratory syncytial virus.

Data were available to inform the increased risk of RSV-related hospitalizations, ED and PC visits depending on the following: quarter of birth, wGA at birth, birth weight, and sex. However, it would have been necessary to apply these increased risks to baseline rates for each reference category. For example, the model would have required the baseline rate to be male specific (i.e. representative of the reference category) to consider the impact of being female on the baseline rate of RSV infections. The baseline RSV infection rates used in the model were representative of the overall population only and were not available for each reference category. Therefore, the incorporation of any increased risk would have been associated with double counting.

8.1.7.2 Clinical effectiveness

The transition probabilities applied to the cohort in the 'no RSV prophylaxis' comparator arm were informed by the baseline RSV incidence rates described in Section 8.1.7.1.

8.1.7.2.1 RSV vaccination with RSVpreF during pregnancy

The efficacy of RSVpreF was informed by MATISSE, a double-blind, Phase 3 trial of RSVpreF versus placebo in pregnant women at 24 to 36 weeks.[78] As per Alvarez et al. (2024), efficacy against severe, RSV-associated, medically attended LRTI from MATISSE was used as a proxy for efficacy against RSV cases requiring hospitalization.[81] Likewise, efficacy against RSV-positive medically attended LRTI from MATISSE was used as a proxy for efficacy against RSV cases treated in the ED or PC setting.[81]

Alvarez et al. (2024) used linear interpolation between cumulative efficacy data from MATISSE to estimate efficacy values for each month up to 6 months of age.[81] The same assumption was applied in the model to generate efficacy estimates for individual months of age. Functionality was included in the model to allow the user to explore the possibility of alternative treatment waning scenarios from 6 months onwards. For example, the Alvarez model assumed that RSVpreF efficacy waned linearly to 0% by age 9 to <10 months.[81] Following a discussion with the clinical expert, it was agreed that treatment waning should be applied in the base case and that an additional scenario with no treatment waning (i.e. equivalence with no RSV prophylaxis from 6 months onwards) should also be presented.

The impact of term status on the efficacy of RSVpreF was also considered. As per Alvarez et al. (2024), efficacy for late preterm infants (32 to 36 wGA) was assumed to be 83.3% of corresponding efficacy values for full-term infants.[81] This application of reduced efficacy for late preterm individuals, and a specific value of 83.3%, was deemed to be suitable by the clinical expert.

Efficacy input values were presented as relative risks in the model and calculated by subtracting the vaccine effectiveness estimates presented by Alvarez et al. (2024) from a value of one.[81] The base case relative risks against RSV infections for RSVpreF compared with no RSV prophylaxis in full-term and late preterm individuals, are presented in Table 50.

It was anticipated that not all mothers in the 'RSVpreF during pregnancy' cohort would elect to receive the vaccination and, therefore, the vaccine coverage would be less than 100%. As RSVpreF is yet to be adopted, the base case vaccine coverage was assumed to be equivalent to the mid-point between the vaccine coverage for pertussis (86.2%) and influenza (49.8%) observed in pregnant women in Switzerland.[104] As such, an RSVpreF vaccine coverage of 68% was used in the base case and deemed to be suitable by the clinical expert. However, this input was flexible to enable it to be varied in sensitivity and scenario analysis. The remaining 32% of individuals in this cohort received no vaccination; these newborns and infants had no RSV immunization. The rates of RSV for these individuals were equivalent to the baseline rates of RSV outlined in Section 8.1.7.1.

Table 50: RSVpreF efficacy against RSV infections

Age (months)	Relative risk against infections requiring hospitalization		Relative risk against infections treated in the ED or PC		Source
	Full-term ≥37 wGA	Late preterm 32 to 36 wGA	Full-term ≥37 wGA	Late preterm 32 to 36 wGA	
0 to <1	0.119	0.266	0.380	0.484	Efficacy up to 6 months (180 days) for full-term live births was taken from Alvarez et al. (2024) who used data from MATISSE.[78] Base case efficacy was assumed to decline linearly to 0% by age 9 to <10 months of age. Values for preterm individuals were calculated by multiplying full-term values by 83.3%, as per the method used by Alvarez et al. (2024).[81]
1 to <2	0.200	0.334	0.423	0.519	
2 to <3	0.280	0.400	0.467	0.556	
3 to <4	0.360	0.467	0.510	0.592	
4 to <5	0.441	0.534	0.553	0.628	
5 to <6	0.521	0.601	0.597	0.664	
6 to <7	0.641	0.701	0.698	0.748	
7 to <8	0.761	0.800	0.799	0.832	
8 to <9	0.880	0.900	0.899	0.916	
9 to <10	1.000	1.000	1.000	1.000	
10 to <11	1.000	1.000	1.000	1.000	
11 to ≤12	1.000	1.000	1.000	1.000	

Abbreviations

ED = emergency department, PC = primary care, RSV = respiratory syncytial virus, wGA = weeks of gestational age.

8.1.7.2.2 RSV prophylaxis in newborns and infants with nirsevimab

The efficacy of nirsevimab against RSV-related ED visits and PC visits was informed by the MELODY Phase 3, randomized double-blind, placebo-controlled trial of nirsevimab versus placebo in healthy late-preterm and full-term infants.[79] The results of a time-to-event analysis showed that infants who received nirsevimab had a lower rate of medically attended, RSV-associated LRTI than those who received placebo (hazard ratio: 0.23; 95% CI: 0.12 to 0.47). Therefore, this hazard ratio was multiplied by the baseline incidence rate (described in Section 8.1.7.1) to estimate the annual rate of RSV infections requiring an ED or PC visit.

In MELODY, the efficacy against medically attended, RSV-associated LRTI was estimated over 150 days of follow-up data.[79] Therefore, it was necessary to include an assumption for the efficacy of nirsevimab against RSV-associated ED and PC visits from 5 months onwards. For consistency with RSVpreF, treatment efficacy was assumed to wane linearly to 0% by age 9 to <10 months.

Furthermore, a scenario analysis was conducted in which treatment efficacy was assumed to instantly decline after 6 months (i.e. equivalence with no RSV prophylaxis from 6 months onwards). This approach was validated by the clinical expert, and the model also included functionality to consider alternative treatment waning scenarios.

A hazard ratio to inform the difference in the rate of newborns and infants requiring hospitalization for an RSV infection between nirsevimab and no prophylaxis was not reported in MELODY. Therefore, the HARMONIE randomized trial (investigating the prevention of hospitalizations due to RSV in infants) was used to estimate the efficacy of nirsevimab against RSV-related hospitalizations.[76] In particular, this trial reported an efficacy of 89.6% (95% CI: 73.8% to 96.8%), which was equivalent to a hazard ratio of 0.104 (1-0.896). Therefore, this hazard ratio was multiplied by the baseline incidence rate (described in Section 8.1.7.1) to estimate the annual rate of newborns and infants requiring treatment for an RSV infection in a hospital.

In HARMONIE, efficacy against RSV-associated LRTI hospitalization was generated using follow-up data over 180 days.[76] Therefore, it was necessary to include an assumption for the efficacy of nirsevimab against RSV-associated hospitalizations from 6 months onwards. For consistency with RSVpreF, treatment efficacy was assumed to wane linearly to 0% by age 9 to <10 months. Furthermore, a scenario analysis was conducted in which treatment efficacy was assumed to instantly decline after 6 months (i.e. equivalence with no RSV prophylaxis from 6 months onwards). This approach was validated by the clinical expert, and the model also included functionality to consider alternative treatment waning scenarios.

As nirsevimab was only recently listed under compulsory health insurance in Switzerland (September 2024),[105] the base case coverage of nirsevimab was assumed equal to vitamin K prophylaxis coverage at birth. Vitamin K prophylaxis is recommended in 85.0% of Swiss healthcare facilities, and there is a 0.5% refusal rate.[106] Therefore, a coverage of 84.6% was used in the base case. This was validated by the clinical expert and was also similar to the value of 90% used by Hodgson et al. (2020) – a study that also used vitamin K prophylaxis coverage as a proxy for nirsevimab coverage.[95] No immunization against RSV was applied to the remaining 15.4% of individuals; the rate of RSV for these individuals was equivalent to the baseline rates of RSV outlined in Section 8.1.7.1. The nirsevimab coverage rate was also flexible so that it could be varied in sensitivity and/or scenario analysis.

8.1.7.2.3 Treatment-related adverse events

No TRAEs were included in the model. Any TRAEs experienced by mothers following vaccine administration in the RSVpreF cohort were not applicable to the model population. Furthermore, MATISSE reported that the percentages of maternal participants with any AEs within one month following treatment were similar in the vaccine group (13.8%) and the placebo group (13.1%).[78] Although the percentages of infant participants with any adverse events reported within one month after birth was higher for the vaccine group compared with the placebo group (37.1% and 34.5%, respectively), the study reported that no serious adverse events in infants were considered to be

related to RSVpreF. Therefore, the exclusion of TRAEs for mothers and newborns/infants was not deemed to have a meaningful impact on the outcomes for the RSVpreF cohort.

TRAEs were not considered for nirsevimab (or palivizumab) in the previous cost-effectiveness models that were reviewed to inform the model protocol development.[83, 85, 87, 95] Furthermore, no substantial safety concerns were identified in HARMONIE, which recruited over 8'000 participants.[76] The marginal increase in AEs for nirsevimab compared with placebo (36.8% vs 33.0%) was markedly similar to the increase observed in the MATISSE trial for RSVpreF (37.1% vs 34.5%). Therefore, TRAEs were also excluded from the nirsevimab cohort.

8.1.7.2.4 Mortality

In alignment with the cost-effectiveness models identified in the rapid systematic literature review, RSV-associated mortality was applied to newborns and infants in the 'hospitalization' sub-health state.[81, 83, 87, 107] A general baseline annual mortality rate of 3.3 per 1'000 was applied to all newborns and infants in the remaining health states.[108] It was anticipated that the risk of mortality for newborns and infants was higher for individuals who were not born at full-term. Therefore, the baseline rate of mortality was also adjusted by term status (as presented in Table 51).

Table 51: Relative risk of mortality based on term status

Term status	Relative risk	Source
Full-term: ≥37 wGA	1.0	Swamy et al. (2024)[109]
Late preterm: 32 to 36 wGA	6.3	

Abbreviations

wGA = weeks of gestational age.

RSV-associated mortality in the 'RSV infection: Hospitalization' health state was specified by the type of hospital admission (i.e. GW or ICU), as presented in Table 52. Firstly, the mortality rate associated with a GW admission was informed using data from Martinón-Torres et al. (2023).[110] The mortality rate was calculated with deaths reported from late preterm individuals excluded so that it was specific to full-term individuals. An additional relative risk of GW mortality of 12.9 was then applied to late preterm individuals. This relative risk was calculated by dividing the reported preterm mortality risk by the full-term mortality risk (12.90/0.14). This relative risk may be slightly overestimated because the study sample may have included early preterm and extreme preterm individuals.

A mean in-hospital fatality risk for an ICU hospital admission was informed using data from Gunville et al. (2010) that was specific to full-term individuals.[111] Therefore, an additional relative risk of ICU mortality was applied to late preterm individuals. This relative risk was also calculated from Gunville et al. (2010) by dividing the risk of ICU mortality in late preterm individuals by the risk of ICU mortality in full-term individuals.

Table 52: RSV hospitalization mortality

Type of hospitalization	Value	Source
GW: Mean in-hospital mortality risk	0.12%	Martinón-Torres et al. (2023)[110]
GW: Relative mortality risk for late preterm individuals	12.90	
ICU: Mean in-hospital mortality risk	3.66%	Gunville et al. (2010)[111]
ICU: Relative mortality risk for late preterm individuals	1.65	

Abbreviations

GW = general ward, ICU = intensive care unit, RSV = respiratory syncytial virus.

8.1.7.3 Utility

In alignment with the approach adopted in previous cost-effectiveness models,[81, 83] individuals were assigned a baseline utility level of one (equal to full health) when residing in the 'No RSV infection' or 'Post-RSV infection' health state. A QALY loss per RSV infection event was applied as a utility decrement adjusted by the duration of illness simultaneously in the month (cycle) of infection occurrence. No QALY losses in the Swiss population were identified during the rapid systematic literature review. The corresponding QALY loss for each type of RSV infection considered in the model is presented in Table 53.

Utility values previously used in a Canadian cost-effectiveness model by Gebretekle et al. (2024) were assumed to apply to the Swiss population and were applied to newborns and infants when experiencing hospital admission (either GW or ICU).[82] Data from Getaneh et al. (2023), which used data from 4 European countries, were assumed suitable for use in a Swiss population and applied to newborns and infants when requiring ED or PC visits.[83]

Although the QALY loss sourced from Gebretekle et al. (2024) for GW hospital admissions was taken from an American study, the value was deemed to have strong face validity when compared with the QALY losses proposed for the other types of RSV infection.[82] Furthermore, although Getaneh et al. (2023) reported a QALY loss for hospitalizations using data from 4 European countries, the study applied the same QALY loss to both hospitalizations and ED visits.[83] It is anticipated that

the QALY loss for hospitalization would be greater than an ED visit and, therefore, the use of Gebretekle et al. (2024) for the GW hospital admission QALY loss was deemed preferable to Getaneh et al. (2023).[82, 83]

Table 53: RSV-associated QALY loss

RSV infection by care setting	QALY loss per event	Source
Hospitalization: ICU	0.0245	Gebretekle et al. (2024)[82]
Hospitalization: GW	0.0169	
ED	0.0102	Getaneh et al. (2023)[83]
PC	0.0063	

Abbreviations

ED = emergency department, GW = general ward, ICU = intensive care unit, PC = primary care, QALY = quality-adjusted life year, RSV = respiratory syncytial virus.

8.1.7.4 Costs

8.1.7.4.1 Treatment costs

As presented in Table 54, individuals in the RSVpreF cohort were assigned a vaccine unit cost (a single intramuscular injection of 120 µg)[78] upon model entry (subject to coverage). The vaccine unit cost was varied by CHF 100 and various percentage reductions within scenario analyses to assess the impact of alternative values on model outcomes (as presented in Section 0). The clinical expert also advised that a vaccine administration cost would not be relevant for RSVpreF because RSVpreF would be administered simultaneously with a scheduled obstetrician visit during pregnancy.

Table 54: RSVpreF treatment and administration unit costs

Parameter	Cost	Source
RSVpreF 120 ug dose	CHF 207.53	Assumed to be equal to the listed German pharmacy price.[112] Converted from EUR to CHF using a 2023 average annual EUR to CHF exchange rate of 0.9717 provided by the Swiss National Bank.[113]

Individuals in the nirsevimab cohort were assigned a treatment cost (subject to coverage). Although the dosage of nirsevimab is informed by an individual's weight (i.e. 50 mg if they weigh <5 kg or a

dose of 100 mg if they weigh ≥5 kg),[79] FOPH list prices for nirsevimab are equivalent across doses (Table 55). Therefore, a single price was applied to all newborns and infants. Furthermore, the clinical expert advised that individuals receiving nirsevimab should also be assigned a treatment administration cost because an additional scheduled outpatient appointment would be required around the time of birth for administering nirsevimab (Table 55).

Table 55: Nirsevimab treatment and administration unit costs

Parameter	Cost	Source
Cost per dose (including VAT)	CHF 395.60	Preparations specialty list. FOPH.[105]
Administration cost	CHF 150.00	Assumed to equal the unit cost of an RSV-associated PC visit (see Table 56)

Abbreviations: FOPH = Federal Office of Public Health, PC = primary care, RSV = respiratory syncytial virus, VAT = value added tax.

8.1.7.4.2 RSV-associated healthcare costs

As outlined in Section 8.1.6.1, the occurrence of each RSV infection that was considered in the model required treatment in a specific care setting (i.e. hospitalization, ED or PC). The values used to inform the cost of each element, as well as values used in the scenario analysis that adopted alternative hospitalization unit costs, are presented in Table 56. In accordance with the clinical expert's judgment, additional medication costs prescribed to treat an RSV infection were not included in the model due to their negligible contribution to the treatment of RSV in practice.

Table 56: RSV-associated healthcare resource use unit costs

RSV-associated care setting	Cost	Source
PC visit	CHF 150.00	Provided by the clinical expert and the FOPH. TARMED codes listed as: 00.0010, 00.0015, 00.0025, 00.0030, 00.0416, 00.0615, 00.0715. The tax points were multiplied by a Swiss average tax point value of CHF 0.89. Analysis List (AL): 4700.00, 1245.00, 3159.00. The tax points were multiplied by the value of CHF 1.0.
ED visit	CHF 194.00	Assumed to be equal to the unit cost of an RSV-associated PC visit (CHF 150.00) plus the cost of an emergency consultation TARMED code 00.2510 (Notfall-Inkonvenienzpauschale A, Mo-Fr 7-19, Sa 7-12) equal to CHF 44.00.
Hospitalization: GW	CHF 5'415	Provided by the FOPH. Swiss DRG codes E70B and E77B (without ICU) based on a base rate of CHF 9'467 estimated for children <1 year old.

Hospitalization: ICU	CHF 30'535	Provided by the FOPH. Swiss DRG codes E90C, E36D, and E36B (requiring ICU) based on a base rate of CHF 9'467 estimated for children <1 year old.
Hospitalization: GW (scenario value)	CHF 6'393	A value of CHF 6'479 reported in Stucki et al. (2024)[36]. Inflated from 2021 to 2024 using the FSO inflation index for health.[114]
Hospitalization: ICU (scenario value)	CHF 29'758	A value of CHF 30'161 reported in Stucki et al. (2024)[36]. Inflated from 2021 to 2024 using the FSO inflation index for health.[114]

Abbreviations:

DRG = diagnosis-related group, ED = emergency department, FOPH = Federal Office of Public Health, FSO = Federal Statistical Office, GW = general ward, ICU = intensive care unit, PC = primary care, RSV = respiratory syncytial virus.

8.1.8 Uncertainty analysis

8.1.8.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was performed to account for second-order uncertainty around the parameter values. PSA allows the computation of expected values of a model's results, as well as the assessment of the uncertainty around these expected values when input variables are varied using uncertainty parameters. The assessment of expected values and measures of uncertainty is done using simulation with all input variables simultaneously that are subject to uncertainty being varied randomly according to their observed distribution.

To generate the input values for each iteration, distributions were fitted to uncertain parameters within the model. The parameter types described in Table 57 were each selected from a distribution rather than using just one fixed value for each input.

The model used a recommended minimum sample of 1'000 iterations, each iteration producing a different set of values for the inputs, to ensure stable results. The convergence of the PSA results was also recorded to confirm that 1'000 iterations were sufficient to achieve stability.

The ICER generated from each iteration was collected and the spread was examined. This provided information on the robustness of the results in the model. If the ICERs from all iterations are very tightly clustered together, this suggests that the results of the model did not change greatly when the inputs were varied with plausible ranges.

PSA can also provide an estimate of the confidence in the direction of model results by looking at the distribution of results. It identifies the proportion of iterations where the ICER falls below the threshold, indicating the proportion of iterations where the new intervention was estimated to be cost effective. The model reports the mean incremental costs and QALY outcomes per person. Therefore, an ICER was calculated per iteration. Standard errors (SEs) were obtained from the literature, where possible, to define the level of uncertainty associated with each parameter and are presented in Appendix 2.1. In the absence of appropriate data, SEs were assumed to be equal to 20% of the mean estimate.

The outputs of the PSA included the mean outcome of all iterations across all key results. The results were also presented graphically, in the form of a cost-effectiveness plane and a cost-

effectiveness acceptability curve (CEAC). The cost-effectiveness plane presented the incremental costs and incremental QALYs from each PSA iteration, the deterministic result, and the cost-effectiveness threshold. The CEAC displayed the probability of a decision maker accepting either the intervention, or the comparator, at various cost-effectiveness thresholds. PSA convergence was also assessed, to indicate the approximate number of PSA iterations required for probabilistic outcomes to converge.

Table 57: PSA variation included in the model

Parameter	Variation method
Proportion of births <32 wGA	Beta
Proportion of live births full-term	Beta
Baseline RSV rates	Gamma
Proportion of hospitalizations requiring ICU	Beta
Distribution of RSV cases throughout the year	Conditional beta
Vaccine coverage	Beta
Efficacy in late preterm vs full-term	Beta
Relative RSV risk vs no prophylaxis	Log-normal
Cost per RSV-related healthcare resource use	Gamma
RSV-associated QALY loss	Gamma
Baseline annual mortality risk	Gamma
Relative risk of mortality for late preterm individuals	Log-normal
Hospitalization mortality risk per episode	Beta

Abbreviations

ICU = intensive care unit, QALY = quality-adjusted life year, RSV = respiratory syncytial virus, wGA = weeks of gestational age.

8.1.8.2 Deterministic sensitivity analyses

All model input parameters were tested in deterministic sensitivity analysis (DSA) to account for first-order uncertainty around the data. DSA involved altering the value used for individual parameters, within realistic ranges, to see the impact on the model results. The main output from the DSA

was a tornado diagram, which summarized the impact of changes to each parameter on the model results. This enabled the user to quickly identify the parameters that had the most substantial impact on the results.

Where possible, the range applied to each parameter was based on 95% confidence intervals obtained from the original data source. Where statistical parameters were not available from the literature, a range of values (+/- 25%) were applied around the point estimate that was used in the base case analysis. The corresponding upper and lower value for each parameter included in the DSA is presented in Appendix 2.1.

8.2 Budget Impact Analysis

8.2.1 Objective

The objective of the budget impact analysis (BIA) was to estimate the absolute and incremental budget impact of adding RSV vaccination with RSVpreF during pregnancy to the existing treatment landscape in Switzerland.

8.2.2 Patient population

The BIA estimated the number of mothers who would be eligible to receive the RSV vaccination with RSVpreF during pregnancy in Switzerland over the next 5 years. The first input required to estimate this number was the annual incident population of live births in Switzerland between October and March: 38’844 as presented in Table 45. The proportion of births with a term status less than 32 wGA (0.679%), as defined in Section 8.1.1, was then subtracted from this value.[101]

The BIA also included inputs for the proportion of women and newborns eligible for the RSV vaccination with RSVpreF or nirsevimab; to prevent overcomplication, the same input was used to inform the eligibility of both treatments. In the base case analysis, eligibility was set to 100% of these individuals. However, this input was flexible.

The final annual eligible population was 38’580 live births (38’844*(1-0.679%)). The model did not consider population growth for simplification purposes. Furthermore, it was assumed that all women who received the RSV vaccination with RSVpreF between 32 and 36 weeks would birth a live newborn. Therefore, the total annual eligible population may be slightly overestimated.

8.2.3 Technology

The BIA estimated the total healthcare costs, and budget impact, for the following 2 scenarios:

– 'A scenario without RSV vaccination using RSVpreF during pregnancy', in which newborns and infants in Switzerland receive RSV prophylaxis with nirsevimab or no RSV prophylaxis.

– 'A scenario with RSV vaccination using RSVpreF during pregnancy', in which vaccination with RSVpreF during pregnancy is introduced as a treatment strategy in Switzerland.

8.2.4 Time horizon

The BIA estimated outcomes over a conventional 5-year time horizon. Outcomes were also disaggregated to present the budget impact in years one to 5 separately.

8.2.5 Perspective

The analysis was performed from a healthcare payers' perspective. Costs of healthcare services covered by the Swiss mandatory health insurance were analyzed, irrespective of the actual payer (mandatory health insurer, other social insurer, government [federal government, cantons, communities] out-of-pocket). The analysis did not include indirect costs due to informal care or productivity losses and additional non-medical costs for patients, such as travel costs.

8.2.6 Model description

An incidence cohort-level modelling approach was taken to construct the BIA. Forecasted market shares were then used to estimate the number of mothers and/or newborns/infants receiving the RSV vaccination with RSVpreF, nirsevimab, or no RSV prophylaxis in each scenario.

The annual costs per newborn/infant associated with each treatment strategy were determined by the one-year outcomes from the cost-effectiveness model. These costs were, therefore, dependent on the incidence, efficacy, and cost data used in the cost-effectiveness model (which is described in Section 8.1).

The total healthcare cost in each scenario was calculated by multiplying the forecasted number of pregnant mothers and newborns receiving each strategy by the average annual costs per individual associated with each strategy. The incremental budget impact of introducing RSV vaccination with RSVpreF during pregnancy was then calculated by subtracting the total cost in the scenario with RSVpreF from the total cost in the scenario without RSVpreF. A schematic representation of the BIA is displayed in Figure 5.

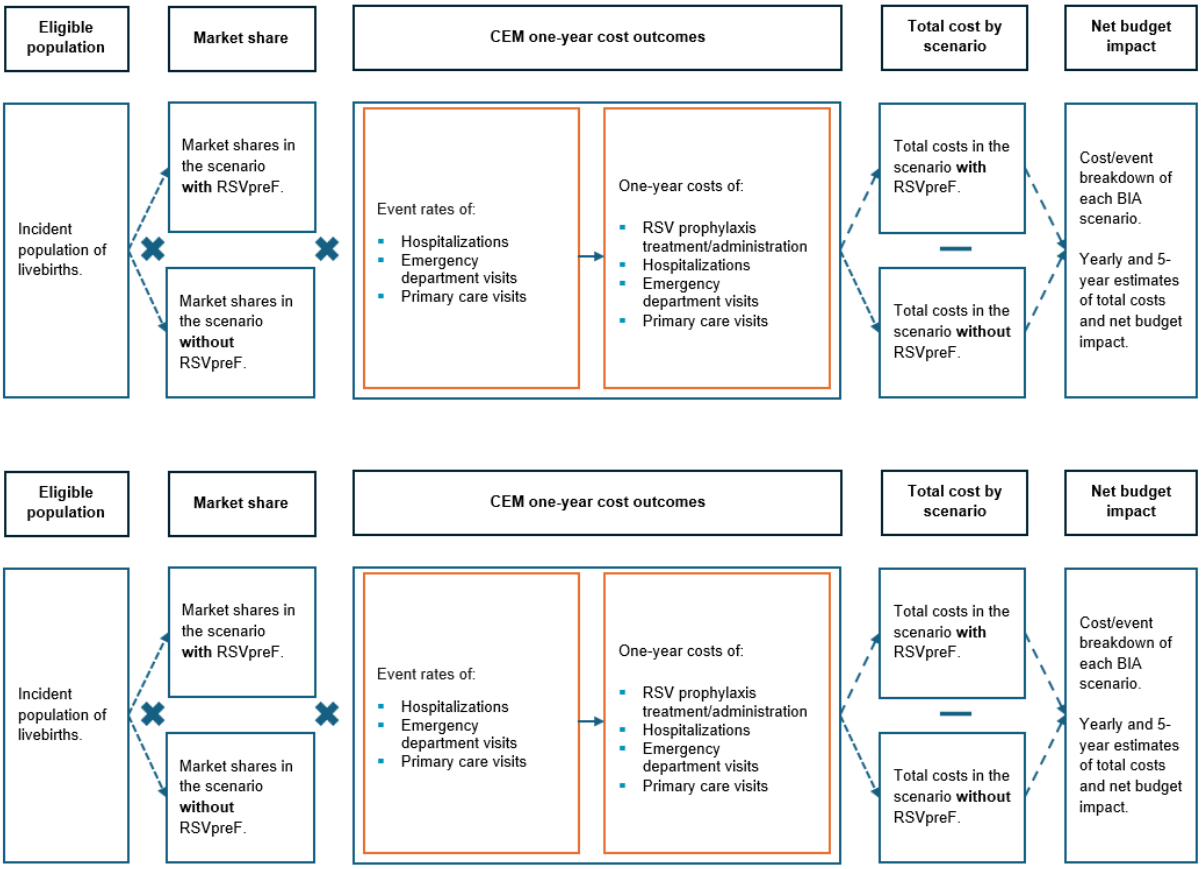

Figure 5: Schematic representation of the BIA

Abbreviations

BIA = budget impact analysis, CEM = cost-effectiveness model, RSV = respiratory syncytial virus.

8.2.7 Input data

8.2.7.1 Market share inputs

Even though pregnant women in the population estimated in Section 8.2.2 were considered eligible for vaccinations with RSVpreF, it was expected that only a proportion would receive the vaccination, at least initially. This is because RSVpreF would be new to the market and widespread adoption would not take place straight away. Therefore, market shares would be required to calculate the number of individuals receiving each treatment strategy and the subsequent overall total healthcare costs of each scenario. The market shares, which were informed by clinical expert opinion, are presented in Table 58 and Table 59.

Table 58: Example market shares in a scenario without RSVpreF

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
Nirsevimab	75%	80%	85%	85%	90%
No RSV prophylaxis	25%	20%	15%	15%	10%
Total	**100%**	**100%**	**100%**	**100%**	**100%**

Abbreviations

RSV = respiratory syncytial virus.

Table 59: Example market shares in a scenario with RSVpreF

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
RSVpreF	20%	25%	30%	35%	35%
Nirsevimab	60%	60%	55%	55%	55%
No RSV prophylaxis	20%	15%	15%	10%	10%
Total	**100%**	**100%**	**100%**	**100%**	**100%**

Abbreviations

RSV = respiratory syncytial virus.

8.2.7.2 Cost inputs

The annual, undiscounted per-person costs associated with each model strategy were estimated within the cost-effectiveness model. All resource use and unit cost inputs that were used to inform the cost-effectiveness and BIA are described further in Section 8.1.7.4. In particular, the BIA considered treatment and acquisition costs of RSVpreF and nirsevimab, as well as RSV-associated healthcare costs for all strategies.

8.2.8 Base case and scenario analyses

The base case analyses are described and justified throughout the following sections. Unless stated otherwise, outcomes were estimated for an annual cohort of live births, a one-year time horizon was adopted, and an annual discount rate of 5% was applied to costs, QALYs and life years.

The following scenarios were conducted during the scenario analyses:

– Including treatment waning for RSVpreF and nirsevimab until 12 months.
– Including no treatment waning for RSVpreF and nirsevimab.
– Increasing and decreasing the unit cost of RSVpreF by CHF 100.
– Reducing the unit cost of RSVpreF in a range of ‘price reduction’ scenarios.
– Increasing the annual market share of RSVpreF by and absolute value of 10% and decreasing the market share for nirsevimab and no RSV prophylaxis proportionally.
– Adopting an increased baseline rate of RSV-associated hospitalizations using Spanish-specific data (see Table 47).
– Adopting alternative unit costs for GW and ICU hospitalizations (see Table 56).

8.2.9 Model software and validation of the model

Please see Section 8.1.6.2.

9. Results Economic Evaluation and Budget Impact Analysis

Summary statement economic evaluation and budget impact analysis

RSVpreF vs nirsevimab

For an annual cohort of live births in Switzerland, RSVpreF decreases costs and QALYs by CHF 9'781'506 and 18.2, respectively, which results in an ICER of CHF 538'075 per QALY lost. The percentage of cost-effective iterations for RSVpreF marginally decreases as the adopted value of the cost-effectiveness value increases (i.e. 100.0% at CHF 50’000 and 99.9% at CHF 200’000), and RSVpreF is cost saving in 100.0% of iterations. Outcomes from the DSA and scenario analyses align with the PSA and indicate that the likelihood of RSVpreF being cost effective is robust.

RSVpreF vs no RSV prophylaxis

For an annual cohort of live births in Switzerland, RSVpreF increases costs and QALYs by CHF 430'224 and 27.8, respectively, which results in an ICER of CHF 15'497 per QALY gained. The percentage of cost-effective iterations for RSVpreF increases as the adopted value of the cost-effectiveness value increases (i.e. 80.0% at CHF 50’000 and 100.0% at CHF 200’000), and RSVpreF is cost saving in 27.8% of iterations. Outcomes from the DSA and scenario analyses align with the PSA and indicate that the likelihood of RSVpreF being cost effective is robust.

Budget impact analysis

The BIA analysis estimates that adopting RSVpreF in each annual cohort of live births in Switzerland over a 5-year time horizon would reduce cumulative total costs by CHF 14’832’734. The conclusion that adopting RSVpreF reduces total costs is robust to all scenarios considered.

9.1 Economic Evaluation

9.1.1 Base case results

The cost-effectiveness results for an annual cohort of full-term and late preterm live births in Switzerland over a one-year time horizon are displayed in Table 60 and Table 61.

Table 60: Deterministic results: RSVpreF compared with nirsevimab

Outcome	RSVpreF	Nirsevimab	Incremental
Total cost	CHF 12'172'946	CHF 21'954'452	-CHF 9'781'506
Total QALYs	37'823	37'841	-18.2
Total life years	37'881	37'883	-1.4
Incremental cost-effectiveness ratio			CHF 538'075

Abbreviations

QALY = quality-adjusted life year.

When compared with nirsevimab, RSVpreF reduces both total costs and total QALYs. Because RSVpreF reduces both costs and QALYs, a higher ICER indicates that RSVpreF is more cost effective.

Table 61: Deterministic results: RSVpreF compared with no RSV prophylaxis

Outcome	RSVpreF	No RSV prophylaxis	Incremental
Total cost	CHF 12'172'946	CHF 11'742'721	CHF 430'224
Total QALYs	37'823	37'795	27.8
Total life years	37'881	37'878	2.9
Incremental cost-effectiveness ratio			CHF 15'497

Abbreviations

QALY = quality-adjusted life year.

When compared with no RSV prophylaxis, RSVpreF increases both total costs and total QALYs. Because RSVpreF increases both costs and QALYs, a lower ICER indicates that RSVpreF is more cost effective.

9.1.1.1 Cost breakdown

A breakdown of total discounted costs for a cohort of full-term and late preterm live births in Switzerland over a one-year time horizon is presented in Table 62 and Table 63.

Table 62: Cost breakdown: RSVpreF compared with nirsevimab

Outcome	RSVpreF	Nirsevimab	Incremental
Treatment	CHF 5'430'944	CHF 12'880'140	-CHF 7'449'196
Prophylaxis administration	CHF 0.00	CHF 4'883'774	-CHF 4'883'774
PC visits	CHF 499'772	CHF 382'127	CHF 117'644
ED visits	CHF 509'633	CHF 366'099	CHF 143'534
GW admissions	CHF 2'706'639	CHF 1'625'283	CHF 1'081'356
ICU admissions	CHF 3'025'958	CHF 1'817'028	CHF 1'208'930
Total	CHF 12'172'946	CHF 21'954'452	-CHF 9'781'506

Abbreviations

ED = emergency department, GW = general ward, ICU = intensive care unit, PC = primary care.

When compared with nirsevimab, RSVpreF reduces total treatment and administration costs. Although RSVpreF increases expenditure on healthcare required to treat RSV infections that result in healthcare-seeking behavior, the decrease in treatment and administration costs results in an overall decrease in total costs. The reduction in treatment costs is the largest contributor to RSVpreF reducing overall costs compared with nirsevimab, which is a result of both a higher coverage (84.6% vs 68.0%) and treatment unit cost (CHF 395.60 vs CHF 207.53) for nirsevimab compared with RSVpreF.

Table 63: Cost breakdown: RSVpreF compared with no RSV prophylaxis

Cost category	RSVpreF	No RSV prophylaxis	Incremental
Treatment	CHF 5'430'944	CHF 0.00	CHF 5'430'944
Prophylaxis administration	CHF 0.00	CHF 0.00	CHF 0.00
PC visits	CHF 499'772	CHF 647'566	-CHF 147'795
ED visits	CHF 509'633	CHF 695'650	-CHF 186'018
GW admissions	CHF 2'706'639	CHF 4'910'114	-CHF 2'203'475
ICU admissions	CHF 3'025'958	CHF 5'489'391	-CHF 2'463'432
Total	CHF 12'172'946	CHF 11'742'721	CHF 430'224

Abbreviations

ED = Emergency department, GW = general ward, ICU = intensive care unit, PC = primary care, RSV = respiratory syncytial virus.

When compared with no RSV prophylaxis, RSVpreF increases total costs. Although RSVpreF reduces expenditure on healthcare required to treat RSV infections that result in healthcare-seeking behavior, the increase in treatment costs outweighs the reduction in RSV-associated healthcare expenditure.

9.1.1.2 Healthcare seeking RSV infection outcomes

A summary of total healthcare-seeking RSV infection outcomes for a cohort of full-term and late-preterm live births in Switzerland over a one-year time horizon is presented in Table 64 and Table 65.

Table 64: Healthcare-seeking RSV infection outcomes: RSVpreF compared with nirsevimab

Outcome	RSVpreF	Nirsevimab	Incremental
PC visits	3'383	2'595	789
ED visits	2'661	1'917	744
GW admissions	505	304	201
ICU admissions	100	60	40
Total	6'650	4'876	1'774

Abbreviations

ED = emergency department, GW = general ward, ICU = intensive care unit, PC = primary care, RSV = respiratory syncytial virus.

Table 65: Healthcare-seeking RSV infection outcomes: RSVpreF compared with no RSV prophylaxis

Cost category	RSVpreF	No RSV prophylaxis	Incremental
PC visits	3'383	4'373	-990
ED visits	2'661	3'625	-963
GW admissions	505	914	-409
ICU admissions	100	181	-81
Total	6'650	9'093	-2'443

Abbreviations

ED = emergency department, GW = general ward, ICU = intensive care unit, PC = primary care, RSV = respiratory syncytial virus.

When compared with nirsevimab, RSVpreF increases the total number of RSV infections that result in healthcare-seeking behavior. As outlined in Section 8.1.7.2.1 and Section 8.1.7.2.2, this is a consequence of nirsevimab being more effective in preventing RSV infections that result in healthcare-seeking behavior compared with RSVpreF.

When compared with no RSV prophylaxis, RSVpreF decreases the total number of RSV infections that result in healthcare-seeking behavior. This outcome is a result of individuals in the no RSV prophylaxis model arm receiving no protection against RSV infections compared with individuals who receive RSVpreF receiving protection against RSV infections.

9.1.2 Probabilistic sensitivity analysis

PSA results over 1'000 iterations for a cohort of full-term and late preterm live births in Switzerland over a one-year time horizon are presented in Table 66 and Table 67. The corresponding cost-effectiveness planes and CEACs are also presented below in Figure 6 and Figure 7, respectively.

Table 66: Probabilistic results: RSVpreF compared with nirsevimab (mean, 95% credible intervals)

Outcome	RSVpreF	Nirsevimab	Incremental
Total cost	CHF 12'245,311 (CHF 10’722’696 to CHF 14’249’323)	CHF 22'124'049 (CHF 18’055’038 to 24’180’200)	-CHF 9'878'738 (-CHF 12’154’926 to -CHF 5’925’016)
Total QALYs	37'819 (37’795 to 37’839)	37'837 (37’811 to 37’858)	-18.4 (-36.2 to 2.3)
Total life years	37’881 (37’866 to 37’894)	37’882 (37’867 to 37’896)	-1.3 (-3.6 to 0.5)
Total RSV infections	6’906 (5’768 to 8’111)	5'170 (4’006 to 6’909)	1'736 (-149 to 3’294)
Incremental cost-effectiveness ratio			CHF 536'008
Percentage of cost-saving iterations			100.0%
Percentage of QALY-increasing iterations			6.4%
Percentage of cost-effective iterations (CHF 50'000 per QALY)			100.0%
Percentage of cost-effective iterations (CHF 100'000 per QALY)			100.0%
Percentage of cost-effective iterations (CHF 150'000 per QALY)			99.9%
Percentage of cost-effective iterations (CHF 200'000 per QALY)			99.9%

Abbreviations

QALY = quality-adjusted life year.

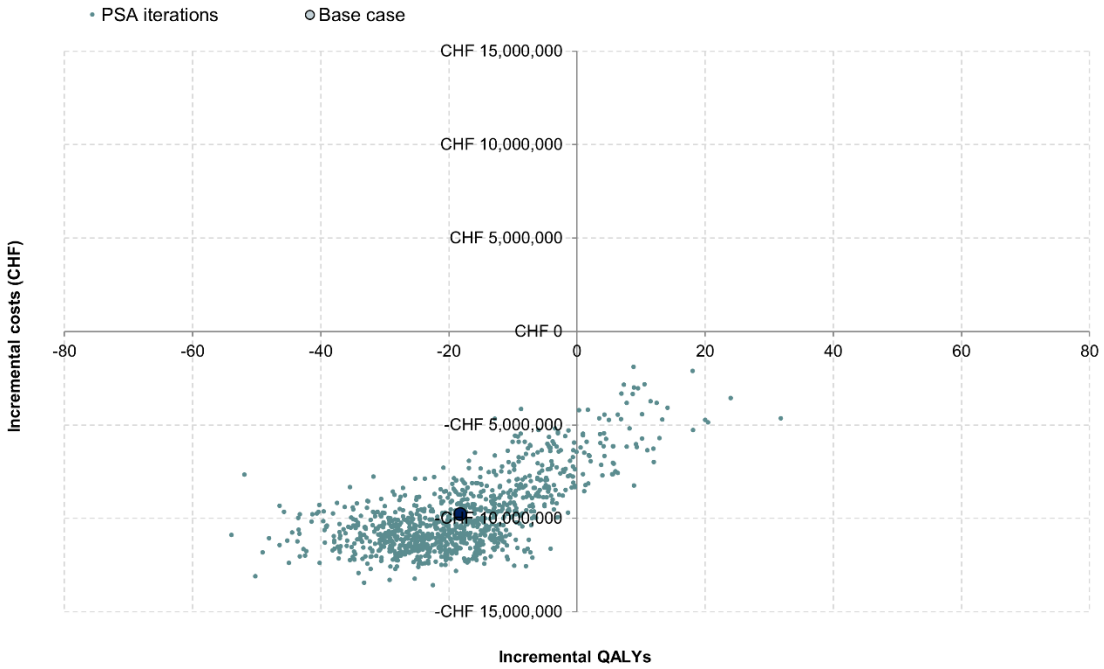

Figure 6: RSVpreF vs nirsevimab cost-effectiveness plane

Abbreviations

PSA = probabilistic sensitivity analysis, QALY = quality-adjusted life year.

As outlined in Table 66, RSVpreF reduces both total costs and total QALYs when compared with nirsevimab. Because RSVpreF reduces both costs and QALYs, a higher ICER indicates that RSVpreF is more cost effective. Convergence of probabilistic outcomes was achieved after approximately 250 iterations.

As indicated in Figure 6, 100.0% of PSA iterations lie below the x-axis, which indicates that RSVpreF reduces total costs in each iteration compared with nirsevimab. Furthermore, 6.4% of iterations are to the right of the x-axis, which indicates the iterations in which RSVpreF increases total QALYs compared with nirsevimab. When adopting cost-effectiveness threshold values of CHF 50'000 or CHF 100'000, RSVpreF is cost-effective in 100% of iterations. When adopting a higher threshold value of either CHF 150’000 or CHF 200'000, RSVpreF remains cost-effective in 99.9% of iterations.

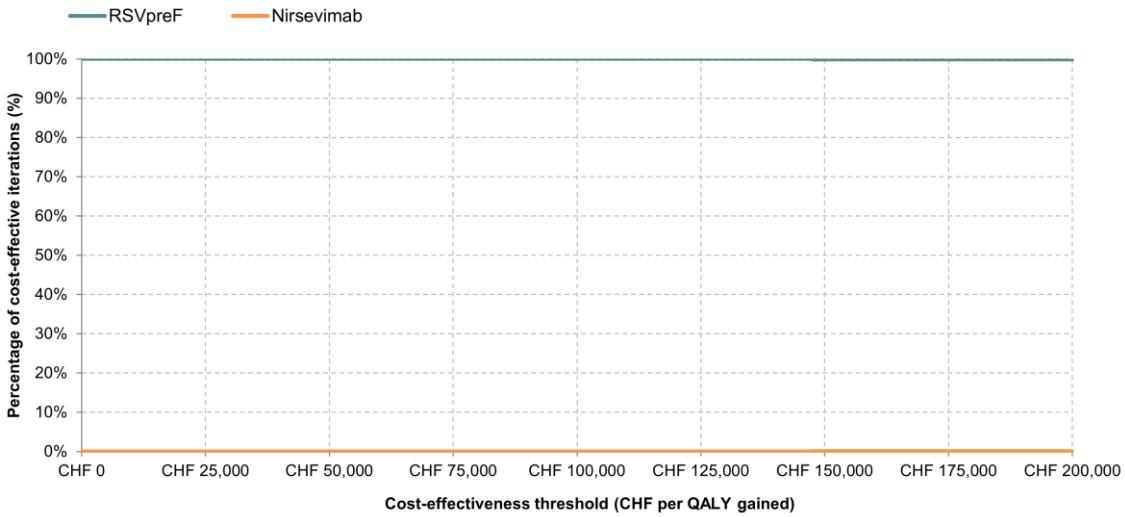

Figure 7: RSVpreF vs nirsevimab cost-effectiveness acceptability curve

Abbreviations

QALY = quality-adjusted life year.

As indicated in Figure 7, the percentage of cost-effective PSA iterations for RSVpreF compared with nirsevimab is approximately equal to 100.0% at all threshold values considered. Although higher threshold values increase the value of the health outcome forsaken by adopting RSVpreF compared with nirsevimab, the accompanying reduction in total costs with RSVpreF means that even when the highest threshold value considered of CHF 200'000 is adopted, RSVpreF remains cost-effective in 99.9% of iterations.

Table 67: Probabilistic results: RSVpreF compared with no RSV prophylaxis

Outcome	RSVpreF	No RSV prophylaxis	Incremental
Total cost (95% CRI)	CHF 12'252,856 (CHF 10’626’750 to CHF 14’176’676)	CHF 11'782'415 (CHF 8’921’735 to 15’135’443)	CHF 470'441 (-CHF 1’117’844 to CHF 1’887’302)
Total QALYs (95% CRI)	37'818 (37’791 to 37’838)	37'791 (37’756 to 37’814)	27.1 (14.8 to 44.4)
Total life years (95% CRI)	37’880 (37’865 to 37’894)	37’877 (37’862 to 37’891)	-2.9 (1.1 to 5.8)
Total RSV infections (95% CRI)	6’896 (5’767 to 8’056)	9'087 (8’343 to 9’880)	-2'191 (-3’111 to -1’237)
Incremental cost-effectiveness ratio			CHF 17'377
Percentage of cost-saving iterations			27.8%
Percentage of QALY-increasing iterations			100.0%
Percentage of cost-effective iterations (CHF 50,000 per QALY)			80.0%
Percentage of cost-effective iterations (CHF 100,000 per QALY)			97.3%
Percentage of cost-effective iterations (CHF 150,000 per QALY)			99.8%
Percentage of cost-effective iterations (CHF 200,000 per QALY)			100.0%

Abbreviations

QALY = quality-adjusted life year, RSV = respiratory syncytial virus.

As outlined in Table 67, the PSA estimates that RSVpreF increases both total costs and total QALYs when compared with no RSV prophylaxis. Because RSVpreF increases both costs and QALYs, a lower ICER indicates that RSVpreF is more cost-effective. Convergence of probabilistic outcomes was achieved after approximately 200 iterations.

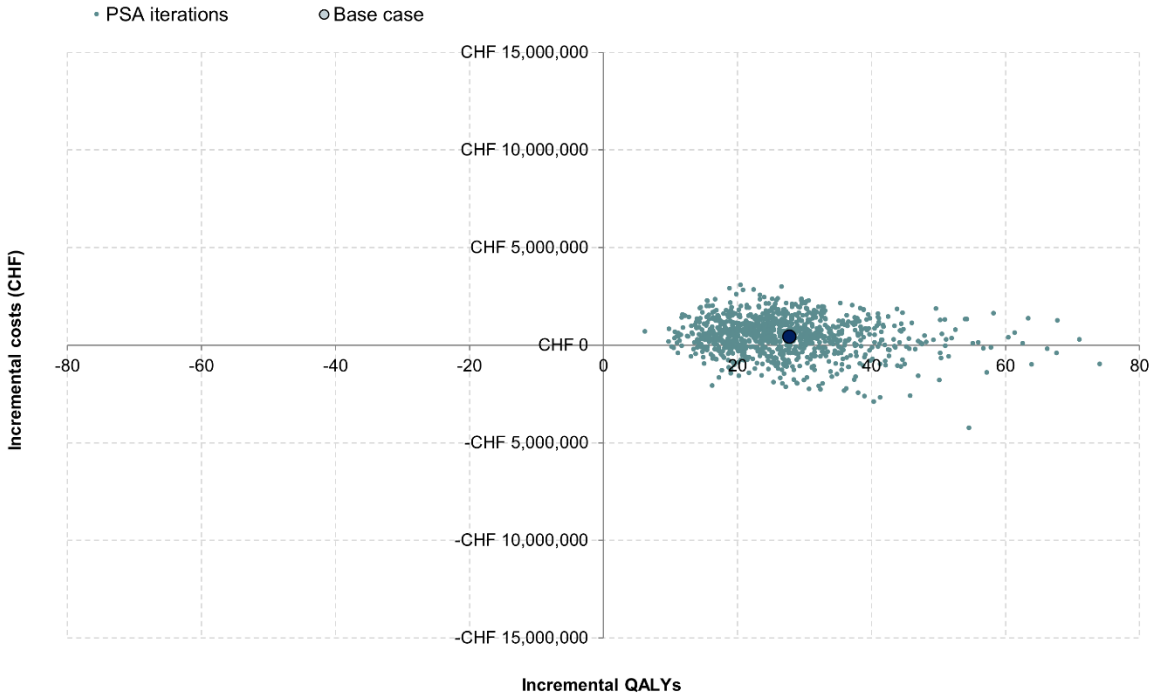

Figure 8: RSVpreF vs no RSV prophylaxis cost-effectiveness plane

Abbreviations

PSA = probabilistic sensitivity analysis, QALY = quality-adjusted life year.

As indicated in Figure 8, 100.0% of PSA iterations lie to the right of the y-axis, which indicates that RSVpreF increases total QALYs in each iteration compared with no RSV prophylaxis. Furthermore, 27.8% of iterations are below the x-axis, which indicates the iterations in which RSVpreF reduces total costs compared with no RSV prophylaxis. When adopting cost-effectiveness threshold values of CHF 100'000, CHF 150'000, and CHF 200'000, RSVpreF is cost-effective in close to or equal to 100% of iterations. When adopting a lower threshold value of CHF 50'000, RSVpreF remains cost-effective in 80.0% of iterations.

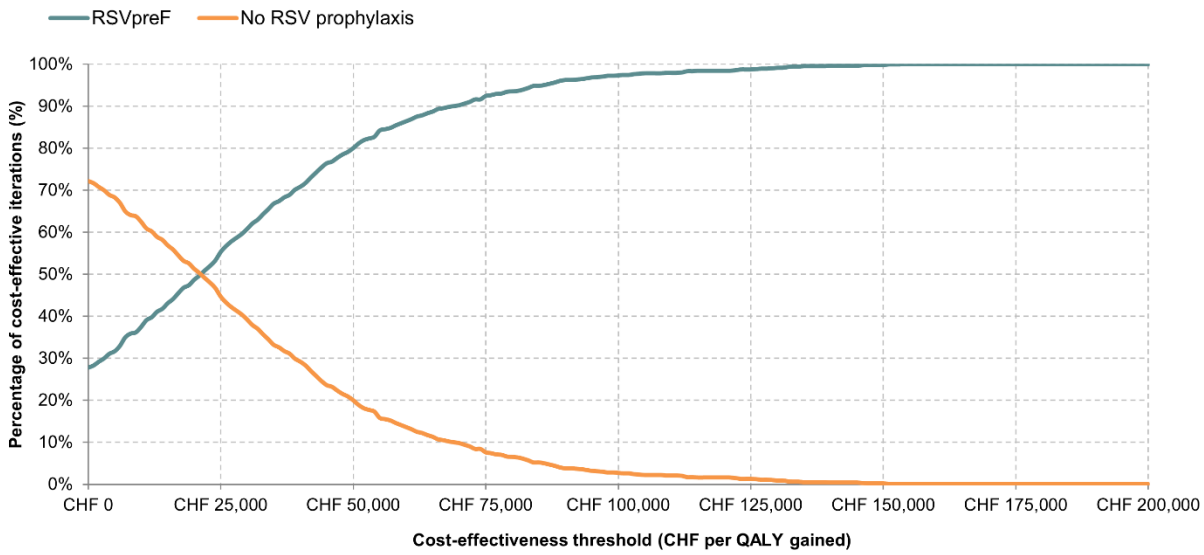

Figure 9: RSVpreF vs no RSV prophylaxis cost-effectiveness acceptability curve

Abbreviations

RSV = respiratory syncytial virus, QALY = quality-adjusted life year.

As indicated in Figure 9, the percentage of cost-effective PSA iterations for RSVpreF compared with no RSV prophylaxis increases as the cost-effectiveness threshold value adopted increases. This is due to RSVpreF increasing total QALYs compared with no RSV prophylaxis. In particular, the increase in health outcome is more valued at higher threshold values, which compensates for RSVpreF increasing total costs compared with no RSV prophylaxis.

9.1.3 Deterministic sensitivity analyses

The univariate impact for a range of parameters was tested during the DSA, as described in Section 8.1.8.2. Given that the overall QALY difference was marginal between the treatment strategies, the DSA results presented in Figure 10 and Figure 11 display the impact on the incremental costs. The ranges that the parameters were varied by are displayed in brackets on the y-axis and parameters are ranked from most impactful on the incremental cost to least impactful.

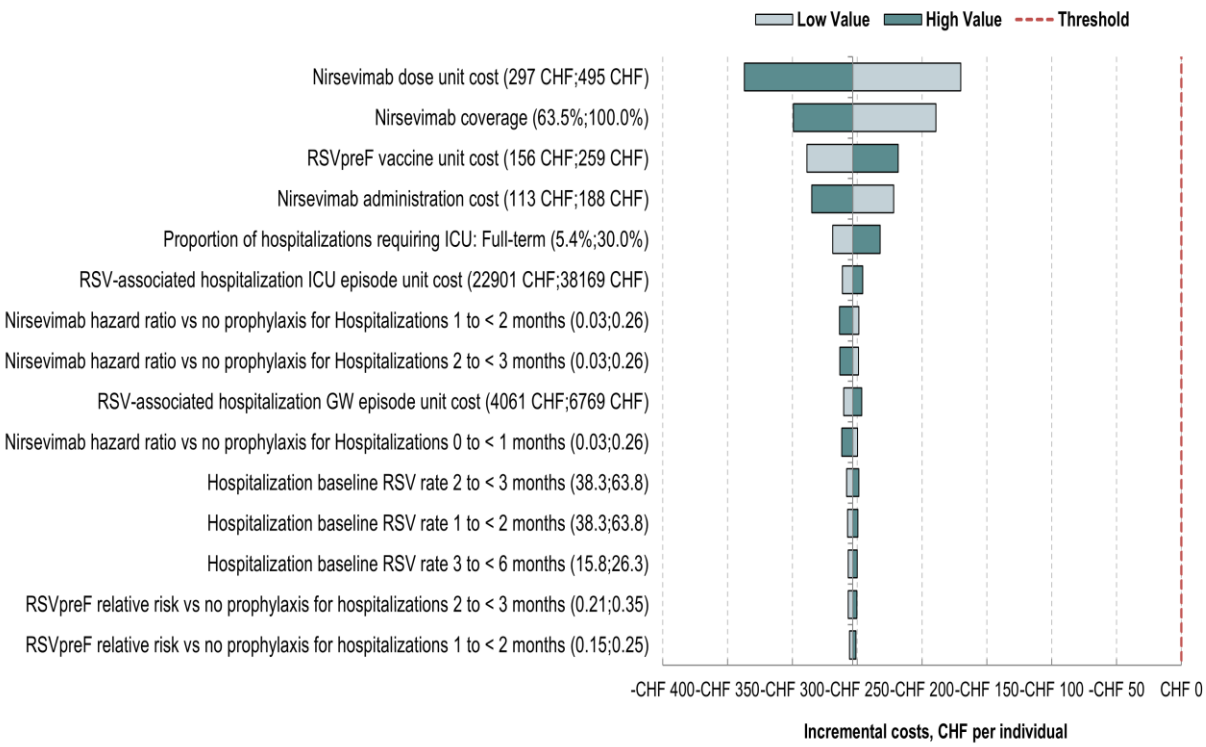

Figure 10: RSVpreF vs nirsevimab univariate sensitivity analysis

Abbreviations

GW = general ward, ICU = intensive care unit, RSV = respiratory syncytial virus.

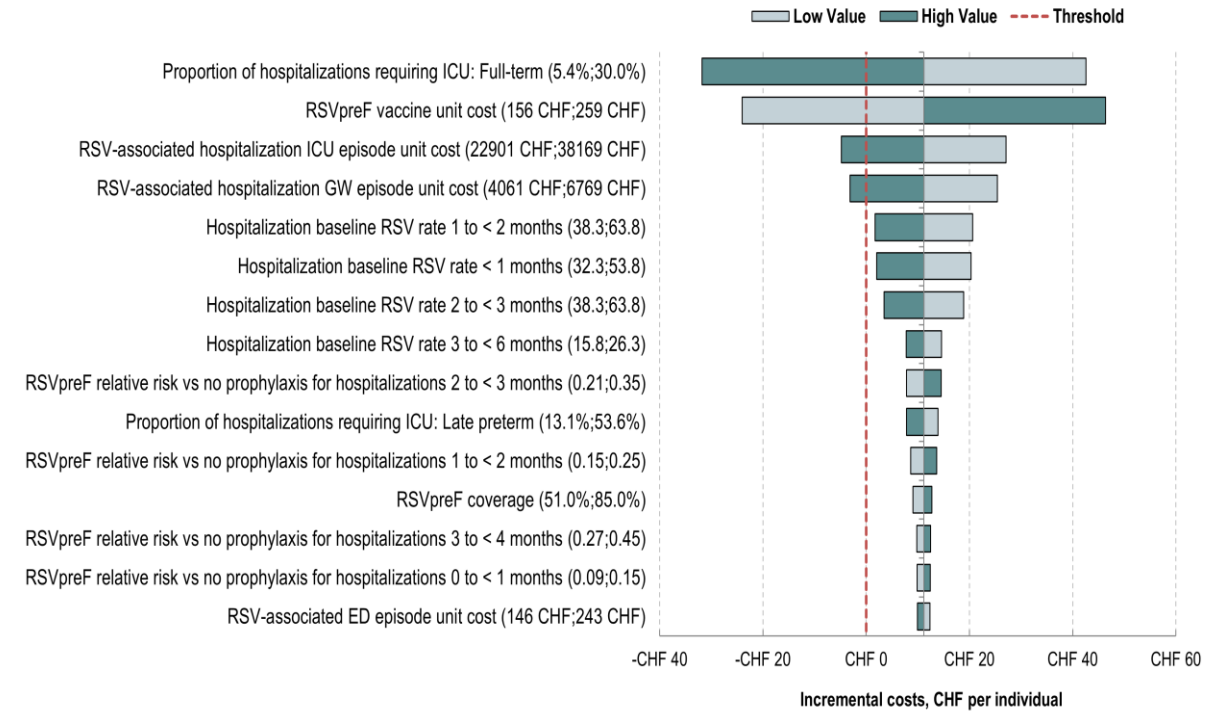

Figure 11: RSVpreF vs no RSV prophylaxis univariate sensitivity analysis

Abbreviations

ED = emergency department, GW = general ward, ICU = intensive care unit, RSV = respiratory syncytial virus.

As indicated in Figure 10, individually changing any of the parameters included in the DSA to either their low or high values does not change the conclusion that RSVpreF reduces overall costs compared with nirsevimab. The treatment unit cost for nirsevimab and RSVpreF are two of the parameters that have the largest impact on overall costs (ranked first and third, respectively). The coverage and administration cost of nirsevimab contribute substantially to the overall difference in incremental costs (ranked second and fourth, respectively).

As indicated in Figure 11, individually changing some of the parameters included in the DSA does result in the conclusion that RSVpreF becomes cost saving. These parameters include changing the proportion of hospitalizations requiring an ICU admission to a high value, the RSVpreF vaccine unit cost to a low value, the unit cost of an ICU episode to a high value, and the unit cost of a GW episode to a high value.

9.1.4 Scenario analyses

The results for various scenario analyses are presented in

Table 68 and Table 69. Outcomes are presented for a cohort of full-term and late preterm live births over a one-year time horizon.

Table 68: Scenario analysis: RSVpreF compared with nirsevimab

Scenario	Incremental costs	Incremental QALYs	ICER
Base case	-CHF 9'781'506	-18.2	CHF 538'075
Discount rate (costs and QALYs): 0%	-CHF 9'795'119	-18.3	CHF 535'063
Discount rate (costs and QALYs): 5%	-CHF 9'772'624	-18.1	CHF 540'038
Treatment waning: instant equivalence	-CHF 9'818'605	-17.2	CHF 571'503
Treatment waning: 12 months	-CHF 9'714'089	-18.9	CHF 513'094
RSVpreF coverage rate: 50%	-CHF 9'866'428	-25.7	CHF 384'023
RSVpreF coverage rate: 75%	-CHF 9'754'194	-15.2	CHF 640'701
Increased baseline hospitalization rate	-CHF 6'193'697	-26.9	CHF 230'399
Stucki et al. GW and ICU hospitalization unit costs	-CHF 9'616'966	-18.2	CHF 529'024
RSVpreF unit cost CHF 100 decrease (CHF 107.53)	-CHF 12'398'501	-18.2	CHF 682'034

Scenario	Incremental costs	Incremental QALYs	ICER
RSVpreF unit cost CHF 100 increase (CHF 307.53)	-CHF 7'164'511	-18.2	CHF 394'115
RSVpreF unit cost 10% decrease (CHF 186.77)	-CHF 10'324'600	-18.2	CHF 567'950
RSVpreF unit cost 25% decrease (CHF 155.64)	-CHF 11'139'242	-18.2	CHF 612'763
RSVpreF unit cost 50% decrease (CHF 103.76)	-CHF 12'496'978	-18.2	CHF 687'451
RSVpreF unit cost 75% decrease (CHF 51.88)	-CHF 13'854'714	-18.2	CHF 762'140
RSVpreF unit cost 90% decrease (CHF 20.75)	-CHF 14'669'355	-18.2	CHF 806'952

Abbreviations

GW = general ward, ICER = incremental cost-effectiveness ratio, ICU = intensive care unit, QALY = quality-adjusted life year, RSV = respiratory syncytial virus.

Table 68, RSVpreF reduces total costs and QALYs in each scenario considered when compared with nirsevimab. The scenario in which an increased baseline rate of RSV infections requiring hospital admission is adopted (see Table 47) is the scenario which results in the least favorable outcomes for RSVpreF. This is due to an increase in the incremental increase of RSV-associated hospitalizations with RSVpreF compared with nirsevimab. Furthermore, the scenario in which the unit cost of RSVpreF is decreased by 90% is the scenario that results in the most favorable outcomes for RSVpreF.

Table 69: Scenario analysis: RSVpreF compared with no RSV prophylaxis

Scenario	Incremental costs	Incremental QALYs	ICER
Base case	CHF 430'224	27.8	CHF 15'497
Discount rate (costs and QALYs): 0%	CHF 417'363	27.9	CHF 14'939
Discount rate (costs and QALYs): 5%	CHF 438'533	27.6	CHF 15'861
Treatment waning: instant equivalence	CHF 445'205	27.6	CHF 16'145
Treatment waning: 12 months	CHF 381'497	28.4	CHF 13'452
RSVpreF coverage rate: 50%	CHF 345'302	20.2	CHF 17'053
RSVpreF coverage rate: 75%	CHF 457'536	30.7	CHF 14'895
Increased baseline hospitalization rate	-CHF 7'406'106	46.8	-CHF 158'235 (Dominant)
Stucki et al. GW and ICU hospitalization unit costs	CHF 94'941	27.8	CHF 3'420
RSVpreF unit cost CHF 100 decrease (CHF 107.53)	-CHF 2'186'770	27.8	-CHF 78'768 (Dominant)
RSVpreF unit cost CHF 100 increase (CHF 307.53)	CHF 3'047'219	27.8	CHF 109'762
RSVpreF unit cost 10% decrease (CHF 186.77)	-CHF 112'870	27.8	-CHF 4'066 (Dominant)
RSVpreF unit cost 25% decrease (CHF 155.64)	-CHF 927'512	27.8	-CHF 33'409 (Dominant)
RSVpreF unit cost 50% decrease (CHF 103.76)	-CHF 2'285'247	27.8	-CHF 82'315 (Dominant)
RSVpreF unit cost 75% decrease (CHF 51.88)	-CHF 3'642'983	27.8	-CHF 131'221 (Dominant)
RSVpreF unit cost 90% decrease (CHF 20.75)	-CHF 4'457'625	27.8	-CHF 160'565 (Dominant)

Abbreviations

GW = general ward, ICER = incremental cost-effectiveness ratio, ICU = intensive care unit, QALY = quality-adjusted life year, RSV = respiratory syncytial virus.

As indicated in Table 69, RSVpreF increases total QALYs in all scenarios when compared with no RSV prophylaxis. When compared with the base case outcomes, 4 scenarios result in an increase in incremental costs for RSVpreF compared with no RSV prophylaxis:

– Discount rate (costs and QALYs): 5%

– Treatment waning: instant equivalence

– RSVpreF coverage rate: 75%

– RSVpreF unit cost CHF 100 increase (CHF 307.53)

In all other scenarios, incremental costs for RSVpreF decrease. Furthermore, in 7 of the scenarios considered, incremental costs become negative. Given that RSVpreF also increases total QALYs in these scenarios, the ICER should be interpreted as dominant compared with no RSV prophylaxis (i.e. RSVpreF reduces total costs and increases total QALYs). The scenario in which an increased rate of hospitalizations is adopted (see Table 47) is the scenario which results in the most favorable outcomes for RSVpreF compared with no RSV prophylaxis.

9.2 Budget Impact Analysis

9.2.1 Base case results

Illustrative results from a Swiss healthcare payers' perspective are presented in Table 70. The outcomes presented compare 2 scenarios – a scenario with all 3 treatment strategies considered (budget with RSVpreF) and a scenario with only nirsevimab and no RSV prophylaxis considered (budget without RSVpreF).

In the base case analysis, the introduction of RSVpreF in the eligible population (38'580 live births per year) results in a cumulative cost of CHF 94'085'187, based on the market shares adopted for each RSV prophylaxis strategy presented in Table 58 and Table 59. These market shares result in a cumulative incremental budget impact of -CHF 14'832'734 over a 5-year period.

Table 70: Cumulative total budget impact

Year	Budget with RSVpreF	Budget without RSVpreF	Net budget impact
Year 1	CHF 19'130'554	CHF 20'825'383	-CHF 1'694'829
Year 2	CHF 38'286'557	CHF 42'249'641	-CHF 3'963'084
Year 3	CHF 56'869'134	CHF 64'272'776	-CHF 7'403'642
Year 4	CHF 75'477'161	CHF 86'295'910	-CHF 10'818'750
Year 5	CHF 94'085'187	CHF 108'917'921	-CHF 14'832'734

9.2.2 Scenario analyses

The BIA scenario analyses results, over a 5-year time horizon, are presented in Table 71. In all scenarios considered, the adoption of RSVpreF results in a decrease in total expenditure over a 5-year period. The scenario in which the unit cost of RSVpreF is decreased by 90% is the scenario that results in the largest decrease in overall costs. Furthermore, when compared with the base case

outcomes, the scenario in which the unit cost of RSVpreF is increased by CHF 100.00 (to CHF 307.53) is the scenario that results in the least favorable outcomes for the adoption of RSVpreF. However, the net budget impact is still negative (-CHF 9’238’614).

Table 71: Cumulative net budget impact by scenario

Scenario	Budget with RSVpreF	Budget without RSVpreF	Net budget impact
Base case analysis	CHF 94’085’187	CHF 108’917’921	-CHF 14’832’734
Treatment waning: instant equivalence	CHF 94’301’260	CHF 109’183’724	-CHF 14’882’464
Treatment waning: 12 months	CHF 93’570’402	CHF 108’326’502	-CHF 14’756’100
Increased market shares of RSVpreF by 10%	CHF 89’515’113	CHF 108’917’921	-CHF 19’402’808
Increased baseline hospitalization rate	CHF 127’164’809	CHF 141’192’545	-CHF 14’027’736
Stucki et al. GW and ICU hospitalization unit costs	CHF 95’410’991	CHF 110’192’131	-CHF 14’781’140
RSVpreF unit cost: CHF 107.53	CHF 88’491’068	CHF 108’917’921	-CHF 20’426’853
RSVpreF unit cost: CHF 307.53	CHF 99’679’307	CHF 108’917’921	-CHF 9’238’614
RSVpreF unit cost 10% decrease (CHF 186.77)	CHF 92’924’262	CHF 108’917’921	-CHF 15’993’659
RSVpreF unit cost 25% decrease (CHF 155.64)	CHF 91’182’875	CHF 108’917’921	-CHF 17’735’046
RSVpreF unit cost 50% decrease (CHF 103.76)	CHF 88’280’562	CHF 108’917’921	-CHF 20’637’359
RSVpreF unit cost 75% decrease (CHF 51.88)	CHF 85’378’250	CHF 108’917’921	-CHF 23’539’671
RSVpreF unit cost 90% decrease (CHF 20.75)	CHF 83’636’862	CHF 108’917’921	-CHF 25’281’059

Abbreviations

GW = general ward, ICU = intensive care unit.

10. Discussion

Nirsevimab was approved and reimbursed in Switzerland in September 2024 for use in newborns and infants in their first RSV season (as well as children with certain risk factors in their second RSV season).[98] In August 2024, RSVpreF was also approved in Switzerland for use in pregnant women to protect newborns and is recommended for women between the 32nd and 36th week of pregnancy between October and February.[98] While RSVpreF is not currently reimbursed by the Swiss mandatory health insurance, this is under review.[98]

10.1 Rapid Systematic Review

The rapid systematic review set out to summarize the clinical and cost effectiveness of prophylaxis with nirsevimab in neonates or vaccination with RSVpreF in pregnant women and infants.

The review of clinical evidence identified 4 trials evaluating the safety and efficacy of nirsevimab in infants (3 comparing to placebo[75, 77, 79] and one to no intervention)[76] and 2 trials comparing maternal vaccination with RSVpreF to placebo.[78, 80] No RCTs comparing nirsevimab to RSVpreF were identified.

The 6 trials were generally favorable towards both nirsevimab and RSVpreF. Both RSVpreF vaccination and nirsevimab prophylaxis appear to be safe and effective when compared with placebo or standard of care. However, all 6 trials had moderate or high risk of bias, which limits confidence in these results. For all but 2 outcomes, the trials also failed to report whether differences against the comparator arm were statistically significant. This is particularly true for safety outcomes (for which statistical significance was not reported by any trial) and trials of RSVpreF (neither of these trials reported statistical significance for any outcome).

Efficacy was assessed in infants, regardless of whether the study drug was administered to infants (the 4 trials of nirsevimab)[75-77, 79] or pregnant women (both trials of RSVpreF).[78, 80] Safety was assessed in the treated population, i.e. infants[75-77, 79] or both infants and mothers.[78, 80] No included trials reported evidence for treatment coverage, emergency room visits associated with RSV or PC visits related to RSV.

10.1.1 Summary of main results

The most commonly reported efficacy outcomes were hospitalization due to RSV LRTI (reported by 5 RCTs)[76-80] and medically attended RSV LRTI (reported by 4 RCTs).[77-80] However, not all trials calculated or reported the statistical significance of efficacy findings.

The only outcomes for which any trials reported statistical significance were rates of medically attended, RSV-confirmed LRTI, and rates of hospitalization due to RSV-confirmed LRTI. Nirsevimab was statistically significantly better than placebo for preventing medically attended, RSV-confirmed LRTI and hospitalization due to RSV LRTIs. Nirsevimab also appeared numerically better than placebo for preventing all-cause LRTI hospitalization, ICU admission for medically attended RSV LRTI,

mechanical ventilation related to RSV, all-cause medically attended LRTI, overall TRAEs, overall serious AEs, and death. The key outlier to these general trends was Domachowske (2018).[75] However, as discussed in Section 7.2.3, this trial was small, unbalanced, and is likely to have been subject to bias.

The trial evidence suggests that RSVpreF and nirsevimab were both safe and well tolerated. Rates of TRAEs were generally low; 2 nirsevimab trials[77 79] reported similar rates across arms (2.3% and 1% in the nirsevimab arms, and 2.1% and 1.4% in the respective placebo arms), while a third[76] reported higher TRAE rates in the nirsevimab (2.1%) than no intervention (0%) arm. The 2 RSVpreF trials reported no TRAEs in infants and up to 0.4% in maternal participants. RSVpreF appeared numerically better than placebo for preventing medically attended RSV LRTI, overall severe adverse events, and death. The evidence was more mixed for other safety outcomes; this was impacted by the smaller of the two RSVpreF trials (Simões 2022),[80] which contained 4 arms (evaluating 3 different doses of RSVpreF). The relative safety performance of RSVpreF in this trial differed by arm, with higher doses generally resulting in more adverse events. However, it remains unknown whether these numeric differences in safety outcomes constitute real effects or are explainable by chance (not statistically significant).

Fear of AEs for both fetus and baby were reported as barriers to vaccination uptake during pregnancy.[115] Therefore, AEs relating to premature labor, premature delivery, premature baby or fetal death were extracted. However, these outcomes were too poorly reported to draw any meaningful conclusions. It remained beyond the scope of the review to evaluate every individual AE reported.

All-cause mortality after nirsevimab treatment was low, ranging from 0% to 0.3% in the nirsevimab arms and 0% to 0.6% in the placebo arms (no statistical significance reported by any trials). No cases of treatment-related mortality in infants occurred in the 2 nirsevimab trials reporting this outcome.[77, 79] Simões 2022 also reported that all-cause maternal mortality up to 12 months after vaccination was zero in all groups.[80] Infant mortality following RSVpreF was also low, with one trial reporting no cases of death (all-cause), and the other a numerically higher mortality in the placebo arm (0.3% in the placebo arm; 0.1% in the RSVpreF arm). Neither RSVpreF trial reported statistical significance in infant mortality or explicitly reported treatment-related mortality.

10.1.2 Completeness and applicability of the evidence (external validity)

None of the studies were conducted in Switzerland. However, all included trials evaluated a population relevant to the Swiss setting: infants ≤12 months of age and entering their first RSV season or women between the 24th and 36th week of pregnancy. No subgroups of interest were highlighted in the review protocol and there are no obvious gaps in the data to indicate the exclusion of relevant participants. Studies on both interventions of interest were identified, though twice as many nirsevimab trials were identified than RSVpreF trials, and no trials directly compared nirsevimab to RSVpreF.

The evidence base is predominantly composed of large trials (5 RCTs randomizing over 500 participants, and 2 randomizing over 7'000 participants), which increases confidence in the precision of results. All trials were also multinational, recruiting participants from between 3 and 23 countries. Although none of the trials were conducted in Switzerland, all but 2[75, 80] included at least one European country.

Evidence gaps were identified for treatment coverage, emergency room visits associated with RSV, and PC visits associated with RSV, which were not investigated by any included trial.

Nirsevimab and RSVpreF are intended to provide protection for infants up to 6 months after birth,[116, 117] and the included trials correspondingly measured efficacy outcomes at up to 12 months following intervention. Safety outcomes were also measured at timepoints of up to 12 months – with the exception of MATISSE, which reported AEs of special interest, serious AEs, and newly diagnosed chronic medical conditions following RSVpreF for up to 24 months after birth.[78]

The 4 nirsevimab trials were heterogeneous in their recruited populations, particularly in terms of gestational age at birth. Although this made it difficult to draw comparisons across the included trials, the overall trend of the results was consistent across trials, finding that efficacy and safety were generally more favorable in the nirsevimab arms. Confidence in the certainty of true effects is reduced due to the scarcity of testing for statistical significance. However, the consistency in findings across the varying nirsevimab populations indicates that the results are generalizable across the breadth of these populations.

Three otherwise eligible trials were excluded at full text review as "ongoing trials without published results" (as reported in Section 1.2 of Appendix A). These include one RCT of nirsevimab versus placebo, reported in 2 trial records,[118, 119] one RCT evaluating RSVpreF versus placebo specifically in women with HIV,[120] and one multi-arm trial comparing RSVpreF with nirsevimab with combination RSVpreF and nirsevimab.[121] Available records indicate that none are likely to fill existing evidence gaps for efficacy outcomes. The direct comparison of nirsevimab with RSVpreF[121] and the placebo-controlled RSVpreF RCT[120] will report safety outcomes and serum concentrations. The placebo-controlled nirsevimab RCT will add to the evidence base for efficacy and safety outcomes addressed by this review.

10.1.3 Strengths and limitations of the included trials (internal validity)

Included trials were all judged to be at either a moderate (4)[77, 79] or high (2)[75, 76, 78, 80] risk of bias. Reporting of the methods for conducting randomization and allocation concealment was generally poor, increasing the risk of selection bias and subsequent imbalances in patient populations at baseline. This was most evident in Domachowske (2018),[75] which contained unbalanced patient numbers and baseline characteristics across the 4 arms.

While the majority of the trials were large, other concerns about the available evidence limit the reliability of the results. None of the 6 trials assessed statistical significance for the majority of reported efficacy outcomes, nor assessed statistical significance for any safety or mortality outcomes.

One trial was not placebo controlled and did not blind participants to the interventions being provided (HARMONIE,[76] which compared nirsevimab with no intervention); this was considered to introduce the risk of ascertainment bias. Ascertainment bias particularly applies to the reporting of adverse events because knowledge of receiving the treatment could influence the perception and experience of these outcomes. The trial's efficacy results did appear to be broadly consistent with those of the blinded nirsevimab trials, but the reported results numerically favored placebo for safety outcomes (overall TRAEs and medically attended adverse events). This was particularly true for TRAEs, which were reported by 86 (2.1%) participants receiving nirsevimab versus none receiving no treatment. Despite this, no apparent difference was found for serious TRAEs. It should be noted that there is low confidence in the safety results for this trial given the lack of blinding, placebo control, and testing of statistically significant differences between arms.

10.1.4 Comparison with other reviews

The searches identified 5 relevant systematic reviews published since 2021 assessing nirsevimab[70, 122-125] and 4 assessing RSVpreF.[67, 68, 126, 127] When these reviews were checked for eligible studies to include in our review, no additional studies were identified. The conclusions of these earlier reviews were consistent with those of the current review: both nirsevimab and RSVpreF were found to be effective, with caveats that further research should be conducted to improve confidence in these conclusions.

Of the 5 systematic reviews identified that evaluated nirsevimab, 3 were focused specifically on nirsevimab[70, 122, 123] and 2 evaluated any monoclonal antibody, including nirsevimab[124, 125]. Three were systematic reviews of RCTs (including one meta-analysis[70] and one network meta-analysis)[125] evaluating the efficacy and safety of nirsevimab[70] (or any monoclonal antibody[124, 125]). Sun et al. (2023) identified 3 monoclonal antibodies (nirsevimab, motavizumab and palivizumab) to be potentially beneficial in the prevention of RSV without a significant increase in AEs over the comparator arm.[125] However, Sun et al. (2023) also highlighted that further evidence was needed to confirm these conclusions.[125] Sevendal et al. (2024) reported nirsevimab and clesrovimab to be the most promising monoclonal antibodies,[124] while Turalde-Mapili et al. (2023) reported that nirsevimab had the potential to prevent RSV infections and hospitalization with no significant differences from the comparator arm in AEs leading to death or AEs of special interest.[70]

The 2 other systematic reviews of nirsevimab included both RCTs and observational data. One was a review by Canada's Drug Agency (CDA-AMC, formerly CADTH) to inform decision making on nirsevimab in the upcoming influenza season. The review concluded that nirsevimab should potentially be given to infants at high-risk of RSV in the upcoming season, although the results of a more comprehensive review are awaited.[122] The final nirsevimab review aimed to evaluate the efficacy of nirsevimab, and reported that nirsevimab was potentially effective in preventing hospital admissions due to lower-respiratory tract diseases, but that further analyses are needed.[123]

Four systematic reviews were identified that evaluated RSVpreF,[67, 68, 126, 127] with all 4 limited to RCTs (including one Cochrane review[67]) evaluating the efficacy and safety of any RSV vaccination during

pregnancy (one also included studies in older non-pregnant adults[127]). All reported positive findings for the safety and efficacy of RSV vaccination in pregnancy, but 2[67, 126] advised caution in decision-making due to the limitations of the available evidence.

Unlike the current review, no existing review reported results separately for RSVpreF. However, the generally positive conclusions in reviews of both RSVpreF and nirsevimab, as well as some concerns about the certainties of the evidence, are consistent with the findings of the current review.

10.1.5 Strengths and limitations of our review

While this was a rapid systematic review, it was conducted in accordance with the principles of systematic reviewing embodied in the Cochrane handbook[62] and guidance published by the Centre for Reviews and Dissemination (CRD).[63] This included the creation of an a priori protocol that guided all subsequent phases of the review.

Consistent with rapid review methods, both trial selection and data extraction were conducted by a single reviewer. This raises the risk of eligible trials being missed or eligible data points not being extracted from included trials. This risk was mitigated by the use of a second reviewer to check a 10% sample of screening decisions and 10% of data points during data extraction.

There were no limits on date or language in this review. However, trials published as conference abstracts only were not eligible. While this increases the risk of missing an as-yet unpublished trial, conference abstracts typically report very limited data, and it is, therefore, unlikely that these sources would be reported in sufficient detail to enable comparison with trials reported in full peer-reviewed publications. Ongoing trials were identified via searches of clinical trial databases.

10.1.6 Recommendations for research

The existing evidence suggests that both nirsevimab and RSVpreF are effective in reducing RSV related outcomes in infants. However, the magnitude of these effects cannot be determined due to a common lack of testing for the statistical significance of outcomes. Future trials should conduct statistical testing to estimate the magnitude and statistical significance of any differences between vaccination and placebo. Furthermore, AEs (particularly those relating to pregnancy outcomes) should be much more clearly and explicitly reported in future studies. The comparative efficacy and safety of nirsevimab and RSVpreF should also be directly assessed.

10.2 Cost-Effectiveness Model

10.2.1 Comparison with nirsevimab

The cost-effectiveness analysis deterministic base case indicates that RSVpreF reduces both total costs and total QALYs resulting in an ICER of CHF 538'075 per QALY lost. Furthermore, because RSVpreF reduces both costs and QALYs, RSVpreF lies in the south-west quadrant of the cost-effectiveness plane when compared with nirsevimab. A higher ICER indicates that RSVpreF is more cost effective.

In terms of clinical outcomes, RSVpreF increases the total number of RSV infections resulting in healthcare-seeking behavior (6’650 vs 4’876) and, as such, increases the total healthcare expenditure required to treat RSV infections. However, the reduction in treatment and administration costs results in RSVpreF decreasing overall costs (Table 62). In particular, the unit cost of RSVpreF is substantially lower than nirsevimab (CHF 207.53 vs CHF 395.60). Furthermore, all individuals receiving nirsevimab are subject to an administration cost of CHF 150.00 compared with no administration cost applied to individuals receiving RSVpreF. The reduction in total QALYs for RSVpreF compared with nirsevimab is a direct consequence of lower efficacy against RSV infections and the resulting increase in RSV infections experienced for individuals receiving RSVpreF compared with nirsevimab (Table 64).

DSA indicates that RSVpreF is associated with cost reductions in all analyses undertaken. For example, RSVpreF is still cost saving when the low unit cost value for nirsevimab is adopted (CHF 297). The least favorable outcomes for RSVpreF are produced in a scenario with an increased baseline rate of RSV infections requiring hospitalization. This is due to an increase in the incremental increase of RSV-associated hospitalizations for RSVpreF compared with nirsevimab and the resulting impact on healthcare costs and HRQoL.

When the model was run probabilistically, RSVpreF is cost effective in approximately 100% of PSA iterations across all feasible cost-effectiveness threshold values, cost saving in 100% of iterations, and QALY-increasing in 6.4% of iterations.

In summary, when compared with nirsevimab, the cost-effectiveness analysis indicates that the reduction in QALYs observed with RSVpreF is compensated by the accompanying reduction in healthcare expenditure. Equivalently, the increase in QALYs estimated by adopting nirsevimab over RSVpreF does not outweigh the increase in costs, which is an outcome highly robust to all cost-effectiveness threshold values adopted and the sensitivity analysis conducted.

10.2.2 Comparison with no RSV prophylaxis

The cost-effectiveness analysis deterministic base case indicates that RSVpreF increases both total costs and total QALYs resulting in an ICER of 15'497 per QALY gained.

In terms of clinical outcomes, RSVpreF decreases the total number of RSV infections resulting in healthcare-seeking behavior (6’650 vs 9’093). Therefore, RSVpreF decreases the total healthcare expenditure required to treat RSV infections. However, the increase in treatment costs results in RSVpreF increasing overall costs (Table 63). This because individuals receiving no RSV prophylaxis are subject to no treatment costs compared with individuals receiving RSVpreF, which costs CHF 207.53. The increase in total QALYs for RSVpreF compared with no RSV prophylaxis is a direct consequence of higher efficacy against RSV infections and the resulting decrease in RSV infections experienced for individuals receiving RSVpreF compared with no RSV prophylaxis (Table 65).

DSA indicates that the conclusion that RSVpreF increases costs compared with no RSV prophylaxis is robust to almost all values considered in the analysis. Parameters that result in RSVpreF

decreasing costs compared with no RSV prophylaxis include changing the proportion of hospitalizations requiring an ICU admission to a high value, the RSVpreF vaccine unit cost to a low value, the unit cost of an ICU episode to a high value, and the unit cost of a GW episode to a high value. Furthermore, the scenario analyses presented in Table 69 indicate that RSVpreF increases QALYs in all scenarios compared with no RSV prophylaxis. Four scenarios result in a marginal increase in incremental costs for RSVpreF and 7 scenarios result in incremental costs becoming negative; this would result in the ICER for RSVpreF becoming dominant compared with no RSV prophylaxis.

When the model is run probabilistically, an increase in the value of the cost-effectiveness threshold value adopted increases the number of iterations that RSVpreF is cost effective. This is because more value is placed on the health outcome gained with RSVpreF treatment compared with no RSV prophylaxis. For example, RSVpreF is cost effective in 80.0% and 100.0% of iterations when adopting a threshold value of CHF 50’000 and CHF 200’000, respectively. Furthermore, RSVpreF is cost saving and QALY-increasing in 27.8% and 100.0% of iterations, respectively.

In summary, when compared with no RSV prophylaxis, the cost-effectiveness analysis indicates that the increase in costs associated with RSVpreF is likely to be outweighed by the accompanying reduction in RSV infections resulting in less healthcare-seeking behavior and a subsequent increase in HRQoL. This conclusion is more likely to be true when higher values of the cost-effectiveness threshold value are adopted, and the sensitivity analysis conducted indicates that model outcomes are robust to the scenarios considered.

10.2.3 Strengths and limitations

The robust model structure is a major strength of this cost-effectiveness model. The structure aligns with the models identified from the rapid systematic literature review and allows for the direct implementation of efficacy data from the key MATISSE clinical trial for RSVpreF and the MELODY and HARMONIE clinical trials for nirsevimab.

This is the first model to estimate the cost effectiveness of vaccination against RSV from a Swiss healthcare payers’ perspective. The number of births, baseline rate of RSV-associated hospitalizations, and unit costs associated with RSV-related healthcare resources were informed by Swiss-specific data. The model is, therefore, generalizable to a Swiss setting.

The primary limitations associated with the modelling approach are related to the assumptions that were necessary due to data limitations. However, all key assumptions were validated by a clinical expert.

The model does not consider the effects of vaccinations on disease transmission and herd immunity because a static modelling approach was used. This static modelling approach was considered preferable over a dynamic transmission model because it allowed the essential consequences of each strategy to be captured without the additional data requirements, additional complexity, and potential uncertainty of a transmission model. Therefore, the cost effectiveness of the prophylactic treatments may be underestimated. The model did also not consider that maternal immunization with RSVpreF

could prevent RSV in mothers, which may further underestimate the benefits associated with RSVpreF.

It was not possible to model risk-group-specific subgroups (for example, people with comorbidities, by term status or weight) because of a lack of baseline RSV infection rates for each reference category and efficacy data stratified by subgroup. The feasibility of different immunization programs to deliver the vaccinations seasonally was also not considered because this was deemed out of scope by the FOPH. Furthermore, MATISSE was not powered to provide estimates of efficacy for late preterm individuals. Therefore, it was assumed that vaccine efficacy for late preterm individuals was equal to 83.3% of the efficacy for full term individuals; this was the approach adopted by Alvarez et al. (2024) and informed by a study of antibody transplacental transfer.[81] This was a necessary assumption, and the clinical expert confirmed that the approach was reasonable.

It was also necessary to seek input from the clinical expert regarding the assumption about the long-term efficacy and subsequent treatment waning associated with the RSVpreF and nirsevimab programs because data were only available for 6 months for RSVpreF and between 5 and 6 months for nirsevimab. In the base case, it was assumed that treatment efficacy waned linearly to 0% by age 9 to 10 months and it was not certain whether a scenario of instant equivalence with no RSV prophylaxis or a longer period of treatment waning would be more reflective of clinical practice. However, as shown by the scenario analyses conducted in

Table 68 and Table 69, the impact of adopting alternative waning assumptions on model outcomes was relatively marginal. This result was due to the months that treatment waning determined the efficacy of each prophylactic treatment generally falling outside of the RSV season at which point the baseline incidence of RSV was much lower (Table 49).

While the model was populated with Swiss-specific data where possible, data to inform the baseline incidence of RSV-related PC visits and ED visits in Switzerland were not available. Therefore, these inputs were informed by a Spanish source, which may not be directly generalizable to the Swiss population. Furthermore, the incidence of RSV is likely to have been underestimated because there will be many cases of RSV that are not identified. Healthcare resource use providers are not required to treat all cases of RSV infections (i.e. asymptomatic or mild cases) and, therefore, these cases will not be recorded. It was also assumed that individuals could only experience one RSV infection over the model time horizon and could not have re-visits to healthcare institutions. However, it should be recognized that the impact of several of the necessary assumptions and alternative sources of data on model outcomes was assessed during the sensitivity analyses and outcomes remained highly robust.

The model does not capture the long-term implications of preventing RSV infections because the time horizon was restricted to one year; this was due to the uncertainty in outcomes associated with a longer time horizon.

The model did not consider that RSVpreF and nirsevimab may have longer-term side effects on newborns. However, these will not be known until large-scale implementation, and there are no

data to model the implications of longer-term side effects. The model also does not capture the potential direct effects of immunization on RSV among vaccinated pregnant women because these people do not fall under the modelled population.

The model did not consider how a reduction in cases of RSV could impact the incidence of other seasonal respiratory diseases, such as Streptococcus pneumoniae. An RSV infection could increase the risk of this disease and, therefore, the prophylactic treatment programs could also reduce other diseases. The model also did not consider long-term sequelae of RSV (i.e. secondary bacterial infections, subsequent respiratory infections, recurrent wheezing, worsening of chronic lung disease among preterm infants, exacerbation of congenital heart disease, and asthma), which may result in additional healthcare resource use and productivity loss. Consequently, the cost-effectiveness of both prophylactic treatment programs may be underestimated.

The anticipated coverage rates associated with both RSVpreF and nirsevimab are uncertain. Furthermore, the RSVpreF vaccine is recommended in the third trimester of pregnancy. This may lead to a proportion of preterm birth mothers not receiving the vaccine before the birth or in time for effective transplacental antibody transfer. Therefore, a lower coverage was assumed in scenario analyses.

There are limitations associated with the utility data used in the model. It is not possible to estimate the general population mortality of newborns and, therefore, this was assumed to be equal to a value of one. It was also not possible to identify Swiss-specific utility data. However, the face validity of the QALY loss estimates, for each RSV infection considered in the model, was confirmed by the consulted clinical expert.

Finally, as per guidance from the FOPH, the model did not consider further monoclonal antibodies such as palivizumab.

10.3 Budget Impact Model

The base results suggest that the adoption of RSVpreF will reduce overall costs over a 5-year time horizon. The model estimates that 5 years after the introduction of RSVpreF into the eligible population the decrease in cumulative costs would be equal to CHF 14’832’734. Furthermore, the outcome that the adoption of RSVpreF is cost saving is consistent in each scenario analysis considered. There is also an increase in the amount of cost savings estimated in scenarios where the unit cost of RSVpreF is decreased. When the unit cost of RSVpreF is increased by CHF 100.00 to CHF 307.53, the BIA still estimates 5-year cost savings of CHF 9’238’614.

The reduction in costs is predominately a result of fewer individuals receiving nirsevimab and an increase in individuals receiving RSVpreF. As indicated by the results of the cost-effectiveness analysis (Section 10.2), RSVpreF reduces costs compared with nirsevimab. Therefore, in the scenario that does not adopt RSVpreF, a greater number of individuals receive nirsevimab. This leads to an increase in total costs compared with the scenario that adopts RSVpreF.

In addition to the limitations discussed in Section 10.2, it was necessary to make several assumptions when designing and populating the BIA. It was assumed that all women who received the RSVpreF vaccination would birth a live newborn. Therefore, the total annual eligible population may be slightly overestimated. There are also uncertainties associated with the market share inputs included in the BIA, which means the analyses presented in the report should be interpreted with caution.

11. Conclusion

The rapid systematic literature review included 6 trials, all of which suggest that both nirsevimab and RSVpreF are safe and effective in preventing RSV-related outcomes in infants. However, several factors limit the certainty of this evidence and confidence in subsequent conclusions. These factors include the lack of statistical significance testing for outcomes (particularly for safety data), the moderate-to-high risk of bias in all included trials, and the relatively small size and high risk of bias of one of the nirsevimab trials.

The cost-effectiveness analysis estimates that RSVpreF increases the number of RSV infections and decreases costs and QALYs when compared with nirsevimab. The PSA estimates that RSVpreF reduces costs by CHF 9'878'738 and QALYs by 18.4, which results in an ICER of CHF 536'008 per QALY lost. RSVpreF is cost effective in approximately 100.0% of PSA iterations across all adopted cost-effectiveness threshold values, QALY-increasing in 6.4% of iterations, and cost saving in 100.0% of iterations.

Outcomes for RSVpreF compared with nirsevimab are robust to the sensitivity analysis conducted. As RSVpreF increases the number of RSV infections, any scenario that increases the consequence or likelihood of experiencing an RSV infection (i.e. more expensive hospitalization unit costs and an increased baseline rate of RSV-associated hospitalizations) leads to less favorable outcomes for RSVpreF. However, when adopting the highest cost-effectiveness threshold value considered in this analysis (CHF 200’000), the ICER for these scenarios are still cost effective.

When compared with no RSV prophylaxis, RSVpreF reduces the number of RSV infections and increases costs and QALYs. The PSA estimates that RSVpreF increases costs by CHF 470'441 and QALYs by 27.1, which results in an ICER of CHF 17'377 per QALY gained. The percentage of cost-effective iterations for RSVpreF increases as the adopted value of the cost-effectiveness value increases (i.e. 80.0% at CHF 50’000 and 100.0% at CHF 200’000). The percentage of QALY-increasing and cost-saving iterations is equal to 100.0% and 27.8%, respectively.

Outcomes for RSVpreF compared with no RSV prophylaxis are robust to the sensitivity analysis conducted. As RSVpreF decreases the number of RSV infections, any scenario which increases the consequence or likelihood of experiencing an RSV infection (i.e. more expensive hospitalization unit costs and an increased baseline rate of RSV-associated hospitalizations) leads to more favorable outcomes for RSVpreF.

The BIA analysis estimates that adopting RSVpreF would reduce cumulative total costs over a 5-year time horizon by CHF 14’832’734. The conclusion that adopting RSVpreF reduces total costs is an outcome that is robust to all scenarios considered and predominantly driven by fewer people receiving nirsevimab and an increase in the number of individuals receiving RSVpreF.

12. References

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