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COST-EFFECTIVENESS OF ABRYSVO® AND BEYFORTUS® AGAINST RSV INFECTIONS IN BELGIAN INFANTS

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
95%CI	95% confidence interval
95%CrI	95% credible interval
AE	Adverse event
aHR	Adjusted hazard ratio
AMB	Ambulatory care
AMSTAR	A measurement tool to assess systematic reviews
aOR	Adjusted odds ratio
ARD	Absolute risk difference
ARI	Acute respiratory illness
BE	Belgium
BIA	Budget impact analysis
CEA	Cost-effectiveness analysis
CHD	Chronic heart disease
CI	Confidence interval
CLD	Chronic lung diseases
CPI	Consumer price index
CrI	Credible interval
CUA	Cost-utility analysis
ED	Emergency department
EMA	European medicines agency
ENL	Expected net loss
EQ-5D-5L	Euroqol's 5-level EQ-5D instrument
EUR	Euro
EVPI	Expected value for perfect information
EVPPI	Expected value for partially perfect information
GP	General practitioner
HC	Health care
hCFR	In-hospital case-fatality ratio
HCP	Health care payers
ICD	International Classification of Diseases
IHI	Innovative Health Initiative
IM	Intramuscular
IQR	Interquartile ratio

IRQ	Interquartile range
ITT	Intention-to-treat
Kg	Kilogram
Lab	Laboratory
LoS	Length of stay
LRTI	Lower respiratory tract infections
MA	Medically attended
mAb	Nirsevimab (Beyfortus®)
MV	Maternal vaccine
N	Number
Nab	Neutralising antibody
NIHDI	National Institute for Health and Disability Insurance
NNT	Number needed to treat
OECD	Organisation for Economic Co-operation and Development
OP	Outpatient
PCR	Polymerase Chain Reaction
(P)ICU	(paediatric) intensive care unit
PROMISE	Preparing for RSV immunisation and surveillance in Europe
PSA	Probabilistic sensitivity analysis
PY	Person-years
QALD	Quality-adjusted life day
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RESCEU	REspiratory Syncytial virus Consortium in EUrope
RoI	Return on investment
RRR	Relative risk reduction
RSV	Respiratory syncitial virus
RT PCR	Reverse transcription polymerase chain reaction
RTI	Respiratory tract infections
RW data	Real world data
RWE	Real-world evidence
SAE	Serious adverse event
SD	Standard deviation
SD	Standard deviation
SE	Standard error

SHC	Superior Health Council of Belgium
SOC	Standard of care
UK	United Kingdom
US	United States
VAS	Visual Analogue Scale
WHO	World Health Organization
WTP	Willingness-to-pay

SCIENTIFIC REPORT

1 BACKGROUND

1.1 Respiratory syncytial virus

Respiratory syncytial virus (RSV) infections in children, and particularly in infants (children <1 year) are a public health problem. First, their frequency is high. It is estimated that approximately 67% of infants experienced an RSV infection in the first year of life and 90% of children within the first 2 years of life.[1]

Second, they can result in serious disease episodes, such as bronchiolitis and pneumonia, requiring hospitalisation and, for a proportion of them, treatment in intensive care units (ICU). In high-income countries, the annual incidence rate of RSV-associated lower respiratory tract infections (LRTIs) is estimated at 24.3 (95%CI: 13.8-42.7) per 1000 children younger than 5 years and 38.5 (95%CI: 21.6-68.8) per 1000 infants.[2, 3] Hospitalisations for RSV-related LRTI occur in around 22.0 per 1000 infants (95%CI: 17.1-28.4), with the highest toll observed in the youngest ones, the hospitalisation rate being 34.7 per 1000 (95%CI: 21.5-56.2) in infants 0-3 months.[2]

Severe RSV infection can be lethal, and RSV is a leading cause of mortality in children worldwide, but the occurrence is rare in high-income countries. The in-hospital case fatality rate in high income countries is estimated at 0.1% (95%CI: 0.1-0.3) in infants.[2]

There is also suggestive evidence that early-life RSV-related LRTIs may predispose to recurrent LRTIs and asthma later in life, but more research is needed for confirmation and evaluation of the effect size.[4]

In Belgium, the burden of disease due to RSV is also high.[5] A retrospective analysis of the population-wide Belgian hospital discharge data set reported that in 2018 there were 8046 hospital episodes due to RSV in infants, corresponding to an incidence of 68.3 per 1000 infants (the incidence was 5 per 1000 in children 1-4 years), and 4 infants died during their hospitalisation.[6] Among very young infants (0-28 days of life), 15.9% of the 965 cases were admitted in an ICU (5.1% in children 1-4 years). The hospital admission rate observed in Belgium was upper or exceeded the typically reported rates in European countries of 20-40 per 1000 infants.[7]

RSV also bears organisational and financial consequences. Because most infections occur during a seasonal peak of 8-12 weeks, the healthcare system is heavily burdened at that time. In Belgium, about 45,000 inpatient bed days in 2018 were related to RSV infections or 300.6 and 19.3 days per 1000 children less than 1 year and 1-4 years of age, respectively, with 20%-40% of occupied paediatric beds due to RSV during the activity peak.[6] In 2018, the annual costs in Belgium associated with RSV hospitalisations of children under 3 years old were estimated to exceed €26 million from the health insurance perspective.[8] In the current study, we evaluated that the total medical costs (paid by the health care payers) to treat RSV in infants (<1 year) amounted to €30 million every year (€28 million for hospitalisations). More details on the epidemiology, burden of disease and costs related to RSV will be presented in chapter 4.

1.2 New tools for prevention

In recent years, two new preventive products directed against the preF protein of RSV A and B strains have become available for passive immunisation of infants and their protection against severe RSV infection. Both products were granted a marketing authorization from EMA.

1.2.1 Maternal vaccine Abrysvo®

Abrysvo® (Pfizer) is bivalent vaccine administered to pregnant women when the delivery is expected during the RSV season (usually from September to March inclusive). Pfizer's RSV preF vaccine contains 120 µg of stabilised prefusion RSV F glycoprotein from RSV A and RSV B strains (60 µg of each) in a lyophilised dosage form for reconstitution. There is no adjuvant. The neutralising antibodies cross the placenta, providing infants with protection up to 6 months after birth. The recommended dose is one single injection into the muscle of the upper arm.

A rapid review of the evidence carried out by KCE in December 2023 reported that, based on interim data, vaccine efficacy for severe medically assisted RSV related LRTI spanned from 81.8% (99.5%CI: 40.6-87.1) to 69.4% (97.6%CI: 44.3-84.1) within 90 days and 180 days of life, respectively (high quality evidence). RSV-associated hospitalisations were reduced by 67.7% (99%CI: 15.9-89.5) at 90 days and 56.8% (99%CI: 10.1-80.7) at 180 days (moderate quality evidence).[9] An updated review of the evidence will be presented in section 2.3.2.

Abrysvo® was granted a marketing authorization from EMA in August 2023 for the use in pregnant women between weeks 24 and 36 of gestation.[10]

1.2.2 Monoclonal antibody Beyfortus®

Nirsevimab (Beyfortus®, Sanofi) is an extended half live monoclonal antibody indicated for the prevention of RSV lower respiratory tract disease in neonates and infants during their first RSV season. A major advantage of nirsevimab over palivizumab (Synagis®, Sobi[a]), the only monoclonal antibody against RSV infection available so far, is that it only needs to be administered once (compared to one injection per month during 5 months for palivizumab). This single intramuscular injection (50 mg if body weight <5 kg; 100 mg if body weight >5 kg) is done either at birth for babies born during the RSV season, or in September for infants aged ≤6 months at the start of the RSV season.

A rapid review of the evidence and meta-analysis carried out by KCE in December 2023 reported that the efficacy against medically attended RSV-confirmed LRTI through 150 days was 75% (95%CI: 66-82), and efficacy against RSV-related hospitalisations was 79% (95%CI: 63-88) (high quality evidence).[11] An updated review of the evidence will be presented in section 2.3.1.

Beyfortus® was granted a marketing authorization from EMA in 2022.[12]

1.3 Belgian context

1.3.1 Recommendations for RSV prevention

In December 2023, the Superior Health Council, informed by the two KCE rapid reviews and in line with recommendations from other high-income countries,[13, 14] recommended to use either Abrysvo® or Beyfortus®. Administering both products is not indicated.

Abrysvo® is recommended for pregnant women being at 28 to 36 weeks of gestation, and expected to deliver between early September and end of March. For pregnant women expected to have a premature delivery or an inadequate immune response to vaccination (immunocompromised status) or decreased transplacental antibody transfer (people living with HIV infection or membrane diseases), the maternal vaccination may not be the best preventive option and the use of Beyfortus® should be favored.

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[a] The original producer of Synagis was AstraZeneca, but AstraZeneca divested the US rights to the drug to Swedish Orphan Biovitrum AB (Sobi) in January 2019.

Beyfortus® is recommended for all babies born from unvaccinated mothers or born prematurely (<30 weeks of gestation) or born within the two weeks following the vaccine administration.[1] These recommendations are in line with

Beyfortus® can be provided:

- At birth (maternity ward) for babies born during the RSV season (October to March) using a single dose of 50 mg (as <5 kg).
- During the regular immunization program (catch up) for those being ≤6 months old at the start of RSV season, using the dose of 50 mg if <5 kg, or 100 mg if >5 kg.

Beyfortus® can be administered with other vaccines.

In children at increased risk of severe RSV infection, Beyfortus should replace palizivumab considering its easier administration schedule and similar safety profile.[b] For these children, Beyfortus® can be given during their first RSV season until age of 11 months at start of the season and if the mother has not been vaccinated or has been vaccinated at the end of the season (January-March). It is also recommended during their second RSV season. The recommended dose is then 200 mg of nirsevimab, administered as two 100 mg injections given at the same time at different injection sites.

1.3.2 Belgian reimbursement rules

Since January 2025, Abrysvo® is reimbursed by INAMI/RIZIV if the reimbursement conditions are met, i.e. when delivery is expected during the RSV season (usually from September to March inclusive). Prior authorization from a medical advisor is required for reimbursement (Chapter IV – *ex ante control*[c]). The list price is €186.01 per dose.

Since May 1, 2024, Beyfortus® is reimbursed by INAMI/RIZIV if the reimbursement conditions are met (see Box 1). Prior authorization from a medical advisor is required for reimbursement in public pharmacies and in hospitals (Chapter IV – *ex ante control*[c]). The list price is €777.58 per dose (same price for Beyfortus® 50 mg or 100 mg). Note that the reimbursement of Beyfortus ® for full-term newborns and infants with a gestational age of 36 weeks or more is temporary (31 May 2026) within Article 111 agreement, i.e. the price is negotiated and lower than the list price, but the real price is not disclosed.

Textbox 1 – Reimbursement conditions of Beyfortus® set by INAMI/RIZIV[d]

- Nirsevimab-based pharmaceutical specialties, Beyfortus® 50 mg and 100 mg, have been included, since May 1, 2024, on the list of reimbursable pharmaceutical specialties under Section 12820100 (for premature newborns and infants) of Chapter IV, and since June 1, 2024, under Section 12820200 (for full-term newborns and infants) for the prevention of severe lower respiratory tract infections caused by respiratory syncytial virus (RSV)

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[b] Children at increased risk of severe RSV disease are children with chronic lung disease or prematurity who required medical support; hemodynamically significant congenital heart disease; immunocompromised states; Down syndrome; cystic fibrosis; neuromuscular disease; congenital airway anomalies.

[c] Drugs in Chapter IV are subject to particular reimbursement conditions and to *ex ante control*, i.e. the prior authorisation by the medical officer of the sickness fund. Restrictions for reimbursement are fixed for health safety reasons (e.g. anti-tuberculosis drugs restricted to tuberculosis patients to prevent resistance) and/or budgetary concern.

[d] Website of INAMI/RIZIV: reimbursement conditions of Beyfortus®

- Section 12820100: Final inclusion for reimbursement for passive immunisation of **premature newborns and infants** with a gestational age of less than 36 weeks. These criteria must be met:
  - The baby is less than 13 months old
  - The baby is experiencing his/her first RSV season
  - The monoclonal antibody is administered before the start of the RSV season, or at birth for infants **born during the current RSV season**
- Section 12820200: Temporary registration based on an Art. 111 agreement for passive immunisation of **full-term newborns and infants** with a gestational age of 36 weeks or more. These criteria must be met:
  - The baby is less than 13 months old
  - The baby is experiencing his/her first RSV season
  - The monoclonal antibody is administered before the start of the RSV season, or at birth for infants born during the current RSV season
  - The mother has not yet been vaccinated with the RSV vaccine. This condition does not apply if the **baby meets the specific conditions indicated by the Superior Health Council**

This temporary registration (under article 111) will end on 31 May 2026.

1.4 Research question

The objective of this research is to evaluate the efficacy, effectiveness, safety, cost-effectiveness and budget impact of Beyfortus® and Abrysvo® against RSV infections in Belgian infants.

This research question was initiated by the Flemish Department of Care (Departement Zorg), which needs the results of an independent economic evaluation before launching the 2025-2026 vaccination campaign. Indeed, in Belgium the competency for health policy is shared between the federal level and the federated entities, and vaccination programmes are mainly under the responsibility of the federated entities. The results of this study will also be relevant to the French- and German-speaking communities to assess the relevance of potentially promoting RSV prevention strategies in their vaccination calendar.

Moreover, the Superior Health Council had emphasised that its 2023 recommendations to use either Abrysvo® or Beyfortus® were temporary and should be updated when relevant data on cost-effectiveness are available. Moreover, additional efficacy and safety data have been published since 2023.

Lastly, the temporary registration of Beyfortus® for infants who are not at increased risk of severe RSV infection will end on 31 May 2026, and conditions of a possible reimbursement by INAMI/RIZIV will be re-discussed at that time.

Methods for the literature review on safety and efficacy of both products; for the evaluation of the quality of life (QoL) and the clinical and economic burden of RSV infections in Belgian children; and for the assessment of the cost-effectiveness and budget impact of RSV prevention strategies in Belgian infants are presented in the corresponding chapters.

This is a rapid HTA, i.e. ethical, organisational aspects, and population preferences were not investigated. This was due to the short time span of this project, as the results were expected for June 2025 at the latest to allow the decision makers organise the 2025-2026 immunisation campaign in due time.

2 SYSTEMATIC REVIEW ON THE EFFICACY AND SAFETY OF BEYFORTUS® AND ABRYSVO®

The present systematic review has been conducted with the objective to synthesise the current literature on the efficacy, effectiveness and safety of nirsevimab (Beyfortus®) and RSVpreF vaccine Abrysvo® in the prevention of RSV infection. The literature review was conducted in two stages with the aim to provide early insights for designing the health-economic model. The initial stage, conducted in October 2024, focused on gathering data on the efficacy/effectiveness, and safety of both molecules to inform the model's development. The subsequent phase, conducted in February 2025, was employed to supply updated evidence on the topic.

2.1 Efficacy, effectiveness and safety of Beyfortus®

KEY POINTS

- Current evidence indicates that nirsevimab is effective against RSV lower respiratory tract infection (LTRI) in both preterm and full-term infants:
  - A meta-analysis of two randomised controlled trials (RCTs) demonstrated a pooled efficacy of 75% (95%CI: 64-82) against medically-attended RSV-LRTI at 150 days (high certainty).
  - A meta-analysis of three RCTs demonstrated a pooled efficacy of 81% (95%CI: 71-87) against RSV-related hospitalisation at 5 to 6 months (high certainty).
  - The effect of nirsevimab on RSV-related mortality could not be reliably estimated due to the low number of observed events.
- Nirsevimab appears to be safe. No increase in adverse events was detected in the 3 RCTs:
  - A meta-analysis of 3 RCTs indicated no significant risk of serious adverse events (pooled risk estimate: 1.05; 95%CI: 0.92-1.19; high certainty), or grade 3 adverse events (pooled risk estimate: 0.94; 95%CI: 0.64-1.36; high certainty) at one year.
- Real-world data (20 included studies) have predominantly assessed the effectiveness of nirsevimab on RSV-related hospitalisations. Their follow-up generally covers a RSV season, and their results closely align with those reported in clinical trial settings. Overall, the quality of real-world studies is good, many of them having a test-negative case-control design:
  - A meta-analysis of 8 studies with an observation period >120 days during the RSV season indicated a pooled effectiveness of 87% (95%CI: 81-91) against RSV-related hospitalisation (moderate certainty). A meta-analysis stratifying results by study design (cohort and case-control designs) showed consistent results.
  - A meta-analysis of 4 studies with an observation period >120 days during the RSV season indicated a pooled effectiveness of 87% (95%CI: 77-93) against RSV-related paediatric intensive care unit admission (moderate certainty).
  - A meta-analysis of 5 studies indicated a pooled effectiveness of 79% (95%CI: 70-86) against emergency department visits (low certainty).
- The current literature reports few data on the safety of nirsevimab. Among these studies only one reported on safety aspects 3 days after injection. At this particular time point, there was no evidence of any safety concerns or adverse events associated with inpatient care. The most frequently reported symptoms were local reactions, fatigue and fever.

- Further research should investigate other impacts of nirsevimab, such as a reduction of long-term respiratory outcomes (asthma), potential emergence of resistance strains and emergence of other viruses causing bronchiolitis.

2.1.1 Methods

2.1.1.1 Search strategy: research questions and selection criteria

The review protocol was prospectively designed in accordance with the standard procedures used by the KCE[e] as well as the AMSTAR-2 guidance.[15] With regard to reporting, we adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guideline (PRISMA).[16]

The research questions were formulated as follows: "*What is the clinical effectiveness of nirsevimab against RSV-infection in children, compared to standard of care?*" and "*Is nirsevimab safe?*". Research questions were translated into a structured *PICOTS* (Participants-Intervention-Comparator-Outcomes-Timeframe-Study design) framework, as presented in Table 1. Only full articles published in English were included. This review is limited to studies conducted in OECD countries to strengthen the contextual relevance of the findings to Belgium. Studies that compared clinical outcomes before and after the introduction of nirsevimab were not considered. The articles were searched by one researcher. The initial screening of documents was performed using titles and abstracts, followed by a full-text review of the selected articles. All retrieved references were imported into EndNote 20, where duplicates were identified through the software's function, supplemented by manual verification after sorting by title.

Table 1 – Inclusion and exclusion criteria

PICOTS	Inclusion	Exclusion
Patients	Infants	
Intervention	Nirsevimab	
Comparators	• For the assessment of efficiency: placebo, or standard of care (including palivizumab) • For the assessment of safety: comparator not mandatory	No comparator /
Outcomes	**Reporting efficacy and safety data:** a. Critical outcomes: • RSV-related mortality • RSV-related ICU admission • RSV-related hospitalisation • Severe RSV-related lower respiratory tract illness (LRTI) • Serious adverse events b. Important outcomes: • RSV-related LRTI • Reactogenicity • Waning of protection • Adverse events	• Data modelisation including data without the use of nirsevimab • In-vitro data • Pharmacokinetics data
Timeframe	No limit	
Setting	Countries from OECD	Study with data exclusively from a country outside of OECD
Type of studies	• For the assessment of efficiency: RCT, observational studies, systematic reviews/meta-analysis*	• Case series, case report, letters, editorials, phase 1 trials, narrative reviews, comments, opinions

[e] http://processbook.kce.fgov.be/

	• For the assessment of safety: all study designs	• /
Language	English	

** As the literature on nirsevimab is rapidly evolving, systematic reviews/meta-analysis were considered to ensure than no study was omitted.*

2.1.1.2 Databases and data extraction

The following bibliographic databases were searched for relevant publications: Ovid-Medline, Embase, and The Cochrane Library. Search queries were developed in collaboration with a medical information specialist and adapted to each database. An initial search was conducted on October 23 (Ovid-Medline), 2024, October 25, 2024 (Embase), and December 19, 2024 (Cochrane). An update in each database was performed on February 20, 2025 (Ovid-Medline), February 22, 2025 (Embase) and February 21, 2025 (Cochrane). Search strategies for each database are available in Appendix 1.1. The database searches were complemented by the identification of additional references through various sources, including citation tracking and exploratory searches within the bibliographic databases of key references. The international clinical trials registry platform, *ClinicalTrials.gov*, was also consulted. Data from each study were extracted using a pre-defined extraction form. Initial data extraction was conducted by a single reviewer, with any discrepancies subsequently discussed and resolved in consultation with a second reviewer.

2.1.1.3 Methodological quality of the studies

The risk of bias for each study was assessed by one reviewer, and doubts resolved with another researcher. Risk of bias 2 tool (Rob-2[f]) was used for RCTs, while the SIGN grid[g] was used for cohort studies and case-control studies.

2.1.1.4 Data synthesis

A meta-analysis was conducted when at least two studies, deemed sufficiently comparable in terms of follow-up duration and risk of bias, were available for a given outcome. The numbers of participants exposed and unexposed to the study drug were extracted from each study, and event ratios were calculated based on the occurrence or absence of the outcome. Owing to the anticipated heterogeneity among the included studies, the Mantel-Haenszel method with a random-effects model was used, as implemented in *Review Manager® (RevMan) Version 5.3* (*Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014)*. This approach accounts for between-study variance, thereby yielding more conservative confidence intervals than those produced by a fixed-effects model. The efficacy, or the effectiveness of immunisation, was calculated for each pooled estimates as *[100% × (1-risk ratio)]* or *[100% × (1-odds ratio)]*, and confidence intervals as follows: *95%CI = [100% × (1-upper bound risk ratio); 100% × (1-lower bound risk ratio)] or [100% × (1-upper bound odds ratio); 100% × (1-lower bound odds ratio)].*

In addition, where applicable, a secondary analytical approach was applied, involving the pooling of the logarithms of adjusted odds ratios (or adjusted hazard ratios) using the inverse-variance method, with standard errors derived from the corresponding 95% confidence intervals[h] in order to meta-analyse estimates which were adjusted for confounding factors in the primary studies. Statistical heterogeneity among studies was assessed using Cochran's Q test and quantified with the I^2 statistic. A threshold of $p<0.05$ was used to determine statistical significance of the pooled estimates, and

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f https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials

g https://www.sign.ac.uk/using-our-guidelines/methodology/

h $Standard\ error\ (log\ (OR)) = \frac{\log(Upper\ bound\ 95\%\ confidence\ interval) - \log(Lower\ bound\ 95\%\ confidence\ interval)}{2 \times 1.96}$

p<0.10 for statistical significance for the test of Higgins (I^2). When a minimum of 8 to 10 studies was available, publication bias was evaluated through visual inspection of funnel plot asymmetry.

The quality of the pooled body of evidence was assessed by implementing the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) framework (i.e., study bias, indirectness, consistency, imprecision and publication bias) according to Cochrane recommendations.[17] The software GRADEpro® was used.

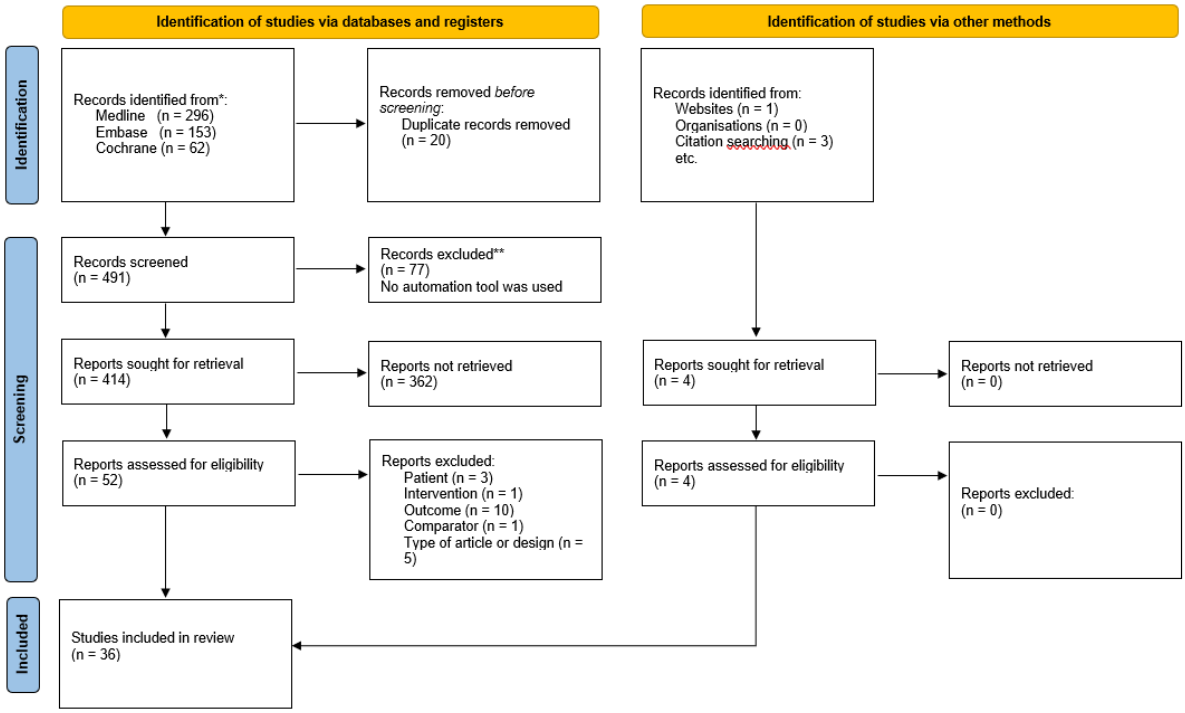
2.1.2 Results

2.1.2.1 Study selection

After removing duplicates, the search yielded 491 records. Following title and abstract screening, 52 articles were assessed for eligibility (Figure 1). A full-text review led to the exclusion of 20 articles. In addition to the 32 remaining studies, 4 more were identified through reference list searches and website screening, bringing the total number of included articles to 36. The list of excluded articles is available in Appendix 1.2. Among the included articles, we identified 6 RCTs, 11 case-control studies, 12 cohort studies, one ancillary study from a RCT, and one cross sectional study which was an online survey. In addition, 5 systematic reviews were identified, but were not included *per se* in the analysis[i].[18-22]

The analysis of RCTs, and the studies using real-world data is addressed in two separate sections (2.1.2.2 and 2.1.2.3).

Figure 1 – Prisma flow diagram for systematic review on nirsevimab



[i] As mentioned in Table 1, systematic reviews/meta-analysis were considered to ensure than no study was omitted since the literature on nirsevimab is currently rapidly evolving.

2.1.2.2 *Randomised controlled trials*

CHARACTERISTICS OF THE STUDIES

- A total of 6 articles were identified, and derived from 4 distinct studies: 4 RCTs assessed the efficacy and safety of nirsevimab[23-26] (one of which was published in two separate publications[24, 25]), while another RCT assessed the safety profile exclusively.[27] In addition, one of the included articles presented pooled data from 2 included RCTs (Griffin et al. and the MELODY trial).[28] Participants came from a wide range of countries in both the northern and southern hemispheres. The main findings are summarised in Table 2 and the characteristics of the included studies are presented in Table 3. Fundings of studies is provided in Appendix 1.3.
- In addition, it is noteworthy to mention that follow-up studies (during the second RSV season) were organised in 2 RCTs[29, 30]: the follow-up from the MELODY trial sought to ascertain whether there was a potential shift in the burden of the disease to the second year of life, while the follow-up of the MEDLEY trial involved a new randomisation to the administration of a second dose of nirsevimab, placebo, or palizivumab, and evaluated its safety and pharmacokinetics in a subgroup of children with heart or lung comorbidities. It should be noted that the present analysis did not incorporate the studies in question, since the participants were over the age of 12 months. A comprehensive overview of each study is presented in Appendix 1.4. The ensuing discussion will address these studies in greater detail.
- An ancillary study was conducted using the data from the randomised controlled trials (RCTs) of Griffin *et al.* and the MELODY trial.[31] The objective of the study was to assess the persistence of RSV-neutralising antibodies following administration of nirsevimab, as well as the natural immune response upon subsequent RSV exposure.

POPULATIONS AND INTERVENTIONS

- Two trials included healthy preterm infants (at least 29 weeks gestational age) under one year of age and entering in their first RSV season,[23, 26] while another RCT considered infants born at term or late preterm (gestational age ≥ week 35) who were also under one year of age, and entering their first RSV season.[24, 25] The MEDLEY trial specifically focused on infants at risk of severe RSV, including those with congenital heart conditions, chronic lung diseases or prematurity <35 weeks.[27]
- The administration of nirsevimab was undertaken in a manner consistent with body weight, categorised as over or under 5 kg, except for the initial RCT, which employed a singular 50 mg dose irrespective of infant weight. The comparator was a placebo in the efficacy trials,[23-25] while standard of care was the control group in the pragmatic trial from Drysdale *et al.*[26] In one RCT nirsevimab was compared to palivizumab.[27]

OUTCOMES AND TIMEPOINTS

The primary outcomes of interest were medically attended[j] RSV low-respiratory tract infection (LRTI) in 2 efficacy RCTs (3 studies[23-25]), and hospitalisation due to RSV disease in one pragmatic trial.[26] Time points for the primary outcome was 150 days after intervention,[23-25] or the time-course of the RSV season in the pragmatic trial (i.e. a follow-up of 6 months).[26] Hospitalisation was addressed as secondary outcome in 2 RCTs (3 articles), and safety events were collected up to 360 days in the four trials. The MEDLEY trial assessed safety, pharmacokinetics, and anti-drug antibody response (over one year).[27]

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[j] The definition includes: a laboratory-confirmed diagnosis of RSV, a physical examination finding indicating involvement of the lower respiratory tract, and signs of severity as detailed in Table 2.

EFFICACY AND SAFETY OF NIRSEVIMAB IN RANDOMISED CONTROLLED TRIALS

Collectively, the evidence based on the RCTs demonstrated that nirsevimab was effective in protecting both healthy, and high-risk infants from RSV-LRTI and hospitalisation, with a favourable safety profile. A summary of the efficacy is presented in Table 2, and points of interest regarding safety are summarised in Table 4.

- The **first published RCT** (2020) evaluated the efficacy of nirsevimab in healthy preterm infants, and revealed that the immunisation following a single dose of 50 mg nirsevimab led to a 70.1% decrease in medically attended LRTI.[23] Furthermore, the incidence of RSV-related hospitalisation was 78.4% lower in the nirsevimab group than the placebo group. The types and frequencies of adverse events were similar in both groups. Five deaths occurred over the 361 days post administration (two deaths in the nirsevimab group and three in the placebo group[k]; see Table 4). Nonetheless, none of these deaths were due to RSV, nor considered to be related to the study drug.
- The **MELODY trial** was published in two articles (preliminary and final results).[24, 25] It assessed nirsevimab efficacy in infants born at term (or late pre-term) and demonstrated that immunisation efficacy against medically-attended RSV-LRTI and hospitalisation were 76.4% and 76.8%, respectively. The safety profile of nirsevimab was consistent with previous findings, showing no clinically meaningful differences between the nirsevimab and placebo groups (death are provided in Table 4).
- A subsequent study of infants participating in the Phase 3 MELODY trial examined the risk of RSV disease during their second RSV season (no new dose of nirsevimab was given prior to the second RSV season).[29] The findings indicated no increase in medically attended RSV lower respiratory tract infections or evidence of antibody-dependent enhancement of infection[l], or disease severity compared to placebo recipients (see Appendix 1.4).
- The **HARMONIE trial** further evaluated the efficacy and safety of nirsevimab in a real-world setting (drug *vs* standard of care).[26] Infants were enrolled between August 2022 and February 2023. The results demonstrated that nirsevimab was 83.2% effective against hospitalisation due to RSV-LRTI in infants under 12 months entering in their first RSV season, in comparison with those who received standard of care. The safety profile of nirsevimab in the HARMONIE trial was consistent with that observed in the previous studies, showing no significant differences between the nirsevimab and control groups (although the follow-up for safety at one year was still ongoing in this first publication of the trial). After the completion of our literature review, updated results of the HARMONIE trial were published and presented extended follow-up time of the majority of participants at 180 days.[32] The efficacy was in line with the efficacy reported in the first publication of the trial and reached 82.7% (95%CI: 67.8-91.5)[m]. In addition, no safety concern was detected up to 365 days.
- The **MEDLEY trial** compared the safety and pharmacokinetics of nirsevimab to palivizumab in infants at high risk for severe RSV disease.[27] This included those with chronic lung disease, or congenital heart disease, or prematurity. The study concluded that nirsevimab exhibited a safety profile comparable to palivizumab, and a similar serum exposure associated with efficacy in healthy infants. The follow-up study investigated the safety of administering a second dose of

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k One death in the placebo group occurred after the trial period (367 days).

l Binding of non-neutralising antibodies or antibodies binding to viral antigens at subneutralising concentrations without adequately blocking or clearing infection has the possibility to lead to antibody-enhancement of infection or diseases severity.

m Up to 180 days after randomisation, hospitalisations due to RSV-associated LRTI occurred in 12 (0.3%) infants in the nirsevimab arm and in 68 (1.7%) infants in the standard of care group. Incidence rates were 0.001 person-months in the nirsevimab group versus 0.003 person-months in the standard of care group.

nirsevimab prior to their second RSV season[n].[30] Participants who received nirsevimab in the first season were given a 200 mg dose before the second season, while those initially on palivizumab were re-randomised to receive either nirsevimab or palivizumab. The findings indicated that the safety profile of nirsevimab was consistent with that of previous studies, and no new safety concerns were identified (see Appendix 1.4).

- A study using the data from the RCTs of Griffin *et al.* and the MELODY trial revealed that nirsevimab provided sustained RSV-neutralising antibody levels throughout the whole RSV season[o].[31] Furthermore, the natural immune response was comparable to that of individuals who had not received nirsevimab, suggesting that nirsevimab does not interfere with the development of natural immunity following RSV infection.

METHODOLOGICAL QUALITY OF THE STUDIES

The risk of bias assessment for each included study is shown in Appendix 1.5. Overall, RCTs were judged as 'low risk of bias'. The ancillary study of the trials focusing on the immunisation response was rated as 'acceptable to high quality' (see Appendix 1.10).[31]

Table 2 – Summary of efficacy of nirsevimab against main outcomes in the main clinical trials (preterm and term infants without comorbidities)

Outcome	Intervention group	Control group	RRR (95%CI)	ARD (95%CI)	NNT (95%CI)
Griffin et al.[23]					
Incidence of medically attended RSV-confirmed LRTI through 150 days	2.6% (25/969)	9.5% (46/484)	72.9% (56.4-83.1)*	6.9% (4.1-9.7)	15 (10-24)
Incidence of hospitalisation for RSV-confirmed LRTI through 150 days	0.8% (8/969)	4.1% (20/484)	80.0% (55.0-91.1)**	3.3% (1.4-5.2)	31 (19-69)
MELODY trial[25]					
Incidence of medically attended RSV-confirmed LRTI through 150 days	1.2% (24/2009)	5.4% (54/1003)	77.8% (64.3-86.2)	4.2% (2.7-5.6)	24 (18-37)
Incidence of hospitalisation for RSV-confirmed LRTI through 150 days	0.4% (9/2009)	2.0% (20/1003)	77.5% (50.8-89.7)	1.5% (0.6-2.5)	65 (41-158)
HARMONIE trial[26, 32]					
Incidence of hospitalisation for RSV-confirmed LRTI through the RSV season (using the most recent update[32])	0.3% (12/4038)	1.7% (68/4019)	82.4% (67.6-90.5)	1.4% (0.96-1.83)	72 (55-104)

*ARD: absolute risk difference, 95%CI: 95% confidence interval, LRTI: low tract respiratory infection, NNT: number needed to treat, RRR: relative risk reduction. * 72.9% was reported using Cochran-Mantel-Haenszel test (observed events) and 70.1% was reported using Poisson regression robust variance, ** 80.0%; was reported using Cochran-Mantel-Haenszel test (observed events) and 78.4% was reported using Poisson regression robust variance.*

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[n] In this follow-up study, only children with chronic lung disease or congenital heart disease were considered (and not those who were born preterm).

[o] Neutralising antibody levels remained 50-fold higher than baseline 151 days after administration, and still 7 fold higher than baseline at day 361.

Table 3 – Extraction of data from RCTs on nirsevimab

Author, year	Design, sample size and setting	Intervention and control	Timeframe and follow-up	Targeted population	Main characteristics *intervention group*	Main characteristics *control group*	Outcomes (intervention vs control) and efficacy (95%CI)
Griffin[23], 2020	Randomised placebo controlled trial (ratio 2:1) N= 1 453 (969/484) 164 sites in 23 countries (68% northern, 32% southern)	Nirsevimab 50 mg (IM) or placebo (IM normal saline)	3 November 2016 and 1 December 2017 Follow-up: 361 days (after intervention)	Healthy preterm infants (29-34 weeks gestational age) and ≤1 year entering in the first RSV season	**Mean age (SD), months:** 3.29 (2.22) **Mean gestational age (SD), weeks:** 32.7 (1.4)	**Mean age (SD), months:** 3.28 (2.31) **Mean gestational age (SD), weeks:** 32.7 (1.5)	**Primary: medically attended$ RSV-LRTI within 150 days, % (n):** • 2.6% (25) vs 9.5% (46); relative difference 70.1% (95%CI: 52.3-81.2) • HR (95%CI): 0.26 (0.16-0.43) **Secondary: RSV-related hospitalisation within 150 days, % (n):** • 0.8% (8) vs 4.1% (20); relative difference: 78.4% (95%CI: 51.9-90.3) • HR (95%CI): 0.19 (0.08-0.44)
Hammitt[24], 2022 (MELODY trial - partial results)	Randomised placebo controlled trial (ratio 2:1) N= 1 490 (994/496) 150 sites in 21 countries (northern hemisphere- one site in South Africa)	Nirsevimab 50 mg (weight <5 kg) or 100 mg (weight ≥5 kg), or placebo	July, 23 2019-March, 15 2020: primary cohort since the study was paused due to COVID-19 pandemic Follow-up: 361 days	Infants born at term or late preterm ≥ week 35 gestational age and ≤1 year, entering in the first RSV season	**Age (months):** • ≤3: 58.0% • >3- ≤6 : 31.9% • >6: 10.1% **Gestational age (weeks):** • ≥35 to <37: 13.3% • ≥37: 86.7%	**Age (months):** • ≤3: 57.5% • >3- ≤6 : 32.7% • >6: 9.9% **Gestational age (weeks):** • ≥35 to <37: 15.4% • ≥37: 84.6%	**Primary: medically attended$ RSV-LRTI within 150 days, % (n):** • 1.2% (12) vs 5.0% (25) • Efficacy (95%CI): 74.5% (49.6-87.1) • HR (95%CI): 0.23 (0.12-0.47) **Secondary: RSV-related hospitalisation within 150 days, % (n):** • 0.6% (6) vs 1.6% (8) • Efficacy: 62.1% (-8.6-86.8) • HR (95%CI): /
Muller[25], 2023 (completion of the MELODY trial)	Completion of a RCT (ratio 2:1) N= 3 012 (2009/1003) 211 sites in 31 countries	Nirsevimab 50 mg (weight <5 kg) or 100 mg (weight ≥5 kg), or placebo	July, 23 2019-October 22, 2021 (paused between March 15, 2020 and April 9, 2021) Follow-up: 361 days (+ phone call at day 511)	Infants born at term or late preterm ≥ week 35 gestational age and ≤1 year, entering in the first RSV season	**Age (months):** • ≤3: 59.2% • >3 - ≤6: 31.7% • 6: 9.1% **Gestational age (weeks):** • ≥35 to <37: 11.9% • ≥37: 88.1%	**Age (months):** • ≤3: 58.6% • >3 - ≤6 : 32.2% • 6: 9.2% **Gestational age (weeks):** • ≥35 to <37: 12.2% • ≥37: 87.8%	**Primary: medically attended$ RSV-LRTI (inpatient or outpatient) within 150 days, % (n):** • 1.2% (24) vs 5.4% (54) • Efficacy: 76.4% (62.3-85.2) **Secondary: RSV-related hospitalisation within 150 days, % (n):** • 0.4% (9) vs 2.0% (20) • Efficacy: 76.8% (49.4-89.4) **Exploratory: hospitalisation with supplementary oxygen or supplementary fluids, % (n):**

							• 0.3% (7) vs 1.7% (17) • Efficacy: 78.6% (48.8-91.0)
Drysdale[26], 2023 **(HARMONIE trial)**	Pragmatic (open-label) randomised placebo controlled trial (ratio 1:1) N = 8 058 (4 037 nirevimab/ 4 021 SOC) 3 countries (UK, France, Germany)	Nirsevimab IM (<5 kg: 50 mg; ≥5 kg: 100 mg)	August, 8 2022-February, 28 2023 Follow-up: 366 days after intervention	Infants ≤1 year, born at a gestational age ≥29 weeks, (entering in RSV season) and not eligible for palivizumab	**Mean age (SD), months:** 4.53 (3.34) **Age (months):** • ≤3: 48.6% • >3 - ≤6 : 23.8% • >6: 27.6% **Gestational age (weeks):** • <37: 14.0% • ≥37: 85.1% *(0.9% missing)*	**Mean age (SD), months:** 4.48 (3.30) **Age (months):** • ≤3: 48.6% • >3 - ≤6 : 23.7% • >6: 27.7% **Gestational age (weeks):** • <37: 13.5% • ≥37: 85.4% *(1.1% missing)*	**Primary: RSV-related hospitalisation (during the RSV season◊), % (n):** • 0.3% (11) vs 1.5% (60) • Efficacy (95%CI): 83.2% (67.8-92.0) • Efficacy in time-event analysis (95%CI): 83.3% (68.2-91.2) **Secondary: very severe‡ RSV associated LRTI:** • 0.1% (5) vs 0.5% (19) • Efficacy: (95%CI): 75.7% (32.8-92.9) • Efficacy in time-event analysis (95%CI): 75.4% (34.0-90.8) *◊: hospitalisation for RSV associated LRTI is presented with a follow-up of 6 months* *‡: hospitalisation and oxygen saturation <90% at any time during hospitalisation and the need for supplemental oxygen*
Domachowske[27], 2022 **(MEDLEY trial)**	RCT (phase 2/3) on safety of nirsevimab in infants eligible for palivizumab (pretem or heart/lung disease) N = 925 (310 CLD/CHD; 615 preterm) 126 sites in 25 countries	• Single fixed IM dose of nirsevimab 50 mg or 100 mg (according to weight <5 kg or ≥5 kg) followed by 4 once-monthly IM doses of placebo • 5 monthly IM doses of palivizumab (15mg/kg per dose)	RSV season in 2019 and 2020 Follow-up: 361 days	Infants at risk for severe RSV (heart, lung diseases or prematurity <35 weeks)	**Age (months)-Nirsevimab group:** • ≤3: 44.5% • >3 - ≤6 : 34.1% • >6: 21.4% **Gestational age (weeks):** • ≥29 to <32: 20.8% • ≥32 to <35: 42.5% • ≥35: 15.6%	**Age (months)-Palivizumab group:** • ≤3: 46.6% • >3 - ≤6 :32.7% • >6: 20.7% **Gestational age (weeks):** • ≥29 to <32: 23% • ≥32 to <35: 40.8% • ≥35: 13.6%	**AE occurring through 360 days after the first dose, %** (total= 918; nirsevimab= 614; palivizumab=304): • ≥1 AE: 67% vs 67% • ≥1 Treatment-related AE: 1.6% vs 1.9% • ≥1 Grade 3 AE: 5.5% vs 6.6% • ≥1 treatment-related grade 3 AE: 0% vs 0% • Any AE with outcome of death: 0.8% vs 0.3% (see Table 4) • ≥1 SAE:11% vs 10% • ≥1 treatment- related SAE: 12% vs 10% • ≥1 AE of special interest#: 2% vs 0% **Pharmacokinetics:** serum levels of nirsevimab at day 151 were similar to those reported in the MELODY trial **Medically attended RSV infection:** 0.6% (nirsevimab) vs 1% (palivizumab)

Simoes[28], 2023	Pooled analysis of Griffin et al. and MELODY RCTs *(excluding participants from the RCT Griffin et al. trial with a birth weight of >5 kg* N= 2 350 (1 564 nirsevimab/786 placebo) *+ Extrapolation of the efficacy of nirsevimab to infants at increased risk of severe RSV infection on the basis of pharmacological data from MEDLEY RCT*	See corresponding RCTs	Infants born between 29 weeks gestational age and full term	**Median age (IQR), months**: 2.02 (1.00-3.58) **Age category (months):** • ≤3: 68% • >3- ≤6: 25% • <6: 6% **Gestational age (weeks):** • ≥29 to <32: 14% • ≥32 to <35: 22% • ≥35 to <37: 9% • ≥37: 55%	**Median age (IQR), months:** 2.00 (0.99-3.71) **Age category (months):** • ≤3: 68% • >3- ≤6: 26% • <6: 6% **Gestational age (weeks):** • ≥29 to <32: 15% • ≥32 to <35: 22% • ≥35 to <37: 10% • ≥37: 53%	**Primary: medically attended RSV-LRTI (follow-up 150 days), % (n):** • 1% (19) vs 6% (51) • RRR (95%CI): 79.5 %(65.9-87.7) • HR (95%CI): 0.183 (0.108-0.310) **Secondary: hospital admission for medically attended RSV-LRTI:** • 1% (9) vs 3% (21) • RRR: 77.3% (50.3-89.7) • HR (95%CI): 0.210 (0.096-0.458) **Exploratory: very severe RSV-LRTI** (*requirement of supplemental oxygen or intravenous fluids)*: • <1% (5) vs 2% (18) • RRR: 86.0% (62.5-94.8) **Extrapolation of efficacy in infants at risk of severe RSV infection:** similar nirsevimab serum concentrations were achieved in the MEDLEY trial as in the MELODY trial and the trial from Griffin *et al.*
Wilkins[31] 2024	Ancillary study of clinicals trials (Hammitt *et al.*, Griffin *et al.*): collection of serum samples at post-dose-time-points (baseline, one month, 5 months and 1 year) N= 2 143 (1 427/716)	*See corresponding RCT*		**Mean ages at randomisation, months:** • Griffin *et al*: 3.4 • Hammitt *et al*: 3.0		**RSV-NAb levels in nirsevimab recipients (compared to baseline value):** • **Day 31:** >140-fold higher than baseline • **Day 151:** levels remained >50-fold than baseline • **Day 361:** levels >7-fold than baseline

$: A diagnosis of medically attended RSV-LRTI requires having a respiratory sample positive for RSV by reverse transcription polymerase chain reaction (RT-PCR) performed at a central laboratory AND a physical examination finding indicating involvement of the lower respiratory tract (rhonchi, rales, crackles, or wheeze) AND at least one indicator of clinical severity including: increased respiratory rate (age: <2 months, ≥60 breaths/min; 2–6 months, ≥50 breaths/min; <6 months – 2 years, ≥40 breaths/min), OR hypoxemia (in room air - oxygen saturation <95% at altitudes ≤1800 meters or <92% at altitudes <1800 meters), OR clinical signs of respiratory distress: new onset apnea, retractions, grunting, nasal flaring, acute hypoxic or ventilatory failure, dehydration secondary to inadequate oral intake due to respiratory distress (need for intravenous fluid), intercostal subcostal or supraventricular retractions (this last sign was used in the Melody trial). # Adverse events of special interest were hypersensitivity, immune complex disease, and thrombocytopenia. AE: adverse event; CLD: chronic lung disease; CHD: chronic heart disease; HR: hazard ratio; IM: intramuscular; IQR: interquartile ratio; Kg: kilogram; LRTI: Low Respiratory Tract Infection; RCT: randomised controlled trial; RRR: relative risk reduction; SAE: severe adverse event; SD: standard deviation; SOC: standard of care.

Table 4 – Points of interest on safety in RCTs on nirsevimab

Author, year	Number of participants analysed for safety	Follow-up for safety	Adverse events ≥grade 3 (intervention vs placebo), % (n)	Serious adverse events and adverse events of special interest (intervention vs placebo), % (n)	Number of deaths and characteristics
Griffin[23], 2020	N = 1447 (968/479: as-treated population)	361 days	8.0% (77) vs 12.5% (60)	**≥1 SAE:** • 11.2% (108) vs 16.9% (81) • Considered related to the trial drug: 0% vs 0% **AE of special interest*:** • Any: 0.5 (5) vs 0.6 (3) • Considered related to the trial drug: 0.5 % (5) vs 0.6% (3)	Five deaths occurred through day 361 (two deaths in the nirsevimab group and three in the placebo group); one death in the placebo group occurred after the trial period (day 367) No deaths were known to be due to RSV or were considered by the investigator to be related to nirsevimab or placebo
Muller[25], 2023 and Hammitt[24], 2022 **MELODY trial (full enrollment)**	N= 2 994 (1 998/ 996: as treated population)	361 days	3.1% (61) vs 3.8% (38) Related to treatment: 0.1% vs 0.1%	**≥1 SAE:** • 6.3% (125) vs 7.4% (74) • Considered related to the trial group: 0.0% vs 0.1% **AE of special interest*:** 0.2% (4) vs 0.0% (0) *All four AE of special interest were limited to cutaneous findings (no anaphylaxis or serious hypersensitivity)*	Four deaths occurred through study day 361 and are included in the safety analysis of the full enrollment cohort. One death occurred after study day 361 (on day 440) and is not included in the safety analysis Deaths: 4 (nirsevimab group) vs 0 (placebo group). All four deaths were assessed by the investigator as being unrelated to treatment: • Study Day 140, cause undetermined. Infant had suspected undiagnosed metabolic disease • Study Day 143, acute gastroenteritis • Study Day 338, acute gastroenteritis • Study Day 286, skull base fracture following road traffic accident.
Drysdale[26], 2023 **HARMONIE trial**	N= 8 035 (4 015/4 020)	(ongoing follow-up; data cutoff date 28 February 2023)	1.2% (48) vs 1.1% (46)	**SAE:** • 2.2% (89) vs 1.7% (67) • Treatment related SAE: <0.1% (1) vs 0% (0) *One infant had a grade 3 SAE (infantile spams-West syndrome) 23 days after the receipt of nirsevimab that was considered related to the trial treatment because the*	No deaths were reported

				relationship to nirsevimab could not be excluded **AE of special interest*:** 0.1% (3) vs <0.1% (1) *Four infants had at least one adverse event of special interest (drug reaction [reported as fever and rash], maculopapular rash, and allergic dermatitis in 1 infant each in the nirsevimab group and food allergy in 1 infant in the standard care group), all of which were assessed to be grade 1 or 2 in severity*	
Munro[32], 2025 Updated results of HARMONIE trial	N= 8 034 (4 016/4 018)	366 days	3.8% (151) vs 3.6% (143)	• Any serious treatment-emergent adverse event: 6.5% (262) vs 5.5% (222) • Treatment related SAE: <0.1% (1) vs 0%	No deaths were reported
Domachowske[27], 2022 **MEDLEY trial**	N= 918	361 days	*See Table 3*	*See Table 2*	6 deaths (5 in nirsevimab group and 1 in palivizumab group): each assessed as not related to study drug: • Multisystem organ failure in the course of respiratory failure requiring mechanical ventilation (palivizumab group) • Respiratory failure due to bronchopneumonia (nirsevimab group) • Respiratory failure following a pneumonia caused by SARS-CoV-2 and requiring mechanical ventilation (nirsevimab group) • Cardiogenic shock and nosocomial sepsis (nirsevimab group) • Congestive heart failure and pulmonary atresia (nirsevimab group) • Acute cardiovascular and respiratory failure, secondary to acute bronchiolitis (nirsevimab group)

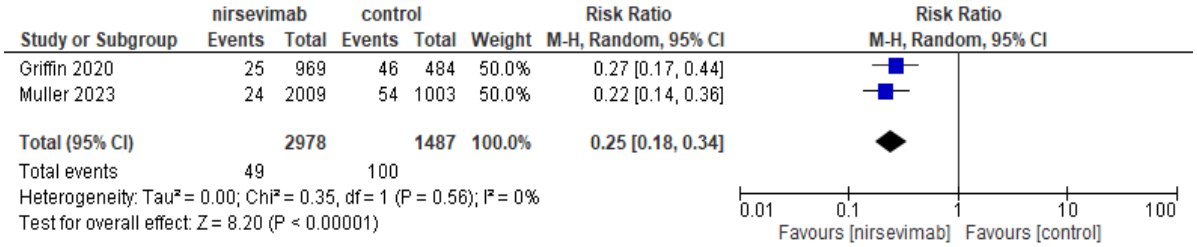
** Adverse events of special interest are hypersensitivity, immune complex disease, and thrombocytopenia. AE: adverse event; N: number; SAE: serious adverse event.*

Data synthesis

MEDICALLY-ATTENDED RSV-LRTI

A meta-analysis was conducted to evaluate the outcome "medically-attended RSV-LRTI[p]" assessed with a follow-up period of 150 days post-intervention. The analysis combined the results of the RCTs on preterm infants (≥29 weeks and <35 weeks gestational age), and those born at a gestational age of at least 35 weeks. Although the doses of nirsevimab in the study of Griffin *et al.* was 50 mg irrespective of the weight[q], the results of the RCT from Griffin *et al.*[23] and the complete results of the MELODY trial (Muller *et al.*[25]) were pooled (4 465 participants). The risk ratio for RSV-confirmed LRTI of nirsevimab *vs* placebo was 0.25 (95%CI: 0.18-0.34) (Figure 2). There was no heterogeneity and the efficacy was 75% (95%CI: 64-82).

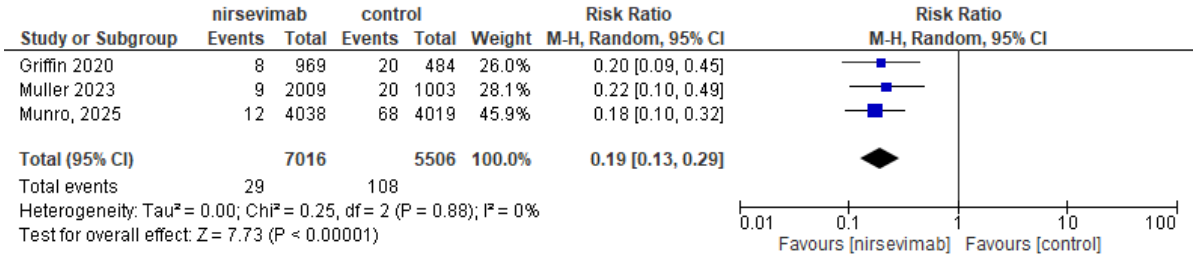
Figure 2 – Efficacy of nirsevimab against medically attended RSV-confirmed LRTI through 150 days



RSV-RELATED HOSPITALISATION

Data on the necessity for hospitalisation was available in 3 RCTs involving 12 522 participants (primary outcome for 1 RCT and secondary outcome for the two other RCTs). As mentioned in the section 2.1.2.2, the most updated results of the HARMONIE trial were used for the meta-analysis.[32] The pooled analysis revealed that nirsevimab reduced the risk for hospitalisation compared to the control arm (RR 0.19; 95%CI: 0.13-0.29) (Figure 3). There was no heterogeneity, and the immunisation efficacy was 81% (95%CI: 71-87).

Figure 3 – Efficacy of nirsevimab against hospitalisation for RSV LRTI (through 5 to 6 months)



SAFETY: SERIOUS ADVERSE EVENTS AND GRADE 3 ADVERSE EVENTS

Main safety data were retrieved from 3 studies, and included the infants who appropriately received any study treatment (as-treated populations). The 3 studies reported adverse events occurring through

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p See definition in Table 3.

q Studies conducted after the trial from Griffin *et al.* considered the dose of 100 mg nirsevimab for infants weighting more than 5 kilograms.

the 361 (or 366) days follow-up period. As mentioned in the section 2.1.2.2, the most updated results of the HARMONIE trial were used for the meta-analysis.[32]

- The meta-analysis indicated no significant risk of serious adverse events associated with nirsevimab, with a pooled risk estimate of 1.05 (95%CI: 0.92-1.19) based on 872 serious adverse events among 12 475 infants (see Figure 4). As shown in Figure 5, the meta-analysis suggested no significant risk of grade 3 adverse events among infants receiving nirsevimab, with 530 such events reported among 12 475 participants (pooled risk estimate of 0.94; 95%CI: 0.64-1.36).

Figure 4 – Serious adverse events through 361 (or 366) days post intervention

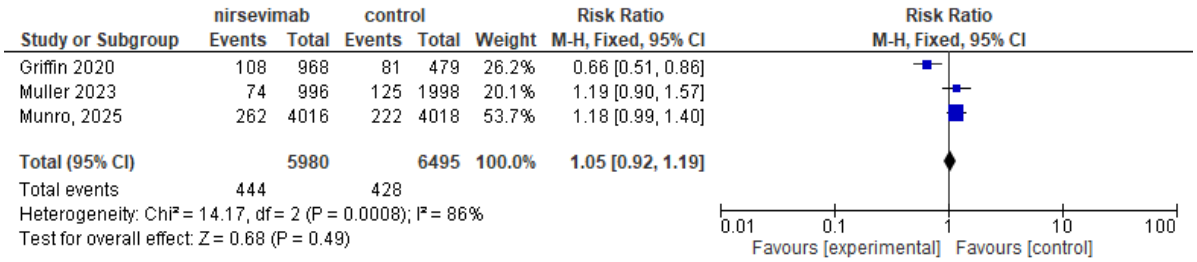
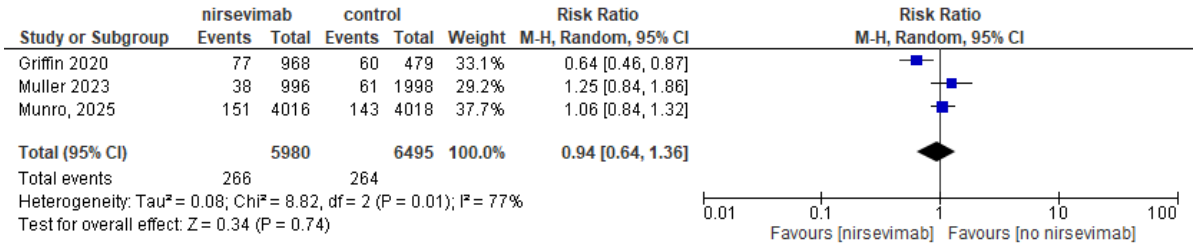


Figure 5 – Grade 3 adverse events through 361 (or 366) days post intervention



2.1.2.3 Studies describing real world data

Characteristics of the studies

- A total of 24 articles reporting on 22 real world studies on the effectiveness of nirsevimab were identified. Studies that appeared to be from the same cohort – based on geographic similarity (same regions within a country) and time period – were considered overlapping evidence. As such, to prevent duplication or overrepresentation of the same participants, four Spanish studies were excluded from the evidence synthesis but were addressed in the discussion section, and are described in Appendix 1.6.[33-36] A total of 20 articles (18 studies) were retained for synthesizing the evidence on effectiveness, and are described in Table 5. The majority of the studies were conducted in Europe, during the 2023-2024 RSV season, Spain being the most represented country (8 articles on 7 studies), followed by France (7 studies), and Italy (1 study). The other studies were conducted in the US and Australia.
- A total of 9 case-control studies were identified, predominantly with a test-negative design. In addition, a cross-sectional study was reported, using an online survey, and 10 cohort studies were included. The majority of studies reported on mixed groups, including predominantly catch-up immunisation along with seasonal ones (only 4 studies analysed exclusively a seasonal cohort[37-40]). One study compared the effectiveness between catch-up and seasonal immunisation.[41] The sample sizes were generally large as data were often population-based, using registries (infectious diseases surveillance system repositories or regional registries). Four studies reported on data collected in multiple centres, and only one of these was a single-centre study (see Table 5).

- The observation time varied between the studies reporting on the incomplete RSV-season, and the studies describing the full RSV season. The majority of studies reported on the LRTI observed during the RSV season (i.e. approximately 5 months). Three studies extended the observation time outside the RSV season.[42-44] The observation durations ranged from 47 days to 251 days. A summary of the dates of duration of observation of the studies and the corresponding dates of availability of nirsevimab, as well as the birth dates of the children to whom nirsevimab was proposed is available in Appendix 1.7.
- The most frequently studied outcomes were hospitalisation due to RSV disease, including PICU admission. Emergency department visit was addressed in 5 studies,[37, 40, 45-47] and 2 studies reported on the primary care attendance.[42, 44] The incidence or RSV-LRTI was addressed in 3 studies.[46, 48, 49] One study reported exclusively on safety.[50]
- The majority of studies (12 articles encompassing 10 distinct studies) included a proportion of infants with comorbidities such as prematurity or chronic cardiac and pulmonary conditions. Additionally, five studies reported effectiveness outcomes stratified by age, comparing infants younger and older than 3 months (subgroup results are provided in Appendix 1.8).
- Details regarding study funding are presented in Appendix 1.9.

Table 5 – Studies using real world data on the use of nirsevimab

Author, year, country (region)	Design and sample size	Timeframe and observation time (days)	Age and characteristics *(immunised vs non-immunised)*	Source of information and settings of included populations	Relevant Outcome(s) by study group	Adjusted effectiveness for RSV-related outcomes *(methods, variables of adjustment)*
Coma[46] (May 2024) Spain (Catalunya)	Retrospective cohort study N= 26 525	1 October 2023- 31 January 2024 122 days	Median age (IQR), days: 106 (52-151) vs 88 (44-134)	Catalan health databases (routinely collected data in primary care and hospitals; regional database)	**RSV-related hospitalisation:** • Nirsevimab 52/23 127 • No nirsevimab: 76/3 398 **RSV-related ICU admission:** • Nirsevimab 8/23 127 • No nirsevimab: 17/3 398 **RSV infection:** • Nirsevimab 71/23 127 • No nirsevimab: 31/3 398 **RSV-related emergency department visit:** • Nirsevimab 604/23 127 • No nirsevimab: 354/3 398	**RSV infection:** • aHR (95%CI): 0.311 (0.200-0.483) • Effectiveness (95%CI): 68.9% (51.7-80.0) **RSV-related hospitalisation:** • aHR (95%CI): 0.124 (0.086-0.179) • Effectiveness (95%CI): 87.6% (82.1-91.4) **RSV-related ICU admission:** • aHR (95%CI): 0.099 (0.041-0.237) • Effectiveness (95%CI): 90.1% (76.3-95.9) *Cox regression: age at the start, sex, area of residence, nationality, socioeconomic status, rurality*
Assad[51] (July 2024) France	Prospective matched case-control study (2:1 ratio) N= 1 035 (690 cases; 345 controls) ***Case=*** *infants <12 months hospitalised*	15 October 2023- 10 December 2023 47 days	Median age (IQR), months : 3.1 (1.8-5.3) vs 3.4 (1.6-5.6) days **Comorbidities:** • Preterm and age <6 months: 4% vs 5.6%	Data from hospital admission (6 tertiary hospitals)	**RSV-related hospitalisation:** • Nirsevimab: 60/157 • No nirsevimab: 630/878 **RSV-related ICU admission:** • Nirsevimab: 27/74 • No nirsevimab: 166/265	**RSV-related hospitalisation (95%CI):** 83.0% (73.4-89.2) *Logistic regression: sex, gestational age at birth, birth weight, risk factors for severe RSV*

	for RSV-related bronchiolitis ***Control=*** *infants hospitalised for diseases unrelated to RSV*		• Chronic lung disease of prematurity: 1.0% vs 1.2% • Congenital heart disease: 1.0% vs 0.6%			
Lassoued[49] (September 2024) France	Prospective case-control study N= 883 (453 cases; 430 controls) ***Case=*** *infants <12 months with RSV-related bronchiolitis* ***Control=*** *infants <12 months with RSV-unrelated bronchiolitis*	15 September 2023- 01 February 2024 139 days	Median age (IQR), months: 7.2 (4.6-9.8) vs 6.3 (4.7-8.2) Preterm birth: 8.9% vs 9.4%	Data extracted from the national based surveillance system PARi including 107 ambulatory paediatricians across the French territory (outpatients)	**RSV-bronchiolitis:** • Nirsevimab: 62/239 • No nirsevimab: 391/644	**RSV-bronchiolitis (95%CI):** 79.7% (67.7-87.3) *Logistic regression: age, sex, birth term, birth weight, previous bronchiolitis, number of children per household, childcare settings, region*
Carbajal[45] (August 2024) France	Case-control study N= 2 786 (864 cases; 1 922 controls) ***Case=*** *infants with bronchiolitis of irrespective cause* ***Control=*** *infants without bronchiolitis*	14 October 2023- 29 February 2024 138 days	Mean age (SD), months (whole cohort): • ≤3: 1.8 (0.7) • 3-≤6: 4.6 (0.8) • <6-12: 8.3 (1.6) **Comorbidities :** • Gestational age <37 weeks: 19% vs 7% • Lung dysplasia: 5% vs 0% • Heart disease: 0% vs 1%	Data from infants admitted to the emergency department of one tertiary hospital	**RSV-related hospitalisation*:** • Nirsevimab: 22/723 • No nirsevimab: 170/1 391 **RSV-related emergency department visit*:** • Nirsevimab: 22/723 • No nirsevimab: 178/1 391 ** primary outcome was emergency department visit for all cause bronchiolitis; one secondary outcome was RSV-related hospitalisation*	**RSV-related hospitalisation (95%CI):** 83% (72-90) **RSV-related emergency department visit (95%CI):** 83% (71-90) *Logistic regression, Mantel Haenszel method: week of ED visit, time, sex, age*

Barbas Del Buey[52] (August 2024) Spain (Region of Madrid)	Prospective population-based observational cohort N= 37 067	01 October 2023- 29 February 2024 151 days	Median age (IQR) at the start of follow-up, months: 0.98 (3.38) vs 2.85 (3.51) **Comorbidities:** • Detected comorbidity: 7.9% vs 6.2% • Prematurity: 6.1% vs 4.4% • Lung pathology: 0.69% vs 0.75% • Cardiac pathology: 0.94% vs 0.95%	Data extracted from registry of endocrine-metabolic diseases (metaB) which contains informations of all newborns in the region and consultation of surveillance systems	**RSV-related hospitalisation:** • **Nirsevimab: 133/29 684** ○ Month 1: 34 ○ Month 2: 50 ○ Month 3: 33 ○ Month 4: 8 ○ Month 5: 7 • **No nirsevimab: 376/7383** ○ Month 1: 46 ○ Month 2: 157 ○ Month 3: 138 ○ Month 4: 24 ○ Month 5: 8 **RSV-related ICU admission:** • **Nirsevimab: 24/29 684** ○ Month 1: 7 ○ Month 2: 12 ○ Month 3: 5 ○ Month 4: 0 ○ Month 5: 0 • **No nirsevimab: 57/7 383** ○ Month 1: 17 ○ Month 2: 25 ○ Month 3: 14 ○ Month 4: 1 ○ Month 5: 0	**RSV-related hospitalisation (95%CI):** • 30 days: 93.6% (89.7-96.1) • 150 days: 87.6% (67.7-95.3) **RSV-related ICU admission (95%CI):** • 30 days: 94.4% (87.3-95.7) • 90 days: 92.1% (64.0-98.3) *Cox regression: sex; age, gestational age, type of delivery, presence of comorbidities (binary variable), percentile of average income per person in their census section of residence, cumulative incidence of suspected RSV in the population under 5 years of age in their census section of residence, calendar week of the start of follow-up*
Ares-Gomez[53] (April 2024) Spain (Galicia) NIRSEGAL study (partial enrollment)	Prospective observational cohort study N= 10 259	25 September 2023- 31 December 2024 97 days Preterm birth (<37 weeks): 6.5% vs 4.7%	Mean age (SD), months: 4.14 (2.44) vs 5.05 (2.29) **Age categories,** months**:** • ≤3:43.2% vs 25.3% • >3 to 6: 35.2% vs 43.0%	Data extracted from different public health registries (vaccine, hospital admission, newborn metabolic disorders screening and the Galician	**RSV-related hospitalisation:** • Nirsevimab: 30/9 408 • No nirsevimab: 16/851 **Severe RSV-LRTI with oxygen support:** • Nirsevimab: 15/9 408 • No nirsevimab: 10/851 **RSV-related ICU admission:** • Nirsevimab: 10/9 408 • No nirsevimab: 0/851	**RSV-related hospitalisation:** 82.0% (65.6-90.2) **Severe RSV-LRTI with oxygen support:** 86.9% (69.1-94.2) *Poisson regression: enrolment group (seasonal, catch-up), residence*

			• <6: 21.6% vs 31.7%	surveillance system)	**Non-invasive mechanical ventilation requirement*:** • Nirsevimab: 7/9 408 • No nirsevimab: 0/851 ** no case requiring invasive mechanical ventilation*	
Mallah[43], 2024 Completion of NIRSEGAL study Spain (Galicia)	Prospective observational cohort study N= 14 476	25 September 2023- 15 April 2024 203 days	Mean age (SD), months: 6.5 (3.5) vs 8.1 (3.3) **Age categories,** months**:** • ≤3:20.1% vs 11.6% • >3 to 6: 25.8% vs 13.8% • <6: 54% vs 74.6% **Preterm birth (<37 weeks):** 6.7% vs 6.1% (missing data for 4.1%)	Data extracted from different public health registries (vaccine, hospital admission, newborn metabolic disorders screening and the Galician surveillance system)	**RSV-related hospitalisation:** • Nirsevimab: 50/13 320 • No nirsevimab: 18/1 156 **Severe RSV-LRTI with oxygen support:** • Nirsevimab: 26/13 320 • No nirsevimab: 17/1 156	**Hospitalisation** (only on catch-up cohort; N= 7 071): 70.7% (42.4-85.1) **Hospitalisation with oxygen support** (only on catch-up cohort; N= 7 071): 80.3% (56.6-91.5) *Cox regression: sex, health district area*
Estrella-Porter[48] (June 2024) Spain (Valencia)	Retrospective cohort study N = 27 362	01 October 2023- 09 January 2024 100 days	Mean age (at immunisation), months: 2.19* **data provided by the authors*	Data extracted from metaB registry (metabolic diseases screening program, vaccination registry and surveillance system network (RedMIVA)	**RSV-LRTI:** • Nirsevimab: 168/24 223 • No nirsevimab: 72/3 139 **RSV-related hospitalisation:** • Nirsevimab: 218/24 223 • No nirsevimab: 49/3 139	**RSV-LRTI:** aOR (95%CI): 0.26 (0.20-0.50) *Logistic regression: breastfeeding intention, country of origin of the mother, gestational weeks, campaign group*

Paireau[54] (April 2024) France	Case-control study N= 288 (238 cases; 50 controls) ***Case=*** *infants admitted in PICU for bronchiolitis positive for RSV* ***Control=*** *infants admitted in PICU for bronchiolitis negative for RSV*	15 September 2023- 31 January 2024 138 days	Numbers by age group: • 0-3 months: 263 (91%) • 4-8 months: 25 (9%)	Data collected from PICU surveillance network (organized by French Public health services)	**RSV-related ICU admission:** • Nirsevimab: 37/58 • No nirsevimab: 201/230	**RSV-related ICU admission (95%CI):** 75.9% (48.5-88.7) *Logistic regression: age group, sex, presence of comorbidities, prematurity and time period*
Moline (a)[55] (March 2024) US	Case control study N= 699 (407 cases, 242 controls) ***Case=*** *hospitalised infants positive for RSV* ***Control=*** *hospitalised infants negative for RSV*	01 October 2023- 29 February 2024 151 days	Numbers by age group, n (%), months: <1: 111 (16) 1-2: 214 (31) 3-4: 131 (19) 5-6: 121 (17) 7-8: 96 (14) 9-10: 23 (3) 11-12: 3 (0) Prematurity: 17% vs 20%	Data collected from the registry 'new Vaccine Surveillance Network' (population-based prospective surveillance platform for acute respiratory illness in children <18 years including 7 pediatric academic centers)	**RSV-related hospitalisation:** • Nirsevimab: 6/59 • No nirsevimab: 401/640	**RSV-related hospitalisation (95%CI):** 90% (75-96) *Logistic regression: age at enrollment, month of illness, enrollment site, presence of conditions for severe RSV disease (list available on demand)*
Moline (b) [44], **2024** US	Test negative case control N= 1 616 (N total= 28 689, including older children and	01 September 2023– 30 April 2024 242 days	**Age categories** (in infants born during or entering their RSV season 2023-2024; N= 1 616):	Data from the surveillance network ' New Vaccine Surveillance Network ' (NVSN)	**RSV-related hospitalisation (in infants born during or entering their first RSV season 2023-2024; N= 875):** • Nirsevimab: 6/73 • No nirsevimab: 525/802	**RSV-related hospitalisation (95%CI):** 93% (82-97) **Medically-attended RSV (95%CI):** 89% (79-94) *Logistic regression: site, age in months, (month of enrolment),*

	previous RSV seasons) *Cases and controls were infants with medically-attended acute respiratory illness with positive and negative RT-PCR tests for RSV, respectively*		• ≤3 months: 54 vs 531 • >3 to 6 months: 54 vs 632 • <6 months: 28 vs 317 **Preterm birth:** • 28-31 weeks: 1 vs 24 • <28 weeks: 4 vs 12 **High risk medical conditions:** 22 vs 33	including 7 academic medical centres	**Medically-attended RSV (in infants born during or entering their RSV season 2023-2024; N= 1 616):** • Nirsevimab: 10/765 • No nirsevimab: 126/851	*presence of high-risk medical condition for severe RSV disease.*
Consolati[56] (May 2024) Italy (Valle d'Aosta)	Prospective observational study N= 537	20 December 2023- 15 February 2024 57 days	Age not mentioned	Data of hospitalisation were obtained through the Local health Unit information systems.	**RSV-related hospitalisation:** • Nirsevimab: 0/369 • No nirsevimab: 14/168	*Not reported*
Ezpeleta[40] (April 2024) Spain (Navarra)	Population-based cohort study N= 1 177	01 October 2024- 28 January 2024 119 days	Median (range), days: 38.5 (14-60)	Data from patients living in the region were extracted from administrative regional databases and epidemiological and virological surveillance registers.	**RSV-related hospitalisation:** • Nirsevimab: 8/1 083 • No nirsevimab: 8/94 **RSV-related emergency department visit:** • Nirsevimab: 11/1 083 • No nirsevimab: 9/94 **RSV-related ICU-admission:** • Nirsevimab: 3/1 083 • No nirsevimab: 2/94	**RSV-related hospitalisation (95%CI):** 88.7% (69.6-95.8) **RSV-related emergency department visit (95%CI):** 87.9% (70.3-95.1) **RSV-related ICU-admission (95%CI):** 85.9% (13.2-97.7) *Cox regression: adjustment on sex*

Jeziorski[38], 2024 France	Prospective cohort study N= 1 086 (RSV positive: 724)	27 October 2023- 29 February 2024 125 days	Mean (SD), months: 3.9 (2.7) Prematurity: 11.1% Risk factor for severe bronchiolitis:7.1%	Data of infants hospitalised for acute bronchiolitis in 6 paediatric wards	**RSV-related hospitalisation:** • Nirsevimab: 102/230 • No nirsevimab: 609/766 **RSV-related ICU admission:** • Nirsevimab: 15/24 • No nirsevimab: 63/69	**RSV-related hospitalisation (95%CI):** 79.5% (71.4-85.3)
Lefferts[42], 2024 US	Test negative case-control study N= 472 (68 cases, 472 controls); 292 entering in first RSV season with age <8 months (39 cases and 253 controls) ***Case=*** *medically-attended infants with positive for RSV* ***Control=*** *medically-attended infants with negative test for RSV*	23 October 2023 to 30 June 2024 251 days	Median, months, range: 9 (0-27) (62% of infants were <8 months)	Data from regional health records (Yukon-Kuskokwim Health Corporation)	**RSV-related hospitalisation** (whole cohort)**:** • Nirsevimab: 3/29 • No nirsevimab: 20/35 **RSV-related hospitalisation** (first season age<8 months)**:** • Nirsevimab: 3/22 • No nirsevimab: 17/27 **Medically-attended RSV-LRTI** (first season age<8 months)**:** • Nirsevimab: 8/161 • No nirsevimab: 31/131	**Hospitalisation, whole cohort (95%CI):** 93% (64-99) **Hospitalisation, first season age<8 months (95%CI):** 89% (32-98) **Medically-attended RSV (95%CI):** 76% (42-90) *Logistic regression: age, sex, calendar month, residence community type, underlying conditions (chronic lung or airway disease, heart disease, immunocompromise, cystic fibrosis, neuromuscular disease, prematurity)*
Lenglart[47], 2025 France	Test negative case control N = 383 (274 cases and 109 controls) *Cases and controls were infants attended at the emergency department with first episode of bronchiolitis with positive and negative*	1 October 2023 to 29 February 2024 151 days	**Median age (Q1-Q3),** months**:** 3.3 (2.0-5.5) vs 2.0 (1.0-4.0) **Chronic conditions, %:** • Respiratory: 0 vs 0 • Cardiac: 0 vs 2.7 • Other: 4.3 vs 9.1	Data from infants presenting to emergency department in 5 university hospitals across France	**RSV-related emergency department visit:** • Nirsevimab: 27/77 • No nirsevimab: 247/306 **RSV-related hospitalisation** (n = 303)**:** • Nirsevimab: 26/225 • No nirsevimab: 36/78	**RSV-related emergency department visit:** 82.5% (68.0-90.8) **RSV-related hospitalisation (95%CI):** 80.5% (60.5-90.3) *Logistic regression: age, sex, chronic disease, prematurity, type of childcare, month, centre of inclusion*

	RT-PCR tests for RSV, respectively					
Chauvel[39], 2024 France	Retrospective observational study N= 83 (season 2023-2024)	2023-2024 RSV season (28 October 2023 to 18 February 2024) *Effectiveness calculated among infants born between 15 September and 31 December 2023: 107 days*	**Median age (IQR), days:** 76 (40-110)	Data from infants born a tertiary centre and hospitalised during the 2023-2024 RSV season	/	**RSV-related hospitalisation (95%CI):** 78.3% (55.9-89.5) *(adjustment on birth week)*
Carcione[50], 2025 Australia	Online survey on post-marketing surveillance N= 1 195 • Nirsevimab alone: 410 • Coadministered with other vaccines): 785	All infants receiving nirsevimab between April, 02 2024 and July, 31 2024	**Median age, months (range):** 4.0 (0-20) **Comorbidities:** 15 (1.3%)	Three days after the injection of nirsevimab, parents received an online invitation to participate to the survey (response rate 27.5%)	• Adverse event within the 3 days after administration: 277 (23.2%) • Fatigue: 172 (14.4%) • Local reaction 140 (11.7%) • Fever: 127 (10.6%) • Gastrointestinal issues:113 (9.4%) • Rash: 23 (1.9%) • Medical attention seeking: 18 (1.22% in who received nirsevimab alone and 1.65% who received coadministration)	/
Perramon-Malavez[37], 2025 Spain	Retrospective cohort study N= 15 341	Infants born and receiving nirsevimab between 1 October	Median age at the end of the study (min-max), days immunized vs non-immunised: 69.0	Catalan health databases (routinely collected data in hospitals,	**RSV-related hospitalisation:** • Nirsevimab: 109/14 055 • No nirsevimab: 34/1 286 **RSV-ICU admission:**	**RSV-related hospitalisation (95%CI):** 74 (62-83) **RSV-related ICU admission (95%CI):** 85 (72-93)

		2023 to 21 January 2024 112 days	(10.0-122.0) vs 60.5 (10.0-122.0)	ED; regional database)	• Nirsevimab: 25/14 055 • No nirsevimab: 14/1 286 **RSV-related emergency department visit:** • Nirsevimab: 56/14 055 • No nirsevimab: 10/1 286	**Emergency department visit (95%CI):** 54 (10-77) *Cox regression: sex, week of birth, rurality, nationality, month of birth, socioeconomic index*
Nuñez[41], 2025 Spain (national level)	Population-based case-control study N= 4 757 • 406 cases/1 623 controls (catch-up immunisation) • 546 cases/2 182 controls (at-birth immunisation) ***Cases=*** *infants born from 1 April 2023 who were admitted in public hospitals* ***Controls=*** *4 controls for each case (matching on being born in the same hospital network, province, date of birth)*	01 October 2023 to 31 March 2024 182 days	Median age at hospital admission (IQR), days: • Catch-up immunisation: 140 (97-190) • At birth immunisation: 43 (27-61)	Clinical and immunisation records (database not mentioned) Cases: clinical and immunisation records from the hospitals Controls: register for screening programs for metabolic diseases	**RSV-related hospitalisation:** ***Catch-up immunisation:*** • Nirsevimab in cases: 205/406 • Nirsevimab in controls: 1359/1623 ***At birth immunisation:*** • Nirsevimab in cases: 399/546 • Nirsevimab in controls: 2039/2182	**RSV-related hospitalisation (95%CI):** ***Catch-up immunisation:*** • Pragmatic[a] : 87.5 (83.1-90.8) • ITT[b]: 71.0 (64.6-76.2) • Per-protocol[c] : 80.3 (75.3-84.4) ***At birth immunisation:*** • Pragmatic[a]: 85.5 (80.5-89.2) • ITT[b]: 78.0 (72.7-82.3) • Per-protocol[c]: 83.1 (78.5-86.8)

aHR: adjusted hazard ratio, aOR: adjusted odds ratio; ED: emergency department; ICU: intensive care unit; IQR: interquartile range; ITT: intention-to-treat; LRTI: low respiratory tract infection; N: number; NAb: neutralizing antibodies; Q1-Q3: first-third quartiles; PICU: paediatric intensive care unit; SD: standard deviation.
[a] logistic regression model based on immunisation status at the matching date and adjusted for sex, gestational age, birth weight, multiple pregnancy, previous non-RSV hospitalisation, comorbidities. [b] obtained from inverse-probability-of-censoring weighted conditional logistic models based on the assigned immunisation among uncensored clones at the end of the intervention period (the first 30 days of campaign for catch-up immunisation and the first 14 days of life for at-birth immunisation). [c] obtained from inverse-probability-of-censoring weighted conditional logistic models based on the assigned immunisation among uncensored clones up to the matching date.

Methodological quality of primary studies

Among the studies evaluating the effectiveness of nirsevimab using real-world data, 4 were assessed as being of high quality, one as acceptable to high, and eight as acceptable. One study was rated as having acceptable to low quality, while two were judged to be of low quality. The cross-sectional survey was rated as 'low' quality. A summary of the quality assessments is presented in Table 6, with detailed evaluations for each publication available in Appendix 1.10. In the cohort studies, the most frequently identified sources of bias were selection bias, as well as detection and confounding bias. In the case-control studies, the main risks of bias were selection and confounding. Given the observational nature of the included studies, it is important to acknowledge that blinding to exposure status is inherently difficult to implement.

Table 6 –Methodological quality of primary studies using real-world data

Cohort studies		Case-control studies	
Author (year)	Quality assessment	Author (year)	Quality assessment
Coma[46], 2024	🔵	Assad[51], 2024	🟢
Barbas del Buey[52], 2024	🔵	Lassoued[49], 2024	🟢
Ares-Gomez[53], 2024 Mallah[43], 2024	🟢	Carbajal[45], 2024	🔵
Estrella-Porter[48], 2024	🔵	Paireau[54], 2024	🔵
Consolati[56], 2024	🔴	Moline (a)[55], 2024	🔵🟢
Ezpeleta[40], 2024	🔵	Moline (b)[44], 2024	🟢
Chauvel[39], 2024	🔴	Lenglart[47], 2025	🔵
Jeziorski[38], 2024	🔵	Lefferts[42], 2024	🔵🔴
Perramon-Malavez[37], 2025	🔵	Nuñez[41], 2025	🔵

🟢 High quality 🔵🟢 Acceptable to high quality 🔵 Acceptable 🔵🔴 Acceptable to low quality 🔴 Low quality

Data synthesis

A meta-analysis was conducted for the following outcomes: hospitalisation, PICU admission, medically attended RSV infection, and overall occurrence of infection. Statistical pooling of studies was undertaken only when follow-up durations were deemed reasonably comparable, defined as either more than 120 days or less. When applicable, an initial meta-analysis was performed including all eligible study designs. A secondary analysis was carried out by stratifying studies according to design type, when applicable. This approach aimed to reduce heterogeneity and enhance the accuracy of the estimated effect sizes. A summary of the main findings is provided in Table 7.

The study by Chauvel *et al.*[39] could not be included in the meta-analysis, as the authors employed the Farrington method[57] to estimate effectiveness, and did not report the number of participants exposed or unexposed to nirsevimab. Similarly, the study by Nuñez *et al.* was not included in the meta-analysis due to its national-level scope in Spain, which overlapped with other included studies and could have introduced duplication of data.[41]

Table 7 – Summary of the pooled estimates of outcomes

Outcome	Pooled estimate odds ratio (95%CI)	Corresponding effectiveness (95%CI)	Heterogeneity (I^2)	Number of studies
RSV-related hospitalisation *(follow-up <120 days)*	• Overall: 0.13 (0.09-0.19) • Case-control studies: 0.17 (0.12-0.24) • Cohort studies: 0.14 (0.08-0.23)	• 87% (81-91) • 83% (76-88) • 86% (77-92)	• 84% • 14% • 90%	8 studies
RSV-related hospitalisation *(follow-up <120 days)*	0.24 (0.13-0.44)	76% (66-87)	86%	5 studies
PICU admission *(follow-up <120 days)*	0.13 (0.07-0.23)	87% (77-93)	57%	4 studies
PICU admission *(follow-up <120 days)*	0.23 (0.12-0.43)	77% (57-88)	47%	3 studies
RSV-related RSV emergency department visit	0.21 (0.14-0.30)	79% (70-86)	69%	5 studies
Incidence of RSV infection	0.27 (0.22-0.33)	73% (67-78)	21%	3 studies

RSV-RELATED HOSPITALISATION

- For the outcome of RSV-associated hospitalisation with a follow-up period of at least 120 days, 8 studies were included. These studies reported a total of 394 hospitalisation events among immunised infants and 1 872 events among non-immunised infants. The pooled analysis, presented in Figure 6, demonstrates that nirsevimab significantly reduced the risk of hospitalisation compared to no immunisation, with an odds ratio (OR) of 0.13 (95%CI: 0.09-0.19). However, this estimate was associated with substantial inter-study heterogeneity (I^2 = 84%). The corresponding estimated effectiveness of nirsevimab against hospitalisation over a period greater than 120 days was 87% (95%CI: 81-91).
- A subgroup meta-analysis including only case-control studies is presented in Figure 7. The pooled estimate favoured nirsevimab, demonstrating an effectiveness of 83% (95%CI: 76-88), with low inter-study heterogeneity (I^2 = 14%). A similar analysis restricted to cohort studies yielded a comparable pooled estimate, with an effectiveness of 86% (95%CI: 77-92) (see Figure 8), with heterogeneity still being high. Several factors may explain the observed heterogeneity among cohort studies. First, variation in follow-up duration was evident, ranging from 122 to 203 days. Second, differences in population characteristics, such as the proportion of children with comorbidities – which was not consistently reported across studies – may have contributed. Lastly, differences in sample sizes across studies may also have played a role. A sensitivity analysis, conducted by excluding the two studies with the smallest sample sizes, led to a marked reduction in heterogeneity while maintaining a highly comparable effectiveness estimate (see Appendix 1.11.1).
- A complementary analysis using the second generic variance method was applied on the 4 case-control studies (pooling the adjusted odds ratio) and showed a pooled estimate of 0.31 (95%CI: 0.19-0.52), which corresponded to a lower effectiveness observed in the previous analysis (see Appendix 1.11.2). However, when excluding one study that was adjusted on variables different than the other, and which was not a test-negative design, the pooled odds ratio was in the range of the results of previous analysis, corresponding to a pooled effectiveness of 77% (95%CI: 71-81) – see Appendix 1.11.3.
- The pooled analysis for the outcome RSV-associated hospitalisation with a follow-up duration of less than 120 days gave a consistent result and is available in Appendix 1.11.4.

Figure 6 – Effectiveness of nirsevimab against hospitalisation for RSV LRTI (studies with follow-up <120 days)

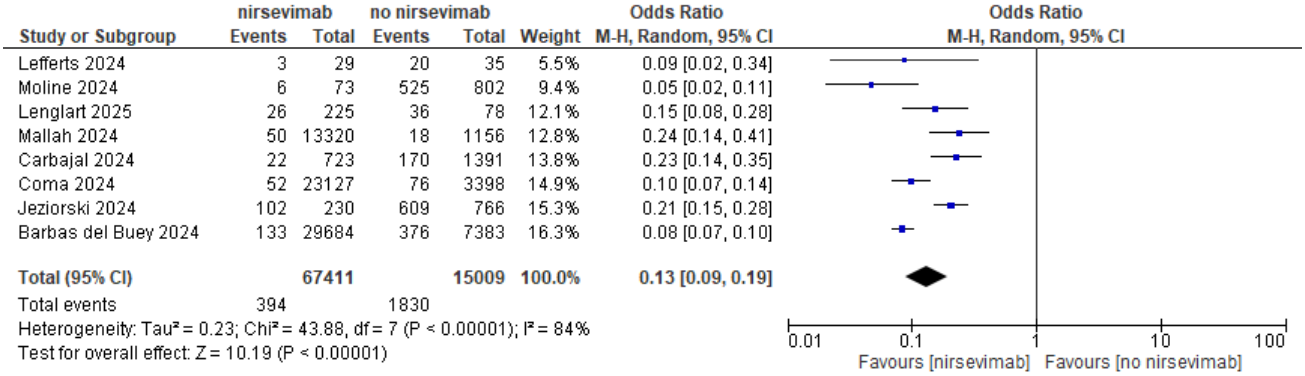


Figure 7 – Meta-analysis of the case-control studies assessing nirsevimab effectiveness against hospitalisation for RSV-LRTI (studies with follow-up <120 days)

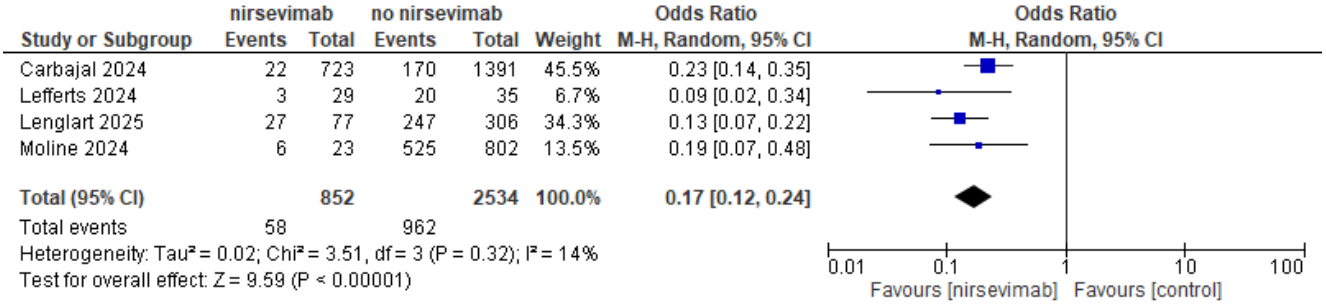
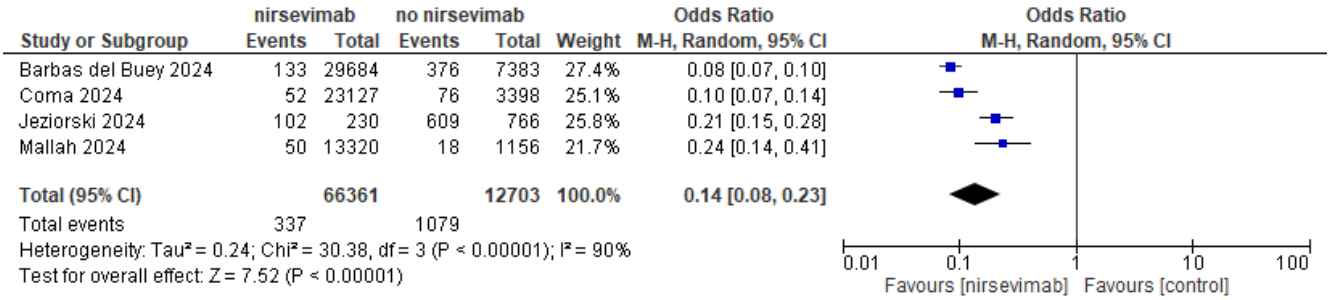


Figure 8 – Meta-analysis of the cohort studies assessing nirsevimab effectiveness against hospitalisation for RSV-LRTI (studies with follow-up <120 days)



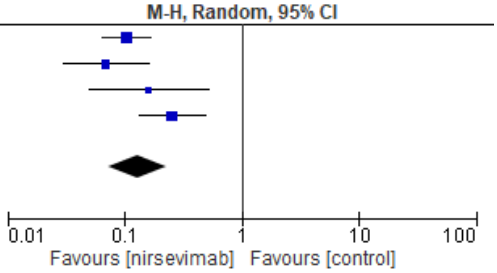
RSV-RELATED PAEDIATRIC INTENSIVE CARE UNIT (PICU) ADMISSION

- When data from four studies with a follow-up period exceeding 120 days, assessing RSV-related PICU admissions, were pooled, nirsevimab was found to be protective, with a resulting odds ratio of 0.13 (see Figure 9). Although substantial heterogeneity was observed in the overall analysis, it was entirely eliminated when restricting the analysis to cohort studies only, yielding a pooled odds ratio of 0.10 (95%CI: 0.07-0.15) – see Appendix 1.11.6.
- The pooled analysis of data on ICU admission retrieved from studies with a shorter follow-up (3 studies) is available in Appendix 1.11.7.

Figure 9 – Effectiveness of nirsevimab against RSV-related PICU admission (studies with follow-up superior to 120 days)

Study or Subgroup	nirsevimab Events	nirsevimab Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Barbas del Buey 2024	24	29684	57	7383	34.2%	0.10 [0.06, 0.17]
Coma 2024	8	23127	17	3398	22.6%	0.07 [0.03, 0.16]
Jeziorski 2024	15	24	63	69	15.3%	0.16 [0.05, 0.51]
Paireau 2024	37	58	201	230	27.9%	0.25 [0.13, 0.49]
Total (95% CI)		**52893**		**11080**	**100.0%**	**0.13 [0.07, 0.23]**
Total events	84		338			

Heterogeneity: Tau² = 0.18; Chi² = 7.08, df = 3 (P = 0.07); I² = 58%
Test for overall effect: Z = 7.07 (P < 0.00001)



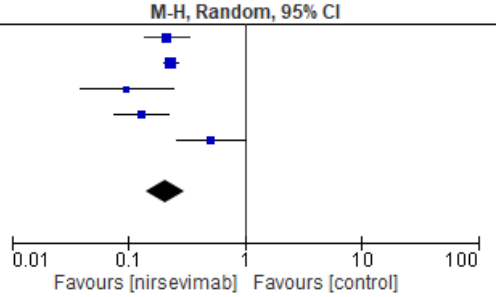
RSV-RELATED EMERGENCY DEPARTMENT ATTENDANCE

There were 5 studies (2 case-control, 3 cohort) examining RSV-related emergency visits, with a timeframe ranging between 112 and 151 days. The pooled analysis revealed that nirsevimab led to a lower likelihood of requiring emergency department visits (see Figure 10). Two other studies reported on medically-attended RSV, specifically in primary care (their pooled analysis is available in Appendix 1.11.8).

Figure 10 – Effectiveness of nirsevimab against RSV-related emergency department visits

Study or Subgroup	nirsevimab Events	nirsevimab Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Carbajal 2024	22	723	178	1391	22.2%	0.21 [0.14, 0.34]
Coma 2024	604	23127	354	3398	31.1%	0.23 [0.20, 0.26]
Ezpeleta 2024	11	1083	9	94	11.3%	0.10 [0.04, 0.24]
Lenglart 2025	27	77	247	306	19.4%	0.13 [0.07, 0.22]
Perramon-Malavez 2025	56	14055	10	1286	16.0%	0.51 [0.26, 1.00]
Total (95% CI)		**39065**		**6475**	**100.0%**	**0.21 [0.14, 0.30]**
Total events	720		798			

Heterogeneity: Tau² = 0.12; Chi² = 13.10, df = 4 (P = 0.01); I² = 69%
Test for overall effect: Z = 8.10 (P < 0.00001)



INCIDENCE OF RSV INFECTION

Data on the incidence of RSV infection (regardless of the type of care) were available from 3 cohort studies, involving 301 events among 47 589 immunised and 494 events among 7 181 non-immunised infants.[46, 48, 49] The pooled odds ratio revealed that nirsevimab reduced the risk of MA LRTI compared with the non-immunised group, with a pooled OR of 0.28 (95%CI: 0.22-0.35) (see Appendix 1.11.9).

STUDIES NOT INCLUDED IN THE POOLED ANALYSIS

- The nationwide, population-based case-control study by Núñez *et al.*,[41] was not included in the meta-analysis to avoid duplication of data: the effectiveness of nirsevimab immunoprophylaxis in preventing RSV-related hospitalisations was assessed gathering data from several regions of Spain during the 2023/24 season. Additionally, the effectiveness was evaluated for the two vaccination strategies, including 406 cases and 1 623 controls for catch-up immunisation[r], and 546 cases and 2 182 controls for at-birth immunisation[s], respectively. In order to correct for a potential immortal bias (i.e. immunised children must remain free from hospitalisation until nirsevimab administration), several modelisations were computed. The effectiveness of the catch-

[r] Nirsevimab administered within the first 30 days of a catch-up immunisation campaign at the season onset.

[s] Nirsevimab administered in the first 2 weeks of life to children born during the RSV season.

up immunisation strategy was 80% (95%CI: 75-84), while the effectiveness of the at birth immunisation was 83% (95%CI: 79-87). It is noteworthy that, a slightly reduced effectiveness was observed in pre-term infants[t] and those with birthweights under 2 500 grams[u], but the precision of the estimation was limited (wide confidence intervals).

- The study by Carcione *et al.* reported on the safety of nirsevimab within 3 days after injection through an online survey.[50] There was no safety concern at this time point, and no adverse events required inpatient care (see Table 5). The most commonly reported symptoms were local reactions, fatigue and fever; seeking medical assessment was rarely reported.

2.1.2.4 Publication bias

Publication bias was assessed only for the outcome "RSV-related Hospitalisation" involving 8 studies with a follow-up <120 days. Publication bias was deemed undetected given the absence of asymmetry of the funnel plot (see Appendix 1.12), but since there were fewer than 10 studies, the interpretation of the funnel plot is limited.

2.1.2.5 Certainty of the pooled of evidence

A GRADE-based assessment of the quality of evidence was conducted separately for clinical trials and real-world evidence studies. While findings were consistent across both study designs, the overall certainty of evidence was inherently lower for studies based on real-world data due to their observational nature.

Randomised controlled trials

The GRADE assessment indicated a high certainty of evidence for the reduction of medically-attended RSV-LRTI and hospitalisation, in infants who received nirsevimab, compared to those who did not. As previously noted, mortality could not be assessed due to the limited number of events. Furthermore, there was a high certainty of evidence that nirsevimab was not associated with an increased likelihood of either serious adverse events, or grade 3 adverse events in comparison to the control group. The certainty assessment is presented in Figure 11.

Real-world data studies

An assessment with the GRADE framework was performed for the 3 main outcomes of the analysis: hospitalisation, PICU admission and the requirement of emergency department attendance:

- Based on studies with an extended follow-up period (i.e., >120 days), the GRADE assessment indicated a moderate certainty of evidence for a reduced likelihood of hospitalisation among infants who received nirsevimab compared to those who did not (see Figure 12). A very large effect size led to upgrading the quality of evidence by one level, given that the pooled odds ratio was below 0.20. Although the number of included studies was limited (fewer than 10), no evidence of publication bias was suspected based on funnel plot analysis.
- The certainty of evidence was rated moderate for the association between nirsevimab use and a reduced risk of PICU admission, relative to standard care (pooled effect considered as 'very large').
- With respect to emergency department consultations for RSV infection, the certainty of evidence suggesting a reduced likelihood among infants who received nirsevimab – as compared to those who did not– was rated as *low*, due to risk of bias in the included studies pooled effect considered as 'large').

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[t] Catch-up effectiveness: 61.5% (95%CI: 28.6-79.3); at birth immunisation: 68.8% (95%CI:37.8-84.3).

[u] Catch-up effectiveness: 66.9% (95%CI: 38.1-82.3); at birth immunisation: 65.8% (25.0-84.4).

Figure 11 – GRADE assessment for pooled outcomes (RCTs)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nirsevimab	Standard of care	Relative (95%CI)	Absolute		
Medically attended RSV-LRTI (follow-up mean 150 days)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[1]	49/2978 (1.6%)	100/1487 (6.7%)	RR 0.25 (0.18 to 0.34)	50 fewer per 1000 (from 44 fewer to 55 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
RSV-related hospitalisation (follow-up 5 to 6 months)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association[2]	29/7016 (0.41%)	108/5506 (2%)	RR 0.19 (0.13 to 0.29)	16 fewer per 1000 (from 14 fewer to 17 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
RSV-related mortality[3]												
3	randomised trials					none	-	-	-	-		CRITICAL
Serious adverse events (follow-up mean 361-366 days)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	444/5980 (7.4%)	428/6495 (6.6%)	RR 1.05 (0.92 to 1.19)	3 more per 1000 (from 5 fewer to 13 more)	⊕⊕⊕⊕ HIGH	CRITICAL[4]
Grade 3 adverse events (follow-up mean 361-366 days)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	266/5980 (4.4%)	264/6495 (4.1%)	RR 0.94 (0.64 to 1.36)	2 fewer per 1000 (from 15 fewer to 15 more)	⊕⊕⊕⊕ HIGH	IMPORTANT

[1] pooled RR <0.50. [2] pooled effect <0.25. [3] Not estimable. [4] Only 1 SAE was considered related to the intervention: one infant had grade 3 SAE (infantile spasms [West ; syndrome]) 23 days after the receipt of nirsevimab that was considered to be related to the treatment because the relationship to nirsevimab could not be excluded (Drysdale et al).

Figure 12 – GRADE assessment for pooled outcomes (real-world data studies)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nirsevimab	Standard of care	Relative (95%CI)	Absolute		
RSV-related hospitalisation (follow-up mean 120 days)												
8	observational studies (case-control and cohort)	serious (majority of included studies rated as 'acceptable')	Serious (heterogeneity present)	no serious indirectness	no serious imprecision	very strong association (pooled odds ratio <0.20)	808 cases 1866 controls and 337/66361 exposed 1079/12703 unexposed		OR 0.13 (0.09 to 0.19)	-	⊕⊕⊕O MODERATE	CRITICAL
PICU admission (follow-up mean 120 days)												
4	observational studies (case-control and cohort)	serious quality of all 4 studies rated as 'acceptable'	Serious (moderate heterogeneity detected)	no serious indirectness	no serious imprecision	very strong association (pooled OR <0.20)	238 cases 50 controls and 47/52835 exposed 137/10850 unexposed		OR 0.13 (0.07 to 0.23)	-	⊕⊕⊕O MODERATE	CRITICAL
RSV-related emergency department visit (follow-up range: 112- 151 days)												
5	observational studies (case-control and cohort)	serious (quality of studies rated as acceptable)	Serious (substantial heterogeneity detected)	no serious indirectness	no serious imprecision	strong association (pooled OR <0.50)	474 cases 1823 controls and 671/38265 exposed 373/4778 unexposed		OR 0.21 (0.21 to 0.30)	-	⊕⊕OO LOW	IMPORTANT

2.2 Efficacy, effectiveness and safety of Abrysvo®

KEY POINTS TABLE

- The current literature on the efficacy of RSVpreF vaccine Abrysvo® is limited. Based on one large randomised controlled trial, Abrysvo® significantly reduced the risk of medically attended severe RSV-LRTI (70.0% at 180 days ; 95%CI: 50.6-82.5; high certainty), medically attended RSV-LRTI (49.2% at 180 days; 95%CI: 31.4-62.8; high certainty), and RSV-related hospitalisation (55.3% at 180 days; 95%CI: 23.8-74.6; moderate certainty), among infants compared to those whose mothers had received placebo. Regarding the RSV-related hospitalisation, the certainty of evidence was rated as moderate mainly because of imprecise results.
- According to the only randomised controlled trial published, Abrysvo® was not associated with a statistically significant increased risk of serious adverse events, either in infants or in pregnant women (moderate quality). The rate of preterm birth was higher in the group that received Abrysvo® compared to the placebo group (5.7% vs. 4.7%), although this difference was not statistically significant, and most cases were classified as late preterm. However, a subgroup analysis in non-high-income countries revealed a statistically significant increase in preterm births among vaccine recipients compared to placebo (7.0% vs. 4.0%).
- There is currently limited data available on real-world effectiveness. Only one recent test-negative case-control study was retrieved. It reported a level of effectiveness higher to that observed in the unique RCT (moderate quality). Unfortunately, the study was not designed to assess safety.
- Real-world data on the safety of Abrysvo® is also currently limited. Two observational studies found no statistically significant association between maternal RSV vaccination and the risk of preterm birth (very low certainty). A post-marketing surveillance study using data from the U.S. Vaccine Adverse Event Reporting System (VAERS) observed a higher-than-expected number of reported preterm births. However, this safety signal is difficult to interpret, as the analysis was not designed to assess causality and did not include clinical data. Long-term monitoring and additional real-world evidence are needed to better assess the potential association between Abrysvo® and the risk of preterm birth.
- Currently, there are no data on the effectiveness or safety of the intervention in pregnancies complicated by obstetrical or fetal conditions, warranting further investigation.

2.2.1 Methods

2.2.1.1 Search strategy: research questions and selection criteria

The research questions were formulated as follows: "*What is the clinical effectiveness of Abrysvo administered to pregnant women, against RSV-infection in infants, compared to standard of care*?" and "*Is Abrysvo safe for pregnant women and infants?*". The structured PICOTS framework is provided in Table 8. Only full articles published in English were included. As for the search on nirsevimab, the review exclusively encompasses research undertaken within OECD countries. The articles were searched by one researcher with the same methodology as described in section 2.1.1.1

Table 8 – Inclusion and exclusion criteria

PICOTS	Inclusion	Exclusion
Patients	Pregnant women	
Intervention	Maternal pre-F vaccine Abrysvo	
Comparators	• For the assessment of efficiency: placebo • For or the assessment of safety: comparator not mandatory	No comparator /
Outcomes	a. Critical outcomes in infants: • RSV-related mortality • RSV-related ICU admission • RSV-related hospitalisation • Severe RSV-related lower respiratory tract illness • Serious adverse events b. Important outcomes in infants: • RSV-related LRTI risk • Reactogenicity • Rate of adverse events c. Critical outcomes in pregnant women: • Rate of serious adverse events d. Important outcomes in pregnant women: • Rate of adverse events	• Data modelisation including data without the use of Abrysvo • In-vitro data • Pharmacokinetics data
Timeframe	No limit	
Setting	Countries from OECD	Study with data only from a country outside of OECD
Type of studies	• For the assessment of efficiency: RCT, observational studies, systematic reviews/meta-analysis* • For the assessment of safety: all study designs	Case series, case report, letters, editorials, phase 1 trials, narrative reviews, comments, opinions /

** As the literature on RSVpreF vaccine Abrysvo® is rapidly evolving, systematic reviews/meta-analysis were considered not for analysis but to ensure than no study is omitted.*

2.2.1.2 Databases and extraction

The following bibliographic databases were searched for relevant publications: Ovid-Medline, Embase, and The Cochrane Library. Search queries were developed in collaboration with a medical information specialist and adapted to each database, and it is presented in Appendix 2.1. The first search was conducted on October, 25 2024 (Ovid-Medline, Embase), and on December 20, 2024 (Cochrane). An update was performed on February 17, 2025 (Ovid-Medline), February 19, 2025 (Embase) and February 17, 2025 (Cochrane). Search in these databases was supplemented by collecting additional references from different sources (identification of cited references, exploratory searches in the bibliographical databases of key-references). The extraction of data was performed as described in section 2.1.1.2. The international clinical trials registry platform '*ClinicalTrials.gov*', was also consulted.

2.2.1.3 Methodological quality of the studies

The risk of bias for each study was assessed as described previously in the section 2.1.1.3.

2.2.1.4 Data synthesis

A meta-analysis was conducted for the studies using real-world data, while a narrative synthesis was undertaken for the sole RCT identified. The quality of the pooled body of evidence was performed using the GRADE methodology, as previously described in the section 2.1.1.4.

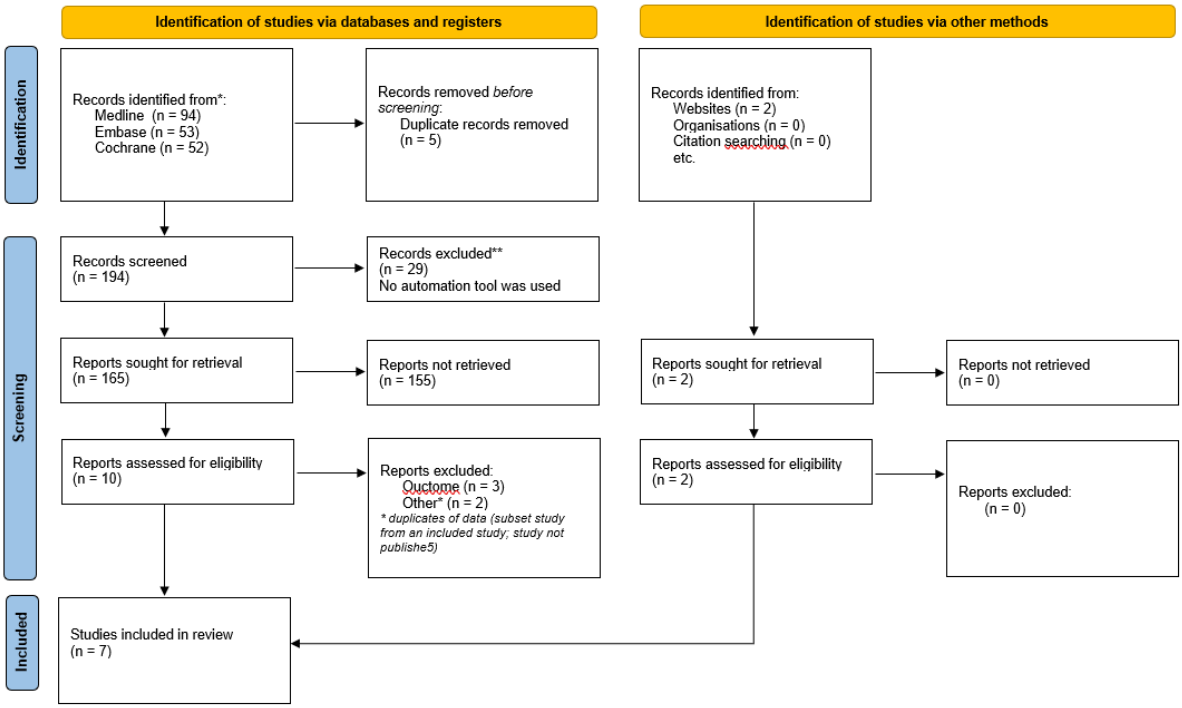
2.2.2 Results

2.2.2.1 Study selection

After removing duplicates, the search yielded 194 records. Following title and abstract screening, 10 articles were assessed for eligibility (Figure 13). A full-text review led to the exclusion of 5 articles. In addition to the 5 remaining studies, 2 more were identified through reference list searches and website screening, bringing the total number of included articles to 7.[58-64] The list of excluded articles is available in Appendix 1.2.

Among the included articles, one RCT (published within two articles[61, 64]) was identified along with a post-hoc analysis of the same RCT[63], 2 cohort studies[59, 62], 1 report on the post-marketing safety from a national health agency (FDA[v])[58], and one systematic review (that is not included *per se* in the analysis[w]).[60]

Figure 13 – Prisma flow diagram for systematic review on Abrysvo



v Food and Drug Administration

w As mentioned in Table 8, systematic reviews/meta-analysis were considered to ensure than no study was omitted since the literature on Abrysvo® is currently rapidly evolving.

2.2.2.2 *Characteristics of included studies*

Randomised controlled trial: the MATISSE trial

- The MATISSE trial was published in 2 publications.[61, 64] The first article presented preliminary findings, based on a partially enrolled study population and incomplete follow-up data.[64] This trial was a phase 3, randomised, double-blind, placebo-controlled study designed to evaluate the efficacy, safety, and immunogenicity of the RSV prefusion F protein vaccine (RSVpreF) administered to pregnant women, with no known increased complication risk.
- Participants were aged 49 years or younger, and received a single 120 µg dose of RSVpreF or placebo at 24 to 36 weeks of gestation. The primary endpoint was defined as the occurrence of severe RSV-associated medically attended LRTI, and medically attended LRTI[x] in infants within 180 days post-birth. A range of timepoints was considered and these are outlined in Table 9 (see Appendix 2.3 for the description of the preliminary results from Kampmann *et al.* [61, 64]). The vaccine demonstrated a 82.4% (95%CI: 57.5-93.9) efficacy against severe RSV-associated MA-LRTI within 90 days and a 70.0% (95%CI: 50.6-82.5) efficacy within 180 days after birth. Efficacy against RSV-related hospitalisation was a secondary outcome and reached 69.7% at 90 days, declining to 55.3% at 180 days (Table 9). The safety profile of Abrysvo was favorable in both pregnant women and their infants, with no new safety concerns identified (safety events of particular interest included pre-term birth or delivery[y], low birth weight (≤2500 grams), developmental delay, or a positive SARS-CoV-2 test) (see Table 10). The incidence of preterm birth was slightly higher in the vaccine group (5.7%) compared to the placebo group (4.7%). A post-hoc analysis of the trial assessing preterm births and neonatal outcomes found that, although the overall difference in preterm birth rates was not statistically significant (RR 1.20; 95%CI: 0.98-1.46), a higher incidence was observed among RSVpreF recipients in non-high-income countries (7.0% vs. 4.0%; RR 1.73; 95%CI: 1.22-2.47).

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[x] The case definitions of medically-attended LRTI and medically-attended severe LRTI are provided in Table 9 (legend).

[y] Birth at <37 weeks' gestation.

Table 9 – Extraction of data from RCTs on RSVpreF vaccine Abrysvo

Author, year	Design, sample size and setting	Intervention and control	Timeframe and follow-up	Targeted population	Main characteristics intervention group	Main characteristics control group	Outcomes (intervention vs control) and efficacy (95%CI)
Simoes[61], 2025 ***MATISSE trial***	Phase 3 Randomised placebo controlled trial (ratio 1:1) N= 7 420 pregnant women (3711/3709) N= 7 307 infants (3 660/3 647) International (both hemispheres)	Unadjuvanted RSVpreF vaccine Abrysvo IM 120 µg or placebo	June 17, 2020 to October 27, 2023 Mean follow-up for children (vaccine vs placebo): 398 vs 392 days	**Pregnant participants:** healthy pregnant (≤49 aged); gestational age 24 to 36 weeks **Infant participants:** infants born to participants who received the investigational product at least 14 days before delivery	**Median age of maternal participants** (range), years: 29 (16-45) **Gestation at injection**, median (range), weeks: 31.3 (24.0-36.6) **Gestational birth** (weeks), %: • 24 to <28: <0.1 • 28 to <34: 0.6 • 34 to <37: 5.1 • 37 to <42: 93.6 • ≥42: 0.7	**Median age of maternal participants** (range), years: 29 (14-47) **Gestation at injection**, median (range), weeks: 31.3 (24.0-36.9) **Gestational birth** (weeks), %: • 24 to <28: <0.1 • 28 to <34: 0.3 • 34 to <37: 4.4 • 37 to <42: 94.3 • ≥42: 0.9	**Primary outcome: medically attended severe* RSV-associated LRTI in infants <6 months, % (n) – efficacy (95%CI):** • Within 90 days: 0.2 (6) vs 1.0 (34)– 82.4% (57.5-93.9) • Within 120 days: 0.4 (13) vs 1.4 (49) – 73.5% (50.3-86.8) • Within 150 days: 0.5 (18) vs 1.7 (61) – 70.5% (49.4-83.6) • Within 180 days: 0.6 (21) vs 2.0 (70) – 70.0% (50.6-82.5) **Primary outcome: medically attended[$] RSV-associated lower respiratory tract illness in infants, % (n) – efficacy (95%CI):** • Within 90 days: 0.7 (25) vs 1.7 (59) – 57.6% (31.3-74.6) • Within 120 days: 1.1 (40) vs 2.5 (88) – 54.5% (33.2-69.5) • Within 150 days: 1.5 (55) vs 3.1 (110) – 50.0% (30.3-64.5) • Within 180 days: 1.9 (67) vs 3.7 (132) – 49.2% (31.4-62.8) **Secondary outcome: RSV-related hospitalisation, % (n) – efficacy (95%CI):** • Within 90 days: 0.3 (10) vs 0.9 (33) – 69.7% (37.1-86.7) • Within 120 days: 0.4 (15) vs 1.1 (39) – 61.5% (28.6-80.3) • Within 150 days: 0.5 (18) vs 1.2 (42) – 57.1% (23.9-76.8) • Within 180 days: 0.6 (21) vs 1.3 (47) – 55.3% (23.8-74.6) • Within 360 days: 1.4 (50) vs 1.9 (66) – 24.2 (-11.1- 48.6) **Exploratory endpoint: efficacy against RSV associated medically-attended LRTI with SpO_2 <90% or supplemental oxygen, % (n) – efficacy (95%CI):** • Within 90 days: 0.1(4) vs 0.5(17) – 76.5%(27.9-94.2) • Within 180 days: 0.4 (13) vs 0.7 (25) – 48.0% (-5.6-75.6)
Madhi[63], 2025	Post-hoc descriptive analysis of MATISSE trial regarding	see corresponding RCT *Simoes et al., 2025*			**Pre-term delivery,** n= 378 (206 RSVpreF vs 172 placebo)		**Proportions of events (% of the whole study population; Abrysvo vs placebo)** • Preterm birth[##] (<37 weeks): 5.7% vs 4.7% • Low birth weight: 5.1% vs 4.3%

	preterm birth frequency and outcomes in infants N= 7 386 pregnant women (3 698 received Abrysvo and 3 688 received placebo) N= 7 305 infants		Gestational age at vaccination, weeks in participants with preterm delivery (n=378), abrysvo vs placebo: ○ 24-<28: 30.1% vs 34.3% ○ 28-<32: 35.3% vs 30.8% ○ 32-36: 34.5% vs 34.9% ○ 36: 0% vs 0% **Term delivery**, n= 6 921 Gestational age at vaccination, weeks, in participants with term delivery (n= 6 921), abrysvo vs placebo: ○ 24-<28: 24.9% vs 24.0% ○ 28-<32: 28.8% vs 30.5% ○ 32-36: 46.2% vs 45.3% ○ 36: <0.1% vs 0.2%	• Preterm birth (<37 weeks) and low birth weight: 2.4% vs 1.9% • SAE-related hospitalisation: 2.3% vs 2.2% • AEs within 1 month after birth: 38.0% vs 35.4% • Low APGAR scores**: 1.5% vs 1.3% • Death within 24 months[$$]: 0.2% vs 0.4% **Relative risks of events (95%CI):** • Preterm birth[##] (<37 weeks): 1.20 (0.98-1.46) • Low birth weight: 1.17 (0.95-1.44) • Preterm birth (<37 weeks) and low birth weight: 1.25 (0.92-1.71) • SAE-related hospitalisation: 1.03 (0.76-1.40) • AEs within 1 month after birth: 1.07 (1.01-1.14) • Low APGAR scores**: 1.17 (0.79-1.72) • Death within 24 months[$$]: 0.57 (0.24-1.36) *[##] Preterm birth occurred predominantly between gestational age 34 to <37 weeks* *** First score <4 and last score <7* *[$$] one RSV-associated death occurred in the placebo group. Of 3 pre-term deaths, 1 occurred in the Abrysvo group due to prematurity-related complications (young age was identified as underlying preterm birth risk factor and the death was not considered as vaccine-related).*

** Severe medically attended RSV-associated LRTI=medically attended visit for respiratory tract infection and a RSV RT-PCR positive test result (central laboratory or by certified laboratory with nucleic acid amplification test for RSV) and at least one of the following: fast breathing (respiratory rate ≥70 breaths per minute for <2 months of age, ≥60 breaths per minute from 2 to less than 12 months of age, or ≥50 breaths per minute in 1 to 2 years of age), SpO2 <93% , high-flow nasal cannula or mechanical ventilation (invasive or non-invasive), ICU admission for more than 4 hours, unconscious infant/failure to respond. [$] medically attended RSV-associated LRTI= medically attended visit for respiratory tract infection and a RSV RT-PCR positive test result (central laboratory or by certified laboratory with nucleic acid amplification test for RSV) and at least one of the following: fast breathing (respiratory rate ≥60 breaths per minute for <2 months of age, ≥50 breaths per minute from 2 to less than 12 months of age, or ≥40 breaths per minute in 1 to 2 years of age), SpO2 <95%, chest wall indrawing.*

Table 10 – Extraction of data on safety from the MATISSE trial

Author, year	Pregnant participants safety (RSVpreF vs placebo)	Infants safety (RSVpreF vs placebo)

Simoes[61], 2025
 	
MATISSE trial
	• Any AE reported one month after vaccination (95%CI), %: 14.0 (12.9-15.1) vs 13.2 (12.2-14.4)
	• AE considered drug related (after drug administration to 6 months after delivery), %: 0.4 vs 0.1
	• AE of special interest (occurring 1 months after vaccination): 2.8% vs 2.6%
	• SAE (occurring 1 months after vaccination)*, %: 4.3 vs 3.8
		• Any AE within 1 month (95%CI),%: 38 (36.4-39.6) vs 35.4 (33.9-37.0)
		• SAE, %: 16.3 vs 16.1
		• Special interest AE (from birth to 24 months), %: 8.4 vs 7.3:
		  ○ Low birth weight, %: 5.1 vs 4.3
		  ○ Premature birth,%: 5.7 vs 4.7
		  ○ SARS-CoV-2 test positive, %: 3.3 vs 3.0
		  ○ Developmental delay, %: 0.1 vs <0.1
		  ○ Newly chronic medical conditions, %: 3.9 vs 4.5
		  ○ Asthma-like respiratory symptoms, %: 6.8 vs 6.3
		• Death (from birth to 24 months), n: 8 vs 14

** Three serious adverse events considered vaccine related were reported in RSVpreF recipients (severe extremity pain, premature labor, eclampsia), and one was reported in the placebo group (moderate premature placenta separation); all resolved. AE: adverse event, SAE: serious adverse event.*

Studies on real-world data

Three studies were identified and are presented in Table 11. Two studies were retrospective,[59, 62] and one study was a report from the US Food and drug Administration (FDA).[58]

- One retrospective study was conducted across two hospitals in the USA and assessed the rate of preterm birth[z] and hypertensive disorders among pregnant women who received RSF-pre-F vaccine, compared to those who did not.[62] Adverse neonatal outcomes[aa] were also recorded. Preterm birth was observed in 6.5% of the cohort. No significant association was found between preterm birth and vaccination. However, a modestly significant association was found between vaccination and hypertensive disorders of pregnancy, and mainly due to the detection of gestational hypertension. No differences were reported on the incidence of pre-eclampsia and eclampsia incidence (see Table 11).
- The second retrospective study, conducted at a single-centre, investigated the uptake of the RSVpreF vaccine in pregnancy and of nirsevimab in newborns, in the US.[59] Among 647 pregnant women, 64% received the vaccine, while 70% of newborns received nirsevimab. Vaccinated individuals exhibited lower rates of preterm delivery.[bb] To further explore the potential association between RSVpreF vaccine and pre-term birth, the authors conducted a nested case-control study by matching 75 cases of preterm delivery with 519 controls who delivered at term. In multivariate analysis, no statistically significant association was identified between preterm delivery and vaccination (see Table 11).
- The third article reported that the FDA mandated new safety warnings for the RSV vaccines (Arexvy® and Abrysvo®) due to a potential increased risk of Guillain-Barré syndrome occurring within 42 days post-vaccination.[58] This decision was based on data from clinical trials, and post-

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z Pre-term birth was defined as any birth occurring at less than 37 weeks' gestation.

aa Stillbirth, small gestational age, intensive care admission, respiratory distress, jaundice or hyperbilirubinemia, hypoglycemia, sepsis.

bb Pre-term delivery was defined as delivery at less than 37 weeks' gestation.

marketing observations among persons ≥65 years old, which suggested an excess of 7-9 Guillain-Barré syndrome cases per million vaccine doses. Despite this, the FDA maintained that the benefits of these vaccines outweigh the potential risks.

2.2.2.3 Within-study methodological quality

- The MATISSE trial was deemed at low risk of bias (see Appendix 2.4.1).
- Among studies presenting real-world data, both were rated as 'acceptable' (see Appendix 2.4.2). The report from the FDA was not rated as it only communicated complications without a particular study design.

Table 11 – Real-world data on the use of Abrysvo

Author, year, country (region)	Design and sample size	Timeframe and observation time (days)	Age and characteristics *(immunized vs non-immunized)*	Source of information and settings of included populations	Relevant Outcome(s) by study group	Adjusted estimates of outcomes
Son[62], 2024 US	Retrospective observational study N = 2 973 participants who delivered at 32 weeks' gestation or later	September, 22 2023 to January 31, 2024 131 days	Median age (IQR) years: 35.3 (33.1-38.1 vs 34.6 (31.9-37.3) Mean gestational age at vaccination, weeks (SD): 34.5 (1.4)	Electronic health records from 2 hospitals (New York City)	Preterm-birth, % (n= 191; 6.5% of the cohort): • Vaccine: 5.9% (60/1 011) • No vaccine: vs 6.7% (131/1 962) Hypertensive disorders of pregnancy: • Vaccine: 20.1% (203/1 011) • No vaccine: 18.1% (355/1 962) *Other results on pregnancy outcomes and neonatal outcomes are available on demand.*	**Preterm-birth:** • aOR (95%CI): 0.87 (0.62-1.20) • aHR (95%CI): 0.93 (0.64-1.34) **Hypertensive disorders of pregnancy:** • aOR (95%CI): 1.10 (0.90-1.35) • aHR (95%CI): 1.43 (1.16-1.77) *Adjustment for: maternal age, race, ethnicity, insurance type, parity, delivery hospital site, in vitro fertilization pregnancy, pregestational diabetes, BMI<30 kg/m^2 at delivery encounter admission*
Blauvelt[59], 2025 US	Retrospective cohort study on the uptake of RSVpreF vaccine and nirsevimab N = 647 pregnant participants + nested case-control analysis including 75 cases (preterm birth	October 2023, 15 to April 15, 2024 183 days	Mean age (SD), years: 34.6 (6.2)	Single academic centre California Immunisation Registry (CAIR2)	**Outcomes** (414 vaccinated vs 233 unvaccinated) • Mean gestational age at delivery (SD), weeks: 39.0 (1.4) vs 38.4 (2.1)* • Preterm delivery: 8.5% vs 18.5%* • Preterm labour: 2.2% vs 3.0% • Preterm premature rupture of membranes: 3.1% vs 4.7% • Fetal growth restriction: 6.5% vs 5.6% • Pregnancy-induced hypertension: 23.9% vs 30.5% • Oligohydramnios: 3.1% vs 2.2% • Chorioamnionitis: 11.4% vs 11.2% • Cesarian delivery: 32.6% vs 27.5%	**aOR for preterm birth (95%CI)** – nested case control design (75 cases/519 controls)**:** 1.03 (0.55-1.93) *Adjustment on: age at delivery, parity, race and ethnicity, type if insurance, parent cardiovascular disease, pregestational diabetes, multiple gestation, use of assisted reproductive technology, early fetal growth restriction, Tetanos Diphteria, Pertussis vaccination during pregnancy*

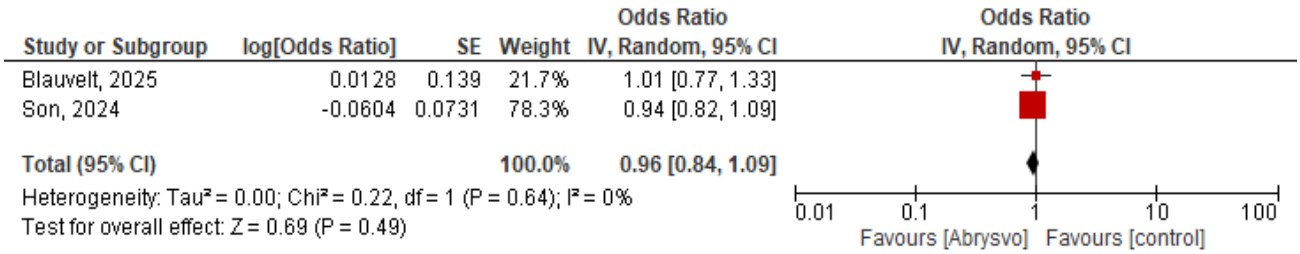
	<37 weeks) and 519 controls (term birth ≥37 weeks)				• Postpartum haemorrhage: 20.0% vs 16.3% • Mean birth weight (SD), grams: 3289 (517) vs 3150 (601)* • NICU admission: 11.1% vs 22.8%* • Stillbirth: 0% vs 0.86% ** p-value <0.05*	
No author[58], 2025	Warning from FDA	May 2023 to July 2024	Adults ≥65 years old	Vaccine Adverse Event Reporting System (VAERS), Medicare data, post marketing study	increased risk of Guillain-Barré syndrome within 42 days of vaccine administration: 9 additional cases per million doses	/

aHR: adjusted hazard ratio, aOR: adjusted odds ratio, IQR: interquartile range, N: number; NICU: neonatal intensive care unit; SD: standard deviation.

2.2.2.4 *Data synthesis*

Using the generic variance method, the pooled analysis of the two studies reporting adjusted OR for preterm delivery showed no statistically significant association between preterm delivery and vaccination (Figure 14).

Figure 14 – Association between RSVpreF vaccine and preterm delivery



2.2.2.5 *Quality of evidence*

- The only available RCT reported that vaccination with Abrysvo significantly reduces the risk of medically attended severe RSV-LRTI and medically attended RSV-LRTI with high certainty (Figure 15). For the efficacy against RSV-related hospitalisation, the quality of the evidence was rated moderate. This rating was based on the following consideration: given that Abrysvo® is relatively expensive and there is a suspicion of a possible increased risk of premature delivery, clinicians would require a large protective effect of the vaccine to reach a balanced risk-benefit ratio, say at least 70%. This target is not met (even for a target efficacy of 50%).
- The only available RCT also found that there was no statistically significant increase in serious adverse events, including prematurity. The evidence was rated moderate because of the large confidence intervals around the point estimates, including both protective and harmful effects. However, for prematurity, the risk ratio was close to statistical significance (RR 1.20; 95%CI: 0.98-1.46), and this potential adverse event should be monitored closely in future studies (see Figure 16).
- The evidence retrieved from the two real-world studies provided very low-certainty, suggesting no statistically significant association between maternal RSV vaccination and preterm birth.

Figure 15 – GRADE assessment for outcomes on efficacy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Abrysvo	No Abrysvo	Relative (95%CI)	Absolute		
Medically-attended severe RSV- LRTI (follow-up mean 90 days)												
1	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	None[1]	6/3585 (0.17%)	34/3563 (0.95%)	RR 0.175 (0.074 to 0.417)	8 fewer per 1000 (from 6 fewer to 9 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Medically-attended severe RSV- LRTI (follow-up mean 180 days)												
1	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	none[1]	21/3585 (0.59%)	70/3563 (2%)	RR 0.298 (0.183 to 0.484)	14 fewer per 1000 (from 10 fewer to 16 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Medically-attended RSV- LRTI (follow-up mean 90 days)												
1	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	none[1]	25/3585 (0.7%)	59/3563 (1.7%)	RR 0.421 (0.264 to 0.671)	10 fewer per 1000 (from 5 fewer to 12 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
Medically-attended RSV- LRTI (follow-up mean 180 days)												
1	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	none[1]	67/3585 (1.9%)	132/3563 (3.7%)	RR 0.504 (0.377 to 0.674)	18 fewer per 1000 (from 12 fewer to 23 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
RSV-related hospitalisation 90 days (follow-up mean 90 days)												
1	randomised trials	no serious risk of bias	not applicable	no serious indirectness	serious[2]	None[1]	10/3585 (0.28%)	33/3563 (0.93%)	RR 0.301 (0.149 to 0.610)	6 fewer per 1000 (from 4 fewer to 8 fewer)	⊕⊕⊕O MODERATE	CRITICAL
RSV-related hospitalisation 180 days (follow-up mean 180 days)												
1	randomised trials	no serious risk of bias	not applicable	no serious indirectness	serious [2]	none[1]	21/3585 (0.59%)	47/3563 (1.3%)	RR 0.444 (0.266 to 0.741)	7 fewer per 1000 (from 3 fewer to 10 fewer)	⊕⊕⊕O MODERATE	CRITICAL

[1] Publication bias not applicable. [2] Large confidence interval, see section 2.2.2.5.

Figure 16 – GRADE assessment for pooled outcomes on safety

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RSVpreF Abrysvo	Standard of care	Relative (95%CI)	Absolute		
Serious adverse events (pregnant women) occurring one month after vaccination												
1	randomised trials	no serious risk of bias	not applicable	no serious indirectness	serious[2]	none[1]	159/3698 (4.3%)	141/3687 (3.8%)	RR 1.124 (0.9 to 1.404)	5 more per 1000 (from 4 fewer to 15 more)	⊕⊕⊕O MODERATE	CRITICAL
Serious adverse events (infants) occurring 1 month after birth												
1	randomised trials	no serious risk of bias	not applicable	no serious indirectness	serious[2]	none[1]	597/3659 (16.3%)	587/3646 (16.1%)	RR 1.013 (0.913 to 1.125)	2 more per 1000 (from 14 fewer to 20 more)	⊕⊕⊕O MODERATE	CRITICAL
Premature birth (based on one RCT)												
1	randomised trials	no serious risk of bias	not applicable	no serious indirectness	serious[2]	none[1]	206/3656 (5.7%)	172/3643 (4.7%)	RR 1.193 (0.98 to 1.454)	9 more per 1000 (from 1 fewer to 21 more)	⊕⊕⊕O MODERATE	CRITICAL
Low birth weight (based on one RCT)												
1	randomised trials	no serious risk of bias	not applicable	no serious indirectness	serious[2]	none[1]	186/3659 (5.1%)	158/3646 (4.3%)	RR 1.17 (0.95 to 1.44)	7 more per 1000 (from 2 fewer to 19 more)	⊕⊕⊕O MODERATE	IMPORTANT
Premature birth (based on real world data studies)												
2	observational studies	serious (retrospective studies)	not applicable	no serious indirectness	serious[2]	none[1]	95/1425 (6.7%)	174/2195 (7.9%)	RR 0.841 (0.66 to 1.07)	13 fewer per 1000 (from 27 fewer to 6 more)	⊕OOO VERY LOW	CRITICAL

1 Publication bias not applicable. [2] Large confidence interval, including both protective and harmful effect.

2.3 Discussion and conclusion

2.3.1 Beyfortus®

This literature review confirms that nirsevimab is effective in preventing RSV infections and associated healthcare utilisation in infants during their first RSV season. Both pivotal and pragmatic clinical trials have consistently demonstrated its efficacy in reducing the incidence of medically attended RSV-associated lower respiratory tract infections and hospitalisations, with significant relative risk reductions. Furthermore, these studies have established a favorable safety profile comparable to that of placebo. Following this initial evidence, real-world data from multiple countries have corroborated the effectiveness of nirsevimab during the RSV season, closely aligned with that observed in clinical trials.

POPULATIONS

The benefits of nirsevimab have been predominantly documented in full-term and preterm infants without major comorbidities. Clinical trials have assessed the efficacy of nirsevimab in both full-term and preterm populations. Notably, the MEDLEY trial specifically evaluated safety in infants at elevated risk for severe RSV infection due to prematurity or underlying cardiopulmonary conditions – populations traditionally eligible for palivizumab.[27] The MEDLEY study demonstrated a safety profile for nirsevimab comparable to that of palivizumab. While it did not directly assess clinical efficacy, it provided indirect evidence through serum nirsevimab concentrations that were consistent with those observed in the MELODY trial, which focused on otherwise healthy infants.[25]

Complementary evidence from real-world observational studies has included infants with cardiopulmonary comorbidities. National immunisation campaigns have supported the broad use of nirsevimab, extending coverage to preterm infants, those with comorbidities, and older children with chronic cardiac or pulmonary conditions (see Table 5). In these studies, effectiveness estimates were generally adjusted for the presence of risk factors for severe RSV disease. However, detailed subgroup analyses specifically addressing effectiveness in high-risk populations is limited (see Appendix 1.8). Additionally, the proportion of at-risk infants was often small or not explicitly reported, likely due to the administrative nature of the datasets used. For instance, Assad *et al.* observed a trend toward reduced effectiveness of nirsevimab in infants with risk factors for severe bronchiolitis, though the difference did not reach statistical significance (64.8%; 95%CI: -17.2-89.4).[51]

TIMEFRAME: COVERAGE OF NIRSEVIMAB AND EVOLUTION OF RSV INFECTIONS

Overall, both clinical trials and real-world studies have assessed the efficacy of nirsevimab throughout the RSV season (*i.e.* on average 150 days). Clinical trials have monitored the safety outcomes up to approximately one year following administration. Some real-world studies have extended their observation periods beyond the end of the RSV season.

Following the introduction of a widespread immunisation, potential shifts in the epidemiological and virological characteristics of RSV infection were explored. These include the possibility of temporal displacement of RSV circulation and the emergence of viral variants with altered characteristics, including potential resistance to monoclonal antibody prophylaxis:

- The MELODY trial followed the participants through their second RSV season (without administration of an additional dose of nirsevimab).[29] The objectives of this follow-up study were to determine whether there was a temporal shift in disease burden to the second year of life, and to evaluate the risk of antibody enhanced diseases severity (see Appendix 1.4). Children were followed from the drug administration to day 511 post-dose. The follow-up data indicated comparable incidence rates of RSV infection between the nirsevimab and placebo groups, suggesting neither an increase in disease severity nor a shift in disease burden to the second RSV season (see Appendix 1.4). Additionally, a post-hoc analysis of the same trial assessed the incidence of all RSV and non RSV infections through day 511, and showed that there was no

replacement of RSV by other respiratory pathogens.[cc][65] These preliminary observations warrant confirmation through further research on the epidemiological impact of widespread nirsevimab use. In this context, a recent study reported clinical and microbiological data from hospitalised infants in two Spanish regions during the 2023–2024 RSV season. The findings indicated a 20% to 30% reduction in hospitalisations due to RSV-associated bronchiolitis compared to the 2021-2022 and 2022-2023 seasons. Conversely, an increase of 10% to 20% was observed in bronchiolitis cases associated with rhinovirus and human metapneumovirus.[66]

- The *POLYRES* study aimed to monitor the potential emergence of viral escape mutations to nirsevimab during the first year of widespread use in France.[67] The susceptibility to nirsevimab was assessed in a cohort of RSV infected infants[dd] treated with or without nirsevimab, during the 2023-2024 RSV season. The findings indicated that all RSV-A strains remained susceptible to nirsevimab, while a limited number of breakthrough infections caused by RSV-B were associated with resistance-conferring mutations. Authors concluded that although rare, resistance might occur in RSV-B and warrants molecular surveillance, particularly in the context of broad-scale prophylactic use of nirsevimab.

STUDIES EXCLUDED FROM THE ANALYSIS AND STUDIES PUBLISHED AFTER THE COMPLETION OF THE LITERATURE REVIEW

- In the present review, four articles conducted in Spain were excluded because of a potential duplication of data (see 2.1.2.1). Three assessed the effectiveness of nirsevimab against hospitalisation.[33-35] They provided results comparable to the included studies, and the pooled estimates through the meta-analysis. One small study assessed the effectiveness of nirsevimab against medically attended RSV infections in primary care settings, through an extensive network including 92 paediatricians and 57 primary care centres (see Appendix 1.6).[36] The study reported an effectiveness of 75.8% (95%CI: 40.4-92.7) in preventing RSV-related medically attended visits.
- After completing the literature review, a study describing the effectiveness of nirsevimab against RSV-related hospitalisation in 3 Australian hospitals was published.[68] Through a test-negative design case-control study (including 184 cases/100 controls), the authors observed an effectiveness of 88.2%[ee] (95%CI: 73.5-94.7).
- A French population based study[ff], including 82 474 infants born between February and September 2023 (end of follow-up in January 2024–median follow-up 118 days), reported an effectiveness of nirsevimab against hospitalisation of 65% (95%CI: 61-69), and 74% effectiveness (95%CI: 56-85) against PICU admission.[69] Subgroup analyses demonstrated consistent effectiveness across key populations, including infants with or without comorbidities, and those born preterm or at term. Effectiveness varied by period of viral circulation, with higher protection observed during the peak RSV activity (November 15 to December 14), estimated at 71% (95%CI: 65-76), compared to the period of lower viral circulation (December 15 to January 31). Overall, the effectiveness observed in this study was slightly lower than that reported in other real-world studies and clinical trials. The authors attributed this difference partly to the high RSV attack rate during the study period.

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cc The incidence of RSV infection was lower in the nirsevimab group, compared to placebo, over the whole follow-up duration (511 days).

dd All infants received medical care (outpatient or inpatient).

ee Adjustment was made on age group, sex, Aboriginality, medical risk factors, prematurity, week and site of enrolment.

ff Nirsevimab recipients were 1:1 matched to unimmunized control, randomly sampled from the set of infants who were yet to receive nirsevimab. The follow-up ended at the earliest following event: nirsevimab receipt, death, monoclonal antibody infusion of the matched control (for the passively immunised infants), or the end of the study period (31 January 2024).

Additional contributing factors may include regional variations in RSV circulation patterns and differences in hospitalisation practices. Another proposed explanation for the lower observed effectiveness, relative to studies conducted in Spain, is the high nirsevimab coverage in Spain, which may have led to fewer hospitalisations and consequently, less precise effectiveness estimates. Lastly, the authors noted that low uptake of monoclonal antibody administration in outpatient settings (12% of eligible infants) may have limited the ability to fully assess effectiveness in the broader population.

- In Belgium, a large observational study on the effectiveness of nirsevimab is ongoing.

METHODOLOGICAL CONSIDERATIONS

Overall, the quality of both clinical trials and real-world studies was good, with consistent findings observed across study types. Notably, many real-world studies employed a test-negative design, and appropriate covariates were frequently included to adjust for potential confounding in statistical analyses. However, several limitations specific to the real-world studies warrant consideration:

- **Variability in hospitalisation criteria:** hospitalisation policies may differ across centers and between countries, potentially affecting comparability. Moreover, the specific clinical criteria prompting hospitalisation – such as the need for non-invasive ventilation or oxygen therapy – are often inadequately reported in the studies.
- **Heterogeneity in RSV testing practices:** testing strategies for RSV infection may vary across settings (for example they can sometimes be limited to more severe cases). This could lead to a selection bias favoring the identification of more clinically severe infections, thereby influencing effectiveness estimates.
- **Limited subgroup analyses in vulnerable populations:** effectiveness data in subpopulations with underlying medical conditions are often insufficient. In particular, stratified analyses by specific comorbidities (rather than grouping all risk factors under a general “presence of comorbidities” category) would provide more nuanced insights.
- **Underreporting of safety outcomes:** safety data are infrequently reported in real-world studies, limiting the post-marketing safety surveillance.
- **Potential incomplete capture of data:** studies relying on administrative databases often do not include data from individuals treated in private healthcare facilities, potentially resulting in incomplete population coverage.
- **Socioeconomic and healthcare access:** indicators of socioeconomic status and access to healthcare services are rarely incorporated into analyses, despite their potential influence on both RSV-related outcomes and the uptake of nirsevimab.

PERSPECTIVES

Further research beyond the effectiveness and safety of nirsevimab could include the following outcomes:

- **Assessment of long-term respiratory outcomes:** further research should investigate whether early protection against RSV infection with nirsevimab reduces the risk of long-term respiratory sequelae, such as recurrent wheezing, or asthma.
- **Evaluation of secondary bacterial infections and antibiotic use:** the prevention of RSV-associated respiratory illness may lead to a decrease in secondary bacterial infections, and consequently, to a reduction in antibiotic prescriptions in infants, with potential implications for antimicrobial stewardship.

- **Comparative effectiveness of new long-acting monoclonal antibodies:** comparative studies with clesrovimab will be necessary to determine their relative efficacy, safety, duration of protection, and cost-effectiveness, should this new drug be approved in the coming years.
- **Monitoring of potential viral resistance and emergences of increase of bronchiolitis associated with other viruses:** the widespread use of nirsevimab may exert selective pressure on RSV, potentially leading to the emergence of resistant strains. In addition, it has been suggested that bronchiolitis due to other viruses could fill the gap of bronchiolitis prevented by nirsevimab, but it remains to be confirmed that such viruses have this potency.

2.3.2 Abrysvo®

This literature review primarily draws upon evidence from a large phase 3 RCT demonstrating that Abrysvo conferred significant protection against severe medically-attended RSV-associated LRTI through 6 months of age.[61] The vaccine efficacy was estimated at 82.4% (95%CI: 57.5-93.9), and 70.0% (95%CI: 50.6-82.5), within 90 and 180 days post-birth (see 2.2.2). Additionally, a prespecified secondary outcome revealed a substantial reduction in RSV-related hospitalisation among infants, with efficacy estimates of 69.7% (95%CI: 37.1-86.7), and 55.3% (95%CI: 23.8-74.6), within 90 and 180 days, respectively. The safety profile of Abrysvo was favorable in both pregnant women and their infants. Although the incidence of preterm birth was slightly higher in the vaccine group (5.7%) compared to the placebo group (4.7%), this difference was not statistically significant but very close to significance (RR: 1.20; 95%CI: 0.98-1.46)[gg]. However, a post hoc analysis indicated a higher relative risk of preterm birth in non-high incomes countries (RR 1.73; 95%CI: 1.22-2.47), with South Africa being the main contributor.[63] Notably, no definitive cause for this regional variation was identified.

Limited literature is currently available regarding the real-world use of Abrysvo. This could hypothetically be linked to the fact that the vaccine was approved later than nirsevimab. Two retrospective studies reported no safety signals concerning an association between its administration and preterm birth.[59, 62] One of them noted an increased incidence of hypertensive disorders during pregnancy; however, this finding was attributable to a higher rate of gestational hypertension, with no observed differences in the occurrence of preeclampsia or HELLP syndrome.[62]

STUDIES PUBLISHED AFTER THE COMPLETION OF THE LITERATURE REVIEW

- During the completion of this systematic review, preliminary results of a real-world use of Abrysvo in Argentina[hh] (NCT066647654; source of funding Pfizer®) were obtained through a multicentre test negative design case-control study involving 286 cases and 219 controls[ii], all aged between 0 and 6 months. The study was published online the 5th of May 2025.[70] The effectiveness of Abrysvo (administered between 32-36 weeks of gestation) against RSV-associated hospitalisation[jj] was

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gg Most preterm newborns were delivered between 34 to <37 weeks of gestation (Abrysvo 89.3% vs placebo 93.0%).

hh RSV season from April, 01 to September, 30 2024.

ii BERNI study. Preliminary results were presented at the 13th International RSV Symposium, 12-15 March 2025, Brazil.

jj All infants admitted to hospital met the definition for LRTI: confirmed RSV infection (PCR or indirect immunofluorescence for cases and PCR for controls) and presence of cough or breathing difficulties, onset of symptoms within 10 days, and at least one of the following: fast breathing (≥60 breaths/minute if aged <2 months, ≥50 breaths/minute if aged 2-6 months); oxygen saturation <95%; chest indrawing.

71.3%[kk] (95%CI: 53.3-82.3) in infants under 6 months of age, and was 78.6%[ll] (95%CI: 62.1-87.9) in those aged 0 to ≤3 months. Furthermore, the effectiveness against severe infection requiring hospitalisation (defined by the presence of at least one of the following criteria: mechanical ventilation high-flow oxygen therapy; SpO2<90%; ICU admission for >4 hours; failure to respond/loss of consciousness) was in the same range of value (76.9%; 95%CI: 45.5-90.3). The study was not designed to assess safety.

- Following the completion of the literature review, a post-marketing surveillance study was identified that assessed the safety profile of the RSVpreF vaccine in the USA between September 2023 and February 2024.[mm71] This study analysed spontaneously reported adverse events submitted to the U*.S. Food and Drug Administration's Vaccine Adverse Event Reporting System* (VAERS). A Bayesian statistical approach – specifically, the Bayesian Confidence Propagation Neural Network– was employed to compare observed reporting rates with expected background rates, allowing for the detection of disproportionate reporting patterns. During the study period, a total of 77 adverse events potentially associated with RSVpreF vaccination were reported, of which 42 were classified as serious. Among non-pregnancy-related events, the most commonly reported adverse effects were headache, injection site pain, and erythema. Among the pregnancy-related adverse events, preterm birth was the most commonly reported (n = 27). Notably, approximately two-thirds of these preterm births occurred within one week of vaccine administration. A signal of disproportionality was detected for preterm birth along with caesarian section and premature rupture of membranes and cervical dilatation. This indicates that those events were reported more frequently than expected relative to other vaccine-event pairs in the VAERS database. No signal was identified for haemorrhage in pregnancy, gestational hypertension, stillbirth and preeclampsia as the number of events was limited and below the evaluation threshold. The authors mention that critical clinical information (e.g. maternal history, use assisted reproductive technology, clinical exam, ultrasound results) related to pregnancy were not available in the analysis, and that report was not designed to assess a potential causality. Nevertheless, they mentioned that the observed safety signal, particularly concerning preterm birth, underscores the need for further investigation. A pharmacovigilence study conducted in the US is ongoing[nn].

PERSPECTIVES

Although the efficacy of RSVpreF vaccine Abrysvo has been demonstrated, knowledge gaps remain:

- **Need for real-world effectiveness data:** further studies using real-world data are essential to evaluate the vaccine's effectiveness in routine clinical settings, and across diverse populations.
- **Uncertainty regarding preterm birth risk**: concerns persist regarding a potential increased risk of preterm birth following vaccination, especially given that women at high risk for preterm delivery were excluded from the pivotal trial, and given that there are up to now few studies that have reported this outcome.

[kk] Adjusted on site, conception date, calendar date of hospitalisation, infant age at hospitalisation, inverse probability of treatment weights.

[ll] Adjusted on site, conception date, calendar date of hospitalisation, inverse probability of treatment weights, and infant sex.

[mm] The article was identified in the first search of literature but not retained as it was a preprint, not yet peer reviewed.

[nn] *A Rapid Surveillance and Cohort Post-Marketing Safety Study to Evaluate the Safety of Respiratory Syncytial Virus Vaccine (ABRYSVO™) Exposure During Pregnancy in the United States (C3671027).*

- **Lack of data on particular subgroups:** to date, there are no data on the use of Abrysvo in pregnancies complicated by maternal or fetal conditions, as this population has not been studied. This represents a significant gap in the current evidence base.

3 INCIDENCE AND COST OF RSV-RELATED HOSPITALISATIONS IN BELGIUM

KEY POINTS

- Two sources of routine hospital data were used:
  - The "Technical Cell – Cellule Technique" (TCT) database links data from each hospitalisation to reimbursement data from the sickness funds. Data on patients aged 0-4 years with respiratory tract infections identified through the ICD 9/10 codes were available for the years 2008-2014 and 2016-2022.
  - The BELSARI-NET data comes from a surveillance network of 10 hospitals aimed at measuring the incidence of seasonal influenza or other acute respiratory infections. Cases of severe acute respiratory infection (SARI) aged 0-4 years were available to complement our analysis for the years 2023-2025.
- A total of 118 025 RSV infection episodes (119 002 hospitalisations) were identified over 14 RSV transmission seasons.
- The annual incidence of RSV hospitalisation per 1000 children aged 0-4 year varied between 13.3 in 2008 and 22.2 in 2022. In children <1 year, the incidence of RSV hospitalisation by 1000 children varied between 51.0 in 2008 and 80.8 in 2022.
- The number of RSV hospitalisations peaked between September/October and January/February, with the exception of the season affected by the COVID-19 pandemic (2020-2021). The BELSARI-NET data suggest that the pre-COVID pattern of incidence was observed again in the two most recent seasons (i.e. 2023-2024 and 2024-2025).
- More than two thirds (71.6%) of RSV hospitalisation occurred in patients aged <1 year
- Among children 0-4 years, 4.1% stayed at least one day in an ICU.
- The incidence of ICU hospitalisation for RSV per 1000 children varied between 0.35 in 2008 to 1.08 in 2022 in children aged 0-4 years, and between 1.54 in 2008 to 4.71 in 2022 in infants (<1 year). The total costs (NIHDI and patient shares) of RSV-related hospitalisations in children aged 0-4 year were €21.35 million in 2008 and €47.15 million in 2022.

3.1 Introduction

This section aims to describe the incidence and costs of RSV hospitalisations in children aged 0-4 years in Belgium.

3.2 Source of data and methodology

3.2.1 The TCT database

The "Technical Cell – Cellule Technique" (TCT) links every year the Minimal Hospital Data (MZG–RHM, see below) to the Sickness Funds reimbursement data in hospital (Hospital Billing Data, see below) for the analysis of links between the expenditures of the health care insurance and the treated pathology and for the elaboration of financing rules, accreditation standards and quality conditions in the context of an effective health policy. KCE has direct access to TCT data, regulated by the same law as the Technical Cell (Law of 29 April 1996), meaning that no informed consent from patients is required. The linkage between the Minimal Hospital Data and the Hospital Billing Data is not possible for patients who

do not have a healthcare insurance in Belgium. In the present study, linkage was successful in 95.7% of cases, representing 4 168 RSV infection episodes over 14 years. These infection episodes were only included in the evaluation of the disease burden (not in the cost analysis).

Minimal Hospital Data (MZG–RHM): all general hospitals are required to submit twice a year a large set of data on all inpatient and day-care hospital stays and emergency room contacts: the Minimal Hospital Data (MZG–RHM defined in the Royal Decree of 27/04/2007) which are transferred to the FPS Public Health, Food Chain Safety and Environment. Day-care stays include all surgical and non-surgical day-care stays for which day-care lump sum can be charged, or are of a specific type (e.g. geriatric, paediatric, oncological). In the MZG–RHM, the year 2015 is missing, so the database is analysed for the periods 2008-2014 and 2016-2022.

Hospital Billing Data (AZV–SHA and ADH–HJA): the Hospital Billing Data contains all reimbursements by the NIHDI related to hospital stays: fees charged by physicians and other healthcare providers, pharmaceuticals, implants, per admission and per diem lump sum payments, etc. In practice, hospitals bill the patient's sickness fund for the provided services for the part covered by the health insurance on the basis on the NIHDI nomenclature. A subset of the data available on these transactions is passed yearly from the sickness funds to the NIHDI: Anonymous Hospital Stays (AZV–SHA) for inpatient stays and Anonymous Day-care Stays (ADH–HJA) for day-care stays.

3.2.1.1 Selection of data

The inclusion criteria were all patients aged 0-4 years who presented as **principal or secondary diagnosis** at least one of the selected ICD-9/10 codes related to RSV or other respiratory infections (used in the RESCEU and PROMISE studies, see Table 12 and Table 15). The description of the codes is provided in Appendix 3. The selection of ICD-9/10 codes was broad, in order to capture all stays related to an RSV infection episode. The selection encompasses all respiratory tract infections (RTIs), including those not specifically related to RSV. The determination of episodes of infection will be made (see next paragraph), and the specific RSV infection episode will be defined as the presence of a specific ICD 9/10 code during the unique or multiples hospitalisations which occur during the infection episode.

Table 12 – List of ICD-9/10 codes used for the selection of patients in the TCT database

Diagnosis classification	ICD-9 (before 2016)	ICD-10 (from 2016)
Respiratory Syncytial Virus	**0796**	**B97.4**
URTI - Acute upper respiratory tract infection	460 4610 4611 4612 4613 4618 4619 462 463 46400 46401 46410 46411 46420 46421 46430 46431 4644 46450 46451 4650 4658 4659	J00 J02.0 J02.8 J02.9 J03.0 J03.8 J03.9 J04.0 J04.1 J04.2 J05.0 J05.1 J06.0 J06.8 J06.9
LRTI - Pneumonia & Influenza	4800 **4801** 4802 4803 4808 4809 481 4820 4821 4822 48230 48231 48232 48239 48240 48241 48249 48281 48282 48283 48284 48289 4829 4830 4831 4838 4841 4843 4845 4846 4847 4848 485 486 4870 4871 4878 514	J09 J10.0 J10.1 J10.8 J11.0 J11.1 J11.8 J12.0 **J12.1** J12.2 J12.3 J12.8 J12.9 J13 J14 J15.0 J15.1 J15.2 J15.3 J15.4 J15.5 J15.6 J15.7 J15.8 J15.9 J16.0 J16.8 J17.0 J17.1 J17.2 J17.3 J17.8 J18.0 J18.1 J18.2 J18.8 J18.9
LRTI - Bronchiolitis & Bronchitis	4660 **46611** 46619	J20.0 J20.1 J20.2 J20.3 J20.4 **J20.5** J20.6 J20.7 J20.8 J20.9 **J21.0** J21.1 J21.8 J21.9 J40
Unspecified LRTI	5198 (not exact map)	J22
SARS-CoV-2/COVID-19	-	U07.1 U07.2 U08-10

The codes in red are RSV specific. LRTI: lower respiratory tract infection, RSV: respiratory syncytial virus, URTI: upper respiratory tract infection.

3.2.1.2 Calculation of the episodes of infection

A hospitalisation stay (either inpatient or daycare) is an admission to a hospital. Hospital stays were grouped into **infection episodes** according to the following methods. An infection episode for a patient with multiple hospitalisations was defined as all hospitalisations of the same patient within 0 to 14 days of the previous hospitalisation. For example, a patient arrives at the emergency department, leaves the hospital the same day and is admitted to an inpatient unit the next day. These 2 different hospital stays within a 2-day interval for the same patient and for the same infection are grouped into one infection episode. The limit of 14 days for an infection episode was determined based on individual RSV-specific hospitalisations (more than 99% of the hospital stays do not exceed 14 days).

A selection process was used to identify episodes of infection among the 532 757 hospital stays identified in the TCT database for the periods 2008-2014 and 2016-2022. First, a distinction was made between patients who were hospitalised once (319 686 single-patient hospitalisations) and those hospitalised multiple times (83 618 patients with several (213 070) hospitalisations). These multiple hospitalisations were either consecutive, indicating that they were related to the same episode of infection, or non-consecutive indicating that they were due to two different infections. Second, multiple consecutive hospitalisations, with a period of less than 14 days between each, were grouped together in a single infection episode. A total of 176 010 non-consecutive and 37 060 consecutive hospitalisations were identified, the latter resulting in 16 912 infection episodes. The selection process yielded a total of **512 608 episodes of infection**, which includes

- 319 686 infection episodes corresponding to single hospitalisations in unique patients,
- 176 010 infection episodes corresponding to multiple hospitalisation for the same patient, separated by a minimum of 14 days,
- 16 912 infection episodes corresponding to multiple hospitalisation for the same patient, separated by less than 14 days.

A distinction is made between RSV and non-RSV cases based on the ICD-9/10 diagnosis code. An RSV infection episode occurs when an RSV ICD-9/10 diagnosis code is reported in the hospitalisation, or in at least one hospitalisation if there are multiple hospitalisations for the same patient.

A total of 119 002 RSV specific infection episodes were identified, for the periods 2008-2014 and 2016-2022. Table 13 shows the annual number of RSV hospitalisations and the corresponding RSV-specific infection episodes.

Hospitalisations in an intensive care unit (ICU) correspond to hospital stays with at least 1 day in an ICU during the infection episode. The definition is based on the unit of the hospital in which the patient was admitted (specific ICU or pediatric ICU).

The severity of illness (SOI) is a variable that measures the health status and the severity of illness of a patient upon admission. This index has four levels and each level is determined by 7 conditions: the disease stage, complications of the principal condition, concurrent interacting conditions that affect the course of hospitalisation, dependency on hospital staff, extent of non-operating room life support procedures, rate of response to therapy or rate of recovery, impairment remaining after therapy for the acute aspect of the hospitalisation.[72] The SOI can be used as a hospital case-mix, and as a risk adjustment factor in quality reporting and inter-hospital comparisons.

Table 13 – Number of RSV-specific hospitalisations and number of RSV-specific infection episodes, per age during the years 2008-2022 (2015 excluded)

	Number of hospitalisations			Number of infection episodes		
	Infants	Children 1-4 year	Children 0-4 year	Infants	Children 1-4 year	Children 0-4 year
2008	6 614	1 821	8 435	6 342	1 785	8 127
2009	4 200	1 697	5 897	3 995	1 650	5 645
2010	6 026	1 980	8 006	5 717	1 938	7 655
2011	6 361	2 254	8 615	6 034	2 218	8 252
2012	7 440	2 506	9 946	7 059	2 455	9 514
2013	6 112	2 157	8 269	5 744	2 112	7 856
2014	5 861	1 999	7 860	5 462	1 934	7 396
2016	6 871	2 271	9 142	6 448	2 219	8 667
2017	7 112	2 453	9 565	6 599	2 386	8 985
2018	8 211	2 562	10 773	7 605	2 498	10 103
2019	7 024	2 451	9 475	6 530	2 389	8 919
2020	1 680	452	2 132	1 516	437	1 953
2021	8 830	4 610	13 440	8 116	4 512	12 628
2022	10 368	3 822	14 190	9 587	3 715	13 302
Mean over 2016-2019	7 305	2 434	9 739	6 796	2 373	9 169

Source: TCT

3.2.1.3 Incidence

RSV incidence was calculated as the ratio of the number of infection episodes divided by the number of children per year of registration. The number of children in each age group and calendar year was obtained from Statbel, the Belgian statistics office.[oo] The incidence rate was expressed per 1000 individuals, and was computed for the 0-4, under 1 and 1-4 year age groups.

3.2.1.4 Costs computations

The hospital billing data are present in the AZV–SHA data. These data were not available for some RSV infection episodes (n=4 168) because of no possible linkage with MZG–RHM data.

The costs are presented by RSV infection episode. The hospital per diem, laboratory testing, medical imaging and pharmaceutical costs were computed according to the rules defined in the second edition[pp] of the guidelines for economic evaluations (KCE report 183B).[73] The costs to the patients are the official out-of-pocket payments listed in the nomenclature, apart from additional payments ("supplements") required by some hospitals or doctors.

EXTRAPOLATION TO 100% HOSPITAL PER DIEM COSTS (NON-MEDICAL HOSPITAL ACTIVITIES)

Each hospital is allocated an annual budget (i.e. the budget of financial means, BFM-BMF) for the financing of its non-medical hospital activities (i.e. capital expenditures for housing and medico-technical facilities, hotel function, nursing care, etc.). The payment of this budget consists of two parts: a fixed part and a variable part. The fixed part is paid by the sickness funds based on monthly advances and

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[oo] https://statbel.fgov.be/fr/themes/population/structure-de-la-population

[pp] Meanwhile, a third edition has been published (May 2025): https://kce.fgov.be/en/publications/all-reports/belgian-guidelines-for-economic-evaluations-and-budget-impact-analyses-third-edition.

represents about 80% of the price of non-medical hospital activities. The second part is paid via an invoice, based on the number of admissions and the number of nursing days. The AZV-SHA database only records the invoices (i.e. the variable part of the budget), which represents about 20% of the total per diem costs. Twice a year, the NIHDI publishes the amount per admission and per diem[qq]. These amounts are specific to each hospital and depend on the type of bed (e.g. acute, burned, elderly, psychiatric, palliative and chronic disease care). To correctly assess the per diem price, the price of the lump sum codes registered in the AZV-SHA database has to be removed and replaced by the 100% per diem price published by the NIHDI.

LUMP SUMS FOR LABORATORY TESTING, MEDICAL IMAGING AND PHARMACEUTICALS

Laboratory testing, medical imaging and pharmaceuticals administered to patients hospitalised in a general hospital are financed through a combined system of retrospective and prospective payments.

- For laboratory testing, there is a mixed system of fee-for-service (where the hospital retrospectively charges the sickness funds 25% of the honorarium fees of each test performed) and lump sum payments: a prospective lump sum per inpatient day to cover the procedures delivered, and a lump sum per admission for the remuneration of the biologists.
- For medical imaging, there is a mixed system of fee-for-service (where the hospital retrospectively charges the sickness funds roughly 70% of the honorarium fees of each act performed) and lump sum payments: a prospective lump sums per inpatient admission to cover the procedures delivered, and an allocation per admission for the remuneration of the radiologists.
- For pharmaceuticals, prospective payments are limited to the forfaitized drugs. For these drugs, up to 2024, there was a mixed system of fee-for-service (where the hospital retrospectively charges the sickness funds 25% of the reimbursement basis of each delivered drug) and a prospective lump sum payment per patient admission. Pharmaceutical products outside the forfait are reimbursed as fee-for-service (according to their reimbursement categories) and represent real consumption.

Except for the lump sums for the remuneration of the biologist or radiologist (which are fixed), all lump sums are hospital-specific and depend on the case mix (APR-DRG) of each hospital, taking into account the severity of illness.

The patients' contribution is fixed and is limited to €7.44 per admission for laboratory testing, €6.20 per admission for medical imaging and €0.62 per inpatient day for pharmaceuticals. Note that these patients' lump sums remained unchanged since 2002 (last check 2024) and should therefore not be indexed.

In order to value the real consumption of the laboratory testing/medical imaging acts performed and of the forfaitized pharmaceuticals delivered during an inpatient stay, taking into account this dual system of financing, the prospective lump sums payments were identified (via (pseudo)nomenclature codes) and removed from the cost computation; and the remaining fee-for-service parts were multiplied by an extrapolation factor. All other costs were aggregated as such. To derive the extrapolation factors for the fees clinical biology, medical imaging and the forfaitized drugs, the yearly (2008-2021) NIHDI specific expenses (in lump sums, fee-for-service and in total) for all inpatient stays were obtained based on the full NIHDI accountancy records. Extrapolation factors were then obtained as the ratio of the total expenses to the fee-for-service expenses for each year. The extrapolation factors are presented in Table 14.

Further, as the lump sums paid by the patients (€7.44 per admission for laboratory testing, €6.20 per admission for medical imaging and €0.62 per inpatient day for pharmaceuticals) are not recorded in the TCT database, they were added to depict the real costs of the patients.

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qq https://www.inami.fgov.be/fr/themes/soins-de-sante-cout-et-remboursement/les-prestations-de-sante-que-vous-rembourse-votre-mutualite/soins-dans-les-hopitaux/prix-de-la-journee-d-hospitalisation

Table 14 – Extrapolation factors from fee-for-service expenses to total expenses for hospitalised patients (2008-2022)

Years	Medical imaging	Clinical biology	Drugs (forfaitized)
2008	1.62	5.09	4.32
2009	1.65	5.09	4.19
2010	1.57	4.89	4.20
2011	1.74	5.53	4.10
2012	1.63	5.38	3.96
2013	1.63	5.38	3.78
2014	1.66	5.32	3.81
2015	1.66	5.26	3.90
2016	1.66	5.52	3.84
2017	1.66	5.47	3.86
2018	1.65	5.29	3.97
2019	1.77	5.34	4.03
2020	1.69	5.01	3.55
2021	1.69	4.88	3.49
2022	1.74	5.00	3.74

INDEXATION

In the economic evaluation (see Chapter 4), costs are expressed in Euro for the year 2024. To compute the average hospitalisation costs based on the TCT database, costs from previous years were updated to this reference year using health consumer price indices[74] when relevant. Indeed, as stated in the KCE guidelines (KCE Report 183[73]), in some cases, indexation will not be relevant for specific products or services. In this analysis, no indexation was applied to the reimbursement basis for pharmaceuticals. Indeed, an in-depth analysis of the costs of reimbursed drugs was conducted (data not shown), revealing a decrease in the costs over the years in the TCT database.

3.2.2 BELSARI-NET data

The TCT dataset has two limitations. It is routine data, and it may underestimate the incidence of RSV-related hospitalisations as a confirmatory PCR test is not carried out in every patient, although the proportion of patients tested has been increasing over the years. Moreover, the TCT data are only available until 2022.

In an attempt to overcome these limitations, the BELSARI-NET dataset was consulted. Although not reliable before November 2023 (personal communication: Laurane De Mot, Sciensano), data are available until January 2025, and include additional useful parameters. BELSARI-NET data are hosted by Sciensano[rr], the health institute of Belgium, and contains cases of Severe Acute Respiratory Infections (SARI). They are collected from a surveillance network of hospitals, with the aim of reporting signs of increased severity of seasonal influenza or other acute respiratory infections to the relevant health authorities. Since 2012, the network has initially comprised 6 hospitals, and has been extended to ten since 2023.

An admission to BELSARI-NET is defined as a hospital admission of at least 24 hours for severe symptoms of acute respiratory infection, which occurred suddenly (in the last 10 days before admission), and in which nosocomial infections are excluded. Before November 2023, the symptoms were defined as fever ≥38° and cough and/or shortness of breath. From November 2023, the symptoms are defined

[rr] https://www.sciensano.be/en/projects/severe-acute-respiratory-infection-surveillance-a-sentinel-network-hospitals

by the presence of at least two signs of respiratory tract infection, as follows: fever ≥38°, cough, signs of respiratory distress, abnormal lung auscultation and, for children; apnea or cyanosis. In patients admitted to the BELSARI-NET, a swab sample is taken from each patient's throat and/or nose, and is tested for respiratory viruses by the National Reference Center for Influenza[ss].

3.2.2.1 Selection of data

The study's inclusion criteria were SARI patients aged 0-4 years included during the last two transmission seasons (2023-2024 and 2024-2025). All SARI cases were selected, distinguishing between different test results. The study included the following viruses: influenza, all coronaviruses (SARS-CoV-2 and seasonal coronaviruses), RSV, human metapneumovirus, enterorhinovirus, parainfluenza, adenovirus, paraechovirus, and bocavirus. The requested variables included age, gender, transfer to the ICU, death in hospital, RSV immunisation status (maternal vaccine and/or monoclonal antibody), presence of risk factors (intrauterine growth retardation or prematurity), coinfection with RSV and the type of infection. For data protection reasons, the exact number by variable was not given if the number of patients was less than 5.

3.3 Results

3.3.1 Distribution of the clinical diagnosis and exploration of the co-infections

Table 15 shows the distribution of the clinical diagnosis of respiratory infections registered in the hospital stays, according to the ICD-9/10 classification appearing as principal and/or secondary diagnosis (see Table 12) in the TCT database. A distinction was made between RSV-related infections and other respiratory tract infections. RSV-specific infections can be registered in the diagnosis classification "Lower respiratory tract infection" as pneumonia, bronchitis or bronchiolitis, or separately in the diagnosis classification "Respiratory syncytial virus".

Table 15 – Distribution of respiratory infections per hospitalisation for the years 2008-2022 (2015 excluded)

	0-4 years		<1 year	
	n	%	n	%
Upper respiratory tract infections	154 548	29,0%	63 957	24,1%
Lower respiratory tract infections				
- *Influenza*	28 434	5,3%	9 992	3,8%
- *Pneumonia*				
- *Coronavirus*	6 422	1,2%	4 473	1,7%
- *Mycoplasma*	3 747	0,7%	294	0,1%
- *RSV*	6 776	1,3%	2 380	0,9%
- *Adenovirus*	1 446	0,3%	575	0,2%
- *Haemophilus influenza*	765	0,1%	243	0,1%
- *Haemophilus Parainfluenza*	563	0,1%	196	0,1%
- *Streptococcus*	2 959	0,6%	531	0,2%
- *Other/unspecified*	71 149	13,4%	17 894	6,8%
- *Bronchitis/Bronchiolitis*				
- *Mycoplasma*	454	0,1%	82	0,0%
- *RSV*	104 764	19,7%	80 591	30,4%
- *Haemophilus influenza*	62	0,0%	17	0,0%
- *Haemophilus Parainfluenza*	594	0,1%	297	0,1%
- *Streptococcus*	45	0,0%	9	0,0%

[ss] https://www.sciensano.be/en/nrc-nrl/national-reference-center-nrc-respiratory-pathogens

- *Other/unspecified*	128 143	24,1%	72 216	27,3%
- *Unspecified*	7 681	1,4%	3 197	1,2%
RSV infection	14 205	2,7%	7993	3,0%
Total RSV-specific ICD codes	125 745	23,6%	90 964	34,3%

Source: TCT data.

ICD codes can be recorded both as principal diagnosis (one code) and as secondary diagnosis (several codes). The majority of the RSV-related hospitalisations were coded with RSV as principal diagnosis (91.8%), while only 8.2% were coded with RSV as secondary diagnosis. For these hospitalisations, we determined the possible presence of a co-infection with Haemophilus influenzae, adenovirus, Haemophilus parainfluenzae, coronavirus, streptococcus and mycoplasma.

The presence of co-infections was relatively low, accounting for 12.5% of all RSV hospitalisations in children aged 0-4 years (Table 16), or 12.7% when RSV was registered as principal diagnosis and 10.0% when RSV was registered as a secondary diagnosis. Co-infections were mostly unspecified.

Table 16 – Co-infections associated with RSV-related hospitalisations (TCT database)

	0-4 year			<1 year		
	RSV as principal diagnosis (n=115 437)	RSV as secondary diagnosis (n=10 308)	Total (n=125 745)	RSV as principal diagnosis (n=84 345)	RSV as secondary diagnosis (n=6 619)	Total (n=90 964)
Co-infection	14 660 (12.7%)	1 035 (10.0%)	15 695 (12.5%)	8 173 (9.7%)	472 (7.1%)	8 645 (9.5%)
- *Coronavirus*	431 (0.4%)	42 (0.4%)	473 (0.4%)	321 (0.4%)	22 (0.3%)	343 (0.4%)
- *Mycoplasma*	236 (0.2%)	16 (0.2%)	252 (0.2%)	54 (0.1%)	4 (0.1%)	58 (0.1%)
- *Adenovirus*	141 (0.1%)	10 (0.1%)	151 (0.1%)	53 (0.1%)	3 (<0.1%)	56 (0.1%)
- *Haemophilus influenzae*	148 (0.1%)	15 (0.1%)	163 (0.1%)	106 (0.1%)	10 (0.2%)	116 (0.1%)
- *Parainfluenzae*	67 (0.1%)	8 (0.1%)	75 (0.1%)	20 (<0.1%)	1 (<0.1%)	21 (<0.1%)
- *Streptococcus*	243 (0.2%)	37 (0.4%)	280 (0.2%)	147 (0.2%)	22 (0.3%)	169 (0.2%)
- *Other/unspecified*	13 394 (11.6%)	907 (8.8%)	14 301 (11.4%)	7 472 (8.9%)	410 (6.2%)	7 882 (8.7%)

Source: TCT data.

In the BELSARI database, coinfections were identified via specific tests done in patients and are described in Table 17. About 10% of patients were co-infected with either an enterorhinovirus or an adenovirus (11.6% and 9.7%, respectively). Further, 5.5% of patients were co-infected with seasonal coronaviruses. Other RSV coinfections were identified in less than 3% of the cases (i.e. 3.0% for bocavirus, 2.7% for parainfluenza, 2.6% for influenza and SARS-CoV-2, 1.0% for paraechovirus and 0.9% for human metapneumovirus).

The proportion of coinfections differs between the two data sources. It can be explained by the objectives of each registry. As BELSARI is an epidemiological surveillance registry, the patients included were tested for all respiratory viruses, not just the suspected ones.

Table 17 – Co-infections associated with RSV-related hospitalisations (BELSARI data)

Co-infection with RSV	Proportion
adenovirus	9.7%
bocavirus	3.0%
SARS-CoV-2	2.6%
enterorhinovirus	11.6%
influenza	2.6%
human metapneumovirus	0.9%
paraechovirus	1.7%
parainfluenza	2.7%
seasonal coronaviruses	5.5%

Source: BELSARI.

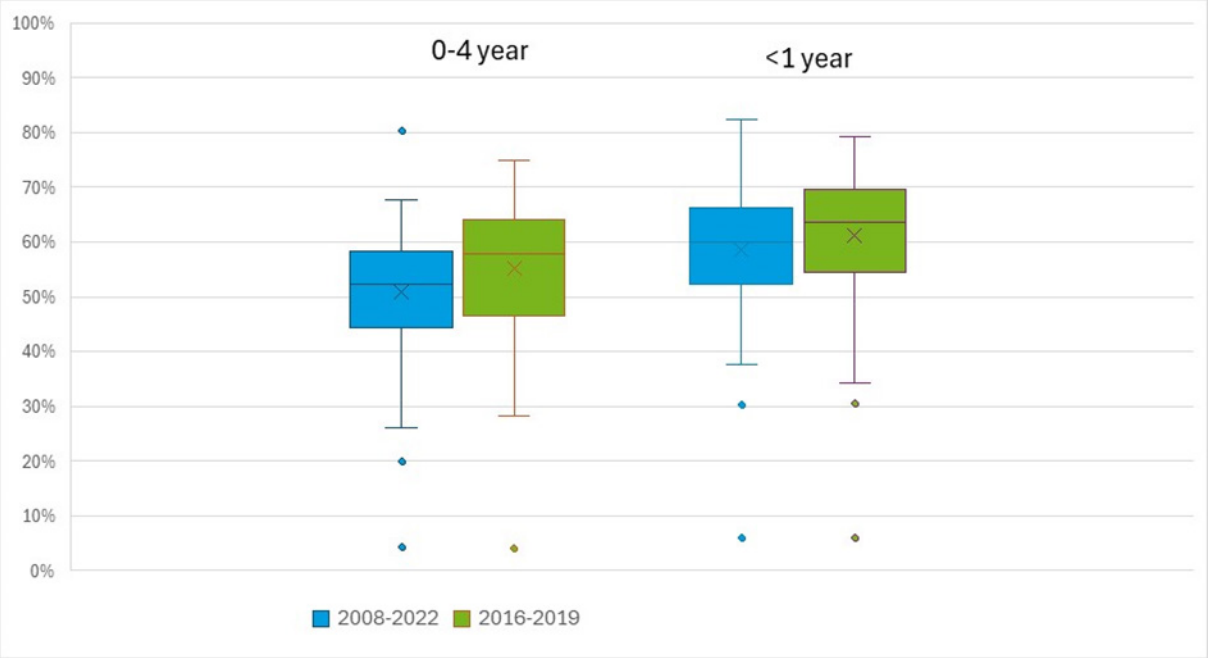
3.3.2 Incidence of RSV-specific bronchitis/bronchiolitis infections by hospital

The absence of routine testing in some hospitals may result in an underestimation of RSV cases. To ensure the representativeness of RSV data across all hospitals, we compared the number of hospitalisations for RSV-specific bronchitis/bronchiolitis versus all bronchitis/bronchiolitis for each hospitals. We obtained a distribution of the rate of RSV-specific hospitalisations. Hospitals situated in the lower 5% of this distribution were considered outliers. The presence of outliers may indicate a systematic difference in testing practices. For this assessment, we focused on the RSV seasons (October to March) over the period 2008-2022 (excl. 2015), with a focus on the period 2016-2019.

There were 87 770 hospital stays (68 507 for children <1 year) for RSV-specific bronchitis/bronchiolitis infections and 86 529 (49 630 for children <1 year) hospital stays for unspecified bronchitis/bronchiolitis infections. The rate of RSV infections was 50.4% (58.0% for children <1 year) on 103 hospitals for the period 2008-2022 (excl. 2015) and 54.5% (61.2% for children <1 year) on 93 hospitals for the period 2016-2019.

Figure 17 shows the distribution of the rate of RSV-specific bronchitis/bronchiolitis infections across hospitals. The median [P25-P75] is 52.1% [43.5%-58.3%] for 2008-2022 (excl. 2015), and 58.1% [47.1%-64.1%] for 2016-2019. In children <1 year, The median [P25-P75] is 59.9% [52.0%-65.9%] for 2008-2022 (excl. 2015), and 63.8% [55.5%-69.5%] for 2016-2019. For children 0-4 years, two hospitals are situated in the lower 5% of the distribution with a rate of RSV-specific bronchitis/bronchiolitis infections lower than 20% for the period 2008-2022, and one hospital for the period 2016-2019. For children <1 year, two hospitals are situated in the lower 5% of the distribution with a rate of RSV-specific bronchitis/bronchiolitis infections lower than 30%. This analysis reflect the variation of testing strategy which is different in each hospital.

Figure 17 – Distribution of the rate of RSV-specific versus all bronchitis/bronchiolitis infections across hospitals



Source: TCT data.

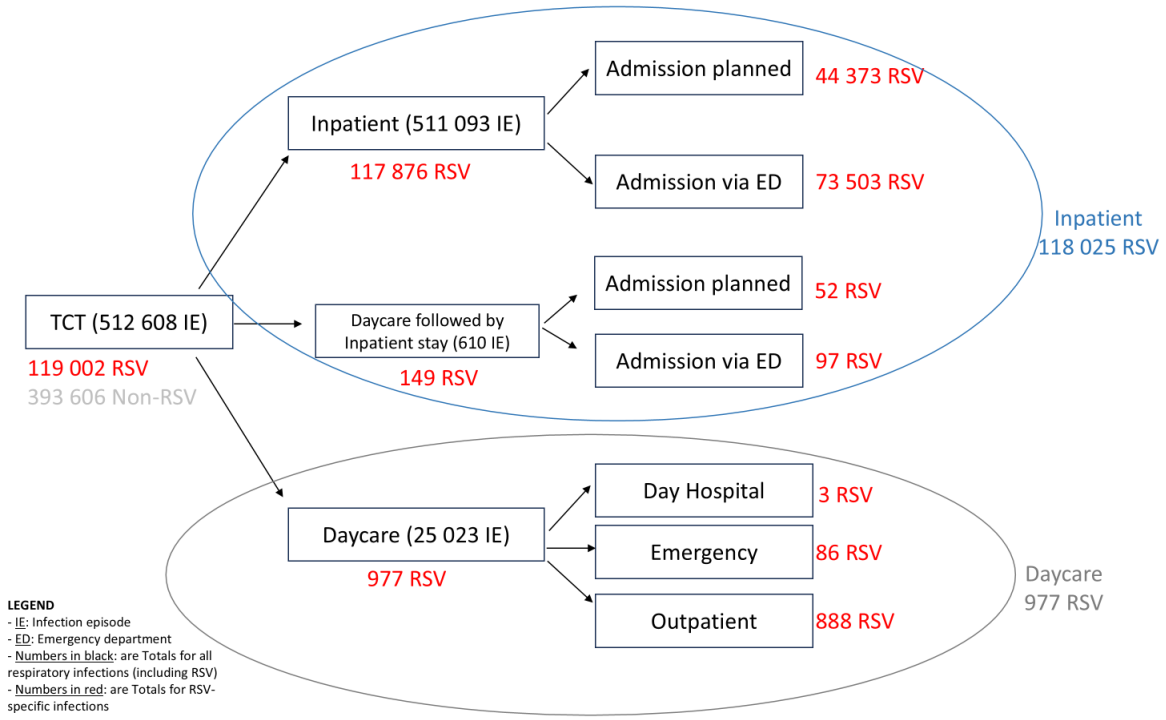
3.3.3 Burden of RSV respiratory tract infections

For the description of the burden of RSV respiratory tract infections, data for the period 2008-2014 and 2016-2022 were analysed with ICD9/10 codes appearing as principal and/or secondary diagnosis. The selection of RSV specific infection episodes is presented in Figure 18.

Daycare data (no overnight stay) totaled 977 RSV-related infection episodes, including 3 day-hospitalisations, 86 emergency department visits and 888 outpatient visits. Inpatient data (at least one overnight stay) for RSV-related infection episodes included a) patients directly admitted to the hospital for at least one night (n=117 876) and b) daycare patients subsequently admitted to the hospital (n=149). For RSV-related infections, this corresponds to 44 425 (44 373 + 52) infection episodes with planned admission and 73 600 (73 503 + 97) infection episodes with emergency admission.

By law, registration of ICD codes for emergency and outpatient (ambulatory and polyclinic) daycare is not compulsory (while it is for inpatient stays and day hospital). The number of day-care stays reported in the TCT database is thus underestimated because not all emergency and outpatient daycare stays could be identified. Therefore, a description of the burden of RSV respiratory tract infections will be done for patients with a minimum of one night in the hospital (i.e. inpatient).

Figure 18 – Distribution of the RSV infection episodes per type of admission for the years 2008-2022 (2015 excluded)



RSV: RSV-specific respiratory tract infection, Non-RSV: non RSV-specific respiratory tract infection, IE: Infection episode, ED: Emergency department, numbers in black are totals for all respiratory infections (excluding RSV), numbers in red are totals for RSV-specific infections.

3.3.3.1 Incidence of respiratory tract infection episodes

Over the period 2008-2022, 118 025 (117 876 + 149, see Figure 18) RSV-related infection episodes were identified in children aged 0-4 year. The number of RSV infection episodes vary from 5 632 in 2009 to 13 208 in 2022, as presented in Table 18. The drop in the number of RSV infection episodes in 2020 is due to the COVID-19 period. In 2021 and 2022, these figures are higher again, even higher than in other years.

Table 18 – Number and incidence (per 1000 individuals) of RSV infection episodes, by year from 2008 to 2022 (2015 excluded)

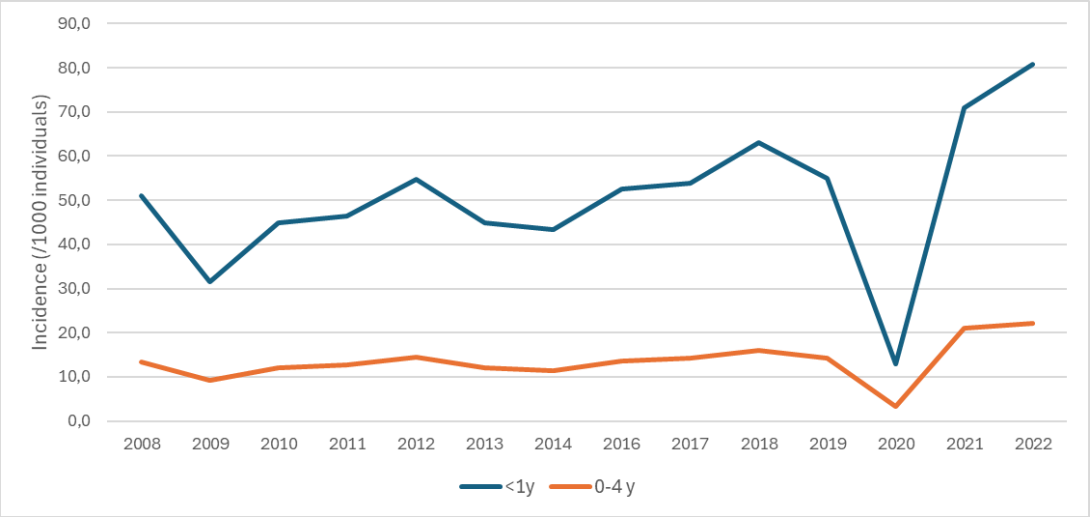
	Annual number of infection episodes			Incidence per 1000 individuals		
	Infants	Children 1-4 year	Children 0-4 year	Infants	Children 1-4 year	Children 0-4 year
2008	6 316	1 766	8 082	51.01	3.64	13.27
2009	3 989	1 643	5 632	31.5	3.35	9.12
2010	5 688	1 924	7 612	44.85	3.83	12.11
2011	6 005	2 195	8 200	46.42	4.29	12.79
2012	7 006	2 424	9 430	54.8	4.67	14.57
2013	5 708	2 093	7 801	44.96	4.01	12.01
2014	5 415	1 917	7 332	43.43	3.68	11.35
2016	6 398	2 180	8 578	52.53	4.25	13.51
2017	6 532	2 356	8 888	53.88	4.64	14.14
2018	7 513	2 448	9 961	63.04	4.88	16.04

2019	6 464	2 347	8 811	54.86	4.73	14.35
2020	1 509	435	1 944	12.88	0.89	3.2
2021	8 073	4 473	12 546	70.98	9.24	20.99
2022	9 538	3 670	13 208	80.79	7.69	22.19
Mean over 2016-2019	6 727	2 333	9 060	56.08	4.63	14.51

Source: TCT data.

The incidence per 1000 children aged 0–4 year varies between 9.1 in 2009 and 22.2 in 2022 and between 32.0 in 2010 and 47.5 in 2022 for the RSV-specific infections (Figure 19). In children <1 year, the incidence per 1000 children varies between 31.5 in 2009 and 80.8 in 2022 for the RSV-specific infections.

Figure 19 – Annual incidence of infection episodes due to RSV



Source: TCT data. RSV: respiratory syncytial virus.

As shown in Table 19, infants accounted for the largest part of all RSV infection episodes with an ICU admission over the observed period. The number of episodes including an ICU admission among infants increased from 136 in 2009 to 556 in 2022.

Table 19 – Number and incidence (per 1000 individuals) of RSV-related infection episodes with an ICU admission, by year from 2008 to 2022 (2015 excluded)

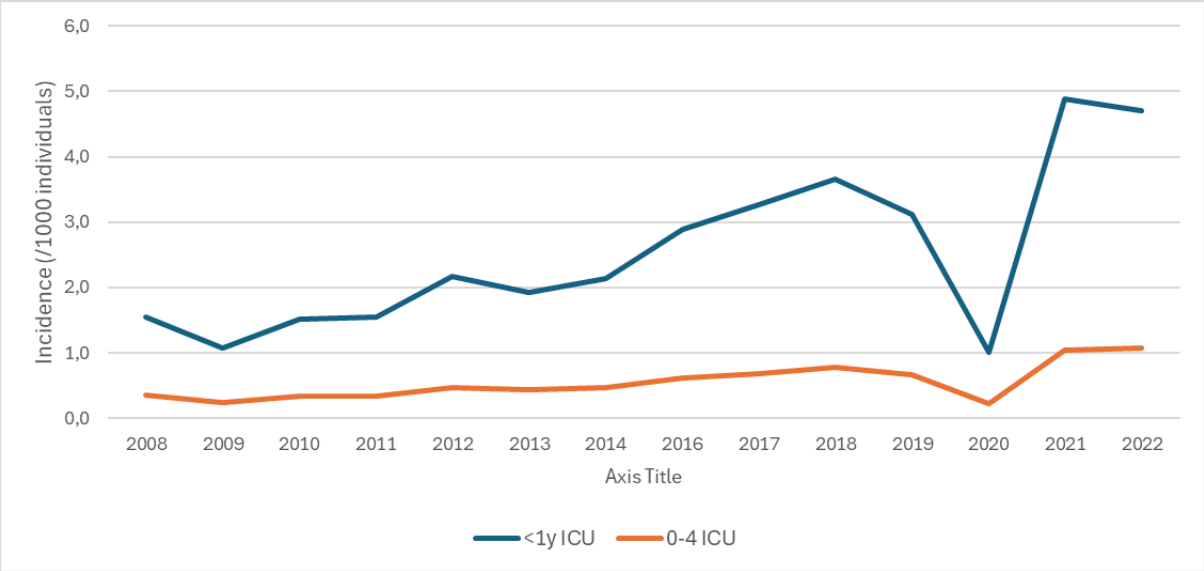
	Annual number of ICU admissions			Incidence of ICU admissions per 1000 individuals		
	Infants	Children 1-4 year	Children 0-4 year	Infants	Children 1-4 year	Children 0-4 year
2008	191	25	216	1.54	0.05	0.35
2009	136	15	151	1.07	0.03	0.24
2010	193	21	214	1.52	0.04	0.34
2011	201	18	219	1.55	0.04	0.34
2012	277	28	305	2.17	0.05	0.47
2013	244	35	279	1.92	0.07	0.43
2014	267	40	307	2.14	0.08	0.48
2016	351	44	395	2.88	0.09	0.62
2017	395	37	432	3.26	0.07	0.69

2018	436	44	480	3.66	0.09	0.77
2019	367	43	410	3.11	0.09	0.67
2020	119	17	136	1.02	0.03	0.22
2021	555	70	625	4.88	0.14	1.05
2022	556	87	643	4.71	0.18	1.08
Mean over 2016-2019	387	42	429	3.23	0.08	0.69

Source: TCT data. ICU: intensive care unit.

The incidence of infection episodes with an ICU admission per 1000 children aged 0–4 year varies between 0.24 in 2009 to 1.08 in 2022 (Figure 20) . In children <1 year, the incidence per 1000 children varies between 1.07 in 2009 to 4.88 in 2021.

Figure 20 – Annual incidence of RSV-related infection episodes with an ICU admission



Source: TCT data. RSV: respiratory syncytial virus, ICU: intensive care unit.

3.3.3.2 Respiratory tract infections by age and gender

There are more males than females (54.2% vs. 45.8% in RSV-specific RTI), especially in the group <1 year old (Table 20).

Table 20 – Number of RSV-specific infection episodes according to age and gender, years 2008-2022 (2015 excluded)

	RSV-specific RTI			
	Total	Male	Female	Unknown
<1 year	84 480	46 251 (54.7%)	38 225 (45.2%)	4
1 year	17 562	9 469 (53.9%)	8 093 (46.1%)	0
2 years	10 092	5 195 (51.5%)	4 897 (48.5%)	0
3 years	4 464	2 331 (52.2%)	2 133 (47.8%)	0
4 years	1 427	711 (49.8%)	716 (50.2%)	0
Total	118 025	63 957 (54.2%)	54 064 (45.8%)	4

Source: TCT data. RSV: respiratory syncytial virus., RTI: respiratory tract infection.

More than two thirds (84 480/118 025=71.6%) of RSV-specific infection episodes occur in patients aged <1 year. In contrast, non-RSV-specific infection episodes occur in 43.5% (=162 270/372 894) of the patients aged <1 year (Table 21). These infections are more common in hospitalised patients aged over 1 year. Among patients <1 year, one third (34.2%) are patients with RSV-specific infection episodes (=84 480/ (84 480+162 270)).

Table 21 – Number of RSV and non-RSV-specific infection episodes according to age, years 2008-2022 (2015 excluded)

	RSV-specific RTI	Non RSV-specific RTI	Total
<1 year	84 480 (34.2%)	162 270 (65.8%)	246 750
1 year	17 562 (24.2%)	54 882 (75.8%)	72 444
2 years	10 092 (12.5%)	70 959 (87.5%)	81 051
3 years	4 464 (8.0%)	51 677 (92.0%)	56 141
4 years	1 427 (4.1%)	33 106 (95.9%)	34 533
Total	118 025 (24.0%	372 894 (76.0%)	490 919

Source: TCT data. RSV: respiratory syncytial virus., RTI: respiratory tract infection.

The distribution of ages in months for patients under one year is shown in Table 22.

Table 22 – Distribution of age for patients under 1 year, for the seasons 2018-2019, 2023-2024 and 2024-2025 (source: BELSARI data)

Age in months	2018-2019 (%)	2023-2024 (%)	2024-2025 (%)
0	8.5%	9,7%	3.9%
1	19.5%	14,2%	13.9%
2	21.6%	15,9%	12.0%
3	10.6%	11,5%	9.7%
4	8.5%	5,3%	6.6%
5	6.8%	9,7%	6.9%
6	5.5%	8,0%	5.4%
7	5.5%	6,2%	7.3%
8	3.0%	6,2%	9.7%
9	4.2%	8,8%	8.5%
10	3.4%	2,7%	8.5%
11	3.0%	1,8%	7.7%
0-5 months	75.4%	66.4%	52.9%
6-11 months	24.6%	33.6%	47.1%

Source: BELSARI.

3.3.4 Hospitalisation characteristics

The characteristics of the infection episodes are presented in Table 23. The primary distinctions between RSV-specific and non-RSV-specific infection episodes were observed in the type of admission and the necessity for intensive care unit (ICU) admission. The proportion of RSV-specific infection episodes that were admitted via the emergency department was 74.9%, compared to 77.4% of the non RSV-specific infection episodes. Furthermore, 4.1% of the infection episodes lasted minimum one day in an ICU for RSV-specific RTI, compared to 2.3% for the non RSV-specific infection episodes. The severity of illness also differed between RSV-specific and non RSV-specific infection episodes, i.e. 40.7% of RSV-specific cases were SOI 1 and 17.8% were SOI 3 while for non RSV-specific cases, the figures were 53.7% and 10.0%, respectively.

Table 23 – Characteristics of the infection episodes, years 2008-2022 (2015 excluded)

	RSV-specific (n=118 025)	Non RSV-specific (n=372 894)
Type of hospital		
- University	7 474 (6.3)	31 831 (8.5)
- General hospital university like	9 586 (8.1)	31 993 (8.6)
- Non university	100 965 (85.5)	309 070 (82.9)
Type of admission		
- Planned	28 285 (24.0)	79 079 (21.2)
- Emergency department	88 374 (74.9)	288 735 (77.4)
- Other	1 366 (1.2)	5 080 (1.4)
Referred by		
- Patient himself	49 493 (41.9)	170 734 (45.8)
- Specialist	45 523 (38.6)	127 638 (34.2)
- GP	13 953 (11.8)	38 637 (10.4)
- Other	9 056 (7.7)	35 885 (9.6)
Discharge		
- After medical advice	116 712 (98.9)	368 480 (98.8)
- Other	1 253 (1.1)	3 928 (1.1)
Destination		
- Home	116 828 (99.0)	368 657 (98.9)
- Transfer to another hospital	662 (0.6)	1 991 (0.5)
- Other	475 (0.4)	1 760 (0.5)
Outcome		
- Admission to PICU	4812 (4.1)	8 532 (2.3)
- Death	60 (0.1)	486 (0.1)
*Severity of illness**		
- SOI 1	48005 (40.7)	200 336 (53.7)
- SOI 2	46600 (39.5)	128 620 (34.5)
- SOI 3	21008 (17.8)	37 221 (10.0)
- SOI 4	2400 (2.0)	6 654 (1.8)

*Source: TCT data. * Severity of illness is missing for 75 RTI infection episodes. GP: General practitioner, PICU: pediatric intensive care unit, SOI: severity of illness.*

The characteristics of the RSV infection episodes by age are presented in Table 24. Of note is the difference in the percentages of infants and children aged 1-4 years who are admitted to intensive care units, which are 5.0% and 1.7%, respectively. The mean case fatality rate (CFR) per 1000 hospitalisations is 0.51 in infants and 0.54 in children 1-4 year for the years 2008-2014 and 2016-2022. For the years 2016 to 2019, the mean CFR (RSV-specific) was 0.41 and 0.43 respectively (Table 25).

Table 24 – Characteristics of the RSV-specific infection episodes, by age, for the years 2008-2022 (2015 excluded)

	Infants (n=84 480)	Children 1-4 year (n=33 545)	Children 0-4 year (n=118 025)
Type of hospital			
- University	5 513 (6.5)	1 961 (5.8)	7 474 (6.3)
- General hospital university like	7 223 (8.5)	2 363 (7.0)	9 586 (8.1)
- Non university	71 744 (84.9)	29 221 (87.1)	100 965 (85.5)
Type of admission			
- Planned	20 437 (24.2)	7 848 (23.4)	28 285 (24.0)
- Emergency department	63 016 (74.6)	25 358 (75.6)	88 374 (74.9)
- Other	1 027 (1.2)	339 (1.0)	1 366 (1.2)

Referred by			
- Patient himself	35 650 (42.2)	13 843 (41.3)	49 493 (41.9)
- Specialist	32 847 (38.9)	12 676 (37.8)	45 523 (38.6)
- GP	9 255 (11.0)	4 698 (14.0)	13 953 (11.8)
- Other	6 728 (8.0)	2 328 (6.9)	9 056 (7.7)
Discharge			
- After medical advice	83 440 (98.8)	33 272 (99.2)	116 712 (98.9)
- Other	998 (1.2)	255 (0.8)	1 253 (1.1)
Destination			
- Home	83 515 (98.9)	33 313 (99.3)	116 828 (99.0)
- Transfer to another hospital	582 (0.7)	80 (0.2)	662 (0.6)
- Other	341 (0.4)	134 (0.4)	475 (0.4)
Outcome			
- Admission to PICU	4 245 (5.0)	567 (1.7)	4812 (4.1)
- Death	42 (0.51)	18 (0.54)	60 (0.51)
*Severity of illness**			
- SOI 1	35 831 (42.4)	12 174 (36.3)	48 005 (40.7)
- SOI 2	31 022 (36.7)	15 578 (46.4)	46 600 (39.5)
- SOI 3	15 821 (18.7)	5 187 (15.5)	21 008 (17.8)
- SOI 4	1 795 (2.1)	605 (1.8)	2 400 (2.0)

*Source: TCT data. * Severity of illness is missing for 75 RTI infection episodes. GP: General practitioner, PICU: pediatric intensive care unit, SOI: severity of illness.*

Table 25 – Mean case fatality rate in years 2016-2019 (per 1000 hospitalisations)

	Infants (n=84 480)	Children 1-4 year (n=33 545)	Children 0-4 year (n=118 025)
CFR (years 2016 to 2019)	0.41	0.43	0.41

Source: TCT data. CFR: case fatality rate.

3.3.4.1 Length of stay

The average length of stay (LOS) for the RSV-specific infection episodes in children aged 0-4 years is 4.8 days. For children <1 year, the LOS increases to 5.1 days. LOS also varies according to severity of illness (SOI) and whether the patient stayed in the ICU (Table 26). Over the years, LOS has decreased from 5.2 days in 2008-2014 to 4.5 days in 2016-2022.

Table 26 – Length of stays in days for the infection episodes, years 2008-2022 (2015 excluded)

	RSV-specific infection episode N=118 025		Non-RSV specific infection episode N=372 894	
	Mean ± SD	Median [IQR]	Mean ± SD	Median [IQR]
Age 0-4 year	4.8 ± 6.8	4 [3-6]	4.1 ± 8.8	3 [2-4]
Age <1 year	5.1 ± 7.2	4 [3-6]	4.6 ± 11.2	3 [2-4]
Age 1-4 year	4.2 ± 5.7	3 [2-5]	3.7 ± 6.4	3 [2-4]
*Severity of illness**				
- SOI 1	3.8 ± 2.2	3 [2-5]	2.9 ± 2.6	2 [2-4]
- SOI 2	4.5 ± 4.8	4 [3-6]	3.9 ± 5.6	3 [2-4]
- SOI 3	6.5 ± 8.3	5 [4-8]	6.1 ± 11.7	4 [2-7]
- SOI 4	17.6 ± 30.3	10 [6-16]	31.7 ± 43.8	16 [8-36]
Admission to PICU				
- Yes	12.7 ± 16.6	9 [6-13]	23.3 ± 34.9	11 [5-23]

- No	4.5 ± 5.8	4 [3-5]	3.6 ± 6.4	3 [2-4]
Years				
- 2008 to 2014	5.2 ± 8.0	4 [3-6]	4.4 ± 9.0	3 [2-5]
- 2016 to 2022	4.5 ± 5.6	4 [2-5]	3.7 ± 8.6	3 [2-4]

*Source: TCT data * SOI is missing for 78 RTI infection episodes. IQR: interquartile range, PICU: pediatric intensive care unit, SOI: severity of illness.*

The annual number of hospital days for RSV varied from 29 215 in 2009 to 56 734 in 2022 in children aged 0-4 years, and from 21 905 in 2009 to 43 938 in 2022 in infants. A peak in the number of hospital days is observed in 2018. The annual length of stay decreased from 7.53 in 2008 to 4.04 in 2022 in children aged 0-4 years. Over the period 2016-2019, the length of stay was 4.6 days (Table 27).

Table 27 – Annual number of hospital days (total and average per hospitalisation) for the RSV-specific infection episodes

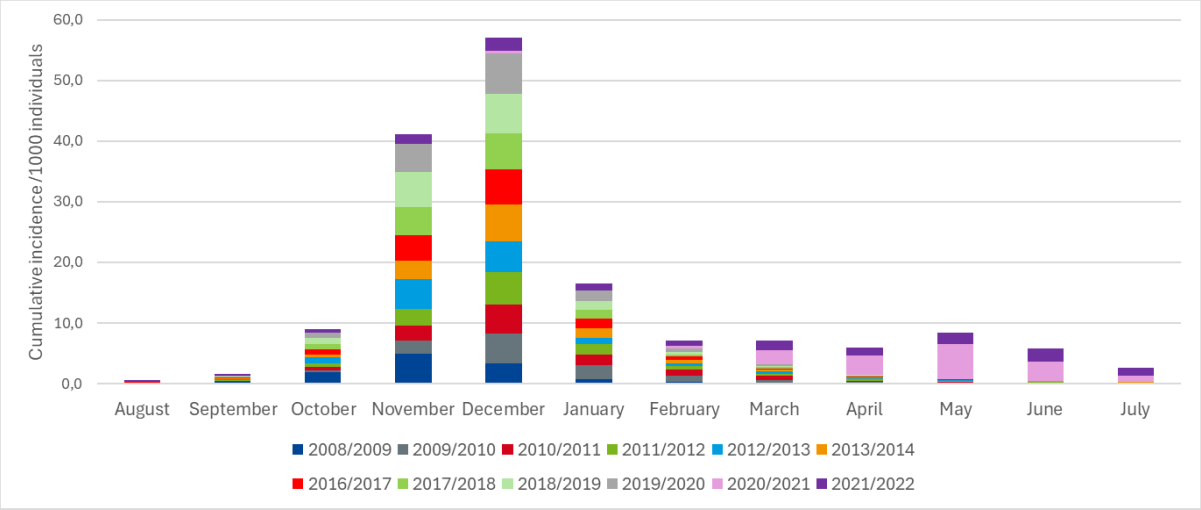
	Annual number of hospital days			Annual length of stay		
	Infants	Children 1-4 year	Children 0-4 year	Infants	Children 1-4 year	Children 0-4 year
2008	24 831	19 667	44 498	5.35	5.72	7.53
2009	21 905	7 310	29 215	5.49	4.45	5.83
2010	32 914	8 203	41 117	5.79	4.26	8.21
2011	32 837	9 073	41 910	5.47	4.13	8.31
2012	38 209	10 639	48 848	5.45	4.39	8.90
2013	29 336	8 602	37 938	5.14	4.11	7.25
2014	29 131	8 481	37 612	5.38	4.42	8.83
2016	32 550	9 177	41 727	5.09	4.21	7.99
2017	31 903	9 829	41 732	4.88	4.17	7.08
2018	35 673	9 485	45 158	4.75	3.87	4.35
2019	31 285	8 693	39 978	4.84	3.7	6.39
2020	8 330	2 003	10 333	5.52	4.6	8.24
2021	38 076	15 919	53 995	4.72	3.56	3.38
2022	43 938	12 796	56 734	4.61	3.49	4.04
Mean over 2016-2019	32 853	9 296	42 149	4.89	3.99	4.66

Source: TCT data.

3.3.5 Seasonality

Figure 21 shows that the cumulative incidence of RSV-specific infection episodes generally increases between October and February, with the exception of the years affected by the COVID-19 pandemic (season 2020-2021). For this season, a decrease is observed, especially from April to December 2020, in the number of RSV-infection episodes. It is also obvious from the figure that the epidemiology of RSV infections was profoundly modified in the years following the COVID-19 pandemic, with a flatter but longer transmission season. Between March and August 2021, the number of RSV-specific infection episodes increases sharply due to late infections, making 2021 the year with the highest number of RSV-specific infection episodes.

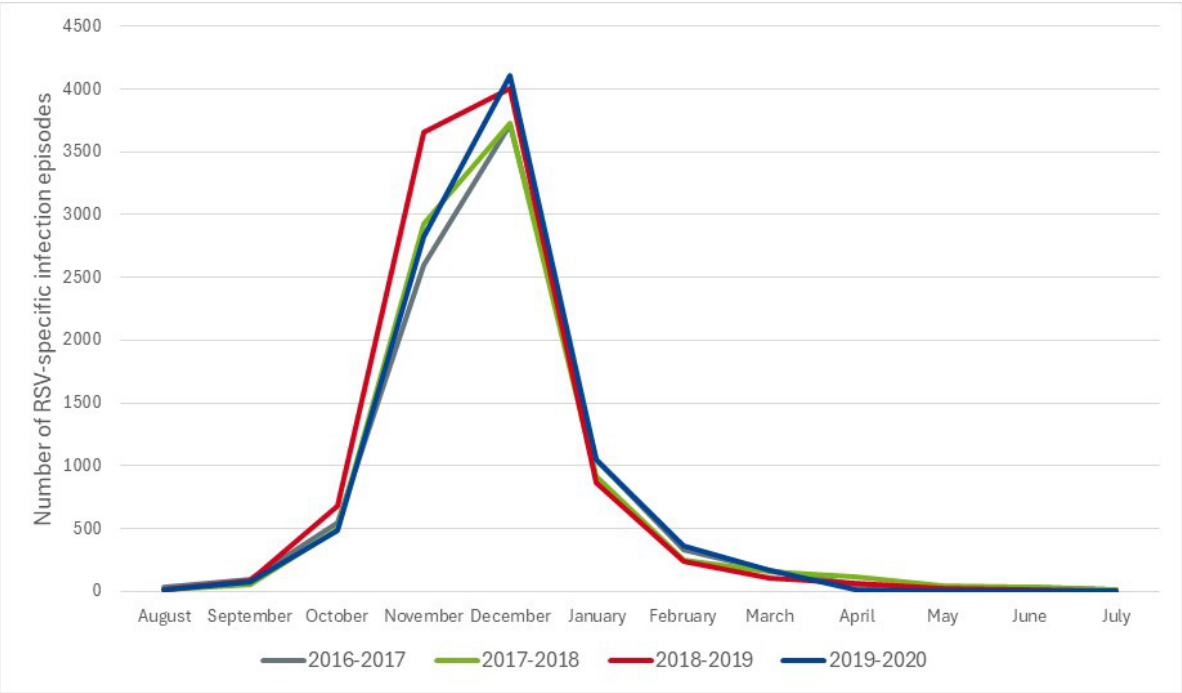
Figure 21 – Cumulative incidence of RSV-specific infection episodes by months for the transmission seasons 2008-2009 to 2013-2014 and 2016-2017 to 2019-2020



Source: TCT data.

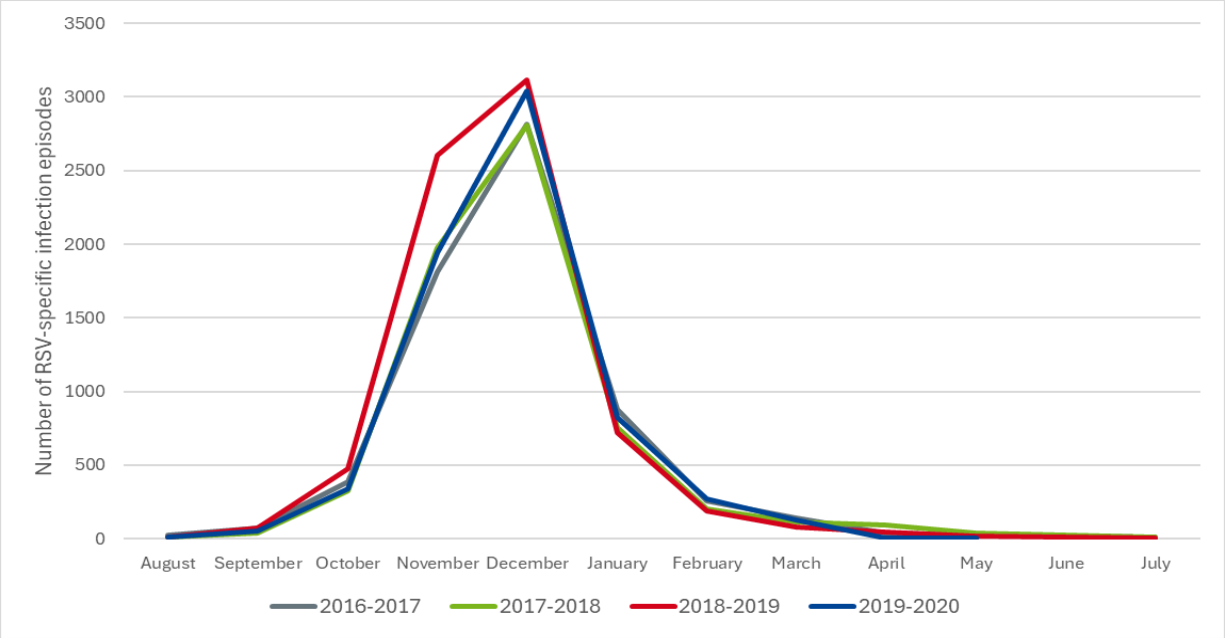
Figure 22 and Figure 23 focus on the years 2016-2019. The increase in the number of RSV infection episodes in children 0-4 years is visible between October and February, reaching 4000 cases in December for the seasons 2018-2019 and 2019-2020. In infants, the number of RSV infection episodes reached 3000 cases in December for the seasons 2018-2019 and 2019-2020.

Figure 22 – Number of RSV-specific infection episodes by months for the transmission seasons 2015-2016 to 2019-2020 in children aged 0-4 years



Source: TCT data.

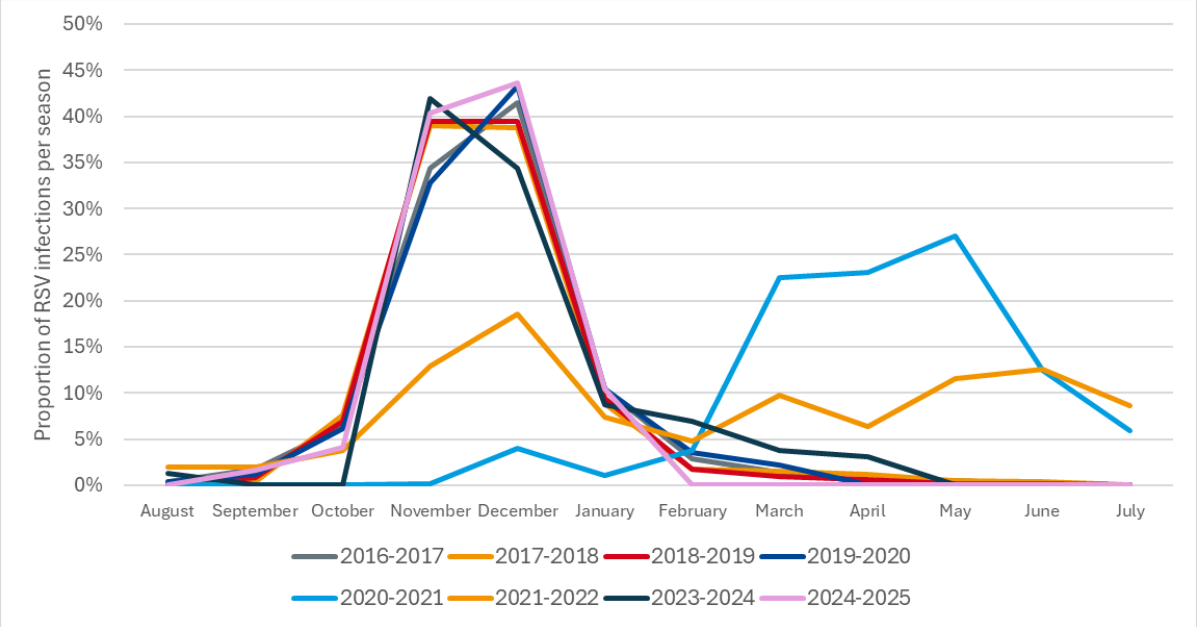
Figure 23 – Number of RSV-specific infection episodes by months for the transmission seasons 2015-2016 to 2019-2020 in infants (<1 year)



Source: TCT data.

The BELSARI analysis provides the most recent data on RSV infections. By expressing the number of RSV infection episodes as a proportion of total infections, per month, it was possible to combine the BELSARI and the TCT data and obtain the distribution of the proportion of RSV infections per season from 2016-2017 to 2024-2025 (no data was available for the season 2022-2023) (Figure 24). It can be seen that the RSV hospitalisations of the two most recent seasons (i.e. 2023-2024 and 2024-2025) have returned to pre-COVID levels, with more cases between October and February.

Figure 24 – Distribution of RSV infection episodes per months per season 2016-2017 to 2021-2022 (TCT data), and 2023-2024 to 2024-2025 (BELSARI data)



Source: TCT data until 2021-2022, BELSARI for 2023-2024 and 2024-2025.

3.3.6 Costs of RSV infection episodes

Of the 118 025 RSV infection episodes, 4 168 could not be attributable to a patient, due to no possible linkage between AZV–SHA and MZG–RHM data. The average cost per RSV-related infection episode was then calculated on 113 857 cases.

3.3.6.1 Hospitalisation costs per RSV-specific infection episodes

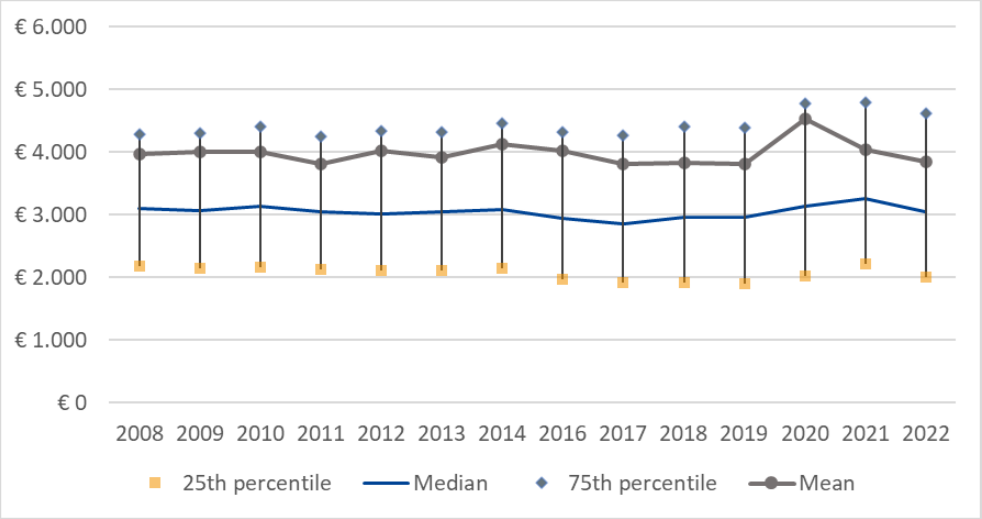
The mean and median hospitalisation costs (NIHDI + patient share) per RSV-specific infection episode among children aged 0-4 years are presented in Table 28 and in Figure 25. All costs were indexed to the reference year (2024). Over the study period (2008-2022, 2015 excluded) the mean costs ranged from €3 832.9 ± €6 365.6 in 2008 to €4 564.0 ± €8 994.0 in 2020. The median costs ranged from €2 871.7 in 2017 (IQR: €1 928.7-€4 297.7) to €3 282.6 (IQR: €2 229.6-€4 818.7) in 2021. For the RSV infection episode including a stay in ICU, the mean costs ranged from €11 993.7 ± €10 822.0 in 2021 to €21 259.2 ± €30 797.5 in 2009. The median costs ranged from €8 676.0 in 2008 (IQR: €4 898.5-€16 206.9) to €12 651.0 (IQR: €5 976.4-€19 577.4) in 2009. For an in-depth analysis see Chapter 4.

Table 28 – Mean cost (NIHDI + patient share) per RSV-specific infection episode and per RSV-specific infection episode with an ICU admission (2008-2022, 2015 excluded)

	Cost per hospitalisation			Cost per hospitalisation in ICU		
	Infants	Children 1-4 year	Children 0-4 year	Infants	Children 1-4 year	Children 0-4 year
2008	3 934.5	4 054.8	3 986.0	13 174.2	21 257.3	15 718.9
2009	4 283.7	3 429.7	4 032.3	21 402.8	19 957.7	21 259.3
2010	4 287.7	3 260.9	4 024.4	15 748.3	7 488.4	14 937.7
2011	4 064.3	3 227.3	3 837.4	15 811.3	14 314.5	15 688.3
2012	4 218.3	3 548.0	4 044.7	15 008.5	25 760.2	15 995.5
2013	4 093.4	3 526.9	3 939.4	14 273.7	14 989.0	14 363.4
2014	4 308.1	3 709.4	4 150.7	16 354.4	20 698.2	16 920.3
2016	4 188.2	3 660.0	4 052.5	16 778.6	27 745.0	18 000.2
2017	4 017.9	3 329.6	3 834.1	13 117.6	25 253.7	14 157.1
2018	4 001.7	3 380.6	3 847.7	12 729.0	18 688.1	13 275.2
2019	4 089.3	3 133.9	3 832.9	14 756.5	10 975.2	14 359.9
2020	4 721.4	4 029.0	4 564.1	17 342.7	18 436.0	17 479.3
2021	4 430.6	3 400.2	4 060.0	11 976.1	12 133.2	11 993.7
2022	4 144.0	3 197.7	3 878.5	12 304.4	11 189.0	12 153.5
Mean over 2016-2019	4 074.3	3 376.0	3 891.8	14 345.4	20 665.5	14 948.1

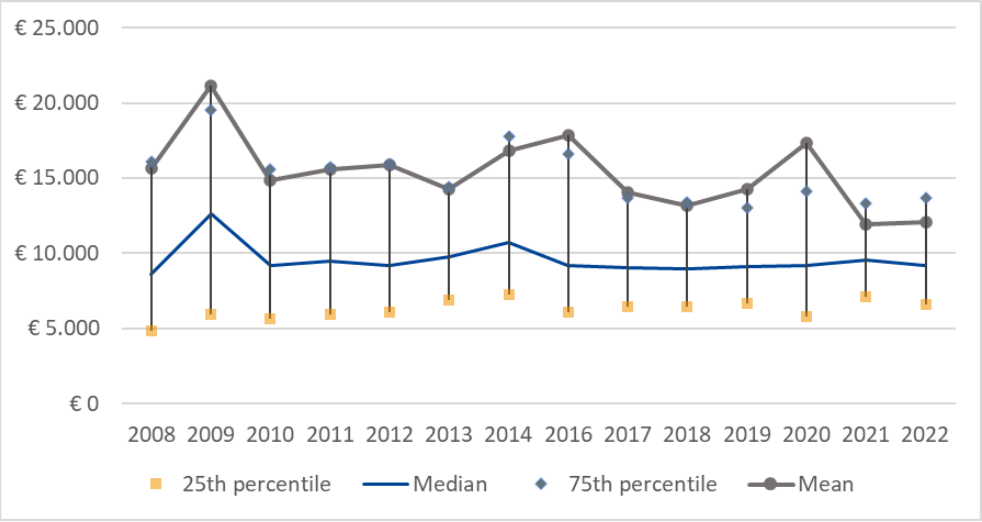
Source: TCT data. All costs were indexed to the reference year (2024).

Figure 25 – Mean and median (and IQR) costs (NIHDI + patients share) per RSV infection episode, per year (age 0-4 years)



Source: TCT data. IQR: interquartile range, NIHDI: National Institute for Health and Disability. All costs were indexed to the reference year (2024).

Figure 26 – Mean and median (and IQR) costs (NIHDI + patient share) per RSV infection episode with an ICU admission, per year (age 0-4 years)



Source: TCT data. IQR: interquartile range, NIHDI: National Institute for Health and Disability. All costs were indexed to the reference year (2024).

3.3.6.2 *Evolution of the total costs of RSV-specific infection episodes*

The analysis of the evolution of total costs is conducted with constant tariffs and prices over the years (not inflated). Total costs are separated between NIHDI and patient's costs[tt].

The total costs of RSV-specific infection episodes in children 0-4 year varied from €15.25 million in 2009 to €31.25 million in 2018, for the pre-COVID period (Table 29). In 2020, the total costs do not exceed €7.41 million. After the COVID-period, the total costs were over €40 million.

Table 29 – Annual total costs (million €) of RSV-specific infection episodes, per age

Year	Infants	Children 1-4 year	Children 0-4 year
2008	12.04	9.31	21.35
2009	11.37	3.88	15.25
2010	16.84	4.33	21.17
2011	17.37	5.1	22.47
2012	21.53	6.32	27.85
2013	17.11	5.5	22.6
2014	17.78	5.51	23.29
2016	20.08	6.05	26.13
2017	20.9	6.33	27.23
2018	24.31	6.94	31.25
2019	21.2	5.96	27.16
2020	5.98	1.43	7.41
2021	29.84	12.78	42.61
2022	36.32	10.82	47.15
Mean over 2016-2019	21.62	6.32	27.94

Source: TCT data. NIHDI: National Institute for Health and Disability.

[tt] Patient's costs (excluding supplements) are not fully available in the AZV-SHA database since patient's shares are only recorded for pharmaceuticals and related deliveries. However, for some 'common' medical acts as well as for medical devices and implants, the patients' shares can vary from minor to important (especially for implants) but these shares cannot be assessed in the data.

4 ECONOMIC EVALUATION OF RSV PREVENTION STRATEGIES IN CHILDREN IN BELGIUM

KEY POINTS

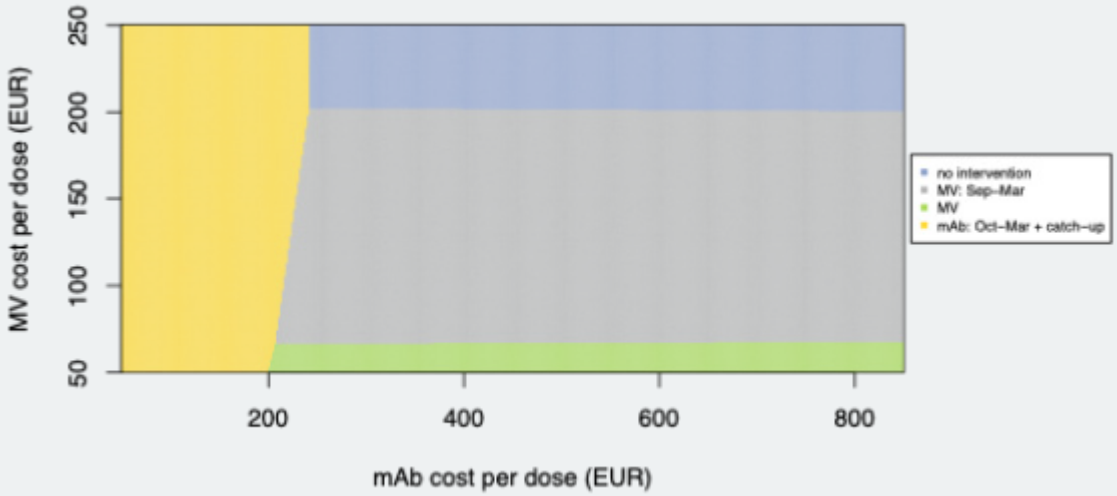
- A static cohort model was used to estimate the RSV disease and economic burden in children under five years of age and to evaluate the cost-effectiveness of RSV interventions in Belgium. Five immunisation strategies were evaluated:
  - Year-round single-dose maternal vaccine (MV) during pregnancy
  - Year-round single-dose nirsevimab (mAb) at birth
  - Seasonal maternal vaccine during pregnancy for infants with a due delivery date in September to March (MV: Sep-Mar)
  - Seasonal nirsevimab given at birth for infants born during the RSV season from October to March (mAb: Oct-Mar)
  - Seasonal nirsevimab (as described above) plus a catch-up program in September for infants (≤6 months) born outside of the RSV season from April to September (mAb: Oct-Mar + catch-up)
- The base case analyses were conducted from the perspective of the health care payers (federal government, federated entities and patients). The immunisation coverage for the MV and mAb strategies were assumed to be 40% and 90%, respectively. The modelled efficacies can be found in the methods section and in Chapter 2.
- Without universal immunisation, but including immunisation of high-risk children with palizivumab, RSV was estimated to cause a substantial burden in children under 5 years, with on average per year:
  - 115,796 RSV episodes, 8,638 (non-ICU) hospitalisations, 428 ICU admissions.
  - 5 deaths per year.
  - A loss of 968 undiscounted QALYs, including 411 life years.
  - €43 million in direct health care costs.
  - A disproportionately large part of the severe burden occurs in infants aged less than 3 months (37% of non-ICU hospitalisations, 57% of ICU admisions, 40% of deaths).
  - Belgium has a comparatively high RSV pediatric hospitalisation and ICU burden, presumably due to differential tertiary care accessibility and patient management.
- The mAb strategies were more clinically effective than the MV strategies, mainly because the uptake is expected to be much higher with mAb (assumed 90%, versus 40% for MV). However, when the same level of coverage was considered (i.e. 90% and 70%) for both mAb and MV strategies, the mAb strategies still yielded a greater clinical benefit.
- The seasonal mAb with catch-up strategy was the most effective strategy, avoiding in infants (children <1 year) 55% of the total RSV episodes, 64% of the (non-ICU) hospitalisations, 66% of the ICU admissions and nearly 2 deaths (65% avoided). It was more effective than year-round mAb immunisation because the doses would, on average, be administered closer to the start of the RSV season.
- Seasonal maternal vaccination is the least effective strategy (even at 90% uptake), but with incremental direct costs per QALY ("ICER") of €11,276, it is also the only potentially cost-effective strategy at current list price level, not explicitly accounting for any serious adverse

event. None of the other strategies would be considered cost-effective at current list prices as they were either dominated, or yielded ICERs exceeding €150,000.

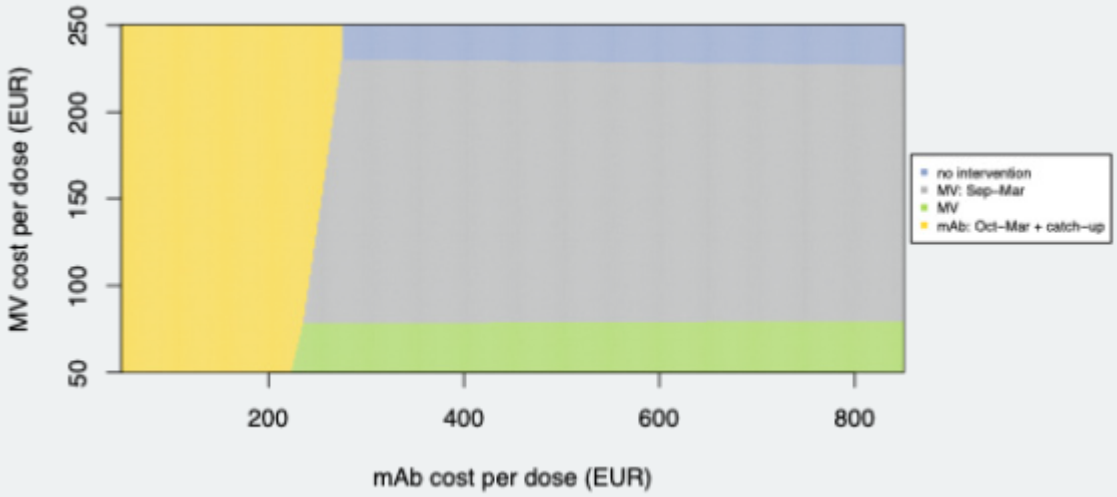
- In the absence of reliable estimates of the administration costs associated with these products, extensive threshold analyses were conducted on "all-inclusive" costs per dose. These costs include purchase, stockage, distribution and delivery of the immunising doses to patients.
- We identified all-inclusive cost-per dose ranges for which either mAb or MV could be deemed cost-effective at different levels of WTP per QALY. Broadly speaking, the immunisation costs per dose needed to reduce much more compared to the public list price for mAb (by about 75%) than for MV (by about 25%), in order to yield a cost-effective result for their use. We found at WTP thresholds ranging from €20,000 to €50,000 per QALY gained:
    - If both immunisation products are costly to implement (i.e. mAb >€210 to >€305 and MV >€200 to >€255 per dose), 'no intervention' would be cost-effective up to €50,000 WTP value, i.e. the preferred choice.
    - If mAb costs <€200 to <€250 per dose, the seasonal mAb plus catch-up strategy would be preferred, regardless of the costs of MV.
    - If MV is relatively cheap (i.e., <€65 to <€85 per dose) and mAb relatively expensive (>€200 to >€250 per dose), then the year-round MV strategy would be preferred.
    - If MV costs <€200 to <€250 per dose and mAb costs >€210 to >€260 per dose, then seasonal MV would be preferred.
    - The seasonal mAb strategy was not preferred, because the seasonal mAb strategy is less costly but also less effective than the seasonal mAb plus catch-up strategy. At the WTP above €20,000 per QALY gained, the seasonal mAb plus catch-up strategy was optimal due higher QALY gained.
    - The year-round mAb strategy was never the optimal strategy, at any WTP value, because it was always dominated by the seasonal mAb plus catch-up strategy.

Intervention cost threshold analysis from HCP perspective (cost per dose including delivery)

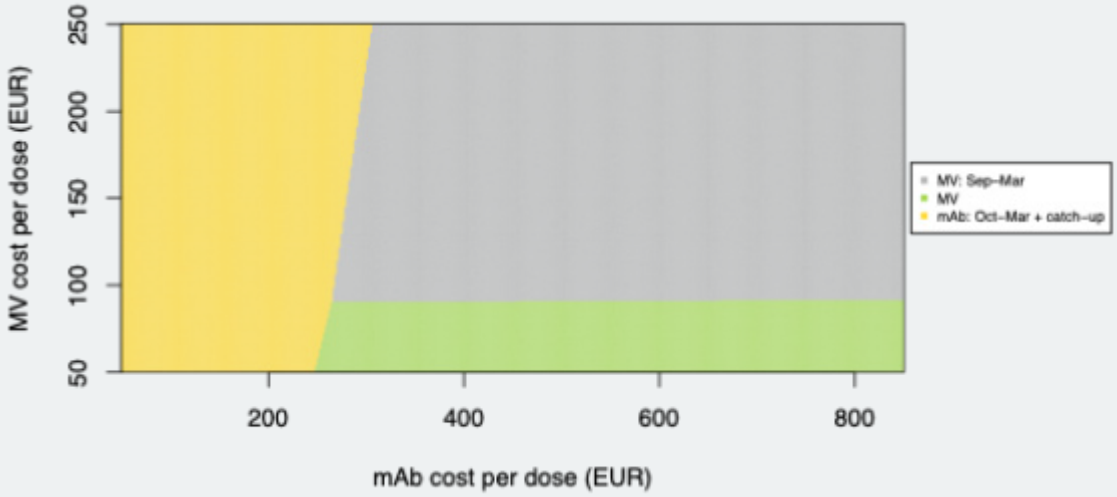
Willingness to pay: €20,000 per QALY gained



Willingness to pay: €35,000 per QALY gained



Willingness to pay: €50,000 per QALY gained



EUR: euro, HCP: health care payers', QALY: quality-adjusted life-year, MV: year-round maternal vaccine, MV: Sept-Mar: seasonal maternal vaccine from September to March, mAb: Oct-Mar + catch-up: seasonal mAb combined with a catch-up strategy.

- Apart from immunisation costs, the results were particularly sensitive to parameterised estimates of the RSV disease burden, selection of hospitalisation-years (non-ICU and ICU) and outpatient rates, as well as the efficacy of the interventions against hospital and ICU admissions, to the extent that they changed the vaccination cost thresholds. Extensive scenario analyses, each including intervention cost-threshold graphs can be consulted.
- Intervention options that use relatively more doses (such as year-round and catch-up programmes) require higher investments upfront. Both mAb and MV are expected to lead to additional costs to the health care system, unless the all-inclusive immunisation costs per dose are lower than €110 for MV year-round and €160 for MV seasonal strategies or lower than €200 for seasonal mAb and €190 for seasonal plus catch-up mAb strategies.
- Future research should aim to:
    - Assess in detail the intervention costs associated with existing individualistic and collective immunisation programmes in Belgium according to payer, and estimate the

marginal costs of rolling out new immunising interventions, as these costs would be important both for cost-effectiveness and budget-impact calculations.

- Establish and quantify the causal relationship between RSV disease and the occurrence of wheezing and asthma, because if such a relationship is causal, it could have an important beneficial impact on the cost-effectiveness of RSV immunisation.

4.1 Literature review

4.1.1 *Methods*

A focused literature review was conducted to identify recent evidence on the disease burden, healthcare resource use, direct and indirect costs, and health-related quality of life (HRQoL) associated with RSV in Belgian children under five years of age. As highlighted in previous research and by a Belgian expert panel, data on RSV disease burden in hospital outpatient, primary care and community settings were limited in Belgium due to limited RSV diagnostic testing.[5, 6, 8, 75] Therefore, this review also aimed to collect data from settings outside of hospital, from large multi-European research consortia and from neighbouring countries of Belgium to address and bridge these data gaps.

PubMed was chosen as the database for this focused review due to its comprehensive, reliable and fast coverage of the biomedical and life sciences literature. Using its advanced search functionality and indexing with Medical Subject Headings (MeSH), it enables rapid retrieval of the most relevant articles and up-to-date evidence. On October 29th, 2024, we searched PubMed using keywords such as “RSV” or “respiratory syncytial virus”, “bronchiolitis” or “cost” or “quality of life”, and “child” for studies published between January 1st, 2014, and the search date, without any language restrictions. The search terms, inclusion and exclusion criteria can be found in Appendix 4.1.1 and Appendix 4.1.2.

The primary reviewer (XL) conducted the literature search and screened titles and abstracts for selection based on the inclusion and exclusion criteria. The second reviewer (ZM) independently screened a random 10% sample of titles and abstracts. Next, the primary reviewer assessed the full texts of the articles, with a random sample of 20% independently reviewed by the second reviewer. Any disagreements were resolved through discussion between the two reviewers. It was reassuring that any initial cause for disagreement was settled in accordance with the primary reviewer’s original assessment.

Data extraction tables were predefined including study characteristics (i.e., study type, period), incidence rate, mortality, health care resource use, direct and indirect cost per episode, HRQoL and study funding. The primary reviewer extracted the data, and the complete data extraction was checked by the second reviewer.

4.1.2 *Results*

The literature search yielded 333 records, and 16 articles met the inclusion criteria. We also identified a systematic review focusing on the global burden of RSV disease in primary care and emergency departments (ED) among children.[76] Therefore, we traced the references and included four additional articles in our review. Moreover, we also included two articles published after our search date: one article evaluated the costs of care for paediatric patients hospitalised for RSV in Belgium[8] and the other reported on the RSV burden in primary care settings across five countries, including Belgium[77] In total, 22 articles were included in the data extraction tables (Appendix 4.2.1).

There are four studies that reported data from Belgium and the details of these studies can be found in Appendix Table 58 and Table 59. Two[6, 8] of them were funded through public funding, one[75] was funded by the European Union Innovative Health Initiative (IHI), a public and private partnership and one[77] was funded by pharmaceutical companies. The funders had no role in the design of any of the four studies.

To summarise, Del Riccio and colleagues[75] used linear regression models to extrapolate the RSV-associated hospitalisation rates among children across 29 European countries, including Belgium. These rates were stratified into detailed age groups, especially for children under one year of age (i.e., 0–2 months, 3–5 months and 6–11 months).[75] Bouckaert and colleagues[6] conducted a retrospective analysis of Belgian hospitalisation claim data from the 2017-2018 RSV season. They estimated RSV-associated hospitalisation rates and reported the number of in-hospital deaths.[6] Tilmanne and colleagues[8] performed a retrospective cohort study across 16 French-speaking hospitals in Belgium covering two calendar years (2018 and 2019). This study evaluated the costs of RSV-associated hospitalisations in Belgian children. Hak and colleagues conducted a prospective cohort study among children under five years of age in primary care settings across five European countries, including Belgium, Italy, Spain, the Netherlands and the UK, over three RSV seasons (2020/2021-2022/2023).[77] Overall, the quality of these studies appears to be relatively high, based on well-established study design hierarchy criteria, although we did not conduct specific quality appraisal for each study regarding (bias in) study execution.[78] In the following section, we explain either how these studies were used directly as input parameters (i.e., resource use, indirect costs) in the cost-effectiveness analysis or how they compare with the input parameters used in our study (i.e. one season hospitalisation data).

We also extracted data on primary care, ED, mortality, health care resource use, direct and indirect costs, and health-related quality of life data (HRQoL) from large multi-country European studies and studies conducted in the countries close to Belgium (Appendix Table 60 to Table 63). Three studies used the data collected from a multi-country, prospective, community-based observational study from the RESCEU (REspiratory Syncytial virus Consortium in EUrope) consortium. One article focused on the incidence rate,[3] another focused on cost and HRQoL of RSV,[79] and the third one on the health care resource use for non-medically attended (non-MA) episodes.[80] We also extracted data from Germany (N=4), the Netherlands (N=4), France (N=1), Spain (N=3), Finland (N=2) and Italy (N=1). In the absence of Belgium-specific data, input from these studies was considered and is explained in the following section.

When estimating national age-specific incidence of primary care, outpatient and hospitalised RSV cases, the hierarchy of study quality depends on factors such as study design, data completeness, and diagnostic accuracy. Prospective cohort studies represent the gold standard, as they enable active surveillance, standardised case definitions, and direct age-stratified case identification, reducing the risk of misclassification bias and enhancing temporal accuracy. However, due to their resource-intensive nature, prospective studies are often limited in sample size and generalisability at the national level. The RESCEU prospective study exhibits these advantageous characteristics, and since it also had a relatively large size it seems most suited for some of our purposes. Indeed, the RESCEU cohort recruited nearly 10,000 newborns to record prospectively pivotal events such as hospital admission (with RSV laboratory test result) before one year of age, and would therefore seem appropriate to estimate the relatively common occurrence of hospital admissions. Within this cohort study of 10,000 infants, a nested cohort of ~1,000 was actively followed during their first RSV season with weekly symptom check-ins (and systematic recording) and nasal sampling during each ARI episode. On the other hand, retrospective studies based on national claims databases offer broad population coverage, enabling nationwide age-stratified incidence estimates over extended time periods. These datasets allow for large-scale analysis, but their reliance on routine clinical coding (i.e. ICD codes) rather than laboratory confirmation combined with symptoms as in the RESCEU cohort study, introduces potential misclassification. While well-validated claims databases with consistent coding practices can provide robust estimates, their quality depends on diagnostic practices, coding accuracy, and healthcare-seeking behaviour. These databases are better suited for estimating the cost per episode, resource utilisation per episode (e.g. length of stay) and probability of the occurrence of an event (e.g. intensive care unit (ICU) admission, death) per recorded episode, rather than the incidence of recorded episodes. Therefore, although both these types of studies have relatively good quality traits, we use them for different purposes, as outlined in appendix tables (Table 60 to Table 62). In addition, modelling studies and extrapolation studies based on regression analyses are generally considered to provide less solid

evidence, but this also depends on the nature of the primary data used in these secondary analyses. In our base case analyses, we do not directly use results from such derived studies as input data.

Generally, our review demonstrated considerable variation in RSV-related primary care consultation and ED visit rates across countries, likely due to differences in primary care systems and heterogeneity in study methodologies. In view of this we did not conduct a meta-analysis. Moreover, we found that RSV mortality data remained scarce, particularly for very young children (e.g., aged 0–2 months and 3–5 months).

4.2 Methods

4.2.1 *Model structure*

We adapted a previously published static cohort model (Multi-Country Model Application for RSV Cost-Effectiveness poLicy: MCMARCEL from Li et al. 2020, 2022[81, 82] and Getaneh et al. 2023[83]) for the Belgian setting. This model was used to estimate the RSV disease and economic burden in children under five years of age and to evaluate the cost-effectiveness of RSV interventions in Belgium.

The static model is deemed appropriate to use in this evaluation. This choice is in line with the World Health Organization (WHO) guide on economic evaluation of vaccines regarding model choice (see chapter 6, WHO guide).[84] Previously, a formal model comparison was performed to investigate the differences between static and dynamic models applied to infant RSV immunisation when using a standard set of input parameters in different models.[85] It showed that static models produced similar results as the dynamic models given that the expected herd immunity impacts remained limited when infants were protected through immunisation mainly in the first year of life. Since only infants are immunised with nirsevimab, and not mother-infant pairs, the herd immunity impact was found to be smaller than with a maternal vaccine. The static models were better equipped than the dynamic models to mimic the monthly incidence of hospitalisations in the first six months of life in the absence of interventions.[85] Furthermore, similar findings were reported in another model comparison study of RSV immunisation in infants.[86] In line with the WHO guide, the existence of two model comparison studies, which found no clear preference for a dynamic over a static model structure for the research questions at hand, offers sufficient basis to opt for a static model for the strategies under consideration.

The model followed the entire cohort of Belgian newborns monthly, including both preterm and full-term infants, over a period of five years. As shown in the model structure (Figure 27), it accounted for costs and loss of quality-adjusted life-years (QALYs) associated with symptomatic RSV cases. This included cases requiring outpatient visits (including primary care visits, hospital outpatient visits and ED visits), hospital admissions (with and without ICU admissions), as well as symptomatic RSV cases that do not require professional medical attention (non-MA). We assumed that RSV-related deaths occur among severe cases requiring hospitalisation in Belgium. The model estimated premature RSV-related deaths by applying non-ICU and ICU case-fatality ratios to the projected ICU and non-ICU hospitalised cases. The number of life years lost was obtained by multiplying the projected premature RSV-related deaths by average life expectancy in Belgium at the age of death. In scenario analyses, we also evaluated the long-term consequences of RSV in infants hospitalised during their first year of life, by including the subsequent development of (i) recurrent wheezing up to 3 years of age, and (ii) recurrent wheezing and asthma up to 13 years of age.[81, 87] We did not explicitly model the long-term consequences of RSV in infants who were not hospitalised (i.e., those who only had outpatient visits) due to a lack of robust data on the occurrence of such consequences in non-hospitalised patients (further details can be found in section 4.2.2.9).

The following immunisation programmes were compared to no program and to each other in a full incremental analysis:

- Year-round single-dose maternal vaccine (MV) during pregnancy
- Year-round single-dose nirsevimab (mAb) at birth

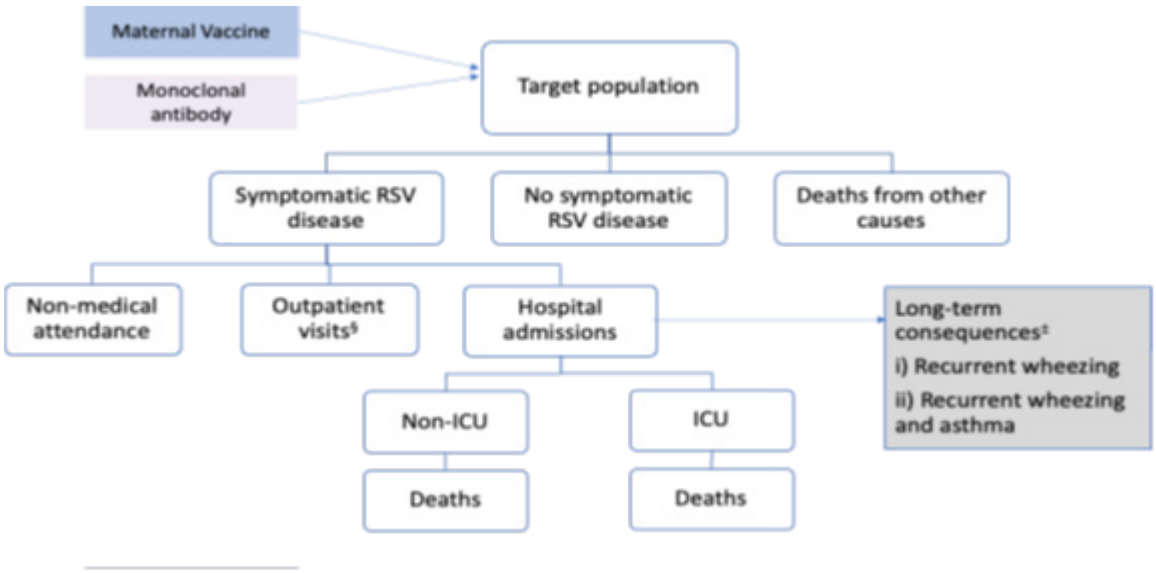
- Seasonal maternal vaccine during pregnancy for infants with due delivery date in September to March (MV: Sep-Mar)
- Seasonal nirsevimab given at birth for infants born during the RSV season from October to March (mAb: Oct-Mar)
- Seasonal nirsevimab (as described above) plus a catch-up program in September for infants (≤6 months) born outside of the RSV season from April to September (mAb: Oct-Mar + catch-up)

Since this economic evaluation focuses on the national immunisation programme, we did not explicitly evaluate an immunisation programme targeting only very high-risk infants (e.g. children with congenital cardiopathy or chronic respiratory insufficiency). It is challenging to accurately estimate the burden of disease for this high-risk population, as the observed burden data we can access is already reduced through the use of palivizumab in high-risk infants (e.g., national hospitalisation data no longer reflect hospital admissions and length of stay of naive, unprotected, high-risk infants). However, the overall influence of the switch from palivizumab to nirsevimab in the high-risk population (averaging 1,397 to 1,566 patients per year[88]) is bound to be limited given a total birth cohort of more than 100,000 infants. Moreover, when transitioning from palivizumab to nirsevimab, one could reasonably expect at least a similar effect at a lower cost. Therefore, we adopted a conservative approach by not incorporating an additional benefit on the effect side from this switch in the high-risk group, which may result in an underestimation of the intervention's impact for this small high-risk group. Our analysis focused on the broader extension of protection through the general use of mAb and MV. Given the relative scales and potential outcomes, we did not explicitly assess the marginal benefit of replacing palivizumab with nirsevimab in high-risk infants. Therefore, our results should be interpreted as relating to the expansion of universal use of mAb and/or MV, after the decision to switch from palivizumab to nirsevimab had already been taken for the high risk group.

The evaluation was conducted according to the KCE guideline for economic evaluation and budget-impact analysis,[89-92] with additional uncertainty analyses (as described in Bilcke & Beutels, 2022[93]). Both a healthcare payers' (federal government + federated authorities + patients) and a societal perspective were employed. For the societal perspective, we considered the parental productivity lost due to RSV illness of their children using the human capital approach.

This model employed a five-year time horizon (in monthly cycles) for incurring infections. The long-term consequences caused by these infections acquired in the first year of life were also accounted for in the scenario analyses. Moreover, the discounted lifetime QALY losses associated with each RSV-associated premature death were included. In scenario analyses, also the costs and QALYs associated with recurrent wheezing and asthma were estimated annually and included over their scenario defined periods (i.e. 3 or 13 years). Discount rates of 3% for costs and 1.5% for effects were applied for all outcomes occurring beyond one year.[91] All costs were inflated to 2024 price levels using the consumer price index (CPI) from the health care sector. Health benefits were measured as QALYs gained. As Belgium does not use an explicit cost-effectiveness threshold, we considered a range of willingness-to-pay (WTP) values, tentatively from €0 to €80,000 per QALY gained. Parametric uncertainty was accounted for with probabilistic sensitivity analysis (PSA, sample size: 1,000).[94, 95] Scenario analyses were conducted to examine uncertainties associated with potentially influential input parameter choices (section 4.2.3).

Figure 27 – Model Structure



RSV: respiratory syncytial virus. § Outpatient visits include primary care consultations (either general practitioners or paediatrician consultation), hospital outpatient consultations and emergency department visits without hospital admission. ± Scenario analysis only: patients with RSV-related hospital admission within the first year of life have age-specific probabilities of (i) recurrent wheezing events up to 3 years of age and (ii) recurrent wheezing and asthma events up to 13 years of age.

4.2.2 *Model input parameters and assumptions*

We adopted input parameters specifically reflecting the Belgian context wherever possible. When data were unavailable, we identified relevant information from neighbouring countries with comparable healthcare systems. We presented these findings to a Belgian expert panel to assess their suitability as bridging data.

Table 47 summarizes the final set of input parameters and details the corresponding reference.

4.2.2.1 Demographic data

Based on demographic data from Statbel, out of a total birth cohort of 108,680 in 2024, 57% of infants were born in Flanders, 30% in Wallonia, and 13% in Brussels.[96] The model follows the birth cohort over a period of five years, to evaluate costs and effects up to this age. The vast majority of infants in Belgium are covered by national health insurance, including access to care and hospital treatments with a small amount of co-payment for families. The age-specific, non-disease-specific probability of death was estimated using life tables published by Statbel (2023).[97]

4.2.2.2 RSV-ICD-coded hospitalisations

Database analyses of RSV-related hospitalisations coded with International Classification of Diseases (ICD) codes were conducted using the “Technical Cell – Cellule Technique” (TCT) database. This national database links the anonymised Minimal Hospital Data (MZG–RHM) to the Sickness Funds reimbursement data in hospitals (more details refer to Chapter 3).

The total number of RSV-ICD-coded hospitalisation episodes was assessed and the number of episodes by month and year is shown in Figure 28. It included episodes based on relevant primary and secondary ICD codes (ICD-9 and ICD-10) from January 2008 to December 2014 and January 2016 to

December 2022[uu]. In total, there were 118,025 hospitalised episodes for RSV in children under 5 years within the 14 calendar years. While our hospitalisation data span full calendar years, we presented them from September to August of the following year to aid visual interpretation of the RSV seasons (Figure 28).

As demonstrated in Figure 28, prior to the COVID-19 pandemic, the highest number of RSV-related hospitalisations was observed predominantly in November and December. As such, between the 2009/2010 and 2019/2020 RSV seasons, the peak of RSV-related hospitalisations consistently occurred in December. During the 2012/2013 and 2018/2019 seasons, hospitalisation numbers in November were also comparable to those observed in December. Notably, during the 2008/2009 season, the peak in hospitalisations occurred in November.

A distinct RSV seasonal pattern was observed during the 2020/2021 season in Belgium, when the peak of RSV hospitalisations occurred in May. This is likely due to voluntary behavioural change and the non-pharmaceutical interventions during the COVID-19 pandemic (i.e. school closure, lockdown, and use of face masks). In the 2021/2022 season, RSV-hospitalisations appeared to have a much lower peak in December but remained constant till July. This trend was comparable to observations reported in several other European countries.[98, 99] Although there are strong indications[33] that the pre-COVID-19 RSV seasonal patterns are returning in Europe, it remains uncertain whether it will be a completely identical annual resumption in years to come, indicating the need for caution and further follow-up. In any case, there was consensus among the expert panel of the current study that pre-pandemic data would provide the most representative baseline for the analysis. Therefore, we excluded data from August 2020 to December 2022, as well as data from incomplete RSV seasons (January 2008 to July 2008, August 2014 to July 2016) observed in Belgium. The excluded data are shaded in grey in Figure 28.

Over the course of 10 RSV seasons, we observed an average of 8300 RSV-coded hospital (ICU and non-–ICU) admissions per year. Notably, there was a gradual upward trend in the average annual number of admissions, despite a decline in the size of the birth cohort. This increase stabilised somewhat during the last 4 seasons prior to the COVID-19 pandemic (2016/2017 to 2019/2020 seasons) to an average annual number of 9066 admissions. A steeper increasing trend was observed in the subgroup of ICU admissions during the same 4 pre-pandemic seasons (Figure 43). These observed patterns are likely due to more diagnostic testing and improved coding practices. Moreover, from 2016 there was a transition in the ICD coding system: the ICD-9 version has no longer be used, replaced by the ICD-10 version, and TCT data of the calendar year 2015 are unavailable due to technical errors. Clinical expert assertion and interim results of an ongoing in-depth study in paediatric care suggested that the most recent pre-COVID-19 ICD-10 based estimates would be most representative of the (pre-long acting mAb) incidence of RSV hospital and ICU admissions in Belgium (personal communications Dr Sophie Blumental (ULB), Dr Laurane De Mot (Sciensano), Dr Marc Raes (Jessa Hospital), May 2025). Therefore, in view also of the switch to ICD-10 coding, we used the non-ICU and ICU admissions from the most recent 4 RSV seasons (Figure 28, red area starting in 2016-2017) prior to the COVID-19 pandemic in our cost-effectiveness analysis for the base case, but we also expanded the selection to all 10 RSV seasons pre-COVID-19 for which TCT data were available, as a scenario analysis. The annual average numbers of non-ICU and ICU admissions are listed in Table 30 for the 4 season base case and in Table 64 (Appendix) for the 10 season scenario analysis.

In a Belgian study identified in our literature review, Bouckaert et al. analysed the TCT database for a single season (2017/2018) and reported an RSV hospitalisation rate of 68.3 and 5.0 per 1,000 population in children <1 year and 1 to 4 years of age, respectively.[6] Using the same database and ICD code selections combining 4 and 10 seasons, respectively, we estimated a lower average annual rate of 56.5 and 49.3 hospital episodes per 1,000 population for children under 1 year, but a similar average annual rate of 5.0 and 4.5 hospital episodes per 1,000 population for children aged 1 to 4 years,

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[uu] The year 2015 is not included, because this year is not available in the TCT database.

respectively[vv]. The difference can be explained by the higher admission rate in children under 1 year observed during the 2017/2018 RSV season, relative to the surrounding seasons.

A prospective, multi-centre, observational cohort study among healthy term-born infants was conducted during three RSV seasons (2017/2018-2019/2020) in Scotland, England, Spain, Finland and the Netherlands (hereafter, RESCEU infant study).[3] The RESCEU infant study estimated an overall rate of 1.56 per 1,000 infant-months (18.72 per 1,000 person-years (PYs)) for RSV-hospitalised ARI over these five European countries combined. The rate per 1,000 infant-months varied by country, ranging from 0.87 in Finland to 2.07 in Spain (10.44 to 24.84 per 1,000 PYs, respectively). Nevertheless, these rates were much lower than the hospitalisation rate (49.3 per 1,000 PYs) estimated by the Belgian TCT database in our study, likely due to the study design (prospective active surveillance vs retrospective database analysis) and clinical definitions (RSV-ARI[ww] vs. RSV-ICD-coded hospital episode[xx]).

Furthermore, the RSV hospitalisation rate we estimated based on the Belgian TCT data for children under one year of age was more than 2-fold higher compared with the “blanket” rate for high-income countries of 22 (17.1-28.4) per 1,000 PY reported in the Global Burden of Disease Study.[100]

A multi-country time-series modelling study[101] by Johannesen et al. using routine virological ARI and ICD-coded admission data, estimated RSV-attributed hospital admissions per 1,000 per year and reported the ratio of RSV attributed to ICD-coded RSV admissions. Overall, in children under 1 year of age, this ratio ranged from 0.46 in the 0-2-month age group to 2.0 in the 6-11-month age group in different European countries. In other words, Johannesen et al. reported an age-specific discrepancy, with overdiagnosis due to miscoding in newborns and underdiagnosis due to uncoded RSV in infants over 6 months.[101]

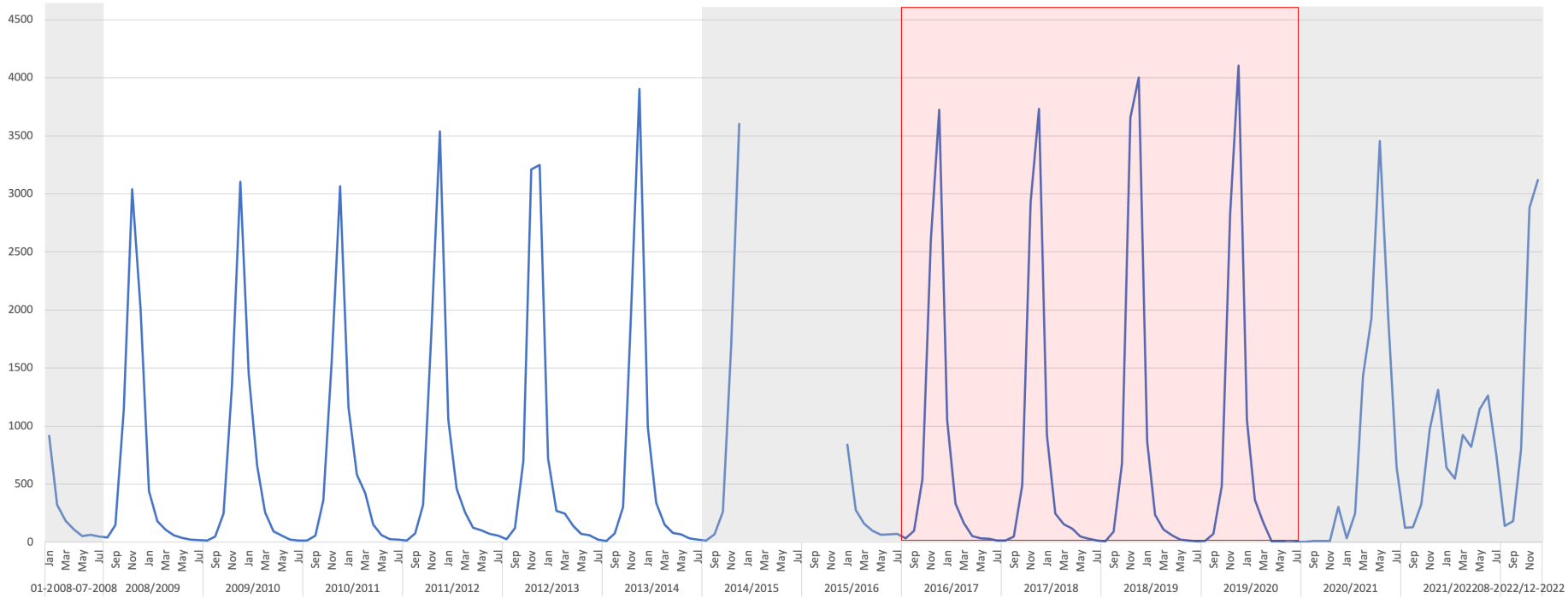
We also conducted a scenario analysis using hospitalisations identified by the primary ICD-code only, to evaluate the impact on cost-effectiveness of RSV interventions.

[vv] These estimates were calculated per 1,000 population to allow comparison with the Bouckaert et al. study. The population of children aged 1–4 years in 2024 was assumed to be four times the size of the birth cohort.

[ww] An ARI episode in the RESCEU infant study was defined as the onset or worsening of any of the following symptoms for at least 1 day: runny or blocked nose, coughing, wheezing, or dyspnoea. An RSV-ARI episode was defined as a positive test result from either in-house RT-qPCR or POCT, or both.

[xx] RSV-ICD-coded hospital episode was identified by the following principal or secondary ICD-10-CM diagnosis codes: B974 (RSV as the cause of diseases classified elsewhere), J121 (pneumonia due to RSV), J205 (acute bronchitis due to RSV) and J210 (acute bronchiolitis due to RSV).

Figure 28 – Number of RSV-ICD-coded hospitalisations in children <5 years by months from 2008-2022*



** TCT data is unavailable in calendar year 2015 due to technical errors. Seasons excluded from the analysis are shown as grey areas (top graph) and dashed lines (bottom graph). The seasons included as base case are shown as red shaded area (top graph).*

Table 30 – Average number of RSV-ICD-coded non-ICU and ICU admissions in children <5 years by calendar month prior to the COVID-19 pandemic (summed over RSV seasons 2016/2017-2019/2020*, divided by 4 (number of seasons) and rounded to nearest integer)

Age	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC
Non-ICU hospital admissions												
0 months	93	21	14	6	3	2	1	2	6	29	158	284
1-11 months	657	193	97	37	16	11	6	8	50	332	1 815	2 491
1 year	5	9	8	5	3	2	2	3	9	97	550	615
2 years	118	35	17	6	3	2	1	1	5	38	216	207
3 years	38	15	6	2	1	1	0	0	2	22	108	81
4 years	11	5	2	1	1	0	0	0	2	7	28	27
ICU admissions												
0 months	16	7	3	1	0	0	0	1	3	7	34	60
1-11 months	32	8	3	3	1	1	0	1	1	16	77	111
1 year	1	0	0	0	0	0	0	1	0	1	8	11
2 years	3	1	1	0	1	0	0	0	0	1	5	3
3 years	1	0	0	0	0	0	0	0	1	0	3	1
4 years	1	0	0	0	0	0	0	0	0	0	1	1

*Source: TCT data. * TCT data is unavailable in calendar year 2015 due to technical errors. ICU: intensive care unit.*

In the TCT dataset, children aged 1–11 months were grouped together. To estimate age-specific RSV hospitalisations by month, we used the BELSARI-NET data on RSV-confirmed admissions (see Chapter 3). BELSARI-NET data is a register from Sciensano[yy] of seasonal influenza and other acute respiratory infections (including RSV). Data have been collected from 2012, from a surveillance network of 6 hospitals, expanded to 10 hospitals from 2023. Table 31 presents the distribution of RSV-confirmed hospitalisations among infants under 1 year of age across two RSV seasons: 2018/2019 (pre-COVID-19 pandemic) and 2023/2024 (post SARS-CoV-2 emergence, termed the "peri-COVID-19" period). Adapted social contact behaviours during SARS-CoV-2 emergence have been well documented in Belgium,[102, 103] and are generally accepted as an explanation for changes in RSV and other ARI seasonal patterns throughout Europe.[104, 105] The BELSARI-NET data show a notable shift in age distribution between the 2018/2019 and 2023/2024 RSV seasons. In 2023/2024, a smaller proportion of hospitalisations occurred in the 0–2 month age group (40% vs. 50%), while the 3–5 month age group remained relatively stable (27% vs. 26%).

Del Riccio et al.[75] extrapolated hospitalisation data stratified by 0–2m, 3–5m, 6–11m age groups. It shows similar proportions to the BELSARI-NET data for the 2018/2019 RSV season. It is uncertain whether the age distribution changes observed in the RSV season 2023/2024 will be sustained in future seasons. Therefore, the 2018/2019 RSV season was used in the base case analysis to redistribute both non-ICU and ICU hospitalisations among infants aged 1–11 months, with the resulting estimates presented in Figure 29. In the scenario analysis, proportions from the 2023/2024 season (peri-COVID19) were applied to evaluate the potential impact of an age shift in RSV hospitalisations.

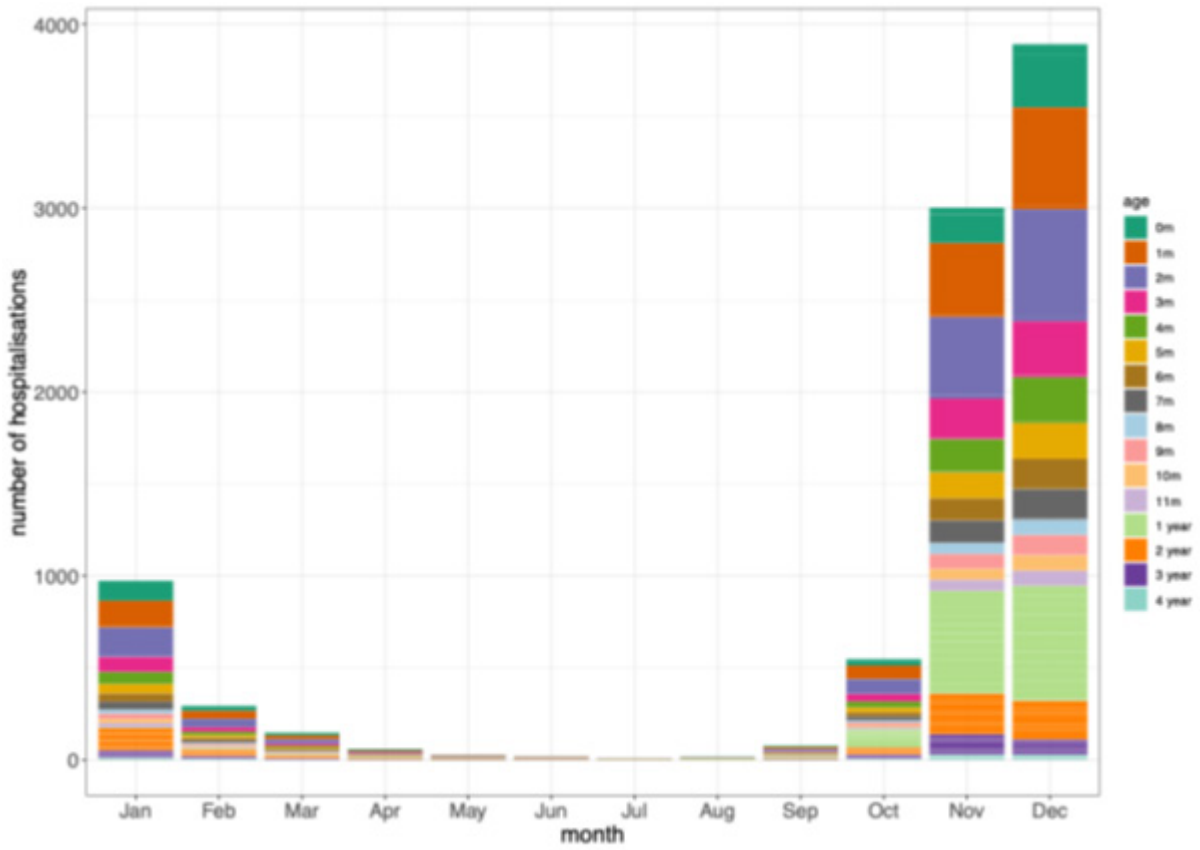
yy https://www.sciensano.be/fr/projets/severe-acute-respiratory-infection-surveillance-par-un-reseau-dhopitaux-vigies

Table 31 – Percentage of RSV hospitalisations per month since birth in children <1 year in the BELSARI-NET database compared with published estimates

Age	2018/2019 (pre-COVID-19)	2023/2024 (peri-COVID-19)	Extrapolation (Del Riccio et al.[75])
0m	8.50%	9.70%	50%
1m	19.50%	14.20%	
2m	21.60%	15.90%	
3m	10.60%	11.50%	27%
4m	8.50%	5.30%	
5m	6.80%	9.70%	
6m	5.50%	8.00%	23%
7m	5.50%	6.20%	
8m	3.00%	6.20%	
9m	4.20%	8.80%	
10m	3.40%	2.70%	
11m	3.00%	1.80%	

m: month.

Figure 29 – Average number of RSV-ICD-coded hospitalisations (including both non-ICU and ICU admissions) by age and calendar month in children <5 years prior to the COVID-19 pandemic (2018/2019 season)



m: month.

4.2.2.3 *RSV-ICD-coded death in hospital*

It remains uncertain whether either RSV prevention programme of mAb or MV would reduce mortality in high-income countries given these have well-established healthcare systems. A review of patient charts and expert assessments suggests that children registered as RSV-related deaths often had severe comorbidities, which would likely have led to premature death even in the absence of RSV infection (Blanken et al. 2018[106]). However, recent real-world effectiveness data indicate that mAbs are highly effective in preventing ICU admissions. The Belgian expert panel of the current study reached a consensus that the prevention of mortality can be attributed to RSV prevention and should be accounted for in the base case analysis, using RSV mortality rates derived from the data outlined below. Due to the uncertainty around this assumption, we also conducted a scenario analysis assuming that RSV prophylaxis would not prevent mortality during the first 5 years of life.

The RSV-coded in-hospital case fatality rate (hCFR) was analysed using the TCT database. We extracted the number of deaths and hospitalisations over a full period of 14 calendar years, as no distinct pattern in RSV-related hCFR was observed before or after the COVID-19 pandemic. A total of 60 RSV-related deaths were recorded among Belgian children under five years of age (Table 32), 27% of deaths occurred outside of the ICU setting. The overall hCFR for children under five years was 0.051%, which was comparable to the hCFR of 0.047% estimated by Bouckaert et al. over a single RSV season.[6]

We assumed that all RSV-related deaths occurred in a hospital setting and therefore applied the hCFR by age group in our model. Since these estimates are based on national claims data and represent in essence census data, consistently collected over 14 calendar years, we did not account for uncertainty around the age-specific hCFR.

Table 32 – Age-specific RSV-coded deaths and hCFR over 14 calendar years (2008-2014 and 2016-2022*)

Age	Hospitalisation without ICU admission			Hospitalisation with ICU admission		
	deaths	admissions	hCFR	deaths	admissions	hCFR
<1m	3	12 158	0.025%	6	1 564	0.384%
1-11m	6	68 077	0.009%	27	2 681	1.007%
1y	3	17 271	0.017%	4	291	1.375%
2y	2	9 931	0.020%	6	161	3.727%
3y	2	4 386	0.046%	1	78	1.282%
4y	0	1 390	0.000%	0	37	0.000%
Total	16	113 213	0.014%	44	4 812	0.914%

** TCT data is unavailable in calendar year 2015 due to technical errors. hCFR: in-hospital case fatality ratio, ICU: intensive care unit, m: month, y: year.*

4.2.2.4 *RSV-related non-hospitalised consultations, including primary care, hospital outpatient and emergency department visits*

As described in our literature review findings (see 4.1.2), there are no age-specific data available on RSV-related primary care or ED incidence in Belgium. Based on our literature review and the systematic review conducted by Heemskerk et al.,[76] a large variation was observed for the RSV outpatient incidence rate per 1,000 PY across European countries. In Italy, Barbieri et al. conducted a retrospective analysis using data from Pedianet, a comprehensive paediatric primary care database of 161 family paediatricians during 2012 to 2019. They reported that the RSV-lower respiratory tract infections (LRTI) incidence per 1,000 PY varied by age, with rates of 8.83 in infants under 1 month, 12.74 in those aged 1–2 months, 10.67 in 2–3 months, 8.5 in 4 months, and declining to 0.59 at 12 months.[107] In Spain, Munoz-Quiles et al. followed a retrospective cohort of children born between 2009 and 2012 from birth to 2 years of age using population and health databases in Valencia, Spain.[108] They estimated that the incidence of ICD-coded bronchiolitis (used as a proxy for RSV infections) was 32 per 1,000 PY in infants aged 0–5 months and 4 per 1,000 in those aged 6–11 months. A prospective study followed 431

newborns over a 10-month period in Finland and estimated the incidence of RSV-confirmed respiratory tract infections (RTI) notably higher, reaching 328 per 1,000 in infants aged 0–3 months in the 2017/2018 RSV season.[109] Another Finnish prospective cohort study among outpatient children estimated this rate at 167 (95%CI: 141-219) and 360 (213-569) per 1,000 children under 1 year of age in the 2000/2001 and 2001/2002 RSV seasons,[110] respectively. It is worth noting that a biannual pattern of RSV MA episodes has been observed in Finland and other Nordic countries.[111, 112] However, such a pattern has not been observed in Belgium (Figure 28).

While the prospective study ComNet followed children across five European countries, including Belgium (N=142),[77] it did not provide primary care incidence data. During 3 RSV seasons (2020/2021 – 2022/2023), children aged younger than 5 years presenting to their general practitioner or primary care paediatrician with symptoms of an acute respiratory tract infection were eligible for RSV testing. Those testing positive were followed up for 30 days via physician reports (day 1) and parent questionnaires (days 14 and 30). The ComNet study reported that 32.4% (95%CI: 24.8-40.8) of recruited Belgian RSV patients reported ED visits. This proportion for Belgium was similar to Spain (31.6%), but much higher than in Italy, the Netherlands and the UK (13.5%, 15.5% and 12.5%, respectively). Moreover, in the ComNet study, Belgium also has the highest proportion of hospital admissions (43.7%) among recruited patients, compared to the other 4 countries (ranging from 3.7% in the Netherlands to 14.6% in Spain). It is worth noting that the Belgian patients were recruited solely from six paediatric centres located in hospitals in Flanders, and not through primary care and paediatrician practices outside of hospital settings, which is a substantial difference with other countries in the ComNet study.

The RESCEU prospective infant study reported both the age-specific MA RSV-ARI incidence rate (including hospitalisations) from a nested active surveillance cohort and the RSV-ARI hospital admission incidence rate from the total RESCEU cohort (Figure 30 and Table 33).[3] Knowing that both the MA RSV-ARI rates and the RSV-ARI hospitalisation rates were estimated based on the same population denominators, we proceeded according to the following steps to estimate the RSV-ARI outpatient rate. First, we doubled the variance of both rates to account for the uncertainties in this approach. Second, we pair-sampled both rates using a lognormal distribution (N=1,000). Finally, we subtracted the hospitalisation rate from the MA rate and estimated the sampled mean and 95%CI (Table 34).

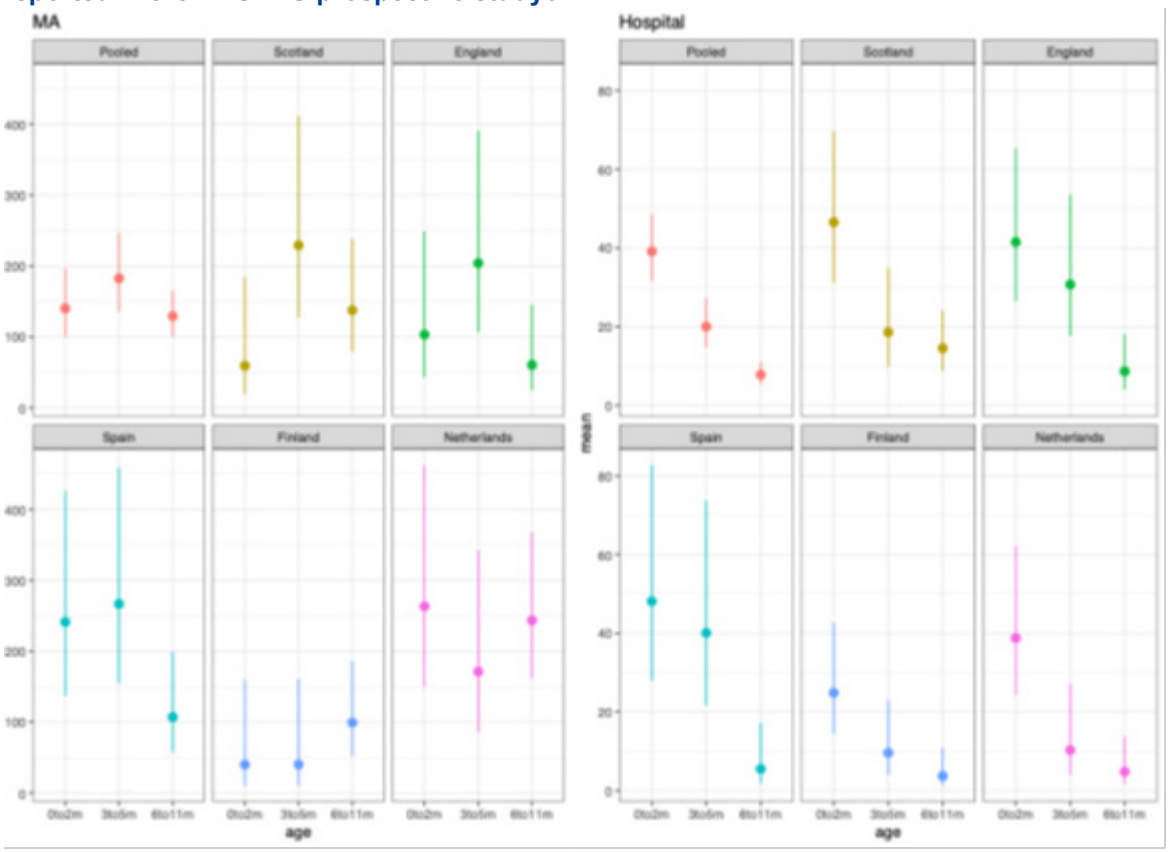
Given the similarities in healthcare-seeking behaviour and the role of paediatricians as primary care providers in both Belgium and Spain as observed by the ComNet study,[77] we adopted the age-distribution of outpatient cases from Spain reported in the RESCEU study[13] as the base case to infer age-specific outpatient RSV cases for Belgium. However, for scenario analyses, we also incorporated the age-specific outpatient rates from the Netherlands and pooled estimates for all 5 countries reported in the RESCEU infant study. Due to a lack of data, we assumed that the outpatient rate in 1–4 year olds would be the same as that in the 6–11 months age group (Table 34).

Table 33 – Country- and age-specific RSV-associated mean medically attended ARI rate and hospital rate per 1,000 person-years over 3 RSV seasons (2017/2018-2019/2020) reported in the RESCEU prospective study3

Country	<3m	3-5m	6-11m	<12m
Medically-attended RSV-associated ARI rate (including hospitalisations) per 1,000 person-years				
Overall (5 countries)	140.28	182.52	129.24	145.32
Spain	241.32	266.64	107.16	181.08
The Netherlands	263.16	171.24	243.36	230.40
Finland	40.08	40.20	98.88	69.48
England	103.32	204.00	60.48	107.76
Scotland	59.40	229.20	137.64	141.00
Hospital admitted RSV-associated ARI rate per 1,000 person-years				
Overall (5 countries)	43.20	20.04	7.80	18.72
Spain	48.12	40.08	5.52	24.84
The Netherlands	38.76	10.32	4.80	14.76
Finland	24.84	9.60	3.72	10.44
England	41.52	30.72	8.64	22.44
Scotland	46.56	18.60	14.52	23.52

Source: RESCEU prospective study.[3] ARI: acute respiratory infection, m: month.

Figure 30 – Country- and age-specific RSV-associated MA ARI rate (left panel) and hospitalisation rate (right panel) per 1,000 PY over 3 RSV seasons (2017/2018-2019/2020) reported in the RESCEU prospective study3



Dots represent the mean and the error bars present 95%CI. MA: medically attended, ARI: acute respiratory infection, m: month, PY: person-year.

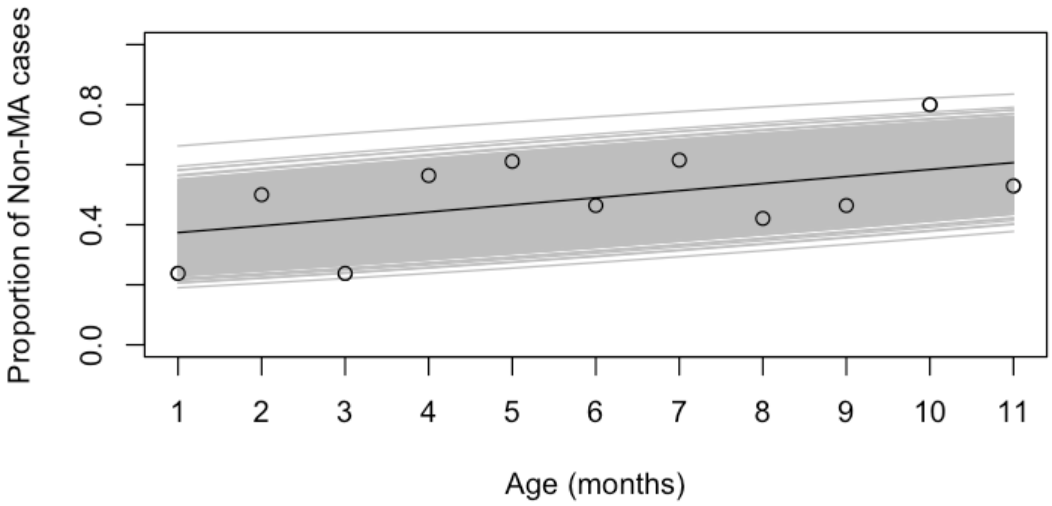
Table 34 – Age-specific RSV-associated outpatient ARI rate per 1,000 person-year (estimated mean and 95%CIs)

per 1,000 person-year	<3 month	3–5 month	6–11 month
Spain	205.87 (71.82-445.14)	239.23 (93.44-488.44)	108.17 (38.41-234.4)
The Netherlands	237.73 (84.68-508.39)	173.92 (52.44-415.72)	245.17 (127.58-415.26)
Overall (5 countries)	103.91 (52.81-174.69)	165.29 (101.63-248.39)	122.91 (82.95-172.24)

4.2.2.5 RSV-related non-medically attended episodes

The RESCEU infant study revealed that non-MA RSV infections in healthy, full-term infants pose a substantial yet often overlooked burden.[3, 79, 80] We utilised data from this study to estimate the age-specific non-MA PCR-confirmed RSV symptomatic cases as a proportion of all medically attended cases by age in children under 1 year.[3, 79] Then, we fitted a generalized linear model (GLM) and simulated the uncertainty around the age-specific proportion (from 1 month to 11 months of age), as illustrated in Figure 31. We assumed the proportion of non-MA cases at 0 in infants under 1 month of age based on the RESCEU infant study and applied the same proportion to the 1–4-year age group as was found for 11-month-old infants (mean: 60.1%, 95% credible interval 45.9-72.8%).

Figure 31 – Proportion of non-MA RSV symptomatic cases over the MA symptomatic cases



Dots represent the data observed in the European observational study (RESCEU),[3, 79, 80] the grey lines represent the fitted values, and the solid black line represents the mean of the fitted value.

4.2.2.6 Resource use, direct and indirect costs

Following the Belgian Pharmacoeconomics guidelines, all costs were valued at the 2024 price level and reported from the perspectives of the National Institute for Health and Disability Insurance (NIHDI), patients, and healthcare payers (HCP).[89] The uncertainty associated with the cost parameters was modelled using gamma distributions, where $\alpha = (\text{mean})^2/SD^2$ and $\beta = SD^2/\text{mean}$.

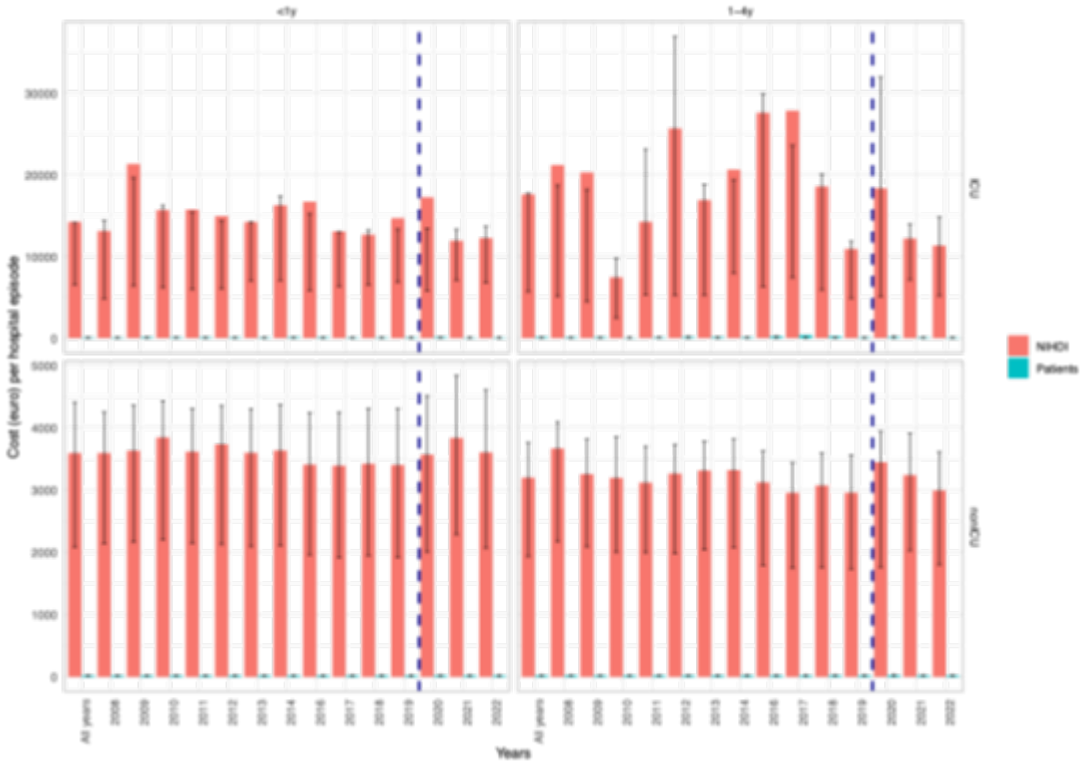
INPATIENT SETTING

Unlike the observed increasing trends in the number of non-ICU and ICU admissions, there was no clear trend in the cost per admission for either category (Figure 25 and Figure 26 in Chapter 3). Therefore, we used the average cost over the full period of data availability, 14 years (appropriately inflated).

Cost per hospitalisation episode was estimated using the TCT database over 14 calendar-years (2008-2014 and 2016-2022). Figure 32 presents the average costs of RSV-coded hospitalisation episodes in Belgian children under 5 years of age, stratified by age and ICU admission status. There is no large observed difference in average costs of RSV-coded hospitalisations before and after the COVID-19 pandemic (indicated by the blue dotted line).

Table 35 illustrates the average cost per ICU and non-ICU hospital episode. Out of the total cost of €14,293 per ICU and €3,613 per non-ICU hospital episode in children under 1 year of age, the majority of the costs were covered by national health insurance, while patients paid an average of €88 and €23 per ICU and non-ICU hospital episode (as per the KCE guideline for economic evaluation, supplements paid by patients or their private insurer are excluded from these analyses). Among children aged 1–4 years, the mean ICU admission cost per episode was higher, while the non-ICU admission cost per episode was lower compared to infants under one year of age. However, all ICU and non-ICU median cost estimates were higher than the median cost estimated by Tilmanne et al. from a hospital perspective[8]: median cost of €7,295 with interquartile range (IQR) of €5,340 to €10,181 per ICU admission and €2,834 per non-ICU admission in children under 3 years of age. The difference is likely due to the use of national data over 14 calendar years as opposed to data from 16 French-speaking hospitals over one year.

Figure 32 – Average RSV-coded hospitalisation costs per admission and per year for ICU (top panels) and non-ICU admissions (bottom panels) in <1 year olds (left panels) and 1-4 year olds (right panels) (€ 2024)



The error bars present the 25th and 75th percentiles. The blue dotted line indicates before and after the COVID-19 pandemic. NIHDI: National Institute for Health and Disability Insurance.

Table 35 – Summary statistics of cost per RSV-coded hospitalisation over 14 calendar years (2008-2014 and 2016-2022*) from NIHDI, patients and health care payers' perspectives (€ 2024)

Perspective	Mean	SD	5th pth	25th pth	Median	75th pth	95th pth
Age under 1 year							
ICU admission							
NIHDI	€ 14 205	€ 20 340	€ 3 717	€ 6 542	€ 9 346	€ 14 112	€ 37 535
Patients	€ 88	€ 191	€ 18	€ 36	€ 54	€ 83	€ 207
Total	€ 14 293	€ 20 490	€ 3 756	€ 6 591	€ 9 411	€ 14 202	€ 37 865
Non-ICU admission							
NIHDI	€ 3 590	€ 3 290	€ 1 095	€ 2 085	€ 3 094	€ 4 401	€ 7 328
Patients	€ 23	€ 24	€ 6	€ 13	€ 19	€ 28	€ 50
Total	€ 3 613	€ 3 306	€ 1 107	€ 2 100	€ 3 114	€ 4 428	€ 7 366
Age 1–4 years							
ICU admission							
NIHDI	€ 17 568	€ 25 697	€ 2 617	€ 5 698	€ 9 726	€ 17 696	€ 64 562
Patients	€ 134	€ 370	€ 17	€ 35	€ 58	€ 108	€ 486
Total	€ 17 702	€ 25 937	€ 2 641	€ 5 721	€ 9 799	€ 17 810	€ 64 969
Non-ICU admission							
NIHDI	€ 3 197	€ 3 416	€ 1 032	€ 1 932	€ 2 701	€ 3 757	€ 6 367
Patients	€ 24	€ 23	€ 7	€ 14	€ 21	€ 29	€ 50
Total	€ 3 221	€ 3 432	€ 1 044	€ 1 949	€ 2 721	€ 3 783	€ 6 407
Overall hospitalisations 0–4 years (including both ICU and non-ICU admissions)							
NIHDI	€ 3 944	€ 5 866	€ 1 094	€ 2 075	€ 3 044	€ 4 425	€ 8 482
Patients	€ 26	€ 53	€ 7	€ 14	€ 20	€ 29	€ 58
Total	€ 3 969	€ 5 904	€ 1 107	€ 2 091	€ 3 065	€ 4 454	€ 8 529

** TCT data is unavailable in calendar year 2015 due to technical errors. ICU: intensive care unit, NIHDI: National Institute for Health and Disability Insurance, pth: percentile, SD: standard deviation.*

OUTPATIENT SETTING

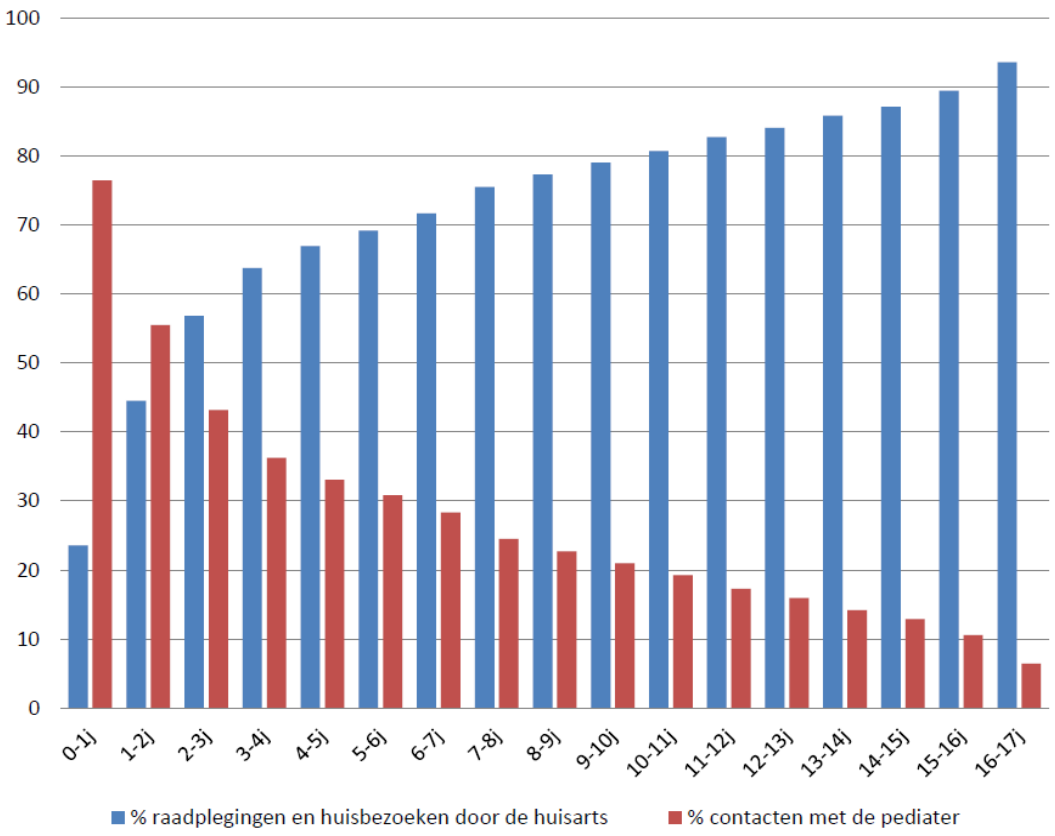
In Belgium, patients can access both general practitioners (GPs) and paediatricians directly. As the cost of a consultation with a paediatrician is higher than that a GP, it is important to document the proportion of consultations (preferably for children under the age of 1) with each of these practitioners.

Proportion of consultations to GPs versus paediatricians in children

De Sadeleer et al.[113] analysed the database of the Christian Mutuality (Christelijke Mutualiteit/Mutualité Chrétienne) in 2014 to derive the proportions of consultations to GPs and pediatricians for children <14 years of age. The Christian Mutuality is the largest health insurance fund in Belgium, with more than 4.5 million members in 2014 (Belgium has a total population of just over 11 million), including more than 700,000 children under 14 years of age.

De Sadeleer et al.[113] found that 76% of all consultations for children <1 year were provided by paediatricians and 24% by GPs. A clear change in consultation type was observed as children grew older (Figure 33). For children aged 3 years, 36% of consultations were done by paediatricians and 64% by GPs (Table 36). Data from 2005 to 2014 showed that the proportion of paediatrician and GP consultations by age group remained stable, and we assume that those figures are still valid.

Figure 33 – Proportion of childhood consultations with GPs and paediatricians by age (2014)



Source: De Sadeleer et al., 2016.[113] Blue bars: percentage of consultations to GPs, Red bars: percentage of consultations to paediatricians, j: year.

Table 36 – Proportion of consultations to general practitioners and paediatricians by age

Type of consultation	<1 year	1 year	2 years	3 years	4 years
GP	24%	45%	57%	64%	68%
Paediatrician	76%	55%	43%	36%	32%

Source: De Sadeleer et al., 2016.[113] GP: general practitioners.

Geographical variations

Differences in the use of consultations to paediatricians in the three Belgian regions (Flanders, Brussels, Wallonia) were analysed in the RIZIV-INAMI report on variations in medical practice – Outpatient paediatric consultation (page 22).[114] The analyses were conducted for the year 2022 and for the whole paediatric population of children under 18 years of age. Data for the age group 0–4 years were obtained from personal communication with the RIZIV-INAMI Appropriate Care Unit in February 2025.

For the age group 0–4 years, the standardized number of consultations to paediatricians was 253,351 per 100,000 insured persons in Belgium, 226,869 in Flanders, 276 645 in Brussels and 295,446 in Wallonia. From these data we can deduce that, compared to the national consultation rate of paediatricians, the rate in Flanders is 10% lower, while in Brussels and Wallonia it is 9% and 17% higher, respectively.

The percentages of regional variation were applied to the proportion of consultations to paediatricians from De Sadeleer et al.[113] The proportion of consultations to GPs was obtained by taking the

complement of the proportion of consultations to paediatricians. It is worth noting that we have extrapolated the mean regional differences observed in the population under 4 years to children aged <1 year (the age groups of interest for RSV immunization), assuming that these differences were constant across all age groups. For children aged <1 year, the percentage of consultations to paediatricians is estimated at 68.1% in Flanders, 83.0% in Brussels and 88.6% in Wallonia (Table 37). These percentages apply to all types of consultations, not exclusively those related to respiratory infections.

Table 37 – Estimated primary health care resource use for paediatric patients under 5 years

Age	<1 year	1 year	2 years	3 years	4 years
Consultation of paediatricians					
Belgium (%)	76.0%	55.0%	43.0%	36.0%	32.0%
Flanders (%)	68.1%	49.3%	38.5%	32.2%	28.7%
Brussels (%)	83.0%	60.1%	47.0%	39.3%	34.9%
Wallonia (%)	88.6%	64.1%	50.1%	42.0%	37.3%
Consultation of GPs					
Belgium (%)	24.0%	45.0%	57.0%	64.0%	68.0%
Flanders (%)	31.9%	50.7%	61.5%	67.8%	71.3%
Brussels (%)	17.0%	39.9%	53.0%	60.7%	65.1%
Wallonia (%)	11.4%	35.9%	49.9%	58.0%	62.7%

Cost per medically-attended RSV outpatient episode

The ComNet study reported that, for Belgium, 54.5% of infants under 6 months and 56.2% of those aged 6 to 11 months had more than one primary care visit per RSV episode in children, with an estimated mean of 2.8 (standard deviation (SD): 2.3) for infants under 6 months and 2.5 (SD: 2.8) for those aged 6 to 11 months.[77] Among children 1–4 years, 53.8% had more than one primary care visit per RSV episode, with a mean of 2.3 (SD: 2.0) visits.[77]

Table 38 – Number of visits per outpatient episode in Belgian children <5 years if more than one visit

Age	≥1 Repeat primary care visits* (Number)	Mean (SD)	Weighted mean (SD)
0–5 month	54.5% (30/55)	2.8 (2.3)	2.0 (1.9)
6–11 month	56.2% (27/48)	2.5 (2.8)	1.8 (2.2)
1–4 year	53.8% (21/39)	2.3 (2.0)	1.7 (1.6)

** All children have an initial visit. SD: standard deviation.*

In addition, the ComNet study also collected data on the costs of medication associated with RSV outpatient episodes in Belgian children. The estimated total medication cost per episode was €13.5 for children under 1 year of age and €11.8 for those aged 1–4 years. Over-the-counter (OTC) medications accounted for 46% and 55% of the medication costs, respectively. We therefore estimated medication costs from different perspectives (Table 39), assuming that patients paid the full cost of OTC medications and a 10% copayment for non-OTC (prescription) medications.

Table 39 – Medication cost per outpatient episode in Belgian children <5 years

Age	<1y	1–4y
NIHDI	€5.85	€4.02
Patients	€7.65	€7.78
Total	€13.50	€11.80

NIHDI: National Institute for Health and Disability Insurance.

The cost per RSV outpatient episode was calculated as the number of outpatient visits (Table 38) multiplied by the healthcare provider distribution (Table 37) and the average unit cost[zz] (Table 65 in Appendix), as well as the associated medication cost.

Cost per outpatient episode = number of outpatient visits × (% pediatrician visits × cost per pediatrician visit + % GP visits × cost per GP visit) + medication cost

We estimated the outpatient cost per episode by perspectives as shown in Table 40.

Table 40 – Mean (95%CI) cost per outpatient episode in Belgium and in each region, weighted for health-seeking behaviour

Cost per episode	Belgium	Flanders	Brussels	Wallonia
<1 year				
NIHDI	€77.43 (59.1-95.77)	€77.35 (59.5-95.21)	€86.75 (67.99-105.51)	€80.43 (61.33-99.53)
Patients	€28.58 (23.22-33.94)	€33.49 (28.37-38.61)	€27.61 (22.04-33.18)	€30.08 (24.33-35.82)
Total	€106.01 (82.32-129.71)	€95.54 (72.57-118.52)	€102.66 (78.32-126.99)	€110.51 (85.66-135.35)
1 year				
NIHDI	€70.61 (53.55-87.66)	€73.01 (56.31-89.72)	€79.6 (62.24-96.97)	€72.77 (55.16-90.38)
Patients	€26.21 (21.49-30.93)	€29.55 (25.01-34.1)	€23.06 (18.18-27.93)	€27.29 (22.3-32.29)
Total	€96.82 (75.04-118.6)	€87.01 (65.75-108.26)	€94.62 (72.38-116.86)	€100.07 (77.46-122.67)
2 years				
NIHDI	€67.76 (51.43-84.08)	€70.45 (54.4-86.49)	€76.49 (59.92-93.05)	€69.44 (52.69-86.2)
Patients	€24.78 (20.43-29.14)	€28.27 (24.05-32.49)	€21.5 (17.02-25.98)	€25.63 (21.06-30.2)
Total	€92.54 (71.86-113.22)	€83.15 (62.89-103.42)	€89.95 (68.9-110.99)	€95.07 (73.74-116.4)
3 years				
NIHDI	€66.09 (50.19-81.99)	€68.95 (53.28-84.61)	€74.66 (58.56-90.75)	€67.52 (51.25-83.78)
Patients	€23.95 (19.81-28.09)	€27.52 (23.49-31.55)	€20.58 (16.34-24.83)	€24.67 (20.34-28.99)
Total	€90.04 (70-110.08)	€80.91 (61.21-100.6)	€87.2 (66.86-107.54)	€92.18 (71.59-112.77)
4 years				
NIHDI	€65.14 (49.49-80.79)	€68.11 (52.66-83.57)	€73.61 (57.78-89.44)	€66.4 (50.42-82.38)
Patients	€23.48 (19.46-27.5)	€27.1 (23.18-31.02)	€20.06 (15.95-24.17)	€24.11 (19.92-28.29)
Total	€88.62 (68.94-108.29)	€79.66 (60.29-99.03)	€85.63 (65.69-105.57)	€90.51 (70.35-110.66)

95%CI: 95% confidence interval, NIHDI: National Institute for Health and Disability Insurance.

[zz] Patient co-payments are €12 per paediatrician visit and €6 per GP consultation.

We did not explicitly model the number of hospital outpatient and emergency department visits separately due to a lack of data. However, the estimated RSV outpatient burden included both types of visits. Given that the cost per ED visit in Belgium is comparable to that of a paediatrician visit, we assumed these costs to be equivalent to the estimated primary care cost per episode (Table 40). In other words, the direct medical cost of RSV outpatient cases was estimated by multiplying the cost per primary care episode (Table 40) by the outpatient age-specific incidence rate (Table 34).

NON-MEDICALLY ATTENDED (NON-MA) EPISODES

The resource use of non-MA episodes was investigated within the RESCEU infant study. According to Mao et al., the mean cost of a non-MA episode was €1.8 (mainly over-the-counter medication) from the healthcare payer's perspective and €44.2 from the societal perspective (in 2021 values) in four European countries.[79] Using data from the same study, Hak et al. reported that 37.9% of infants received painkillers, while 20% received a nasal spray.[80] We used the average cost of €8 per pack/bottle for paracetamol (in children) and €7 for a nasal spray (at 2018 values) from the healthcare payers' (paid by patients, not reimbursed by NIHDI) perspective based on a micro-costing approach for non-hospitalised influenza-like-illness cases.[115] The cost was estimated based on the assumed new purchase of paracetamol and nasal spray per RSV-ARI episode. The unit cost of a bottle of paediatric paracetamol reflected market-weighted prices across the pharmacy network.[115] After adjusting the unit costs to 2024 values using the HCPI, we estimated the cost per non-MA episode to be €4.43 from the healthcare payers' perspective with no uncertainty distribution applied for these unit costs.

PRODUCTIVITY LOSSES

The ComNet study reported 64% of Belgian parents lost workdays, with a mean of 2.7 (SD: 3.3) days per outpatient episode and 76% of parents reported a mean of 4.6 (SD: 4.4) days per hospitalisation for children under 1 year of age. For children aged 1–4 years in Belgium, 80% and 69% of parents reported work losses of 4.3 (SD: 4.2) days and 8.1 (SD: 10.7) days for outpatient and hospital episodes, respectively. The human capital approach was used to value the reported workdays lost. We attributed productivity losses only for RSV episodes in infants older than 3 months, assuming conservatively that all mothers would be on maternity leave in the first three months post-partum and would be able to take care of the sick infant. The average productivity cost per day was €376.8 based on the average labour costs including employee wages and/or salaries and employers' social security contributions in 2023.[116]

Table 41 – Cost of parental productivity loss per RSV episode

Episode	Age	% lost workdays	Mean (SD)	Weighted mean cost per episode (SD)
Outpatient	<1y	64%	2.7 (3.3) days	€ 636 (798)
	1–4y	80%	4.3 (4.2) days	€ 1296 (1257)
Inpatient	<1y	76%	4.6 (4.4) days	€ 1318 (1261)
	1–4y	69%	8.1 (10.7) days	€ 2107 (2790)

SD: standard deviation, Y: year.

4.2.2.7 Interventions' characteristics: efficacy, durability and costs

EFFICACY VALUES Reported in phase 3 randomized controlled trials

A systematic review of the literature on efficacy, effectiveness and safety of nirsevimab and Abrysvo was previously conducted by KCE. For more details, please refer to Chapter 2. Both nirsevimab and RSV-preF MV published their phase 3 randomized controlled trial (RCT) results.[117, 118] The efficacy of RSV interventions by severity was reported as follows by the RCTs: MA RSV-LRTI (as a proxy for non-MA and outpatient RSV episode) and hospital admissions for RSV-LRTI (as a proxy for hospital admissions with RSV). We used the reported MV efficacy values and pooled RCT efficacy values for mAb in our base case analyses, assuming that the efficacy against non-MA, and outpatient episodes equalled the efficacy against MA RSV-LRTI. Similarly, the efficacy against hospital admission was

based on the efficacy for hospital admissions due to MA RSV-LRTI, while the efficacy against ICU admission and death was aligned with the efficacy against severe MA RSV-LRTI (Figure 34). Extensive sensitivity analyses were performed to investigate the impacts of the vaccine efficacy assumptions (see section 4.2.4 below).

For the RSV-preF MV study, the final analysis published by Simoes et al.[61] (2025) confirmed the findings of the primary analysis by Kampmann et al.[119] (2023). Overall, the final analysis included a larger sample of newborns and infants (vaccine n=3,660, placebo n=3,647) and reported narrower 95% confidence intervals compared to the primary analysis (vaccine n=3,495, placebo n=3,480). In the final analysis, monthly cumulative cases of RSV-MA-LRTI and severe RSV-MA-LRTI were reported, and the efficacy was presented as cumulative efficacy from day 0 to each corresponding time point (90 to 180 days). For the current cost-effectiveness analysis, efficacy values on a month-by-month basis were needed. As such, we obtained time-specific point estimates with uncertainty based on the reported cases and risk groups in the final analysis of Simoes et al. (2025)[61] using the following steps.

Although cumulative and incremental cases were reported over 180 days at 30-day intervals (Figure 1 in Simoes et al.[61]), the number of infants at risk in both the vaccine and placebo groups were reported at 90-day intervals from day 0 to day 720 (Appendix Figure 7 in Simoes et al.[61]). In other words, the number of infants at risk in both groups was not available for days 30, 60, 120 and 150. Therefore, we assumed a linear decrease in the risk population between days 0–90 and days 90–180 to obtain monthly numbers. Similarly, incremental hospitalised cases were not reported at the 30-day and 60-day time points. Therefore, we approximated these cumulative numbers based on the reported figures at 90 days (vaccine group n=10, placebo group n=33), assuming the same time-specific trends as observed in the reported severe RSV-MA-LRTI cases (Table 42).

Table 42 – Inferred RSV cases and population at risk over time based on the RSV-MA-LRTI MATISSE trial[61] (Number: population at risk)

Population	Arm	Day 0	Day 30	Day 60	Day 90	Day 120	Day 150	Day 180
MA cases	Vaccine	0 (N:3585)	2 (N:3563)	12 (N:3540)	11 (N:3518)	15 (N:3494)	15 (N:3470)	12 (N:3446)
	Placebo	0 (N:3563)	15 (N:3522)	23 (N:3482)	21 (N:3441)	29 (N:3409)	22 (N:3377)	22 (N:3345)
Severe MA cases	Vaccine	0 (N:3585)	1 (N:3569)	3 (N:3552)	2 (N:3536)	7 (N:3521)	5 (N:3506)	3 (N:3491)
	Placebo	0 (N:3563)	10 (N:3530)	18 (N:3498)	6 (N:3465)	15 (N:3445)	12 (N:3425)	9 (N:3405)
Hospitalisation	Vaccine	0 (N:3585)	2 (N:3567)	5 (N:3550)	3 (N:3532)	5 (N:3518)	3 (N:3505)	3 (N:3491)
	Placebo	0 (N:3563)	10 (N:3530)	17 (N:3498)	6 (N:3465)	6 (N:3452)	3 (N:3439)	5 (N:3426)

MATISSE: Maternal Immunization Study for Safety and Efficacy, RSV: Respiratory syncytial virus, MA: medically attended, LRTI: lower respiratory tract infections.

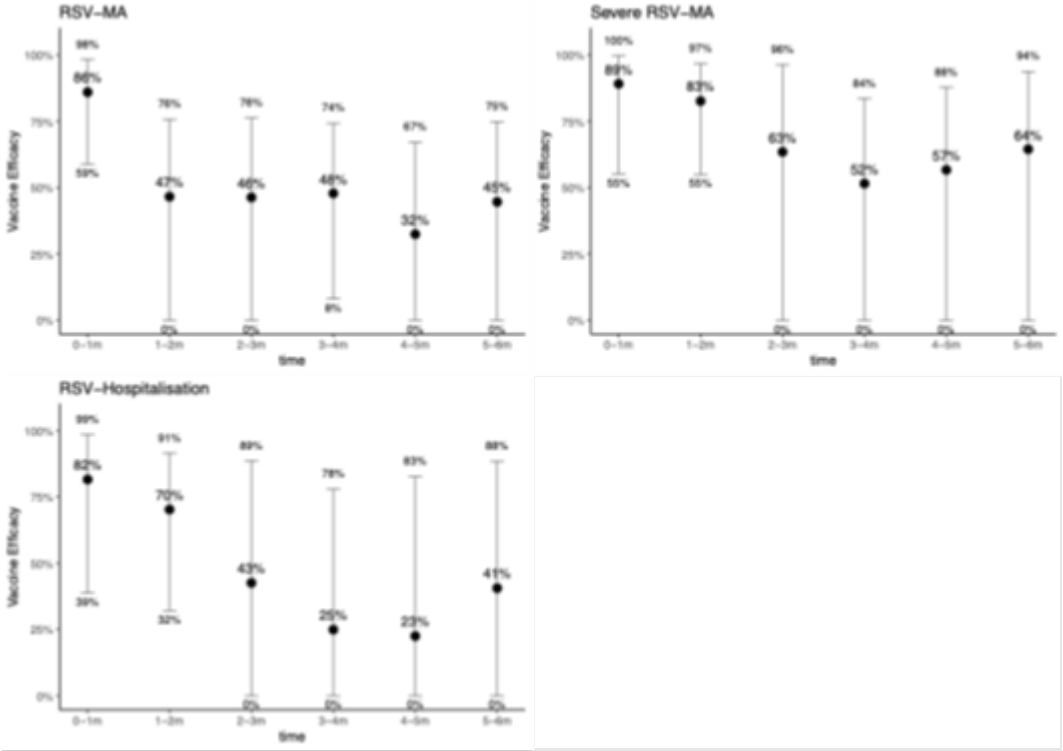
To obtain time-specific efficacy estimates with credible intervals we adopted a Bayesian approach. As such, we specified for each time point between 30 and 180 days a beta distribution based on the reported cases and populations at risk. Each beta distribution is specified by α, representing the number of events reported at a time point, and β, representing the corresponding at-risk population minus the number of events. From these distributions, we sampled for each time point a number of cases in both the vaccine and placebo groups and calculated efficacy as VE=1–(P/[1–P]), where P is the proportion of cases in the vaccine group relative to the total number of cases. In cases where the independent sampling resulted in more cases in the vaccine group than in the placebo group, the VE was set to 0. The sampling procedure was repeated 5,000 times to obtain a mean with 95% credible intervals. The result is shown in Figure 34.

DURATION OF PROTECTION AND WANING

For nirsevimab, efficacy values were assessed at 150 days in the phase 2b and phase 3 RCTs,[24, 28, 120] but the phase 3b trial demonstrated 180-day efficacy of nirsevimab against hospitalisation.[32] Alternatively, the efficacy values of pre-F maternal vaccine[61] were reported at 30, 60, 90, 120, 150 and 180 days as described above. Our Belgian expert panel reached consensus to use the latest clinical trials data as the base case for both interventions. We assumed constant protection over 6 months for nirsevimab and the monthly efficacy (as described above) for the maternal vaccine over 6 months. From month 7 onwards, efficacy is assumed to be 0% for both products.

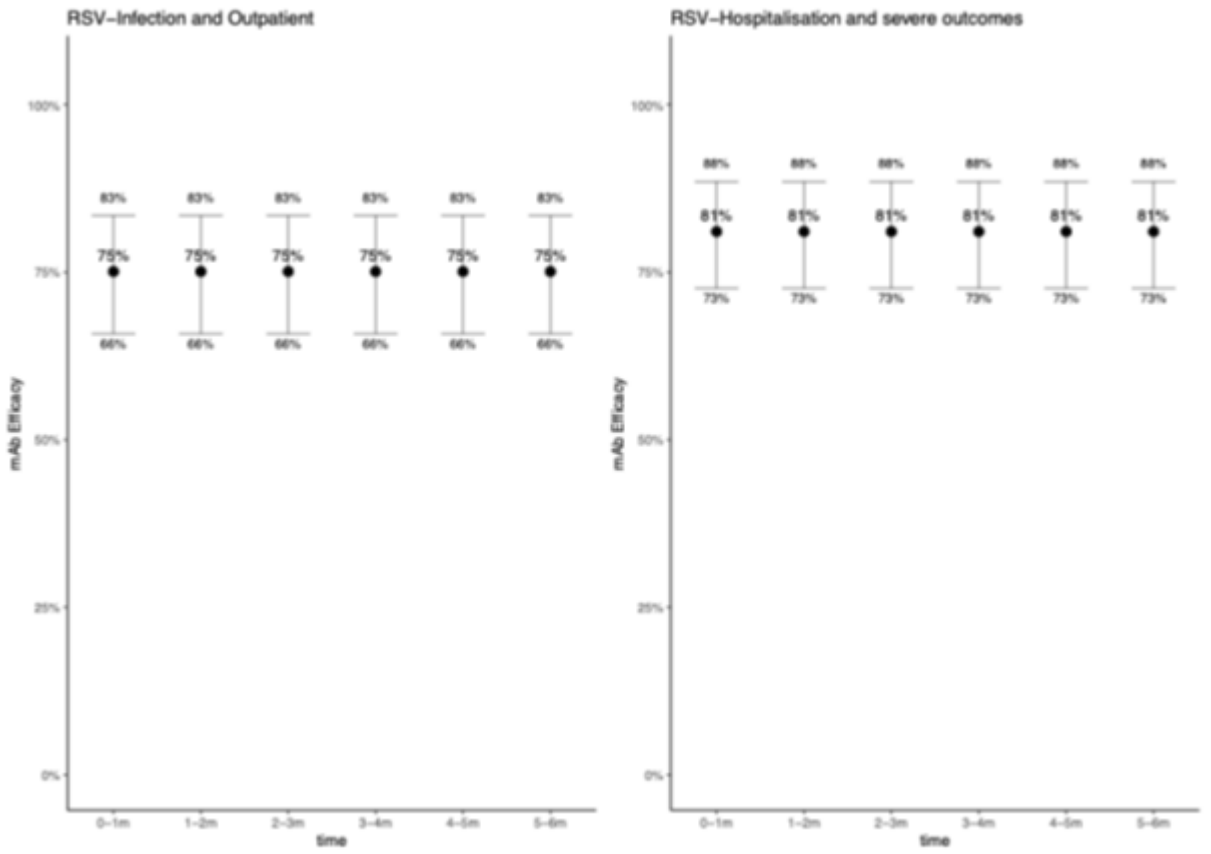
The efficacy over time of MV and mAb used as base case analysis in our cost-effectiveness analysis are illustrated in Figure 34 and Figure 35. We also incorporated real-world evidence (RWE) studies reporting the effectiveness of nirsevimab into our scenario analyses, including a scenario with waning effectiveness over time (see section 4.2.4).

Figure 34 – Estimated maternal vaccine efficacy values over 180 days (base case)



m: month, MA: medically-attended cases.

Figure 35 – Reported nirsevimab efficacy value over 180 days (base case)



m: month.

PARAMETRIC UNCERTAINTY FOR THE EFFICACY OVER TIME

In the PSA, we accounted for parametric uncertainty by varying the efficacy based on the estimated mean and corresponding 95%CI or Credible Interval (CrI). In the case of a constant efficacy profile over time, efficacy values were sampled from a logit normal distribution. First, standard errors (SE) were derived from the 95%CI or CrI using the delta method, i.e. SE = (upper limit – lower limit) / (2 * 1.96). Next, the mean and standard error were transformed to the logit scale to convert from the probability to a continuous scale. Samples were then drawn from the resulting normal distribution and transformed back to the probability scale using the inverse logit function. Each sampled efficacy value was held constant over the specified number of months. This procedure was applied to mAb in the base case. Note that a logit normal distribution was chosen over a beta distribution to maintain consistency with the time-specific efficacy profile by using the multivariate extension, as described in the next paragraph.

The logit multivariate normal distribution allows incorporating dependency between time points to preserve an overall efficacy pattern over time while incorporating uncertainty. In this case, a covariance matrix was assumed with 1 on the diagonal and 0.8 elsewhere. Following logit transformation of time-specific mean and SE estimates, samples were drawn from the resulting multivariate normal distribution and transformed back using the inverse logit function. This procedure was applied to MV in the base case and when time-specific efficacy values were adopted in sensitivity analyses.

COVERAGE AND PRICE

Following the first year of RSV MV implementation in England, the estimated coverage for September 2024 and October 2024 was 33.6% and 39.4%, respectively.[60] Other data from a subset of GPs in England indicated that out of 16,152 women who gave birth in October 2024, 6,369 (39.4%) had

received the RSV vaccine. Coverage varied by ethnic group, with the highest uptake among the 'Other ethnic groups - Chinese' category (65.5%) and the lowest in the 'Mixed - any other mixed background' category (18.6%). Routine maternal RSV vaccination has also been initiated in the US, Argentina and Australia. Preliminary data indicates that 32.6% of eligible pregnant women have received the RSV vaccine in the US,[61] no such data were found yet for Argentina and Australia. Over the past decade, maternal vaccination coverage against influenza and pertussis in Belgium has shown significant regional variations. For pertussis vaccination, coverage has been highest in Flanders, where it reached 69.3% in 2016 and increased to 85.5% by 2020.[62-64] In Wallonia, coverage was lower, with an estimated 39% in 2017 and a slight increase to 40% by 2020.[121, 122] The Brussels region had the lowest recorded uptake, with coverage at 31% in 2017, decreasing slightly to 30% by 2020.[121, 122] For influenza vaccination, uptake among pregnant women has generally been lower. In Flanders, it was about 47.2% in 2016.[62] In Wallonia, the estimated coverage was only around 10% in 2017, while in Brussels, it was slightly higher at 19% in the same year.[64] Based on all the above information, we assumed a 40% coverage rate for MV in Belgium in our cost-effectiveness analysis. The immunisation coverage for mAb was assumed to be 90%, based on recent data from Spain, where national uptake was 92% in infants born in the season and 87% for infants born before the season (the latter estimate showed regional variations from 45% to 97%).[123, 124] Also for France, mAb uptake was high in the 2023-2024 season: close to 80%, despite shortages of mAb doses.[124]

The uptake of other comparable immunizations early in life in Belgium is high. A coverage rate exceeding 90% has been achieved for complete primary vaccination (1 to 4 doses, depending on the vaccine) for all vaccines included in the recommended basic vaccination schedule, except for the rotavirus vaccine.[125-128] The national vaccination coverage for the complete schedule (4 doses) of the hexavalent vaccine is 94%, with comparable coverage rates in all Belgian regions. The hexavalent vaccine combines protection against six diseases in one injection (diphtheria-tetanus-pertussis (DTP), hepatitis B (HepB), Haemophilus influenzae type b (Hib), and poliomyelitis (polio)). The coverage rates for meningococcal vaccines (92%) and pneumococcal vaccines (94%), as well as the first dose of the measles, mumps, and rubella (MMR1) vaccine (96%), show limited regional variations. The rotavirus vaccine is the only recommended vaccine for children that is not provided through the free vaccination program of the regions and uptake varies by region (uptake 92% in Flanders, 81% in Wallonia and 70% in Brussels). The vaccination coverage studies conducted for Flanders in 2016 and 2020 showed coverage for the first dose of the hexavalent vaccine and the first pneumococcal conjugate vaccine dose (recommended at 8 or 12 weeks) to clearly exceed 95%, with respective values of 98.5% and 97.8% reported for 2020.[125, 129] Based on the above information and in consultation with our expert panel, we assumed that uptake of 90% would be achievable in the Belgian context, given a well- organized mAb programme, for both seasonal mAb and catch-up mAb administrations.

It is important to note that, as a static model was used, in which all costs are variable, immunisation coverage does not influence the cost-effectiveness results.[130] However, it does affect the estimated disease burden averted and budget impact figures.

The list price for nirsevimab is €777.58[131, 132] and €186.01 for Abrysvo[132, 133] and these prices are used in our base case analysis. However, the actual negotiated prices are expected to be substantially lower for the Belgian healthcare payer[aaa]. In order to allow for an intuitive easy comparison in the scenario analyses, we assumed cost-parity per dose for both products. I.e. we assumed the same cost per dose of €200 to show the relative efficiency at cost parity for both interventions. These costs per dose should be interpreted to include purchase, distribution and administration costs required to achieve the assumed uptake. In addition, extensive cost sensitivity analyses (including up to the public list price costs) were performed to explore the relationship between the cost of the different options for intervention and the selection of the optimal immunisation strategy given different WTP values per QALY

[aaa] In 2025, nirsevimab is temporarily reimbursed under a managed entry agreement, including confidential price discounts.

gained. More specifically, we considered a cost range of €50 to €250 per dose for MV, and €50 to €850 per dose for nirsevimab (see more details in the section 4.2.4 below).

RSV INTERVENTION DELIVERY COST IN BRUSSELS, FLANDERS AND WALLONIA

Distribution and delivery costs include cost of cold chain transportation, cold chain storage at distributional centres, as well as fixed and variable costs associated with health care facilities preparing, including training of personnel, and administering these immunisations, including purchase and disposal of specific medical equipment (e.g., syringes), and potential wastage. Furthermore, the introduction of these immunisation products will entail the organisation of awareness and information campaigns, specific safety monitoring, registering and reporting.

Based on discussions with the expert panel of the current study, using the experience and data available up to the time of the analytical set-up of the model implementation in this report (end of January 2025), the 2024-2025 season RSV immunisation programme and potential implementation options in the next few seasons can be summarised as follows. Nirsevimab was implemented in each region in the 2024-2025 season. As the MV, Abrysvo®, has only been reimbursed since 01/01/2025 in Belgium, it was not used during the 2024-2025 RSV season in Belgium.

The nirsevimab programme was expected to achieve more effective implementation in the 2025-2026 season through enhanced preparation. However, relatively few details were available on how this is expected to be done.

Long acting monoclonal antibody nirsevimab (Beyfortus®)

- The administration of long-acting RSV monoclonal antibodies (such as nirsevimab) for newborns, when they are born within the RSV season, can be implemented by a hospital nurse for in-hospital births (estimated to constitute 99% of births in Flanders).[134] Although mAbs might be kept in stock at hospitals, it would require a consulting clinician (most likely a pediatrician) to file an online (age-based) request first, as it is medication reimbursed from the federal budget under Chapter IV (*ex ante* control[bbb]).[135] It was at the time of writing this report unclear whether these acts would require costing in addition to a nurse's time, the charge of an extra specialist consultation to obtain chapter IV approval.
- For infants born outside the RSV season, multiple scenarios are possible, depending on whether the federated Mother & Child consultation clinics (Kind & Gezin (K&G), Office de la Naissance et de l'Enfance (ONE)) would be involved for the implementation, and whether or not the program would be funded from the federal budget (responsible for chapter IV medication, and for physicians and nurses remuneration for reimbursable medical acts) only, or also from the federated budget (responsible for collective prevention, including routine vaccination and screening programs).
- For the out-of-season catch-up component of the program to be most effective, it would need to be administered not long before the start of the RSV season, and therefore would concentrate a lot of activity in the months of September and October. In case the program is funded from the federal budget, and implemented without the involvement of federated Mother & Child Clinics, it is expected to require a physician (most likely a GP or a pediatrician) to provide the prescription and obtain the Chapter IV approval to allow the child's caregivers to purchase and collect the product at the pharmacy, and rejoining subsequently the physician for the mAb to be administered to their infant. In Flanders, Brussels and Wallonia, the administrator-physician is expected to be a pediatrician in 67%, 87% and 89% of these consultations for infants, respectively.[113, 114] It is as yet unclear whether

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bbb Drugs in Chapter IV are subject to particular reimbursement conditions and to ex ante control, i.e. the prior authorisation by the medical officer of the sickness fund. Restrictions for reimbursement are fixed for health safety reasons (e.g. anti-tuberculosis drugs restricted to tuberculosis patients to prevent resistance) and/or budgetary concern.

these acts would require costing in addition to a physician consultation for administration, an extra consultation to obtain a prescription and chapter IV approval, and whether the products could be stocked directly in the physician offices during this peak period. If on the other hand, federated Mother & Child Clinics would be tasked with the implementation, while funding was federal, the mAb administration step of the procedure could take place in the Mother & Child Clinics instead.

- Since for many infants, regular health care visits occur regardless, it was not clear at the time of writing the report, whether there would be need to cost an extra consultation to obtain a prescription and a chapter IV certificate and to visit the pharmacy to obtain the product, before visiting the Mother & Child clinic. If the programme would be funded by the federated entities, then the products would no longer be subject to a federal prescription and chapter IV authorisation, and therefore they could be made directly available to the Mother & Child clinics, while limiting the time losses to caregivers.
- Furthermore, it proved difficult for regional experts to provide estimates for each region for the costs of implementing this extra, specific program to the Mother & Child Clinics' workload in September and October.

RSVpreF vaccine F (Abrysvo®)

- Regarding RSV maternal vaccination, at the time of writing experts and the gynaecological medical society were actively engaged in discussions and preparations to introduce the RSV maternal vaccine from the 2025-2026 season onwards.
- Here too several scenarios are possible. The vaccine could be administered in the gynaecologist office, or a gynaecologist may provide an e-prescription, and the vaccine can then be administered by a GP after the patient obtains a vaccine from a pharmacist. Gynaecologists must request (Chapter IV) approval online (gestation age-based).
- Based on the experience with maternal pertussis and influenza vaccination in Flanders, most likely gynaecologists will refer to GPs rather than administer the vaccines themselves, as only about 16% and 9% of the time a gynecologist or a midwife, respectively, would perform the vaccination.[125]

In summary, for all strategies under consideration in this report there is considerable uncertainty about the costs of implementation, not only because it is uncertain who will deliver the immunization, but also how it will be financed, distributed, stocked, registered and reimbursed.

Since the estimation of the marginal intervention costs of an additional component to the federated immunisation programmes is a complex, fundamental issue for program evaluation in Belgium, that exceeds the means and timelines of the current study, it would be advisable to investigate this in depth in a separate study.

If we were to cost the implementation options as described above, based on multiple assumptions, we would not only end up with wide administration cost ranges with high uncertainty, but we may also inadvertently present scarce estimates that may subsequently be taken to be authoritative in other, future studies.

Additionally, it is also important to note that the negotiated prices for purchasing mAb or MV in large quantities would likely be affected by how these products would be administered, and that these prices are by definition fully unknown, but expected to lie well below the list prices.

Therefore, we decided to use all-in costs per dose in this report, including purchase, distribution and delivery, without explicitly attempting to estimate what proportion of these costs would be for administration and what proportion would be for purchase of these products. So when a certain strategy is found cost-effective at a certain immunization cost per dose, the reader should interpret that cost per dose to combine both purchase and administration costs. Program managers may want to distinguish fixed and variable administration costs. To interpret fixed vaccination costs in the context of our study,

they should divide these costs by the number of doses under a given scenario, and add that to the variable costs per dose they wish to consider.

The base case analysis included list prices per dose, and these were taken to include the costs for delivery and program setup. In the scenario analysis assuming cost parity, an all-in cost of €200 per dose is assumed.

4.2.2.8 Quality of life loss

As highlighted in our literature review above (section 4.1.2), the RESCEU infant study[79] used EQ-5D-5L questionnaires with Visual Analogue Scale (VAS) to estimate the utility scores in both infants and caregivers. This study was an observational prospective multi-country cohort study that recruited healthy term-born infants in four European countries (Finland, Spain, the Netherlands, and the UK). The study collected health-related quality of life data from infants and their caregivers, enabling the estimation of RSV-associated health utility loss, expressed as quality-adjusted life-day (QALD) loss in this study, for both groups.

Initially, the QALD loss was calculated using each country's EQ-5D value set, as reported in the original publication.[136] For this analysis, we obtained the primary data on the health state descriptions from the four countries and we recalculated the QALD loss using the Belgian value sets to reflect the preference of the Belgian general population. Specifically, we recalculated the QALD loss for infants using the Belgian EQ-5D-Y value set,[137] while the QALD loss for caregivers was derived using the Belgian EQ-5D-5L value set.[138] The QALD results are presented in Table 43.

Table 43 – Infant and their caregivers' quality-adjusted life-day (QALD) loss per RSV episode, stratified by health care resource utilisation

		Mean (95%CI)	Median [IQR]	Sample size in the cohort
Infant	Infant pooled	1.75 (1.57 - 1.94)	1.61 [0.77 - 2.52]	180
By healthcare resource utilisation	Outpatient	2.15 (1.90 - 2.43)	2.05 [1.26 - 2.72]	81
	Non-MA	1.23 (1.04 - 1.45)	0.97 [0.42 - 1.79]	90
	Hospitalised	3.59 (3.07 - 4.18)	3.47 [3.06 - 4.02]	7
Caregivers	Caregivers pooled	0.08 (-0.03 - 0.17)	0.03 [0.00 - 0.29]	164
By healthcare resource utilization	Outpatient	0.19 (0.06 - 0.32)	0.12 [0.00 - 0.33]	75
	Non-MA	-0.10 (-0.26 - 0.04)	0.00 [-0.03 - 0.10]	81
	Hospitalised	1.06 (0.59 - 1.64)	0.72 [0.63 - 1.37]	6

Non-MA: non-medical attendance, CI: confidence interval, IQR: interquartile range. In the cost-effectiveness analysis, we convert quality-adjusted life-day to quality-adjusted life-year.

In the RESCEU cohort, caregivers were asked to record daily the health-related quality of life (HRQoL) of their children as well as their own HRQoL from symptom onset for 14 days or until the child was symptom-free. The differences in HRQoL scores between baseline and each diary day were calculated for each episode, representing their QALD loss for each day. Caregivers' HRQoL, collected around their infant's first birthday, was treated as their baseline HRQoL, while infants were assumed to have full health at baseline. The total QALD loss for each episode was then obtained overall, as well as in subgroups, stratified by type of healthcare resource use (non-MA, outpatient or hospitalised). The 95%CI of the mean QALD loss were calculated by bootstrapping (number of samples: 1,000).

In our base case analysis, we included only the QALY losses (converted from QALDs) in infants, 0.003 (95%CI: 0.003-0.004) per non-MA episode, 0.006 (0.005-0.007) per MA outpatient episode, and 0.010 (0.009-0.011) per hospitalisation. However, in the scenario analysis, we additionally incorporated the QALY losses experienced by parents (see section 4.2.4 below). In the PSA, gamma distributions were used to account for the uncertainties around QALY losses.

In this analysis, we applied age-specific QoL weights to life-years lost due to RSV-related deaths, using population norm data for the QoL data. Van Wilder et al.[139] reported the most recent nationally representative Belgian population norm using the EQ-5D-5L instrument for ages 15 years and older. Since QoL weights cannot be directly elicited from young children, Van Wilder et al. chose not to estimate population norm data for those aged under 15. Bilcke et al's[140] earlier Belgian population norm included estimates for children using caregiver proxy valuations of their child's health, which showed overall good correspondence between the self-valuations at age 15 and the valuations-by-proxy at younger ages.[140] We assumed therefore the population norm weight estimated at age 15 by Van Wilder et al. (0.9) would also apply to all younger age groups.[139] For example, if an infant were to die from RSV at one month of age, the associated life-years lost would correspond to life expectancy at birth (averaged across genders: 82.29 years). Each of these lost life years was then weighted by the age specific population norm QoL weight corresponding to the age, during which the life year would have been lived if the infant had not died.

4.2.2.9 Long-term consequences

The relation between early childhood RSV infection and the later development of wheezing or asthma remains a topic of debate. The randomized, placebo-controlled MAKI trial with continuous follow-up showed that RSV preventions by palivizumab had no major effect on asthma or lung function at age 6 years in preterm healthy infants. While some studies have limitations, they have identified a statistically significant association between RSV infection in childhood and an increased risk of recurrent wheezing and/or asthma in later years (Shi et al.[141] 2020; Perez-Yarza et al.[142] 2007). The studies further suggested that the association weakens progressively with age. Similarly, Bont et al. (2004)[143] reported a significant decline in recurrent wheezing within the first three years following hospitalisation for RSV lower respiratory tract infections in infants.

As described in a previously published study (Li et al.[81] 2022), we evaluated the impact of recurrent wheezing up to three years of age and the combination of recurrent wheezing and asthma up to 13 years of age on cost-effectiveness outcomes for infants who had RSV-related hospitalisation during their first year of life. The annual probabilities of developing recurrent wheezing and asthma following RSV hospitalisation before one year of age were derived from the six studies identified in two previously published systematic reviews[141, 142] which investigated the association between RSV in infancy and recurrent wheezing and asthma. We also aim to investigate the impact of recurrent wheezing and asthma following RSV outpatient visits. However, there is insufficient data to determine the probability of developing wheezing and asthma after an RSV outpatient episode without hospitalisation (more details in the subsections below).

RSV-HOSPITALISATION RELATED RECURRENT WHEEZING ALONE UP TO 3 YEARS OF AGE

A longitudinal study reported that wheezing severity decreased over a three-year period among infants hospitalised with RSV in their first year of life.[143] Therefore, we conducted a scenario analysis incorporating recurrent wheezing outcomes over three years.

During the first year of life, the probability of developing recurrent wheezing following RSV hospitalisation was 31% (beta distribution; α=13, β=42-13), based on a prospective hospital-based study conducted among full-term infants in Germany.[144] The probability of recurrent wheezing also decreased with age. In infants ≥32 weeks of gestation with uncomplicated RSV-related hospitalisations in their first year, Escobar et al.[145] (2013, N=504) found the probability of recurrent wheezing was 27% (135/504) and 17% (87/504) in the second and third year, respectively. To reflect uncertainty, beta distributions were defined for these probabilities (Table 44). Two other studies with smaller sample sizes reported cumulative probabilities over the first three years of life as 21% (Sigurs et al.[146] 1995, N=47) and 28% (Henderson et al.[147] 2005, N=96), but these did not specify annual probabilities.

Table 44 – Scenario analysis: probability of recurrent wheezing and asthma up to 3 years of age for infants who were hospitalised with RSV during their first year of life

Scenario	Age (years)	Annual probability of recurrent wheezing/asthma (uncertainty distribution)
Age 0–3 years	0–1	31% ~ Beta (α =13, β =19)
	1–2	27% ~ Beta (α =135, β =269)
	2–3	17% ~ Beta (α =87, β =417)

Based on a Dutch study in preterm infants, the annual treatment cost of recurrent wheezing was estimated as the cost of 5.5 primary care visits and one beta-agonist inhaler.[148] A study in Belgian pre-schoolers estimated the medication cost per asthma-like case at €42.72 (2014 value).[149] Although the cost from national health insurance and patients' perspectives were not explicitly reported, based on the division for commonly prescribed relevant medication we estimated that 10% of these costs were paid from the patients' perspective.

Overall, the annual cost of recurrent wheezing and asthma are presented in Table 45, they were estimated by multiplying the unit cost of a primary care consultation at three years of age (Table 40) with 5.5 consultations, to which a cost was added for medication of €49.41 per year (in 2023 value, of which, 10% is paid by patients).

Table 45 – Undiscounted cost of recurrent wheezing and asthma per year used in scenario analysis

Cost per episode	Belgium	Flanders	Wallonia	Brussels
NIHDI	€ 215.02	€ 212.41	€ 217.28	€ 219.13
Patients	€ 49.82	€ 48.57	€ 50.91	€ 51.80
Healthcare payers	€ 264.84	€ 260.98	€ 268.19	€ 270.93

NIHDI: National Institute for Health and Disability Insurance.

Since no Belgian studies appear to report HRQoL data for children with wheezing or asthma, we conducted a literature search on asthma-associated HRQoL studies in children and identified three studies reporting HRQoL data from EU countries, namely Sweden,[150] Spain,[151] and the Netherlands.[152] To use all available data, we pooled the findings and calculated a weighted average proportion for each level of problem in each EQ-5D-Y dimension. The Belgian value set was then applied to derive an expected average health utility of 0.9217 for child patients with asthma. Compared to the Belgian EQ-5D-3L population norm for children under 16 years (estimated at 0.94),[140] this resulted in an estimated annual QALY loss of 0.0183 due to asthma.

Therefore, we estimate an asthma case to incur an annual loss of 0.0183 QALYs, which corresponds to 6.8 QALDs. By contrast, for instance an acute ambulatory case of RSV incurs an annual loss of 2.15 QALDs, or 0.00589 QALYs. Of course, an acute ambulatory case of RSV, incurs a quality-of-life loss over a relatively short period of illness (here empirically derived over a 14-day period), while the health status over the remainder of the year (365 – 14 days) is unaffected by RSV.

Note that the quality-of-life loss per RSV episode shown in Table 43 was calculated for the acute disease period (14 days in total). To obtain the daily quality of life loss during this acute period, we can divide the values in Table 43 by 14, resulting in losses of 0.256, 0.154, and 0.088 per day for hospitalised, outpatient, and non-MA patients, respectively. Therefore, while the average disutility experienced during the illness is higher for an ambulatory case of RSV (0.154) than for asthma (0.0183), the period over which it is incurred, is much longer for asthma. For instance, for an ambulatory RSV case we have (0.154*14 + (0*(365-14))/365) = 0.00589 QALYs lost per year; whereas for an asthma case we have (0.0183 * 365)/365 = 0.0183 QALYs lost per year.

Overall, the total undiscounted treatment costs and QALY losses associated with recurrent wheezing among children hospitalised with RSV during their first year of life were calculated as:

$$\text{Total Cost} = \text{Nr of hospitalisations}_{\text{(age 0-11 months)}} \times P_{\text{(year)}} \times \text{Annual treatment cost}$$

$$\text{QALY loss} = \text{Nr of hospitalisations}_{\text{(age 0-11 months)}} \times P_{\text{(year)}} \times \text{QALY loss per hospitalised case}$$

Where P_{year} represents the probability of recurrent wheezing and asthma at a given age. The mean and uncertainty distribution are reported in Table 46.

RSV-HOSPITALISATION RELATED RECURRENT WHEEZING ALONE UP TO 13 YEARS OF AGE

In this scenario, the long-term consequences of recurrent wheezing and asthma were included up to 13 years of age after an RSV-related hospitalisation during the first year of life. For the first three years, we assumed the same probabilities as those used for recurrent wheezing (see previous section). Based on Escobar et al.,[145] probabilities of recurrent wheezing were 16% (80/504) in the fourth year and 10% (50/504) in the fifth year. From ages 5 to 13, the probability was assumed to remain the same as in the fifth year.

Several studies with smaller sample sizes (N=35–76) have reported an association between RSV-related hospitalisation in children under one year and recurrent wheezing or asthma at ages 7–9 years.[147, 153, 154] The overall probabilities were consistent with those reported in the Escobar 2013 study (40%).[145] Similarly, the WHISTLER study found a comparable probability of 39% (63/158) for clinically diagnosed asthma at age 6.[155]

Sigure et al.[156, 157] published two studies examining asthma patterns 13 and 18 years after severe RSV bronchiolitis in infancy. However, due to the small sample size (N=46), we did not consider this study as a basis to model recurrent wheezing and asthma beyond 13 years of age.

Table 46 provides an overview of the probabilities and uncertainty distributions used in this scenario analysis.

Table 46 – Scenario analysis: probability of recurrent wheezing and asthma up to 13 years of age for infants who were hospitalised with RSV during their first year of life

Scenario	Age (years)	Annual probability of recurrent wheezing/asthma (uncertainty distribution)
Age 0–13 years	0–1	0.31 ~ Beta (α =13, β =19)
	1–2	0.27 ~ Beta (α =135, β =269)
	2–3	0.17 ~ Beta (α =87, β =417)
	3–4	0.16 ~ Beta (α =80, β =424)
	4–5	0.10 ~ Beta (α =50, β =454)
	5–13	Same as age 4–5

RSV-OUTPATIENT EPISODE RELATED RECURRENT WHEEZING AND ASTHMA

We attempted to investigate the impact of recurrent wheezing and asthma following RSV outpatient visits. As described in the previous section, long-term follow-up studies have primarily focused on infants hospitalised due to RSV. There are limited studies examining the association between RSV outpatient cases and recurrent wheezing or asthma in children who had RSV outpatient visits but did not require hospitalisation. This is likely because respiratory viruses, including RSV, are not routinely tested in outpatient settings in Europe, and most children contract RSV by the age of two. Therefore, conducting a prospective observational study or a retrospective and representative database analysis in this context is highly challenging, particularly because recurrent wheezing and asthma can also be caused by other factors such as environmental exposures.

Two large prospective population-based birth cohort studies were reviewed, namely, the Respiratory Syncytial Virus Consortium in Europe (RESCEU) Birth Cohort Study[3] and the Infant Susceptibility to Pulmonary Infections and Asthma Following RSV Exposure (INSPIRE) in the US.[158] The RESCEU infant study was described in the previous section, and part of its data were used as input parameters of our cost-effectiveness analysis. However, as the study is ongoing and only the first year of data has been published, it is not yet possible to estimate the association between RSV infections and the consequences of recurrent wheezing and asthma beyond one year based on this study.

The INSPIRE study assessed the association between RSV infection during infancy and childhood asthma.[159] This is a large, population-based birth cohort of term-born, healthy infants recruited from 11 paediatric practices in Tennessee, USA, between 2012 and 2013. RSV infection status in the first year was determined through active and passive surveillance (N=1,741). This study estimated the proportion of asthma cases by age 5 years that could be prevented by avoiding RSV infection during infancy to be 15% (95%CI: 2.19-26.84).

In this study, the incidence of RSV infection was 54% which is higher than in other studies.[3] Given the study only included children born between June and December, and younger infants (under six months) were at higher risk of severe RSV disease than older children, the preventable fraction of asthma might be overestimated. Moreover, these findings were challenging to reconcile with the lack of a significant relationship between infant RSV infection and recurrent wheezing beyond age 3.

According to the European Respiratory Society clinical practice guidelines, asthma is difficult to diagnose before age 5 years since lung function tests, as an objective diagnostic tool for asthma, are unreliable in younger children.[158] In the INSPIRE study, “current asthma by age 5 years" was defined as “*parental report of physician-diagnosed asthma or use of asthma medications at any timepoint before age 5 years and any of the following symptoms during the 12 months before the 5-year visit: asthma symptoms, asthma-related systemic steroid use, or acute health-care utilisation for asthma.*”[159] In Belgium, Trabelsi et al.[149] estimated that 36.40% of children under five had asthma medication purchases. However, the prevalence of 5-year “current asthma” in Belgium remains unclear when using the same definition as the INSPIRE study. Medication purchases do not necessarily equate to a clinical diagnosis of asthma, as they may include other respiratory conditions. Hence, we did not perform an additional scenario analysis for all outpatient related recurrent wheezing and asthma. Most importantly, as highlighted by authors of INSPIRE study[158] and the accompanying commentary,[160] convincing evidence for causality should come from large efficacy trials showing that RSV maternal vaccines and monoclonal antibody would reduce childhood asthma by including asthma endpoints in RSV efficacy trials.

4.2.2.10 Overview of the input parameters

An overview of the input parameters is provided in Table 47.

Table 47 – Input parameters used in the cost-effectiveness analysis and uncertainty distribution for the PSA

Parameter	Mean value (95%CI , SD or SE)	Reference/source and uncertainty distribution
Target population (birth)	Birth cohort: 108 680 The cohort is followed over time up to the age of 5 years.	2024 birth cohort, Statbel[96] Fixed
RSV disease burden		
RSV hospital admissions (numbers)	Age- and calendar-month specific	National hospital database TCT data. See 4.2.2.2. Fixed
RSV-related in hospital-deaths	Age-specific	National hospital database TCT data. See 4.2.2.3. Fixed
RSV-related primary care incidence	Base case: Age-specific based on the Spanish data Scenario analysis: Dutch data and the pooled 5 European countries	RESCEU infant cohort study, see 4.2.2.4. Lognormal distribution
Proportion of non-MA over the MA cases	Age-specific 0m: 0% (assumption) 1-11m: 37.3% - 60.1% Assume 1-4 y same as 11 month	RESCEU infant cohort study, see 4.2.2.5. Uncertainty was estimated by the GLM
Probability of recurrent wheezing and asthma given RSV hospitalisation within first year of life	Scenario analyses only: Decrease by age	See 4.2.2.9, Table 44 and Table 46 Beta distribution
Quality-adjusted life-year losses		
QALY loss per hospital admitted episode	0.010 (95%CI: 0.009-0.011)	Re-analysis of RESCEU infant cohort study using Belgian value set. See 4.2.2.8. Gamma distribution
QALY loss per episode seen in primary care	0.006 (95%CI: 0.005-0.007)	
QALY loss per non-MA episode	0.003 (95%CI: 0.003-0.004)	
QALY loss of recurrent wheezing/asthma per year (scenario analysis only)	0.0183	See estimation in section 4.2.2.9 above. Fixed
Costs by perspectives in €2024		
Cost of ICU admission	<1y: NIHDI: €14,205 (SE: 312) Patients': €88 (SE: 3) HCP: €14,293 (SE: 314) 1-4y: NIHDI: €17,568 (SE: 1067) Patients': €134 (SE: 15) HCP: €17,702 (SE: 1,077)	See section 4.2.2.6 above. Gamma distribution
Cost of hospitalisation (non-ICU)	<1y: NIHDI: €3,590 (SE: 12) Patients': €23 (SE: 0) HCP: €3,613 (SE:12) 1-4 y: NIHDI: € 3,197 (SE: 19) Patients': €24 (SE: 0) HCP: €3,221 (SE: 19)	See section 4.2.2.6. Gamma distribution
Cost per outpatient episode (Belgium) <1 year of age	NIHDI: €77.43 (59.10-95.77) Patients': €28.58 (23.22-33.94) HCP: €106.01 (82.32-129.71)	Weighted cost by age, region and health-seeking behaviours See section 4.2.2.6. Gamma distribution
Cost per outpatient episode (Belgium): 1 year of age	NIHDI: €70.61 (53.55-87.66) Patients': €26.21 (21.49-30.93)	

	HCP: €96.82 (75.04-118.6)	
Cost per outpatient episode (Belgium): 2 years of age	NIHDI: €67.76 (51.43-84.08) Patients': €24.78 (20.43-29.14) HCP: €92.54 (71.86-113.22)	
Cost per outpatient episode (Belgium): 3 years of age	NIHDI: €66.09 (50.19-81.99) Patients': €23.95 (19.81-28.99) HCP: €90.04 (70.00-110.08)	
Cost per outpatient episode (Belgium): 4 years of age	NIHDI: €65.14 (49.49-80.79) Patients': €23.48 (19.46-27.50) HCP: €88.62 (68.94-108.29)	
Cost per non-MA episode	Patients': €4.43	See section 4.2.2.6 Assumed cost of OTC medication[80] Fixed
Annual undiscounted costs of recurrent wheezing and asthma (Scenario analysis only)	NIHDI: €215.02 Patients': €49.82 HCP: €264.84	See 4.2.2.9 and Table 45 Fixed
Intervention cost per dose	Base case: list price Nirsevimab: €777.58 Abrysvo: €186.01 Scenario analyses cost-parity: both €200 (including purchase, distribution and delivery programme costs)	List price based on BCFI [131] [133] Assumption and price threshold analyses were performed
% work absence of outpatient episode	<1y: 64% 1–4y: 80%	ComNet study[77] See section 4.2.2.6. Gamma distribution
Productive days lost per outpatient episode	<1y: 2.7 (SD: 3.3) days 1–4y: 4.3 (SD: 4.2) days	
% work absence of hospitalisation episode	<1y: 76% 1–4y: 69%	
Productive days lost per hospitalisation episode	<1y: 4.6 (SD: 4.4) days 1–4y: 8.1 (SD: 10.7) days	
Average productivity cost per day	€376.8	Statbel[116] Fixed
Intervention characteristics		
MV efficacy against hospital admissions	0–1m: 82% (33-99%) 1–2m: 70% (32-91%) 2–3m: 43% (0-89%) 3–4m: 25% (0-78%) 4–5m: 23% (0-83%) 5–6m: 41% (0-88%)	See Figure 34 and section 4.2.2.7. Logit multivariate normal distribution
mAb efficacy against hospital admissions	81% (73-88%)	See Figure 35 and section 4.2.2.7. Logit normal distribution
MV efficacy against ICU admissions and deaths	0–1m: 89% (55-100%) 1–2m: 83% (55-97%) 2–3m: 63% (0-96%) 3–4m: 52% (0-84%) 4–5m: 57% (0-88%) 5–6m: 64% (0-94%)	See Figure 34 and section 4.2.2.7. Logit multivariate normal distribution Sensitivity analysis: no efficacy against deaths.
mAb efficacy against ICU admissions and deaths	81% (73-88%)	See Figure 35 Logit normal distribution Sensitivity analysis: no efficacy against deaths.
MV efficacy against primary care visits and non-MA episodes	0–1m: 86% (59-98%) 1–2m: 47% (0-76%) 2–3m: 46% (0-76%) 3–4m: 48% (8-74%) 4–5m: 32% (0-67%) 5–6m: 45% (0-75%)	See Figure 34 and section 4.2.2.7. Logit multivariate normal distribution Sensitivity analysis: no efficacy against non-MA episode.
mAb efficacy against primary care visits and non-MA episodes	75% (66-83%)	See Figure 35 and section 4.2.2.7.

		Logit normal distribution Sensitivity analysis: no efficacy against nonMA episode.
Duration of protection investigated in the studies	Base case: MV: 180 days mAb: 180 days (150 days in one scenario analysis)	See section 4.2.2.7.
Immunisation coverage		
MV coverage	40% (70% and 90% in scenario analysis)	Approximation based on regional maternal vaccine coverage for pertussis in Belgium and the first season RSV maternal coverage data in England.[161] See 4.2.2.7. Fixed
mAb coverage	90% (70% in scenario analysis)	Approximation from the first season coverage data in region of Murcia, Spain,[123] France and coverage for other childhood immunisations in Belgium. See 4.2.2.7. Fixed
Discount rate		
Costs	3%	Belgian guidelines for economic evaluations[91] Fixed
Health outcomes	1.5%	

PSA: probabilistic sensitivity analysis, SD: Standard Deviation, SE: standard error, NIHDI: National Institute for Health and Disability Insurance, QALY: quality-adjusted life year, MV: maternal vaccine, mAb: nirsevimab, ICU: intensive care unit, MA: medically-attended, y: year, CI: confidence interval, HCP: health care payers, OTC: over the counter.

4.2.3 *Uncertainty*

Uncertainty regarding the cost-effectiveness of a program was assessed using two measures: (i) the probability that a program is cost-effective, as illustrated in the cost-effectiveness acceptability curves (CEACs), and (ii) the population expected value of perfect information (EVPI). The probability of cost-effectiveness, defined as the proportion of samples from the PSA (N=1,000 samples, unless specified) in which a program is cost-effective across a range of willingness-to-pay (WTP) values, can be interpreted from the CEACs.[95] A higher probability of cost-effectiveness increases confidence in the optimal program, i.e., the program with the lowest expected net loss. The EVPI for a given WTP value represents the expected net loss of the cost-effective program at that WTP value.[93, 94, 162] Consequently, it accounts not only for the probability of making an incorrect decision but also for the potential consequences of making this incorrect decision. Higher EVPI values indicate greater expected loss and, consequently, higher decision uncertainty. The EVPI is equivalent to the expected net loss frontier (ENLF) at a specific decision point and can be visually interpreted from the expected net loss curve (ENLC) plot. Additionally, the EVPI represents the maximum justifiable investment in research to precisely measure all parameterized uncertain aspects of the RSV disease burden, costs and the impact of the interventions. This would enable the identification of the cost-effective option with complete certainty (100%).

4.2.3.1 Expected Value of Partial Perfect Information (EVPPI)

To identify the most influential uncertain input parameters affecting the cost-effectiveness results, EVPPI values were calculated across a range of WTP thresholds for each uncertain input parameter included in the PSA.[93] The input parameter with the highest EVPPI was considered the most influential. Moreover, the impact of uncertainty in other parameters was assessed through a scenario analysis.

4.2.4 Sensitivity and scenario analysis

The following sensitivity and scenario analyses were implemented:

- RSV-coded hospitalisations:
  - Using 10 seasons ICD-coded data before COVID-19 pandemic (versus base case: 4 seasons)
  - Using season 2023/2024 age distribution data for age-group 1-11 months (versus base case: season 2018/2019 age distribution data)
  - using only the primary diagnosis code to select hospitalisations (versus base case, which included both primary and secondary diagnosis codes)
- RSV-related primary care incidence: alternatively based on Dutch data and pooled estimates from 5 countries (versus base case, which applied Spanish data)
- Using Effectiveness studies of nirsevimab (see section below)
- Different coverages for both mAb and MV strategies
- Inclusion of recurrent wheezing and asthma up to 3 years and 13 years of age
- RSV interventions under consideration have no impact on mortality
- RSV interventions under consideration have no impact on non-MA episodes
- Societal perspective (versus base case HCPs)
- Inclusion of parental QALY losses per RSV episode

4.2.4.1 Effectiveness studies of nirsevimab

For the scenario analysis, we used two sets of effectiveness data for nirsevimab based on real-world evidence (RWE) studies. Firstly, we adopted from the systematic review and meta-analysis of efficacy and effectiveness of RSV interventions conducted by KCE (Chapter 2), the pooled effectiveness against the occurrence of RSV MA infection as a proxy for non-MA and outpatient RSV episodes. In addition, we used the pooled effectiveness against hospital admission for the hospitalisations, and the pooled effectiveness against RSV-related PICU admissions as a proxy for ICU admissions and deaths (Table 48).

Secondly, as identified in the systematic review (Chapter 2), there was one study (a test-negative case-control study in the US) that reported nirsevimab's effectiveness over time since immunisation.[163] It is worth noting that this study was conducted in a population that differed significantly from previous RCT and RWE studies, as acknowledged by the authors, notably due to limited access to nirsevimab and a total of only 21 confirmed RSV cases. Importantly, the results after 14 weeks were not statistically significant (only one hospitalised RSV case remained at this time point). The authors acknowledge that these findings are preliminary and should be interpreted with caution. Nevertheless, this study incorporated time as a categorical variable within a logit model and demonstrated a clear trend of waning effectiveness over time; therefore, we included it as part of our scenario analyses to evaluate waning effectiveness.

Table 48 – Scenario analyses based on two sets of nirsevimab's effectiveness data

	Nirsevimab (pooled real-word studies) with 6-month protection Mean and 95%CI	Nirsevimab (US test-negative case-control study) with 5-month protection Mean[@] and 95%CI
Efficacy non-MA episode	Assume same as outpatient episode	0-1 month: 76% (95%CI: 60-87%) 1-2 month: 70% (95%CI: 51-82%) 2-3 month: 61% (95%CI: 34-77%) 3-4 month: 47% (95%CI: 0-72%)[&] 4-5 month: 37% (95%CI: 0-70%)[&] 5-6 month: 0%
Efficacy vs. outpatient episode	73% (95%CI: 67-78%)*	0-1 month: 72% (95%CI: 48-86%) 1-2 month: 64% (95%CI: 38-80%) 2-3 month: 55% (95%CI: 20-76%) 3-4 month: 41% (95%CI: 0-70%)[&] 4-5 month: 32% (95%CI: 0-68%)[&] 5-6 month: 0%
Efficacy vs. hospitalisation	86.0% (95%CI: 70-94%)^	0-1 month: 89% (95%CI: 67-97%) 1-2 month: 83% (95%CI: 53-95%) 2-3 month: 74% (95%CI: 24-92%) 3-4 month: 59% (95%CI: 0-89%)[&] 4-5 month: 48% (95%CI: 0-88%)[&] 5-6 months: 0%
Efficacy vs. ICU admission and deaths	87% (95%CI: 77-93%)*	0-1 month: 94% (95%CI: 75-99%) 1-2 month: 88% (95%CI: 61-97%) 2-3 month: 78% (95%CI: 21-94%) 3-4 month: 58% (95%CI: 0-91%)[&] 4-5 month: 43% (95%CI: 0-89%)[&] 5-6 month: 0
Duration of protection	6 months protection	5 months protection

** Studies with follow-up superior to 100 days. ^ Studies with follow-up through 100 to 150 days. [&] All negative values were set to 0 in the analyses, and the distribution was truncated to align with the mean values. [@] The original article from Xu et al. only reported median, the mean values were provided by the first author via personal communication. ICU: intensive care unit, MA: medically attended, CI: confidence interval, CrI: credible interval.*

4.3 Results of the cost-effectiveness analysis

We assessed the disease burden of RSV in Belgian children under five years of age, as well as the impact of various RSV immunisation strategies as described in methods section 4.2:

- Year-round single-dose MV during pregnancy
- Year-round single-dose mAb at birth
- Seasonal maternal vaccine during pregnancy for infants with due delivery date in September to March (MV: Sep-Mar)
- Seasonal nirsevimab given at birth for infants born during the RSV season from October to March (mAb: Oct-Mar)
- Seasonal nirsevimab (as described above) plus a catch-up program in September for infants (≤6 months) born outside of the RSV season from April to September (mAb: Oct-Mar + catch-up)

We conducted a full incremental cost-effectiveness analysis comparing the above immunisation strategies to no programme and to each other from the healthcare payer perspective. In the base case analysis, we used the list prices of €186.01 for Abrysvo[132, 133] (MV) and €777.58 for nirsevimab.[131, 132] In addition, we conducted a scenario analysis exploring cost parity between the two interventions to enable a direct head-to-head comparison of multiple strategies. A comprehensive set of scenario analyses was also performed, as described in section 4.2.4.

4.3.1 RSV-related disease and economic burden in Belgian children <5 years

In Belgium, RSV led to a substantial disease burden in children under 5 years of age, as illustrated in Table 49. Following the birth cohort over a five-year time horizon, we estimated approximately 116 thousand RSV cases, including 40 thousand non-MA cases, 66 thousand outpatient cases, 8638 non-ICU hospitalisations, 428 ICU admissions and 5 deaths.

Among children hospitalised for RSV, those under 1 year of age experienced approximately 3 and 9 times more non-ICU and ICU admissions, respectively, compared to children aged 1–4 years. RSV-related deaths were also more frequent in infants under 1 year of age than in the 1–4–year age group (3.7 versus 1.3, respectively). The highest number of hospital (both ICU and non-ICU) admissions was projected to occur in the youngest age group (0-2 months). In children under 1 year, the highest number of outpatient episodes was observed in the 3–5 months age group, whereas the highest number of non-MA episodes occurred in children aged 6–11 months. In children aged 1–4 years, we estimated 48 thousand outpatient episodes and 30 thousand non-MA cases, assuming the same outpatient incidence rate and non-MA proportion as in the 6–11-month age group. This assumption may lead to an overestimation of non-MA and outpatient cases in children above 1 year of age.

In children under 5 years, the burden of RSV disease was associated with an estimated 968 undiscounted QALYs lost, of which 48% (467) was attributable to children under 1 year. RSV-related mortality accounted for over 36% of total QALY losses in children under 5 years and over 56% in infants under 1 year. From the HCP perspective, RSV resulted in an undiscounted medical cost of €43 million, of which more than two-thirds was attributable to children under 1 year.

Table 49 – Estimated RSV-related undiscounted burden without new RSV intervention in a birth cohort followed over 5 years (Mean [95%CrI])

Outcome	0–2 months	3–5 months	6–11 months	0–11 months	12–59 months	0–59 months
Non-MA episodes	2,419 [1,282 ; 4,472]	3,598 [1,709 ; 6,947]	4,091 [1,923 ; 8,500]	10,108 [4,944 ; 19,956]	30,373 [11,712 ; 68,439]	40,481 [16,594 ; 88,731]
Outpatient episodes	5,593 [1,951 ; 12,095]	6,524 [2,457 ; 12,958]	6,015 [2,139 ; 13,362]	18,132 [6,544 ; 38,415]	48,117 [17,110 ; 106,898]	66,249 [23,654 ; 145,314]
Hospitalisations (non-ICU)	3,169	1,641	1,519	6,329	2,309	8,638
ICU admissions	245	72	67	384	43	428
Total cases	11,427 [6,805 ; 19,850]	11,835 [6,018 ; 22,074]	11,692 [5,764 ; 23,583]	34,954 [18,587 ; 66,019]	80,842 [31,456 ; 179,436]	115,796 [50,026 ; 245,605]
Deaths	2.0	0.9	0.8	3.7	1.3	5.0
Life years lost	166	72	66	304	108	411
QALY						
QALY loss due to non-MA episodes	8.1 [4.2 ; 15]	12 [5.6 ; 24]	14 [6.2 ; 29]	34 [16 ; 68]	102 [38 ; 227]	136 [54 ; 294]
QALY loss due to outpatient episodes	33 [11 ; 72]	38 [15 ; 78]	35 [13 ; 78]	107 [39 ; 227]	283 [102 ; 623]	390 [140 ; 851]
QALY loss due to hospitalisation	31 [27 ; 36]	16 [14 ; 19]	15 [13 ; 17]	62 [53 ; 72]	23 [19 ; 26]	85 [73 ; 98]
QALY loss due to ICU admission	2.4 [2.1 ; 2.8]	0.7 [0.6 ; 0.8]	0.7 [0.6 ; 0.8]	3.8 [3.2 ; 4.4]	0.4 [0.4 ; 0.5]	4.2 [3.6 ; 4.8]
QALY loss due to deaths	142	61	57	261	92	353
Total QALY loss	217 [192 ; 261]	129 [99 ; 178]	121 [91 ; 177]	467 [380 ; 617]	500 [257 ; 950]	968 [640 ; 1,561]
Cost (€'000)						
Cost due to non-MA episodes	11 [5.7 ; 20]	16 [7.6 ; 31]	18 [8.5 ; 38]	45 [22 ; 88]	135 [52 ; 303]	179 [74 ; 393]

Cost due to outpatient episodes	593 [208 ; 1,347]	692 [267 ; 1,455]	629 [226 ; 1,455]	1,915 [696 ; 4,263]	4,425 [1,589 ; 9,887]	6,340 [2,240 ; 14,049]
Cost due to hospitalisations (non-ICU)	11,451 [11,374 ; 11,527]	5,929 [5,889 ; 5,968]	5,418 [5,386 ; 5,451]	22,797 [22,646 ; 22,945]	7,438 [7,355 ; 7,525]	30,235 [30,070 ; 30,415]
Cost due to ICU admission	3,502 [3,343 ; 3,651]	1,035 [988 ; 1,079]	986 [947 ; 1,027]	5,524 [5,285 ; 5,757]	767 [675 ; 865]	6,291 [6,039 ; 6,548]
Total treatment cost	15,557 [15,121 ; 16,299]	7,672 [7,238 ; 8,441]	7,051 [6,633 ; 7,902]	30,280 [29,031 ; 32,614]	12,764 [9,858 ; 18,304]	43,045 [38,864 ; 50,994]

Grey area: the total columns (0–11 months and 0–59 months), the totals may differ by up to one unit due to rounding. QALY: quality-adjusted life year, non-MA: non-medically attended, ICU: intensive care unit, CrI: credible interval.

4.3.2 Impact of interventions on RSV disease and economic burden

From the HCP perspective, the RSV-related disease and economic burden under the standard of care, as well as following the implementation of the five RSV immunisation strategies, are presented in Table 50. Compared to the standard of care before the 2024-2025 RSV season (no new RSV interventions, hereafter "no intervention" or "standard care"[ccc]), all strategies contributed to a reduced disease burden, leading to lower direct and indirect costs, as well as fewer QALY losses. It is worth remembering that in the base case, in accordance with the available clinical trial data, the mAb and MV strategies were assumed to offer duration of protection for a period of time up to 6 months. As a result, the reduction in disease burden may appear limited, especially for year-round strategies, and when coverage was assumed low, as for the MV strategies, which had an assumed 40% uptake.

Table 51 presents the RSV-related disease and economic burden averted by each immunisation strategy, as well as the associated intervention costs based on list prices, compared to 'no intervention' in children <5 years. Since the duration of protection for both interventions does not exceed 6 months in our base case analysis, the averted disease burden was limited to children <1 year. Seasonal MV and mAb strategies prevented approximately 18% and 45% fewer RSV cases, respectively, than the equivalent year-round strategies. However, the intervention costs of the seasonal MV and mAb strategies were substantially lower, representing 58% (7/12) and 50% (6/12), respectively, of the costs associated with year-round strategies.

The seasonal plus catch-up mAb strategy averted the greatest part of the RSV disease burden in Belgium. At 90% coverage, on average 19,381 RSV cases (55% of total cases averted in children <1 year), including 252 ICU admissions (66% in <1 year), 4,062 non-ICU hospitalisations (64% in <1 year), 9,845 outpatient episodes (54% in <1 year) and 5,222 non-MA episodes (52% in <1 year) could be prevented. Consequently, the seasonal mAb plus catch-up strategy also resulted in the most discounted QALYs gained, 216 (60% in <1 year), as well as the highest treatment costs of €19 million (64% in <1 year) averted.

When intuitively interpreting these estimates, it is important to keep in mind that this strategy is designed, a substantial part of the RSV burden remains unpreventable, despite the high assumed immunisation coverage of 90%. Indeed, the seasonal plus catch-up mAb strategy would, by the end of October (at the start of the RSV season), have administered mAb to 90% of infants up to the age 6 months. This implies that 10% of infants up to 6 months would still be fully unprotected, and 90% will be partially protected against the various outcomes as they are exposed to the high RSV seasonal incidence window during their first year of life. Additionally, none of the infants aged over 6 months at the start of the season would be protected during the season under this strategy. This implies that infants aged 7, 8, 9, 10, 11 months at the start of the season would still experience, respectively, 5, 4,

[ccc] 'Standard care' and 'no intervention' were used equivalently, meaning the absence of any new RSV-specific intervention.

3, 2, 1 months of full, unprotected RSV exposure during their first RSV season, in their first year of life. Furthermore, the 90% of infants up to 6 months of age, who did receive the mAb, would “only” be partially protected, with higher protection conferred against more severe outcomes, e.g. about 81% and 75% efficacy for hospitalisations and outpatients, or a protective effectiveness of 72.9% and 67.5%, respectively, see also section 4.2.2.7. Finally, the 65% to 55% of infants aged up to 6 months, in whom the protective effect “took hold” at the start of the season, were assumed to lose that protection completely towards the tail of their first RSV season (from March onwards), as the duration of protection was limited to 6 months in the baseline (see section 4.2.2.7).

The mAb seasonal plus catch-up strategy was the most effective strategy, but it also incurred the highest intervention cost of €76 million at 90% coverage, due to the large target group and given the public list price of €777.58 per dose. In comparison, the seasonal MV strategy resulted in an intervention cost of €5 million, based on a list price of €186.01 per dose and an assumed coverage of 40%. Moreover, the seasonal mAb plus catch-up strategy incurred the same intervention costs as the year-round mAb strategy, as both were assumed to target the same birth cohort at the same overall uptake rate and costs. However, the mAb seasonal plus catch-up strategy averted more RSV cases and treatment costs and gained more QALYs. This is primarily due to its administration immediately prior to the RSV season, which, given the assumed duration of the protection period (6 months), covers the peak transmission period well.

In a scenario analysis, we also demonstrated the impact of 70% and 90% coverage of both interventions on the prevention of RSV disease and the associated economic burden (Appendix 6). We showed that when the same level of coverage was considered for both mAb and MV strategies (70% or 90% uptake), the mAb strategies still yielded a greater clinical benefit. However, it is important to note that this is a static model; therefore, the coverage level does not influence the incremental cost-effectiveness results.

Table 50 – Disease and economic burden of standard care and 5 RSV strategies in children <5 years from the HCP perspective (Mean [95%CrI])

	No intervention	MV	MV: Sep-Mar	mAb	mAb: Oct-Mar	mAb: Oct-Mar + catch-up
Coverage	*NA*	*40%*	*40%*	*90%*	*90%*	*90%*
Undiscounted cases						
Non-MA episodes	40,481 [16,594 ; 88,731]	39,412 [16,252 ; 86,485]	39,860 [16,374 ; 87,495]	36,442 [14,434 ; 80,988]	39,028 [15,847 ; 86,023]	35,258 [13,884 ; 78,533]
Outpatient episodes	66,249 [23,654 ; 145,314]	63,810 [23,202 ; 140,413]	64,629 [23,316 ; 141,962]	58,122 [20,796 ; 128,752]	62,721 [22,451 ; 138,232]	56,404 [20,206 ; 124,875]
Hospitalisations (non-ICU)	8,638	7,667 [7,072 ; 8,226]	7,843 [7,442 ; 8,280]	5,144 [4,827 ; 5,553]	6,673 [6,494 ; 6,903]	4,577 [4,208 ; 5,052]
ICU admissions	428	335 [309 ; 376]	348 [329 ; 382]	197 [176 ; 224]	267 [253 ; 286]	175 [152 ; 205]
Total cases	115,796 [49,314 ; 243,111]	111,224 [46,835 ; 235,500]	112,680 [47,461 ; 238,119]	99,905 [40,233 ; 215,517]	108,689 [45,045 ; 231,444]	96,414 [38,450 ; 208,665]
Deaths	5.0	4.2 [4.0 ; 4.6]	4.4 [4.2 ; 4.7]	2.9 [2.8 ; 3.2]	3.8 [3.6 ; 3.9]	2.6 [2.4 ; 2.9]
Life years lost	411	345 [324 ; 376]	358 [343 ; 382]	239 [223 ; 259]	306 [297 ; 318]	215 [197 ; 238]
Discounted QALYs (discount rate 1.5%)						
QALY losses due to non-MA episodes	132 [53 ; 286]	128 [51 ; 277]	130 [52 ; 281]	118 [47 ; 260]	127 [51 ; 277]	114 [45 ; 252]
QALY losses due to outpatient episodes	380 [137 ; 828]	365 [132 ; 802]	370 [134 ; 812]	332 [120 ; 737]	359 [129 ; 787]	322 [116 ; 717]
QALY losses due to hospitalisations	84 [72 ; 97]	75 [63 ; 88]	77 [65 ; 90]	50 [42 ; 59]	65 [56 ; 76]	44 [37 ; 53]
QALY losses due to ICU admission	4.2 [3.6 ; 4.8]	3.3 [2.7 ; 3.9]	3.4 [2.9 ; 4.0]	1.9 [1.6 ; 2.3]	2.6 [2.2 ; 3.1]	1.7 [1.4 ; 2.1]
QALY losses due to deaths	205	172 [161 ; 187]	178 [170 ; 190]	118 [111 ; 128]	152 [147 ; 158]	106 [97 ; 118]
Total discounted QALY losses	**805 [471 ; 1,421]**	**743 [410 ; 1,358]**	**758 [424 ; 1,377]**	**620 [322 ; 1,186]**	**706 [385 ; 1,301]**	**588 [296 ; 1,142]**
Discounted cost (€'000) (discount rate 3%)						
Direct cost due to non-MA episodes	170 [70 ; 372]	165 [68 ; 362]	167 [69 ; 366]	152 [61 ; 337]	164 [67 ; 360]	147 [58 ; 326]
Direct cost due to outpatient episodes	6,031 [2,130 ; 13,370]	5,772 [2,046 ; 12,887]	5,859 [2,071 ; 13,089]	5,169 [1,840 ; 11,519]	5,657 [2,001 ; 12,577]	4,986 [1,781 ; 11,123]
Direct cost due to hospitalisations	29,888 [29,725 ; 30,065]	26,380 [24,237 ; 28,448]	27,013 [25,507 ; 28,613]	17,263 [16,105 ; 18,772]	22,786 [22,102 ; 23,625]	15,213 [13,854 ; 16,951]
Direct cost due to ICU admissions	6,251 [6,001 ; 6,502]	4,921 [4,479 ; 5,557]	5,113 [4,740 ; 5,654]	2,955 [2,620 ; 3,370]	3,962 [3,702 ; 4,274]	2,643 [2,286 ; 3,092]
Total discounted treatment cost	42,340 [37,926 ; 50,309]	37,238 [30,830 ; 47,254]	38,152 [32,387 ; 47,722]	25,539 [20,626 ; 33,998]	32,569 [27,872 ; 40,836]	22,989 [17,979 ; 31,492]
Intervention costs (list price*)	0	8,086	4,717	76,057	38,028	76,057

** The cost of the intervention includes the cost per dose of the product (valued at list price), excluding delivery costs. QALY: quality-adjusted life-year, non-MA: non-medically attended, ICU: intensive care unit, CrI: credible interval, MV: year-round maternal vaccine, MV: Sep-Mar: seasonal maternal vaccine from September to March, mAb: year-round nirsevimab, mAb: Oct-Mar: seasonal mAb strategy from October to March, mAb: Oct-Mar + catch-up: seasonal mAb combined with a catch-up strategy.*

Table 51 – Disease and economic burden averted in children <5 years compared to 'no intervention' from the HCP perspective (Mean [95%CrI])

	MV	MV: Sep-Mar	mAb	mAb: Oct-Mar	mAb: Oct-Mar + catch-up
Coverage	*40%*	*40%*	*90%*	*90%*	*90%*
Undiscounted cases averted					
Non-MA episodes	1,069 [321 ; 2,267]	621 [194 ; 1,297]	4,039 [2,009 ; 7,713]	1,452 [770 ; 2,692]	5,222 [2,583 ; 10,125]
Outpatient episodes	2,439 [678 ; 5,578]	1,620 [450 ; 3,688]	8,127 [2,950 ; 16,666]	3,528 [1,220 ; 7,491]	9,845 [3,554 ; 20,302]
Hospitalisations (non-ICU)	971 [412 ; 1,567]	796 [359 ; 1,196]	3,494 [3,085 ; 3,812]	1,966 [1,735 ; 2,144]	4,062 [3,586 ; 4,431]
ICU admissions	93 [51 ; 119]	80 [45 ; 99]	230 [203 ; 251]	160 [141 ; 175]	252 [223 ; 275]
Total cases averted	4,572 [1,941 ; 8,904]	3,116 [1,423 ; 5,776]	15,890 [8,883 ; 28,088]	7,106 [4,191 ; 12,473]	19,381 [10,703 ; 34,815]
Deaths	0.8 [0.4 ; 1.1]	0.7 [0.4 ; 0.8]	2.1 [1.9 ; 2.3]	1.3 [1.1 ; 1.4]	2.4 [2.1 ; 2.6]
Life-years lost	66 [36 ; 88]	53 [30 ; 68]	173 [152 ; 188]	105 [93 ; 115]	197 [174 ; 214]
Discounted QALYs gained (rate 1.5%)					
QALYs gained due to non-MA episodes	3.6 [1.0 ; 7.7]	2.1 [0.6 ; 4.5]	13.5 [6.4 ; 26.4]	4.9 [2.4 ; 9.4]	17.5 [8.3 ; 34.4]
QALYs gained due to outpatient episodes	14.4 [3.9 ; 33]	9.6 [2.6 ; 22]	47.9 [17.3 ; 101]	20.8 [7.2 ; 45]	58.0 [20.8 ; 124]
QALYs gained due to hospitalisations	9.6 [4.0 ; 16]	7.8 [3.6 ; 12]	34.4 [28.2 ; 40]	19.3 [15.9 ; 23]	39.9 [32.8 ; 47]
QALYs gained due to ICU admission	0.9 [0.5 ; 1.2]	0.8 [0.4 ; 1.0]	2.3 [1.9 ; 2.7]	1.6 [1.3 ; 1.9]	2.5 [2.0 ; 2.9]
QALYs gained due to deaths	33 [18 ; 44]	27 [15 ; 34]	86 [76 ; 94]	53 [46 ; 57]	98 [87 ; 107]
Total discounted QALYs gained	61 [40 ; 88]	47 [31 ; 65]	184 [145 ; 248]	99 [81 ; 127]	216 [168 ; 296]
Discounted treatment costs saved (€ '000) (rate 3%)					
Direct cost saved due to non-MA episodes	4.7 [1.4 ; 10.0]	2.8 [0.9 ; 5.8]	17.9 [8.9 ; 34.2]	6.4 [3.4 ; 11.9]	23.1 [11.4 ; 44.9]
Direct cost saved due to outpatient episodes	259 [71 ; 620]	172 [49 ; 409]	862 [317 ; 1,893]	374 [132 ; 843]	1,045 [385 ; 2,315]
Direct cost saved due to hospitalisations	3,508 [1,488 ; 5,653]	2,875 [1,298 ; 4,329]	12,625 [11,138 ; 13,759]	7,102 [6,265 ; 7,739]	14,675 [12,946 ; 15,992]
Direct cost saved due to ICU admissions	1,330 [730 ; 1,701]	1,139 [652 ; 1,421]	3,296 [2,912 ; 3,641]	2,289 [2,022 ; 2,528]	3,609 [3,189 ; 3,986]
Total treatment cost averted	5,102 [2,986 ; 7,271]	4,189 [2,547 ; 5,683]	16,802 [14,792 ; 18,466]	9,772 [8,638 ; 10,689]	19,351 [17,013 ; 21,315]
Intervention and incremental costs (€ '000)					
Intervention costs (list price*)	8,086	4,717	76,057	38,028	76,057
Incremental costs	2,984 [815; 5,5100]	528 [-996 ; 2,572]	59,255 [57,591 ; 61,264]	28,257 [27,339 ; 29,390]	56,706 [54,742 ; 59,044]

*Negative incremental costs indicate savings. * The cost of the intervention includes the cost per dose of the product (valued at list price), excluding delivery costs. CrI: credible interval, QALY: quality-adjusted life year, non-MA: non-medically attended, ICU: intensive care unit, MV: year-round maternal vaccine, MV: Sep-Mar: seasonal maternal vaccine from September to March, mAb: year-round nirsevimab, mAb: Oct-Mar: seasonal mAb strategy from October to March, mAb: Oct-Mar + catch-up: seasonal mAb combined with a catch-up strategy.*

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4.3.3 Cost-effectiveness of RSV immunisation strategies

4.3.3.1 Cost-effectiveness of each strategy versus standard of care

The incremental cost-effectiveness ratios (ICERs) of each RSV immunisation strategy compared to the 'no intervention' are presented in Table 52. When we applied the currently available list prices for both interventions, the seasonal MV strategy was considered cost-effective at a WTP threshold of €11,276 per QALY gained, and the MV year-round strategy had an ICER below €50,000 per QALY gained. In contrast, all mAb strategies had ICERs exceeding €250,000 per QALY gained when compared to standard of care only. Given that these estimates are made without accounting for the costs of distribution and delivery of the doses, it seems safe to state that, apart from seasonal MV (depending on the WTP), none of the strategies would be considered cost-effective when the purchase of the immunising products is costed at current list prices.

Given this observation, using a lower price for nirsevimab in our cost-effectiveness analysis is needed, because nirsevimab is currently temporarily reimbursed under a managed entry agreement, with confidential price discounts already negotiated at the federal level. Excluding these discounts would not accurately reflect the current pricing situation. Moreover, both prices of Abrysvo and nirsevimab will still need to be further negotiated to secure structural reimbursement at either the federal or federated level (e.g., through tenders in Flanders). Therefore, our scenario analyses were conducted using a range of intervention costs, with a large part of these analyses investigating the results under assumed cost parity at €200 per dose for both interventions. These costs should be interpreted to include the costs for purchase, distribution and delivery. At a cost parity of €200 per dose, the seasonal mAb and the seasonal mAb plus catch-up strategies yielded ICERs of €96 and €978 per QALY gained, respectively when compared to 'no intervention'.

Table 52 – Expected incremental cost-effectiveness ratios of each strategy compared to 'no intervention' from the HCP perspective (Mean [95%CrI])

	MV	MV: Sep-Mar	mAb	mAb: Oct-Mar	mAb: Oct-Mar + catch-up
Total discounted QALYs gained	61.40 [39.77 ; 87.51]	46.86 [30.84 ; 64.61]	184.24 [144.82 ; 247.86]	99.08 [80.79 ; 126.91]	216.08 [167.96 ; 296.14]
Total discounted treatment cost averted (€'000)	5,102 [2,986 ; 7,271]	4,189 [2,548 ; 5,683]	16,802 [14,792 ; 18,466]	9,772 [8,638 ; 10,689]	19,351 [170,013 ; 21,315]
Base case: using list prices					
Intervention costs at list price (€'000)	8,086	4,717	76,057	38,028	76,057
Incremental costs (€'000)	2,984 [815; 5,100]	528 [-966; 2,170]	59,255 [57,591 ; 61,264]	28,257 [27,339; 29,390]	56,706 [54,742; 59,044]
ICER per QALY gained	48,607	11,276	321,614	285,190	262,422
Cost parity scenario: €200 per dose for both interventions including delivery costs					
Intervention costs (€'000)	8,694	5,072	19,562	9,781	19,562
Incremental costs (€'000)	3,593 [1,423 ; 5,708]	883 [-611 ; 2,524]	2,760 [1096 ; 4,770]	9 [-908 ; 1,143]	211 [-1,752 ; 2,549]
ICER / QALY gained versus no intervention	58,513	18,846	14,982	96	978

Negative incremental costs indicate savings, QALY: quality adjusted life-year, CrI: credible interval, ICER: incremental cost-effectiveness ratio, MV: year-round maternal vaccine, MV: Sep-Mar: seasonal maternal vaccine from September to March, mAb: year-round nirsevimab, mAb: Oct-Mar: seasonal mAb strategy from October to March, mAb: Oct-Mar + catch-up: seasonal mAb combined with a catch-up strategy.

4.3.3.2 Incremental cost-effectiveness plane: full incremental analysis

A full incremental cost-effectiveness analysis was conducted, comparing all five RSV immunisation strategies to 'no intervention' and to each other. A cost-effectiveness frontier was constructed to identify the most efficient RSV immunisation strategies in terms of health outcomes and costs. This approach involves ranking all strategies by increasing incremental cost and then comparing their ICERs. Strategies that are either dominated or extendedly dominated were excluded from the frontier.

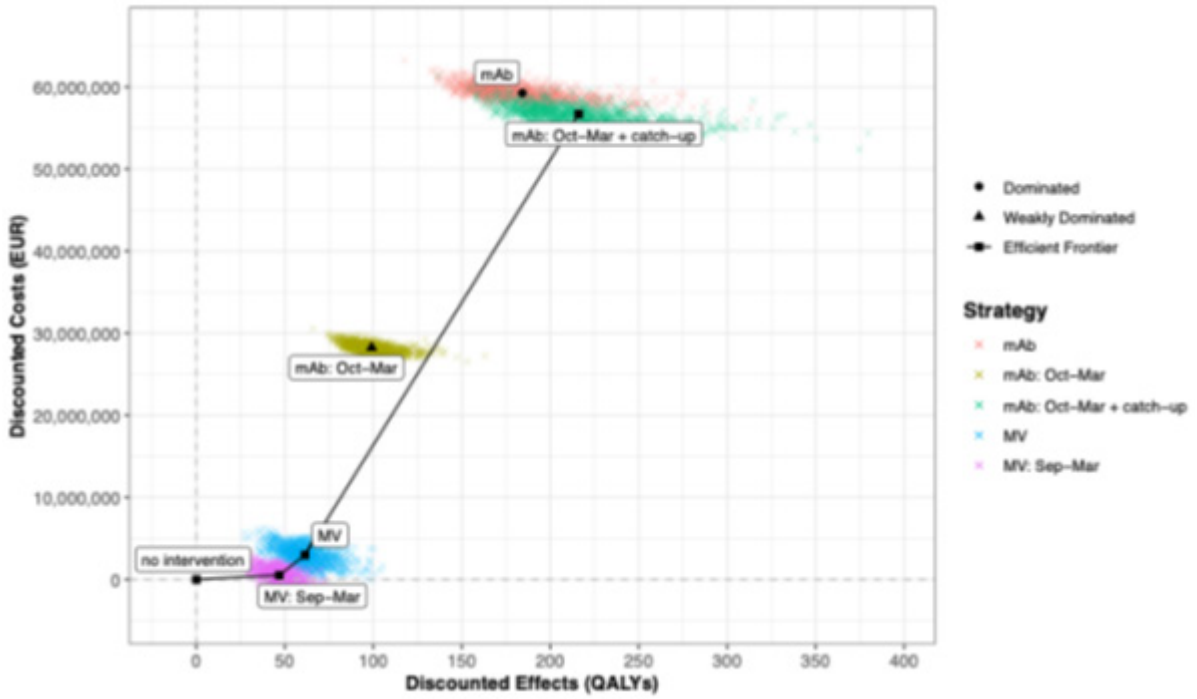
A cost-effectiveness plane is presented in Figure 36 to illustrate the results of PSA (N=1,000). The percentages of ICER iterations falling into each quadrant of the cost-effectiveness plane are provided in Table 53. In the base case analysis using list prices, 71.7% of iterations for the ICER of the seasonal MV strategy fell within the north-east quadrant (more effective and more costly) and 28.3% within the south-east quadrant (more effective and less costly) (Table 53). Furthermore, 99.9% of iterations for the year-round MV strategy fell within the north-east quadrant, with only 0.1% in the south-east. All mAb strategies show 100% of iterations in the north-east quadrant. Assuming cost-parity, as expected the west-east division remains unchanged. Still no iterations fell into the south-west or north-west quadrants, but proportionately more ICERs were situated in the south-east quadrant. Specifically, the seasonal and year-round MV strategies had 83.5% and 100% of iterations in the north-east quadrant, respectively, with the remainder in the south-east. Among the mAb strategies, 48.9% of iterations for the seasonal strategy, 99.9% for the year-round, and 56.8% for the seasonal plus catch-up strategy fell within the north-east quadrant.

As illustrated in the cost-effectiveness plane (Figure 36), when using list prices, the seasonal MV, year-round MV, and seasonal plus catch-up mAb strategies lay on the cost-effectiveness frontier. In the cost parity scenario, where both interventions were assumed to cost €200 per dose (including delivery cost), the mAb seasonal and mAb seasonal plus catch-up strategies formed the new cost-effectiveness frontier, indicating a shift in efficiency under equal intervention cost conditions.

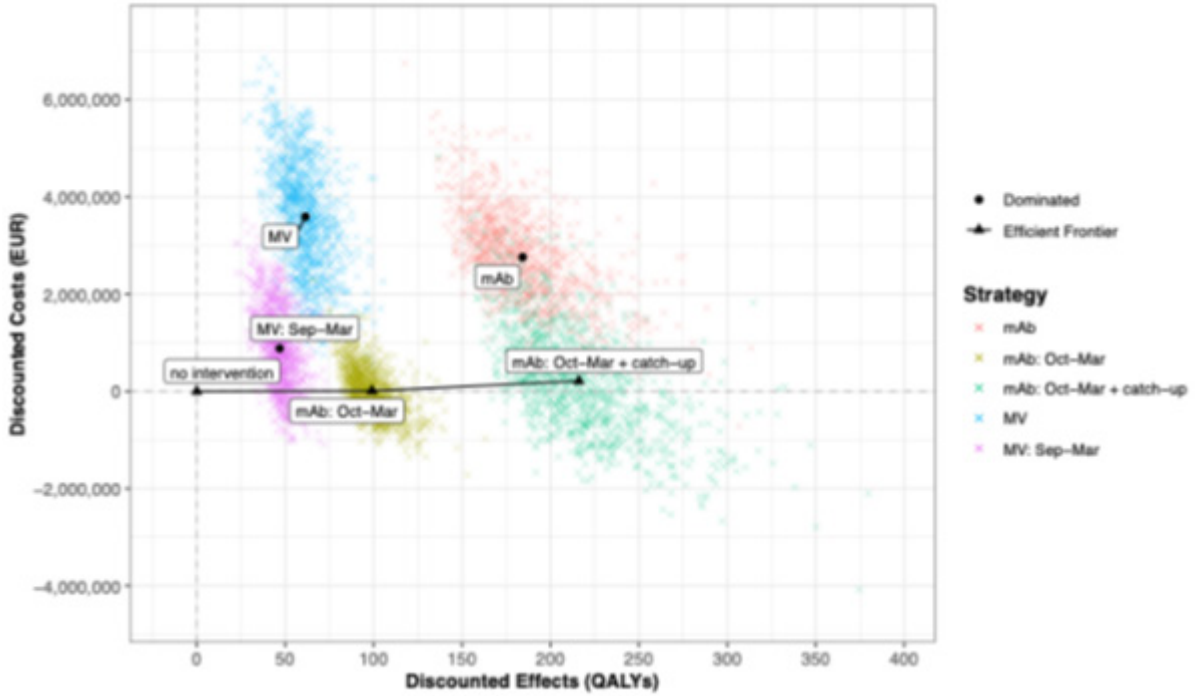
The ICERs of the full incremental analysis, excluding dominated strategies, are reported in Table 54. In the base case analysis using list prices, the estimated ICER for the seasonal MV strategy compared to 'no intervention' was €11,276 per QALY gained, consistent with the value reported in Table 52. The ICER for the year-round MV strategy, when compared to the seasonal MV strategy, was €168,938 per QALY gained. Among all evaluated strategies, the seasonal mAb plus catch-up approach yielded the highest ICER, at €347,290 per QALY gained versus year-round MV. In the cost-parity scenario (Table 54), only the seasonal mAb and seasonal plus catch-up mAb strategies remained on the cost-effectiveness frontier (Figure 36). Both seasonal mAb the seasonal plus catch-up mAb strategies showed substantially lower ICER compared to the base case analysis, because of the assumed considerable reduction in cost per dose (proportionately much larger reductions for mAb). When compared to 'no intervention', the ICER for the seasonal mAb strategy was €96 per QALY gained, consistent with the value reported in Table 52. The mAb seasonal plus catch-up strategy had an ICER of €1,725 per QALY gained when compared to the seasonal mAb strategy.

Figure 36 – The cost-effectiveness plane from the HCP perspective

Base case: list prices (MV: €186.01 and mAb: €777.58)



Scenario: cost parity (€200 per dose including delivery cost)



QALY: quality-adjusted life year, EUR: euro. HCP: health care payers', MV: year-round maternal vaccine, MV: Sep-Mar: seasonal maternal vaccine from September to March, mAb: year-round nirsevimab, mAb: Oct-Mar: seasonal mAb strategy from October to March, mAb: Oct-Mar + catch-up: seasonal mAb combined with a catch-up strategy.

Table 53 – Percentage of incremental cost-effectiveness ratio (ICER) iterations by cost-effectiveness plane quadrant (HCP perspective, versus the next best alternative)

Strategies	Base case: list prices				Scenario: cost parity			
	north-east	south-east	south-west	north-west	north-east	south-east	south-west	north-west
MV	99.9%	0.1%	0%	0%	100%	0%	0%	0%
MV: Sep-Mar	71.7%	28.3%	0%	0%	83.5%	16.5%	0%	0%
mAb	100%	0%	0%	0%	99.1%	0.1%	0%	0%
mAb: Oct-Mar	100%	0%	0%	0%	48.9%	51.1%	0%	0%
mAb: Oct-Mar + catch-up	100%	0%	0%	0%	56.8%	43.2%	0%	0%

HCP: health care payers, MV: maternal vaccine, MV: Sep-Mar: seasonal maternal vaccine from September to March, mAb: year-round nirsevimab, mAb: Oct-Mar: seasonal mAb strategy from October to March, mAb: Oct-Mar + catch-up: seasonal mAb combined with a catch-up strategy.

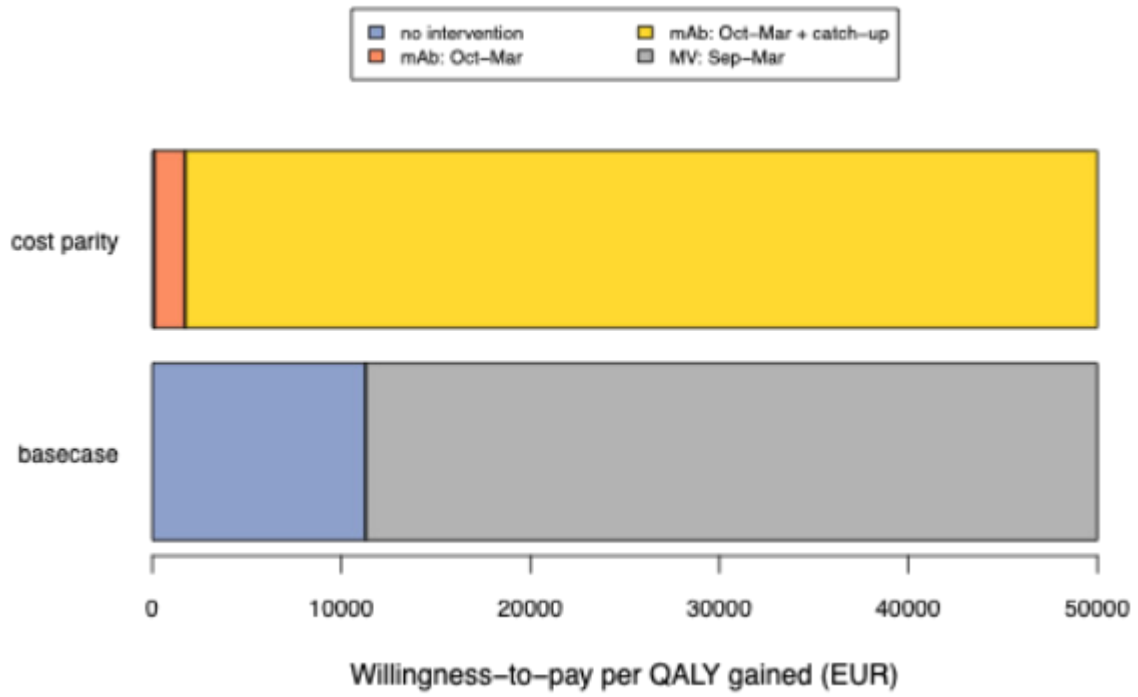
Table 54 – Expected incremental cost-effectiveness ratios of the full incremental analysis (HCP perspective, versus the next best alternative)

Strategies	Strategies compared to	Incremental cost ('000)	Incremental QALY	ICER per QALY gained
Base case: list prices				
MV: Sep-Mar	'no intervention'	528 [-966 ; 2,170]	46.86 [30.84 ; 64.61]	€ 11,276
MV	MV: Sep-Mar	2,456 [1,758 ; 2,965]	14.54 [8.11 ; 23.29]	€ 168,938
mAb	NA	NA	NA	Extendedly dominated
mAb: Oct-Mar	NA	NA	NA	Dominated
mAb: Oct-Mar + catch-up	MV	53,721 [50,694 ; 56,695]	154.69 [111.38 ; 222.01]	€ 347,290
Scenario: cost-parity				
MV: Sep-Mar	NA	NA	NA	Extendedly dominated
MV	NA	NA	NA	Extendedly dominated
mAb	NA	NA	NA	Extendedly dominated
mAb: Oct-Mar	'no intervention'	9 [-908; 1,143]	99.08 [80.79 ; 126.91]	€96
mAb: Oct-Mar + catch-up	mAb: Oct-Mar	202 [-1,752; 2,549]	117.00 [86.15 ; 169.22]	€ 1,725

HCP: health care payers, QALY: quality adjusted life-year, ICER: incremental cost-effectiveness ratio, MV: year-round maternal vaccine, MV: Sep-Mar: seasonal maternal vaccine from September to March, mAb: year-round nirsevimab, mAb: Oct-Mar: seasonal mAb strategy from October to March, mAb: Oct-Mar + catch-up: seasonal mAb combined with a catch-up strategy.

Since Belgium has no official WTP threshold value, Figure 37 presents the cost-effectiveness of the RSV immunisation strategies across a WTP threshold range of €0-50,000 per QALY gained, from the HCP perspective. In the base case analysis using list prices for immunisation costs per dose, 'no intervention' was considered cost-effective at a WTP threshold below €11,276 per QALY gained. At a WTP threshold between €11,276 to €50,000 per QALY, the seasonal MV strategy became the optimal strategy. Note that the public list prices are used here to approximate full immunisation costs per dose. In the scenario analysis assuming cost parity, where both interventions cost €200 per dose (also implicitly assumed to include distribution and delivery costs), the seasonal mAb strategy was considered cost-effective at a WTP threshold below €96 per QALY gained and the seasonal plus catch-up mAb strategy became cost-effective when the WTP exceeded €1,725 per QALY gained. These findings are consistent with the results presented in Table 52, Table 54 and Figure 36.

Figure 37 – Cost-effectiveness analysis from the HCP perspective over a range of WTP threshold values



WTP: willingness-to-pay, HCP: health care payers', EUR: euro, QALY: quality-adjusted life-year. MV: Sep-Mar: seasonal maternal vaccine from September to March, mAb: Oct-Mar: seasonal nirsevimab strategy from October to March, mAb: Oct-Mar + catch-up: seasonal mAb combined with a catch-up strategy.

4.3.3.3 Cost-effectiveness acceptability curves (CEACs) and expected net loss curves (ENLCs)

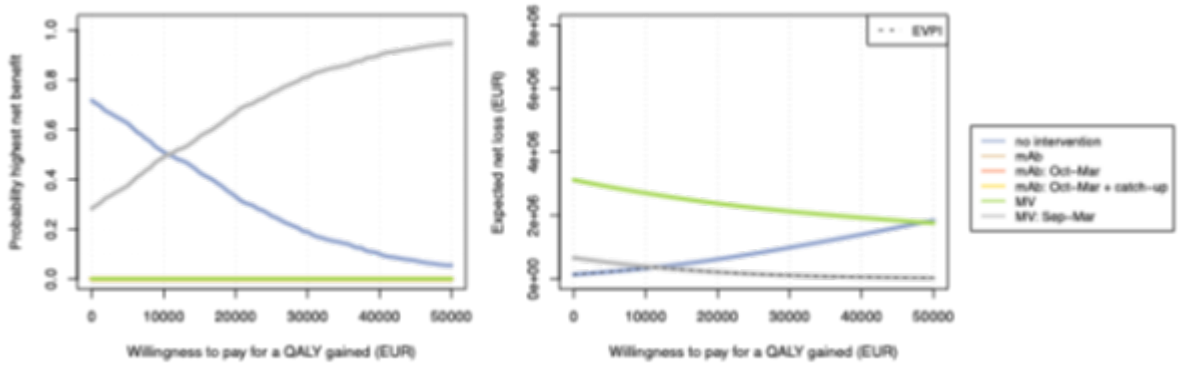
In addition to the cost-effectiveness plane, the ENLCs (Figure 38, right) identify the cost-effective strategy over a range of WTP values per QALY, showing the strategy with the lowest expected net loss. CEACs (Figure 38, left) display the probability of each strategy being cost-effective across WTP values. In the base case analysis using list prices, the 'no intervention' strategy was cost-effective with 70% probability at a WTP of €0 per QALY gained, and this probability declined as the WTP increased. At a WTP threshold of ~€11,000 per QALY, the seasonal MV strategy became the preferred option with a 50% probability, increasing with higher WTP values. All other strategies had a 0% probability. In the cost parity scenario, 'no intervention' was the most cost-effective option at WTP value of €0 per QALY gained with 40% probability, but this probability decreased rapidly with increasing WTP. At a WTP threshold of €2,500 per QALY gained, the seasonal plus catch-up mAb strategy was the most cost-effective strategy with ~50% probability. This probability increased further for all higher levels of WTP considered, exceeding 98% around a WTP of €20,000 per QALY. These findings are consistent with those demonstrated in Figure 36 and Figure 37.

In the right-side panel of Figure 38, the curves show the expected net loss (i.e., the expected cost of uncertainty) for each strategy. In the base case analysis (Figure 38 top panel, right plot), the ENL was the highest for the year-round MV strategy within the range of WTP values from €0 to €49,000 per QALY gained. The seasonal MV strategy showed a higher ENL than the 'no intervention' strategy at WTP values between €0 and ~€11,000 per QALY gained. However, once the WTP exceeded ~€11,000, the ENL for the seasonal MV strategy became the lowest, indicating it as the optimal choice within the WTP range of ~€11,000 to ~€50,000 per QALY gained. This finding is consistent with the results presented in Figure 36, Table 54, and Figure 37.

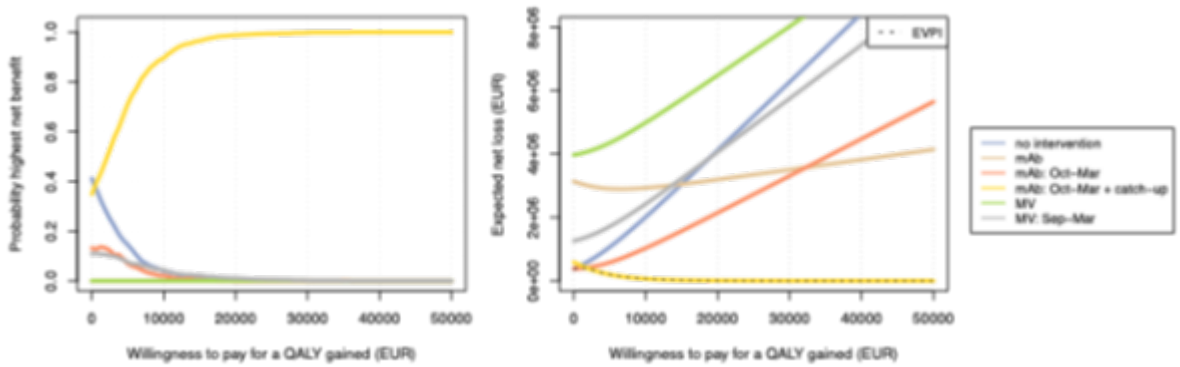
In the cost parity scenario, the ENL was generally highest for both the MV and mAb year-round strategies. The mAb year-round strategy had higher ENL than the seasonal mAb strategy below a WTP of ~€32,000 per QALY, where this relationship switches around (Figure 38). The ENL curve of seasonal mAb strategy was lowest when WTP values were below ~€1,000 per QALY gained. Between the WTP values of approximately ~€2,000 and ~€50,000 per QALY gained, the seasonal plus catch-up mAb strategy had the lowest ENL.

Figure 38 – CEACs (left plots) and ENLCs (right plots) comparing 5 RSV immunisation strategies in children from the HCP perspective

Base case: list price costs (MV: €186.01 and mAb: €777.58 assumed to include delivery costs)



Scenario: cost parity (€200 per dose, assumed to include delivery cost)



CEAC: cost-effectiveness acceptability curve, ENLC: expected net loss curve, MV: year-round maternal vaccine, MV: Sept-Mar: seasonal maternal vaccine from September to March, mAb: year-round nirsevimab, mAb: Oct-Mar: seasonal mAb strategy from October to March, mAb: Oct-Mar + catch-up: seasonal mAb combined with a catch-up strategy.

4.3.3.4 Two-way threshold analysis of interventions' cost

We varied the all-inclusive costs of the interventions per dose (including purchase, distribution and administration/delivery) and presented the results in Figure 39 from the HCP's perspective. For the MV, costs were sampled uniformly within a range of €50 to €250 per dose as indicated on the Y-axis, while for the mAb, the range was €50 to €850 per dose on the X-axis. Each colour represents a predefined RSV strategy. The largest uncertainty occurs at the boundaries between colours, where the preferred strategy changes.

At an arbitrary WTP threshold of €35,000 per QALY gained (Figure 39 middle plot),

- If both interventions are costly (i.e. MV >€240 and mAb >€280 per dose), 'no intervention' would be cost-effective.
- If mAb cost <€210 per dose, the seasonal plus catch-up mAb strategy would be the preferred choice, regardless of the cost of MV.
- If MV is relatively cheap (i.e., <€75 per dose) and mAb relatively expensive (>€220 per dose), then the year-round MV strategy can be the preferred choice.
- If MV cost <€230 per dose and mAb cost between €220-850 per dose, then seasonal MV is the preferred choice.
- The seasonal mAb strategy was not preferred, because the seasonal mAb is less costly but also less effective than the seasonal mAb plus catch-up strategy. At the WTP above €20,000 per QALY gained, the seasonal mAb plus catch-up strategy was optimal due higher QALY gained. The seasonal mAb strategy could be the preferred strategy only over a narrow mAb cost per dose range and given a WTP value of €0 per QALY gained. More specifically, if policy makers are not willing to pay anything to gain QALYs in the population then the seasonal mAb strategy without catch-up could be preferred, if the costs for mAb are around ~€200 per dose and for MV >€160 per dose.
- The year-round mAb strategy was never the optimal strategy because it was dominated by the seasonal plus catch-up mAb strategy (hence it does not show up in these figures)

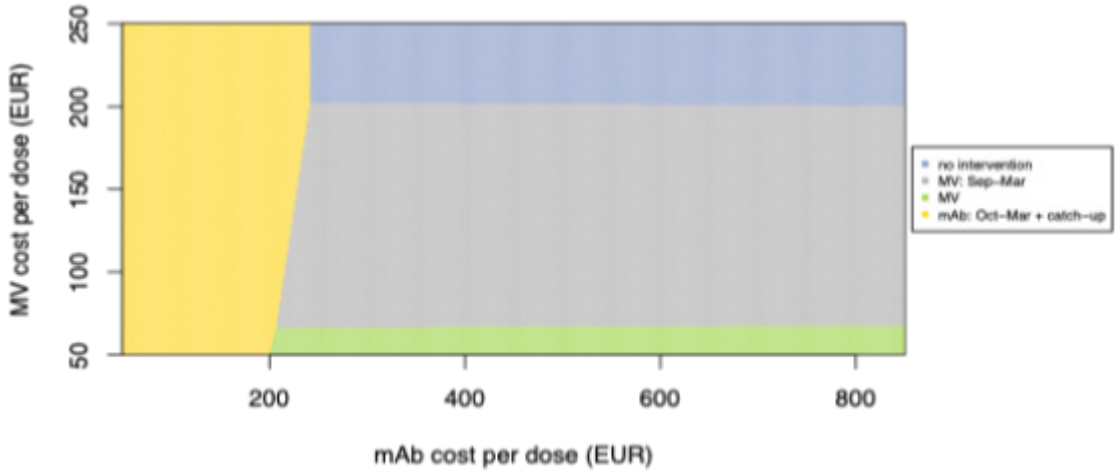
When applying a lower WTP threshold of €20,000 per QALY gained (Figure 39 top plot), the findings were similar to those observed at a WTP of €35,000. However, the colour pattern shifted left and downwards, indicating that with lower WTP, lower intervention costs would be required for a strategy to become the preferred choice. For example, mAb then needs to cost less than €200 per dose for the mAb seasonal plus catch-up strategy to be the preferred choice, regardless of the cost of MV. The MV year-round strategy was the preferred option when the intervention cost was reduced to €52 per dose.

On the other hand, at a higher WTP threshold of €50,000 per QALY gained (Figure 39 bottom plot), the colour pattern shifted right and upwards, suggesting that the interventions could cost more while still remaining preferred over 'no intervention'. When the cost of MV >€255 and mAb >€305, 'no intervention' would be cost-effective, although this region is not shown in the figure.

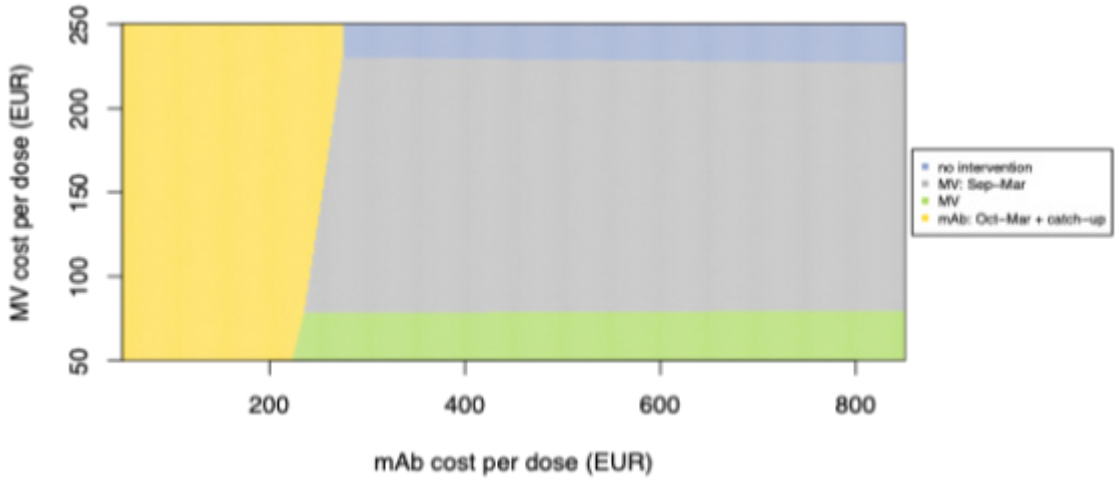
Notably, uncertainty is highest at the boundaries where the preferred strategy changes.

Figure 39 – Intervention cost threshold analysis from HCP perspective (cost per dose including delivery cost)

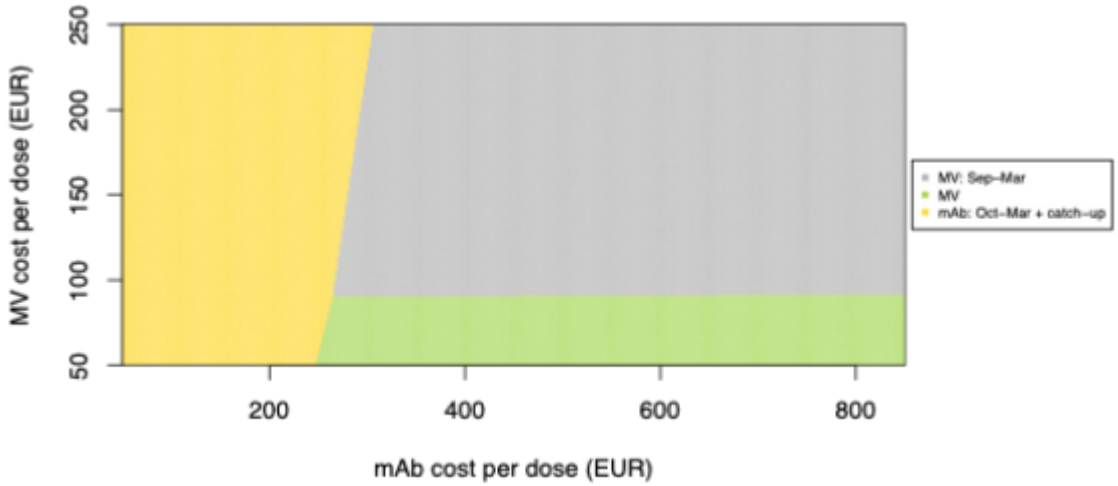
Willingness to pay: €20,000 per QALY gained



Willingness to pay: €35,000 per QALY gained



Willingness to pay: €50,000 per QALY gained



EUR: euro, HCP: health care payers', QALY: quality-adjusted life-year, MV: year-round maternal vaccine, MV: Sept-Mar: seasonal maternal vaccine from September to March, mAb: Oct-Mar: seasonal mAb strategy from October to March, mAb: Oct-Mar + catch-up: seasonal mAb combined with a catch-up strategy.

4.3.3.5 Expected value of partial perfect information

The EVPPI was estimated for each uncertain input parameter across a range of WTP thresholds to identify the parameters contributing most to decision uncertainty. As demonstrated in Figure 40, the higher the EVPPI, the more influential the parameter to which it refers. For this “base case” scenario, aside from the intervention costs, the uncertainties around the efficacies of the interventions and the age-specific outpatient incidence rates were the most influential drivers of decision uncertainty.

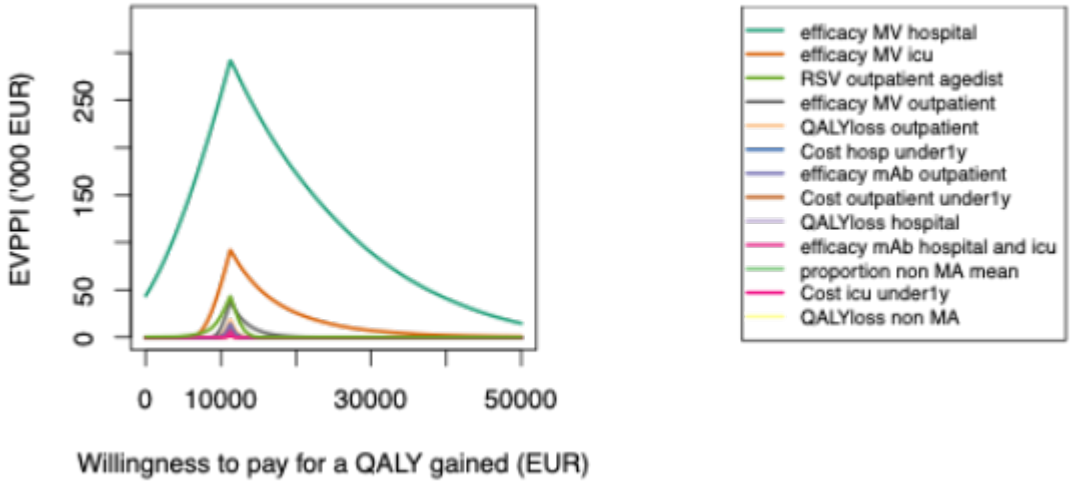
In the base case scenario using list prices, the efficacy of MV against hospitalisation was the most influential driver, with an EVPPI value of €0.3 million. The MV efficacies against ICU admission and the RSV outpatient incidence rate were ranked as the second and third most influential drivers, respectively. However, their influence was significantly lower, each with an EVPPI value of less than €0.1 million. A peak was observed in the EVPPI plot at a WTP value of approximately €11,000 per QALY gained. This corresponds to the WTP threshold at which the preferred strategy shifted from ‘no intervention’ to the seasonal MV strategy. This peak highlighted that decision uncertainty peaks around WTP values marking switches between preferred strategies.

In the scenario using cost parity, the most influential driver was the efficacy of mAb against both hospitalisation and ICU admission, for which equal efficacy was assumed. This assumption was based on pooled estimates from phase 3 RCTs of nirsevimab. The second most influential driver was the RSV outpatient incidence rate. The uncertainties around the outpatient and hospitalisation costs were the third to fourth most influential drivers, respectively. However, the impact of the uncertainty around these parameters was considerably lower than that of the mAb efficacies against hospital and ICU admissions and the RSV outpatient incidence. The peak was observed in the EVPPI plot at WTP values of ~€2,000 per QALY gained.

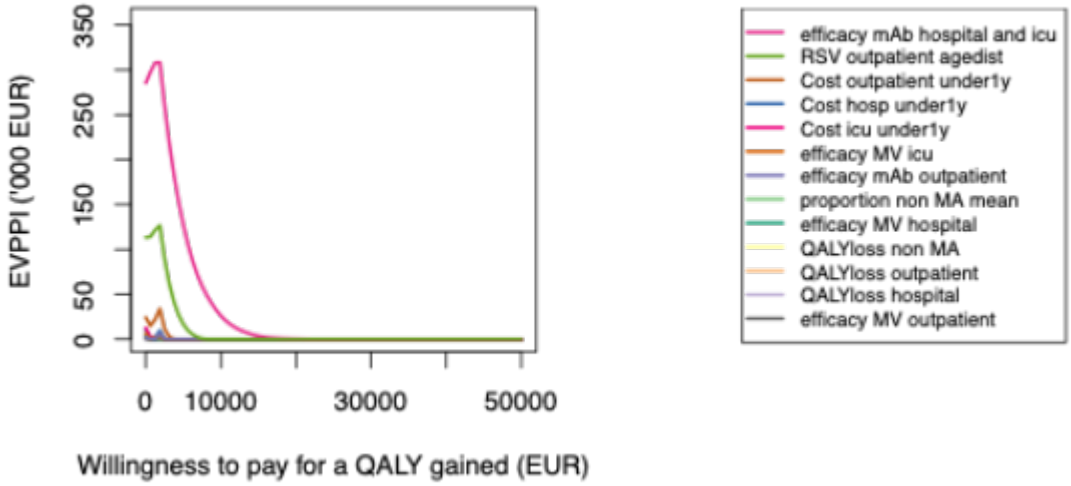
Hence, research that would reduce the uncertainty in our base case analysis the most, would be on estimating the interventions’ efficacies against severe RSV outcomes and RSV outpatient burden. Note that uncertainty around hospitalisation and death was not parameterized within this base case, but was explored in scenario analyses (see below).

Figure 40 – Expected value of partial perfect information

Base case: list prices (MV: €186.01 and mAb: €777.58 assumed to include delivery costs)



Scenario: cost parity (€200 per dose, assumed to include delivery cost)



EUR: euro, QALY: quality-adjusted life-year, EVPPI: expected value of partial perfect information, agedist: combined uncertainty range for age-specific RSV outpatient incidence rate, including age group: 0-2 months, 3-5 months and 6-11 months, MA: medically attendance, MV: maternal vaccine, icu: intensive care unit, mAb: nirsevimab.

4.3.4 Scenario analyses

A list of scenario analyses was described in Methods section 4.2.4 and summarised in Table 55. The results of scenario analyses are presented in Figure 41 and Figure 42. Two-way price threshold analyses of each scenario are presented in Appendix 7.

Table 55 – List of scenario analyses

Label in the graphs	Full name	Comparison of Base Case and Scenario Analyses (Differing from Base Case Assumptions)
Base case	Base case analysis	• Perspective: HCP • Price: list price (no delivery cost) • RSV-coded hospitalisations: both primary and secondary diagnosis codes • TCT data: average 4 seasons: 2016/2017 – 2019/2020 • Age distribution in 1-11m age group: season 2018/2019 • mAb's efficacy values: pooled phase 3 RCT data, constant protection over 6 months • Both interventions' efficacies against mortality: assume same as efficacies against hospitalisation (MV) or ICU (mAb) • Both interventions' efficacies against non-MA: assume same as efficacies against outpatient • Inclusion of recurrent wheezing: no • QALY losses: children only
Cost parity	SA: cost parity	• Cost: €200 per dose for either mAb or MV (including all delivery costs)
Societal perspective	SA: Societal perspective	• Perspective: societal
Hospitalisation data related scenarios		
Average 10 seasons TCT admissions data	SA: using the average of 10 seasons non-ICU and ICU admissions data	• TCT data: average 10 seasons: 2008/2009 - 2013/2014 and 2016/2017 – 2019/2020 (see Figure 28)
ICD primary code only	SA: using only the primary diagnosis code	• RSV-coded hospitalisations: using only the primary diagnosis code to select hospitalisations
S23to24 age primary + secondary codes	SA: using season 2023/2024 age distribution data	• Age distribution in 1-11m age group: season 2023/2024
S23to24 age primary code only	SA: using season 2023/2024 age distribution data and primary diagnosis code	• RSV-coded hospitalisations: using only the primary diagnosis code to select hospitalisations • Age distribution in 1-11m age group: season 2023/2024
Outpatient data related scenarios		
OP incidence: NLD	SA: using the outpatient incidence rate from the Netherlands	• RSV-related primary care incidence: based on Dutch data
OP incidence: pooled (5 countries)	SA: using the pooled outpatient incidence rates	• RSV-related primary care incidence: based on pooled estimates from 5 countries
Interventions' efficacy/effectiveness related scenarios		
Efficacy mAb RWE (6m constant)	SA: effectiveness data of nirsevimab using RWE studies	• mAb's effectiveness values: pooled effectiveness data, constant protection over 6 months, 0% from month 7 onwards
Efficacy mAb wane over 5m	SA: effectiveness data of nirsevimab using a test-negative case-control study	• mAb's effectiveness values: wane over 5 months, 0% from month 6 onwards

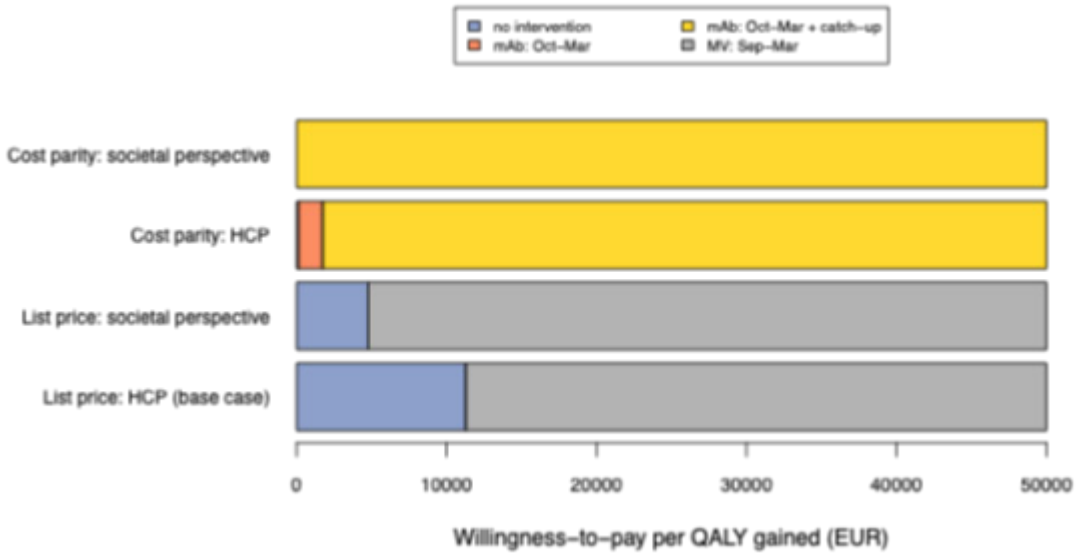
No efficacy against death	SA: no protection against RSV mortality	• Both interventions' efficacies against mortality: assume no protection against RSV mortality
No efficacy against nonMA	SA: no protection against RSV non-MA episode	• Both interventions' efficacies against non-MA: assume no protection against RSV non-MA episode
Asthma wheezing up to 3y	SA: inclusion of recurrent wheezing and asthma up to 3 years	• Inclusion of recurrent wheezing and asthma up to 3 years of age in children who had an RSV hospitalisation before age 1 year
Asthma wheezing up to 13y	SA: inclusion of recurrent wheezing and asthma up to 13 years	• Inclusion of recurrent wheezing and asthma up to 13 years of age in children who had an RSV hospitalisation before age 1 year
Health outcome related scenario		
QALY losses of caregivers	SA: inclusion of parental QALY losses per RSV episode	• Inclusion of parental QALY losses per RSV episode in addition to the children's QALY losses

SA: scenario analysis, HCP: health care payers', QALY: quality adjusted life-year, y: year, m: month, ICD: international classification of diseases, mAb: nirsevimab, non-MA: non-medically attended, OP: outpatient, RWE: real-world evidence, S: season, NLD: the Netherlands.

4.3.4.1 Cost-effectiveness from the societal perspective

Figure 41 presents the cost-effectiveness of the RSV immunisation strategies from the societal perspective, in comparison to the HCP perspective illustrated in the bottom and the third bar from the bottom (same as in Figure 37). In the base case analysis using list prices, the seasonal MV strategy became preferred at a lower WTP value from the societal perspective versus the HCP perspective, due to the averted costs of productivity losses. In the scenario analysis using a cost parity of €200 per dose (including delivery costs), the mAb seasonal plus catch-up strategy was found to be cost-saving from the societal perspective.

Figure 41 – Scenario analyses related to the societal perspective



EUR: euro, HCP: health care payers', QALY: quality-adjusted life-year, MV: Sept-Mar: seasonal maternal vaccine from September to March, mAb: Oct-Mar: seasonal mAb strategy from October to March, mAb: Oct-Mar + catch-up: seasonal mAb combined with a catch-up strategy.

4.3.4.2 Hospitalisation data-related scenarios

From the HCP perspective, RSV-related hospitalisation data were influential. When hospitalisations were identified using only the primary diagnosis code, the intervention bars in the cost-effectiveness plots (Figure 42) shifted to the right. This indicates that both the seasonal MV strategy (under list prices) and the seasonal mAb without and with catch-up strategies (under cost parity) required higher WTP values to become the optimal strategy.

When using the 10-season average TCT data, the average number of non-ICU and ICU hospital admissions in children under 5 years was lower (N=8300) compared to the base case using the most recent 4 pre-COVID-19 seasons (N=9066), with the difference being more pronounced for ICU admissions in children under 1 year (278 vs. 384 in base case). Therefore, using the 10-season average data in this scenario resulted in the MV strategy requiring higher WTP values (~€17,000 per QALY gained) to become cost-effective under list prices. Under the cost-parity assumption, the seasonal mAb strategy was cost-effective at WTP values above ~€1,000 per QALY gained. The seasonal mAb plus catch-up strategy became the optimal option when the WTP exceeded ~€23,000 per QALY gained. This highlights that the selection of hospitalisation data was an influential driver, which led to substantial impact on the cost-effectiveness results.

As described under methods, the TCT data were grouped for ages 1–11 months, and we used the BELSARI-NET data from the 2018/2019 (pre-COVID-19) season to redistribute the proportion of hospitalisations by age in months for the base case analysis. In the scenario analysis labelled as S23to24 age primary + secondary codes, we used data from the 2023/2024 season to inform this age distribution. When using list prices, the seasonal MV strategy required a higher WTP value to become the optimal strategy. Given cost-parity, the seasonal mAb strategy without catch-up was dominated. 'No intervention' was the optimal strategy at low WTP value (~€5,000), and the seasonal plus catch-up mAb programme became the optimal strategy at higher WTP values compared to base case. This showed that the age distribution of hospitalisations had an important impact on the cost-effectiveness results.

When reducing the assumed attributable hospital burden by combining primary (only) ICD diagnostic codes with the 2023/2024 season BELSARI-NET data for the distribution of children aged 1–11 months (labelled as: S23to24 age primary code only), the 'no intervention' strategy remained cost-effective up to a higher WTP value of ~€17,000 per QALY gained.

4.3.4.3 Inclusion of recurrent wheezing and asthma

Including recurrent wheezing and asthma led to substantial changes in the overall results. When using the list price, incorporating recurrent wheezing and asthma outcomes up to age 3 years and 13 years made the seasonal plus catch-up mAb strategy potentially cost-effective at a WTP value around ~€22,000 and ~€10,000 per QALY gained, respectively. Under the cost parity scenario, including wheezing and asthma up to age 3 years and 13 years made the seasonal plus catch-up mAb strategy cost-saving.

4.3.4.4 RSV-related outpatient incidence rate

In the scenario analysis using the Dutch outpatient incidence rate, the results were comparable to those obtained using the Spanish incidence rate in the base case analysis. When applying the pooled outpatient incidence rate from 5 countries, either the MV seasonal strategy in the base case under the list price scenario or the seasonal mAb and seasonal plus catch-up mAb strategies required higher WTP values to be considered the optimal choice compared to the base case.

4.3.4.5 Efficacy and effectiveness of RSV interventions

When assuming that both interventions did not protect against RSV non-MA episodes, the results were comparable to the base case under both the list price and cost parity scenarios. In contrast, when assuming no efficacy against RSV-related deaths for either intervention, 'no intervention' became the cost-effective option under the list price scenario if the WTP range was below ~€27,000 per QALY gained. Under cost parity, the seasonal plus catch-up mAb strategy required a slightly higher WTP value (~€200, ~€2,000,respectively) to be considered cost-effective.

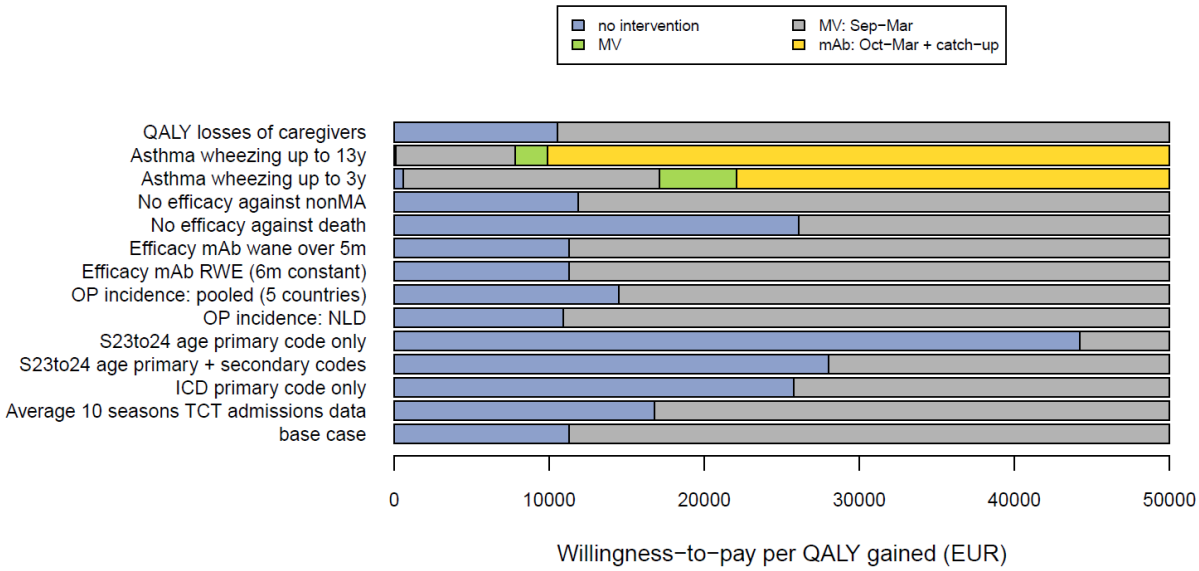
In the base case analysis using the list price, variations in mAb efficacy (6 months constant or waning over 5 months) had no impact on the results at WTP values below €50,000 per QALY gained, as none of the mAb strategies were cost-effective at the list price. However, under cost parity, applying pooled effectiveness data from the RWE studies assuming 6-month protection led to the mAb strategies becoming cost-saving. When waning efficacy was modelled using data from a US study instead of the described stepwise waning function with 5-month protection, the mAb seasonal strategy became cost-effective given a WTP value greater than ~€1,200 per QALY gained. The seasonal mAb plus catch-up strategy required a higher WTP threshold to be preferable over seasonal mAb without catch-up.

4.3.4.6 Inclusion of parental QALY losses

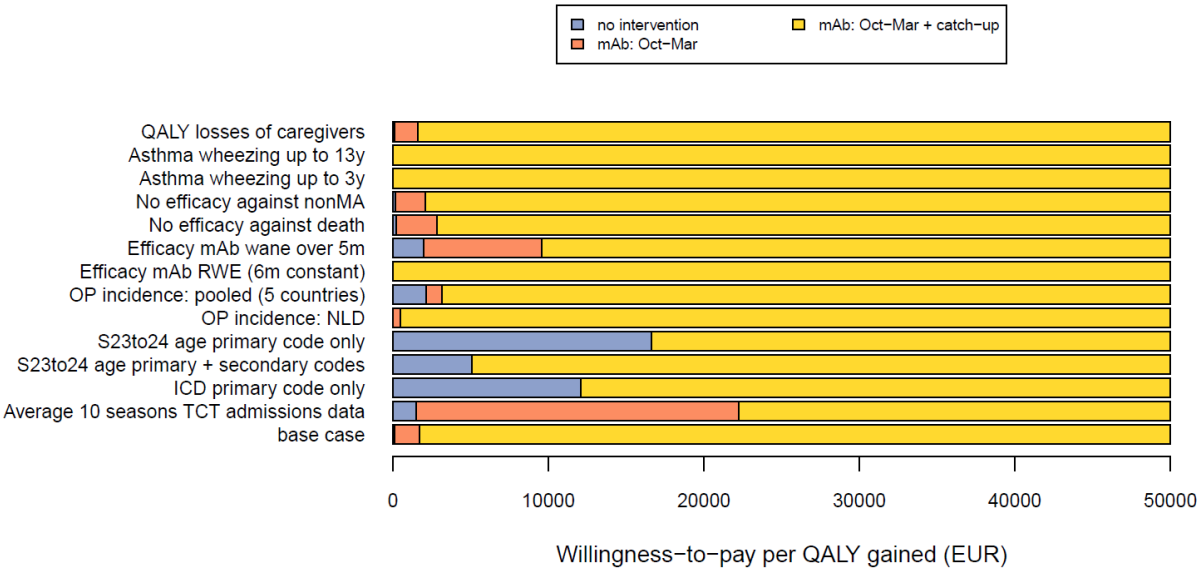
Inclusion of parental QALY losses had limited impact on the overall results, likely due to the small value of QALY losses and because most of the QALY gains came from RSV deaths averted. Note that the implicit assumption in this analysis is that a child's non-fatal disease experience has a temporary impact on the quality of life of the parents, but that a child's death would not have an impact on parental quality of life in excess of the average temporary parental quality of life impact experienced during the average child's non-fatal RSV disease period.

Figure 42 – Scenario analyses from the HCP perspective

Base case: list prices (MV: €186.01 and mAb: €777.58 assumed to include delivery costs)



Scenario: cost parity (€200 per dose, assumed to include delivery cost)



EUR: euro, HCP: health care payers, QALY: quality-adjusted life-year, MV: Sept-Mar: seasonal maternal vaccine from September to March, mAb: Oct-Mar: seasonal mAb strategy from October to March, mAb: Oct-Mar + catch-up: seasonal mAb combined with a catch-up strategy. SA: scenario analysis, QALY: quality adjusted life-year, y: year, m: month, ICD: international classification of diseases, mAb: nirsevimab, non-MA: non-medically attended, RWE: real-world evidence, OP: outpatient, S: season, NLD: the Netherlands.

4.4 Results of the budget impact analysis

A budget impact analysis evaluates the financial feasibility of adopting a new healthcare intervention, focusing on affordability rather than value for money. This analysis estimates the one-year budget impact of introducing an RSV intervention for Belgian children, compared to the current standard of care ('no intervention'). Following Belgian guidelines, only direct costs are considered, with no discounting or inflation adjustments. We also calculated the return on investment (RoI), which relates the net savings from the intervention to its cost. A RoI greater than 1 indicates that the savings exceed the investment and a RoI less than 1 indicates that the intervention costs more than it save to the health care payer.

Results are presented from the overall healthcare payer perspective: Table 56 for MV strategies and Table 57 for mAb strategies. The analysis presents Belgian national data, with demography-driven disaggregation by federated entity (Flanders, Brussels, and Wallonia). The tables depict the impact on the average Belgian health care payers, combining potential impacts on federal (treatment and partial immunisation costs) and federated budgets (partial immunisation costs), depending on how these strategies will be implemented (see section 4.2.2.7 above). Budget holders at the federal and federated level (Flanders, Brussels, and Wallonia) will need to relate these estimates to their budgetary responsibilities to assess the specific impact on the federal and federated budgets.

Under the base case assumptions, the year-round and seasonal MV strategies at 40% coverage were estimated to avoid treatment costs of €5.1 and €4.2 million, respectively (Table 56). However, assuming a cost range of €50 to €250 per dose, the immunisation costs (assumed all-inclusive) for the year-round MV strategy ranged from €2.1 million to €10.9 million, while the costs for the seasonal MV strategy ranged from €1.3 million to €6.3 million in Belgium. The lowest immunisation cost (€50 per dose) resulted in net savings, i.e. the lowest net investment, and, consequently, the highest RoI in direct health care costs (i.e., the ratio of avoided treatment costs to immunisation costs). More specifically, at €50 per dose, for every euro invested in year-round MV, the health care payers would receive €2.4 in return, whereas for seasonal MV they would receive €3.3 in return. At €150 per dose, the health care payers would almost break even, with a 78% return for year-round MV, but would still gain 10% on top of the investment for seasonal MV, given a ROI of 1.10. The seasonal MV strategy yielded a higher, more attractive RoI than the year-round strategy, irrespective of the assumed vaccination costs.

At 90% coverage, the seasonal mAb and the combined seasonal plus catch-up mAb strategies were projected to reduce treatment costs by €9.8 million and €19.4 million, respectively, under base case assumptions (Table 57). Assuming a cost range of €50 to €850 per dose, the immunisation costs (assumed all-inclusive) for the seasonal mAb strategy ranged from €2.4 million to €41.6 million. In comparison, the costs for the seasonal mAb plus catch-up strategy ranged from €4.9 million to €83.1 million in Belgium. The net investment rose substantially with increasing immunisation costs per dose, ranging from net saving to €31.8 million for the seasonal mAb strategy, and from net-saving to €63.8 million for the seasonal mAb plus catch-up strategy. Correspondingly, the RoI declined markedly, from 4.0 to 0.2 for the seasonal mAb strategy and from 4.0 to 0.2 for the seasonal plus catch-up mAb strategy, indicating that the investment became disproportionately large relative to the benefits. Findings across the federated entities of Flanders, Brussels, and Wallonia aligned closely with the national-level results for Belgium. Again, as for MV, the federal and federated budgetary impact assessments will need to be made jointly with the development of implementation strategies. The seasonal mAb strategy consistently showed a greater RoI, and lower net investment, than the seasonal with catch-up mAb strategy, irrespective of immunisation costs per dose.

Table 56 – Treatment costs avoided, immunisation costs, return on investment and direct net benefits per year: MV at 40% coverage versus 'no intervention' from the HCP perspective (Mean [95%CrI])

	Treatment costs avoided ('000 €)		Immunisation costs (assumed all-inclusive*) ('000 €)		Net investment ('000 €)		Return on investment ratio (RoI)	
Cost per dose	MV	MV: Sep-Mar	MV	MV: Sep-Mar	MV	MV: Sep-Mar	MV	MV: Sep-Mar
Belgium (nr of doses)			(43,472)	(25,359)				
€50	5,102 [2,986 ; 7,271]	4,189 [2,547 ; 5,683]	2,174	1,268	-2,928 [-5,097 ; -812]	-2,921 [-4,415 ; -1,280]	2.35	3.30
€100			4,347	2,536	-755 [-2,924 ; 1,361]	-1,653 [-3,147 ; -12]	1.17	1.65
€150			6,521	3,804	1,419 [-750 ; 3,535]	-385 [-1,879 ; 1,256]	0.78	1.10
€200			8,694	5,072	3,593 [1,423 ; 5,709]	883 [-611 ; 2,524]	0.59	0.83
€250			10,868	6,340	5,766 [3,597 ; 7,882]	2,151 [657 ; 3,792]	0.47	0.66
Flanders (nr of doses)			(24,745)	(14,435)				
€50	2,890 [1,686 ; 4,115]	2,374 [1,441 ; 3,214]	1,237	722	-1,652 [-2,878 ; -448]	-1,653 [-2,493 ; -719]	2.34	3.29
€100			2,474	1,444	-415 [-1,640 ; 789]	-931 [-1,771 ; 3]	1.17	1.65
€150			3,712	2,165	822 [-403 ; 2,026]	-209 [-1,049 ; 724]	0.78	1.10
€200			4,949	2,887	2,060 [834 ; 3,263]	512 [-328 ; 1,446]	0.58	0.82
€250			6,186	3,609	3,297 [2,071 ; 4,500]	1,234 [394 ; 2,168]	0.47	0.66
Brussels (nr of doses)			(5,563)	(3,245)				
€50	652 [381 ; 929]	535 [325 ; 726]	278	162	-374 [-650 ; -103]	-373 [-564 ; -163]	2.34	3.30
€100			556	324	-96 [-372 ; 176]	-211 [-402 ; -1]	1.17	1.65
€150			834	487	183 [-94 ; 454]	-48 [-239 ; 162]	0.78	1.10
€200			1,113	649	461 [184 ; 732]	114 [-77 ; 324]	0.59	0.82
€250			1,391	811	739 [462 ; 1,010]	276 [85 ; 486]	0.47	0.66
Wallonia (nr of doses)			(13,164)	(7,679)				
€50	1,548 [906 ; 2,205]	1,270 [774 ; 1,725]	658	384	-890 [-1,547 ; -248]	-887 [-1,341 ; -390]	2.35	3.31
€100			1,316	768	-232 [-889 ; 410]	-503 [-957 ; -6]	1.18	1.65
€150			1,974	1,152	426 [-231 ; 1,069]	-119 [-573 ; 378]	0.78	1.10
€200			2,633	1,536	1,084 [428 ; 1,727]	265 [-189 ; 762]	0.59	0.83
€250			3,291	1,920	1,743 [1,086 ; 2,385]	649 [195 ; 1,146]	0.47	0.66

*HCP: health care payers', MV: year-round single-dose maternal vaccine (MV) during pregnancy, MV: Sep-Mar: seasonal maternal vaccine from September to March, nr: number. * These vaccination costs should cover purchase, stockage, distribution and administration of the listed number of doses. Currently none of these cost items are fully known.*

Table 57 – Treatment costs avoided, immunisation costs, return on investment and direct net benefits per year: mAb at 90% coverage versus 'no intervention' from the HCP perspective (Mean [95%CrI])

	Treatment costs avoided ('000 €)		Immunisation costs (assumed all-inclusive*) ('000 €)		Net investment ('000 €)		Return on investment ratio (RoI)	
Cost per dose	mAb: Oct-Mar	mAb: Oct-Mar + catch-up	mAb: Oct-Mar	mAb: Oct-Mar + catch-up	mAb: Oct-Mar	mAb: Oct-Mar + catch-up	mAb: Oct-Mar	mAb: Oct-Mar + catch-up
Belgium (nr of doses)			(48,906)	(97,812)				
€50	9,772 [8,638 ; 10,689]	19,351 [17,013 ; 21,315]	2,445	4,891	-7,326 [-8,244 ; -6,193]	-14,460 [-16,424 ; -12,122]	4.00	3.96
€150			7,336	14,672	-2,436 [-3,353 ; -1,302]	-4,679 [-6,643 ; -2,341]	1.33	1.32
€250			12,226	24,453	2,455 [1,537 ; 3,588]	5,102 [3,138 ; 7,440]	0.80	0.79
€350			17,117	34,234	7,345 [6,428 ; 8,479]	14,883 [12,919 ; 17,221]	0.57	0.57
€450			22,008	44,015	12,236 [11,318 ; 13,369]	24,664 [22,700 ; 27,002]	0.44	0.44
€550			26,898	53,797	17,127 [16,209 ; 18,260]	34,446 [32,482 ; 36,784]	0.36	0.36
€650			31,789	63,578	22,017 [21,100 ; 23,150]	44,227 [42,263 ; 46,565]	0.31	0.30
€750			36,680	73,359	26,908 [25,990 ; 28,041]	54,008 [52,044 ; 56,346]	0.27	0.26
€850			41,570	83,140	31,798 [30,881 ; 32,932]	63,789 [61,825 ; 66,127]	0.24	0.23
Flanders (nr of doses)			(27,838)	(55,677)				
€50	5,541 [4,897 ; 6,056]	10,956 [9,652 ; 12,043]	1,392	2,784	-4,149 [-4,664 ; -3,505]	-8,172 [-9,259 ; -6,868]	3.98	3.94
€150			4,176	8,352	-1,365 [-1,880 ; -721]	-2,605 [-3,691 ; -1,300]	1.33	1.31
€250			6,960	13,919	1,418 [904 ; 2,063]	2,963 [1,876 ; 4,268]	0.80	0.79
€350			9,743	19,487	4,202 [3,688 ; 4,847]	8,531 [7,444 ; 9,835]	0.57	0.56
€450			12,527	25,054	6,986 [6,471 ; 7,630]	14,098 [13,012 ; 15,403]	0.44	0.44
€550			15,311	30,622	9,770 [9,255 ; 10,414]	19,666 [18,579 ; 20,970]	0.36	0.36
€650			18,095	36,190	12,554 [12,039 ; 13,198]	25,234 [24,147 ; 26,538]	0.31	0.30
€750			20,879	41,758	15,338 [14,823 ; 15,982]	30,801 [29,715 ; 32,106]	0.27	0.26
€850			23,663	47,325	18,121 [17,607 ; 18,766]	36,369 [35,282 ; 37,674]	0.23	0.23
Brussels (nr of doses)			(6,259)	(12,517)				
€50	1,249 [1,104 ; 1,366]	2,472 [2,176 ; 2,720]	313	626	-936 [-1,053 ; -791]	-1,846 [-2,094 ; -1,550]	3.99	3.95
€150			939	1,878	-310 [-427 ; -165]	-595 [-842 ; -298]	1.33	1.32
€250			1,565	3,129	316 [198 ; 461]	657 [409 ; 954]	0.80	0.79
€350			2,190	4,381	942 [824 ; 1,086]	1,909 [1,661 ; 2,206]	0.57	0.56
€450			2,816	5,633	1,567 [1,450 ; 1,712]	3,161 [2,913 ; 3,457]	0.44	0.44
€550			3,442	6,884	2,193 [2,076 ; 2,338]	4,412 [4,164 ; 4,709]	0.36	0.36
€650			4,068	8,136	2,819 [2,702 ; 2,964]	5,664 [5,416 ; 5,961]	0.31	0.30
€750			4,694	9,388	3,445 [3,328 ; 3,590]	6,916 [6,668 ; 7,212]	0.27	0.26
€850			5,320	10,640	4,071 [3,954 ; 4,216]	8,168 [7,920 ; 8,464]	0.23	0.23

Wallonia (nr of doses)			(14,809)	(29,618)				
€50	2,977 [1,797 ; 4,620]	5,908 [3,455 ; 9,177]	740	1,481	-2,223 [-2,504 ; -1,880]	-4,392 [-4,992 ; -3,675]	4.00	3.97
€150			2,221	4,443	-742 [-1,023 ; -399]	-1,430 [-2,030 ; -713]	1.33	1.32
€250			3,702	7,404	738 [458 ; 1,082]	1,532 [932 ; 2,248]	0.80	0.79
€350			5,183	10,366	2,219 [1,939 ; 2,563]	4,493 [3,894 ; 5,210]	0.57	0.57
€450			6,664	13,328	3,700 [3,420 ; 4,044]	7,455 [6,856 ; 8,172]	0.44	0.44
€550			8,145	16,290	5,181 [4,901 ; 5,525]	10,417 [9,818 ; 11,134]	0.36	0.36
€650			9,626	19,252	6,662 [6,382 ; 7,006]	13,379 [12,779 ; 14,096]	0.31	0.31
€750			11,107	22,214	8,143 [7,863 ; 8,486]	16,340 [15,741 ; 17,057]	0.27	0.26
€850			12,588	25,175	9,624 [9,344 ; 9,967]	19,302 [18,703 ; 20,019]	0.24	0.23

*HCP: health care payers', mAb: Oct-Mar: seasonal mAb strategy from October to March, mAb: Oct-Mar + catch-up: seasonal mAb combined with a catch-up strategy, nr: number. * These vaccination costs should cover purchase, stockage, distribution and administration of the listed number of doses. Currently none of these cost items are fully known.*

4.5 Discussion

This analysis estimated the RSV disease burden among Belgian children under five years of age and evaluated the cost-effectiveness and budget impact of various RSV maternal vaccine (MV) and long-acting monoclonal antibody (mAb) programmes administered to infants up to 6 months of age.

Our findings indicated that prior to the 2024-25 season, RSV imposed a substantial annual burden in children under 5 years of age leading to approximately 116 thousand RSV episodes, 8,638 non-ICU hospitalisations, 428 ICU admissions, and 5 deaths annually. The largest part of the severe burden, such as hospital and ICU admission and death, occurred in infants within the first 3 months of life. As a result, RSV led to an annual loss of 968 QALYs, comprising 411 life years lost and approximately €43 million in direct healthcare costs.

Overall, mAb strategies are expected to prevent a greater RSV disease burden than MV strategies. This is not only due to the expectation that coverage of MV would be markedly lower than coverage of mAb in the respective target groups (in our baseline analysis 40% versus 90%, respectively), but also due to mAb's higher overall efficacy and effectiveness over time. Indeed, we also found the mAb strategies to be more effective when we assumed equal coverage levels for mAb and MV. Nonetheless the difference in effectiveness would not be as high as the current difference in list price for these products (mAb: €777.58; MV: €186.01).[131-133] The ratio of prevented hospital admissions for seasonal mAb over seasonal MV would be 2.43:1 assuming the above expected differential coverage and 1.08:1 assuming equal coverage, whereas the ratio of the current list prices per dose is 4.18:1. Furthermore, it is likely that the costs for administration would be greater for mAb than for MV.

In the 2024-2025 season, nirsevimab was administrated in hospital for children born within the RSV seasons, which required an online (age-based) application.[164] For infants born outside the RSV season, the immunisation was not implemented yet in Mother & Child Clinics (K&G and ONE). As demonstrated in our analysis, the seasonal plus catch-up mAb strategy could result in the greatest reduction in disease burden. However, the out-of-season catch-up component presents major implementation challenges. It would need to be administered shortly before the onset of the RSV season, thereby concentrating much of the operational workload in September and October (approximately half of the birth cohort). To ensure successful implementation of the catch-up, a joint effort, along with dedicated funding and resources, will be essential. For MV, experience with maternal pertussis and influenza vaccination in Flanders suggests that gynaecologists are likely to refer patients to a GP with an e-prescription rather than administer the vaccines themselves. This referral process would necessitate additional visits to both the pharmacy and the GP, thereby incurring specific administration costs. Moreover, the MV vaccine has a relatively narrow immunisation window (28 to 36 weeks of gestation) and can be administered concomitantly with seasonal influenza but cannot be co-administered with the pertussis vaccine under current recommendations.[164] A coordinated communication effort could be considered to enhance overall coverage of the seasonal maternal vaccines.

Given different potential approaches to delivering these products, and the lack of essential information to estimate these administration costs accurately while accounting for the diverse regionally funded and federally funded actors involved, we did not attempt to estimate these specifically as part of this report. Instead we varied the all-inclusive intervention costs per dose (which includes the purchase, storage, distribution, and delivery of the immunising doses to patients) for each product extensively, and policy makers will have to consider which part of the indicated threshold costs per dose they would require to deliver either mAb or MV to the target group under a specific strategy in a specific region, and which part they should keep in mind when negotiating the purchase of a product. The negotiated prices for these products would be lower than the list prices, but it is unknown to anyone involved in the current study how much lower these negotiated prices would be. Clearly, given the list price amounts, the uncertainty around the negotiated price is likely to be more influential than the uncertainty around the administration costs.

From the HCP perspective, under the base case assumption of approximating all-inclusive intervention costs per dose by the current list prices, the seasonal MV strategy can be considered cost-effective if the WTP threshold exceeds €11,276 per QALY gained. In contrast, none of the other strategies would be deemed cost-effective at current list prices: both the year-round mAb and seasonal mAb strategies were dominated, while the year-round MV and the seasonal plus catch-up mAb strategies resulted in incremental cost-effectiveness ratios (ICERs) exceeding €150,000 and €300,000 per QALY gained, respectively.

When we considered much lower intervention costs per dose for mAb, by assuming cost-parity for mAb and MV at €200 per dose (again to be interpreted as all-inclusive costs), the seasonal mAb strategy would be borderline cost-saving and the seasonal mAb plus catch-up strategy would be cost-effective with an ICER of €1,725 per QALY. Our bivariate threshold analyses also provided much more extensive and granular estimates through all-inclusive cost-per dose ranges for which either mAb or MV could be deemed cost-effective at three different levels of WTP per QALY. From these explorations, it was clear that the costs per dose would need to be brought down from the list price level much more for mAb than for MV in order to use these products in a cost-effective manner in Belgium.

In addition to intervention costs, our extensive sensitivity analyses revealed that the results were particularly sensitive to the overall burden of RSV hospitalisations. The results indicated that when using the 10-season average TCT data and relying solely on primary diagnostic codes, higher WTP thresholds were required for any strategy to be considered optimal, compared to the base case. Belgium has a high burden of RSV-coded paediatric non-ICU and ICU hospital admissions. The rates are substantially higher than in several other European countries studied during three RSV seasons (2017–2020),[3] and more than twice the average rate of 22 (17.1–28.4) per 1,000 person-years estimated for high-income countries in the Global Burden of Disease Study.[100] This may be partly caused by differences in tertiary care accessibility and patient management practices. Moreover, the number of hospital admissions increased over time prior to the COVID-19 pandemic, despite a gradual decline in the birth cohort size. This trend is likely attributable to several factors, including enhanced diagnostic testing and improved medical coding practices. Additionally, the implementation of other successful childhood (e.g., pneumococcal conjugate and rotavirus vaccination) and maternal (e.g., pertussis and influenza vaccination) immunisation programmes may have contributed to relatively greater availability of paediatric hospital beds during winter seasons, thereby facilitating more admissions.

As demonstrated through the TCT national database analysis in Chapters 3 and 4, an atypical “out-of-season” peak of RSV hospitalisations was observed due to temporary behavioural changes occurring during the emergence and control stages of the COVID-19 pandemic. Given these trends in coding, clinical practice and behaviour, we selected the four pre-COVID-19 seasons as our base case. Additionally, we noted differences in the age distribution of hospitalisations between the 2018/2019 season (pre-COVID-19, base case) and the 2022/2023 season (peri-COVID), based on laboratory-confirmed data from Sciensano. Our sensitivity analysis revealed that applying the age distribution from the 2022/2023 season had a notable impact on the results under the cost-parity scenario. Specifically, a higher proportion of hospitalisations among infants older than six months led to the seasonal mAb strategy becoming dominated and the seasonal mAb plus catch-up strategy requiring a higher WTP per QALY threshold to become the preferred option. Recent data from Belgium and other European countries suggest that RSV seasonality and age distribution returned to pre-COVID-19 patterns.

In scenario analyses, we found the widening of the perspective from that of the health care payer to that of society is unlikely to have an important impact for the interventions considered here, mainly because the impact against the bulk of common acute RSV disease episodes, especially above age 1 year would be limited. Including indirect QALY losses for the caregivers themselves, in addition to direct QALY losses in the infants was found to be of minor impact for our findings for the same main reason.

The impact of RSV immunisation on the occurrence of wheezing and asthma is still uncertain, both in terms of causal pathways and its quantification. When we explored the potential impact of such a longer term effect resulting from preventing severe RSV in infancy (which we quantified through hospital admissions), we found it to have a large influence, to the extent that seasonal mAb plus catch-up may be considered cost-effective nearer to list price level.

Although an increasing number of RSV cost-effectiveness analyses have been published in Europe, most have focused on comparing a single intervention to standard care, with several estimating cost-effective price thresholds based on specific official or arbitrary WTP thresholds. Conducting economic evaluation by constructing a decision environment in which not all available and feasible options are compared head-to-head, will lead to fundamentally misleading results for policy. Therefore, we conducted a full incremental analysis comparing all relevant strategies within the Belgian context in consultation with a diverse advisory panel of Belgian clinical and public health experts. As shown in Table 52 and Table 54, the ICERs for the seasonal plus catch-up mAb strategy were substantially lower (i.e. more attractive) when compared simply to no intervention rather than to the appropriate next best alternative strategy.

Our analysis can be compared with three previously published full incremental cost-effectiveness analyses: Li et al. (2022)[81] in Norway, Getaneh et al. (2023)[83] in six European countries (England, Scotland, Finland, Denmark, Netherlands, Veneto region of Italy) and Hodgson et al. (2024)[165] in England. Our analysis found for comparable intervention options higher threshold intervention costs per dose at which these interventions can be considered cost-effective than Li et al.[81, 83] found for any of the 7 countries using a similar static model structure, two to three years ago. The primary reason is that Belgium has substantially higher RSV-coded hospitalisation rates compared to these six countries. Moreover, in our baseline analysis, in addition to assuming that these interventions prevent RSV attributable infant mortality, we were able to use more recent and more favourable information on efficacy and duration of protection (e.g., 6 months duration of protection for both mAb and MV).

Hodgson et al.[165] used a dynamic transmission model, comparing four strategies both to 'no intervention' and to one another. They also performed a similar two-way threshold analysis using the UK's official WTP threshold of £20,000 per QALY gained. They concluded that a seasonal mAb programme could be cost-effective up to £84, while seasonal MV could be cost-effective up to £80 at all-inclusive cost. The main driver of the difference with our findings for Belgium was again the higher hospitalisation incidence rate used in our analysis. Moreover, the National Health Service costs per GP visit (£35), non-ICU admission (£1,100), and ICU admission (£2,905) were substantially lower than the corresponding costs in Belgium. Furthermore, Hodgson et al. attributed lower QALY losses for both MA and non-MA episodes.

Our study has several strengths. It incorporated age-specific national disease burden data, representative cost and quality of life data, and the pooled clinical evidence from systematic literature review, to inform the model, thus providing valuable information to support evidence-based decision-making. Moreover, we applied a wide range of WTP thresholds and conducted advanced probabilistic sensitivity analyses (including value of perfect information and net loss analyses), scenario analyses and two-way threshold analyses, enhancing the relevance of our findings for decision-makers and programme managers, particularly during price negotiations and public tender processes. Finally, we were able to incorporate the latest real-world effectiveness data.

Our study also has several limitations. First, we employed a static model, which does not account for herd immunity. However, given (a) that no intervention would be targeted at infants over the age of 6 months, (b) the relatively short duration of protection for both MV and mAb, and (c) that the role of infants in RSV transmission is predominantly that of a "sink", rather than a transmitter of the pathogen, the impact of this limitation on our results is likely limited. Furthermore, a model comparison analysis using both static and dynamic frameworks for these types of RSV interventions demonstrated similar outcomes when applying the same set of input parameters.[85] Second, since RSV-associated otitis media[166] was not accounted for in our analysis due to lack of data, the overall health and economic benefits of RSV prevention strategies may be underestimated. Third, our analysis did not account for

MV protection of the pregnant women themselves, as this efficacy was not assessed in RCTs. This may result in a slight underestimation of MV impact. This underestimation is likely limited, given that RSV episodes in healthy adults under 60 years are generally mild, and pregnant mothers constitute a small subgroup in the total adult population at any one time, and are not core transmitters of the pathogen. Finally, although our study used the disease burden observed in the presence of a palivizumab programme for high risk children in Belgium as the 'no intervention' comparator, we did not account for potential cost offsets from replacing palivizumab with nirsevimab in high-risk children, because this decision was considered to be taken, and therefore separate from the expansion of the programme to all infants. It is useful to note that in a full cost-effectiveness framework where all strategies are compared to each other, not just to 'no intervention', this omission is unlikely to affect the preferred strategy, as 'no intervention' is already a strongly dominated option.

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APPENDICES

APPENDIX 1. SYSTEMATIC REVIEW ON EFFICACY/EFFECTIVENESS OF NIRSEVIMAB

Appendix 1.1. Search strategy on nirsevimab

Appendix 1.1.1. Ovid Medline

Search MEDLINE OVID 23 October 2024		
1	nirsevimab.ab,ti,kf.	246
2	beyfortus.ab,ti,kf.	21
3	MED-18897.ab,ti,kf.	0
4	MEDI8897.ab,ti,kf.	15
5	1989556-22-0.ab,ti,kf.	0
6	C170224.ab,ti,kf.	0
7	1 or 2 or 3 or 4 or 5 or 6	258
Update February 20, 2025		
1	nirsevimab.ab,ti,kf	249
2	beyfortus.ab,ti,kf	18
3	MED-18897.ab,ti,kf	0
4	MEDI8897.ab,ti,kf	11
5	1989556-22-0.ab,ti,kf	0
6	C170224.ab,ti,kf	0
7	1 or 2 or 3 or 4 or 5 or 6	256
8	limit 7 to ed="20241023-20250221"	38

Appendix 1.1.2. Embase

Search EMBASE 25 October 2024		
#10	#9 NOT (‘conference abstract’/it OR ‘conference paper’/it OR ‘conference review/it)	119
#9	#8 NOT [Medline]/lim	157
#8	#1OR #2 OR #3 OR #4 OR #5 OR#6	401
#7	#6 NOT [Medline]/lim	7
#6	‘beyfotus’:ab,ti	17
#5	‘c170224’:ab,ti	0
#4	‘1989556-22-0’:ab,ti	0
#3	‘med 18897’:ab,ti	0
#2	‘medi8297’:ab,ti	18
#1	‘nirsevimab’/exp	400
Update February 22, 2025		
#10	#8 NOT (‘conference abstract’/it OR ‘conference paper’/it OR ‘conference review/it) AND [25-10-2024]/sd NOT [22-02-2025]/sd	34
#9	#8 NOT (‘conference abstract’/it OR ‘conference paper’/it OR ‘conference review/it)	147
#8	#7 NOT [Medline]/lim	196
#7	#1OR #2 OR #3 OR #4 OR #5 OR#6	489
#6	‘beyfotus’:ab,ti	20
#5	‘c170224’:ab,ti	0
#4	‘1989556-22-0’:ab,ti	0
#3	‘med 18897’:ab,ti	0
#2	‘medi8297’:ab,ti	18
#1	‘nirsevimab’/exp	488

Appendix 1.1.3. Cochrane

Search Cochrane 19 December 2024		
1	Nirsevimab:ab,ti	36
2	beyfortus:ab,ti	1
3	MED-18897:ab,ti	0
4	MEDI8897:ab,ti	17
5	1989556-22-0:ab,ti	5
6	c170224:ab,ti	0
Update February 21, 2025		
1	Nirsevimab:ab,ti	39
2	beyfortus:ab,ti	1
3	MED-18897:ab,ti	0
4	MEDI8897:ab,ti	17
5	1989556-22-0:ab,ti	5
6	c170224:ab,ti	0

Appendix 1.2. List of excluded studies

Author, year,	Reason(s) for exclusion
Dagan, 2024	Population: as this is a follow-up study of a RCT, age of participants is <12 months
Domachowske, 2023	Population: as this is a follow-up study of a RCT, age of participants is <12 months
Domachowske, 2024 (MUSIC trial)	Comparator: no comparator/ Population: mean age <12 months
Ernst, 2024	Population: mean age <12 months
Perramon- Malavez, 2024	Outcome: before-after design with no data on the group without immunisation by nirsevimab
Xu, 2024	Type of article: article under review
Brault, 2024	Outcome: no crude data on the effectiveness of nirsevimab (modelisation study)
Gil-Prieto, 2024	Outcome: no crude data on the effectiveness of nirsevimab (modelisation study)
Levy, 2024	Outcome: lack of data on how many in total immunized and among them how many developed RSV infection (before-after design)
Alejandre, 2024	Outcome: lack of data on how many in total immunised and among them how many developed RSV infection
Molina Gutierrez, 2024	Outcome: lack of data on how many in total immunised and among them how many developed RSV infection
Kuitunen, 2024	Outcome (and type of article): brief report, no new data: studies included already identified in our search
Mazagatos, 2024	Outcome: calculation of expected and observed hospitalisations, no number of infants immunized with nirsevimab vs non-immunised
Fortunato, 2024	Intervention: no data on nirsevimab
Jimeno-Ruiz, 2024	Design: before after design
Espelata-Fox, 2024	Design: before after design
Sumsuzzman,2025	Type of article: article under review
Gregory-Garcia, 2025	Design: before after design
Wilkins, 2024	Outcome: serologic data after nirsevimab and palivizumab exposure
Arbetter, 2025	Outcome: post hoc analysis of the Melody trial (RSV and no RSV co-infections)

Appendix 1.3. Funding of the clinical trials

Author,/study name,Year,	ClinicalTrials.gov number	Funding
Griffin, 2020	NCT02878330	Astra-Zeneca®, Sanofi Pasteur®
MELODY, 2023	NCT0397313	MedImmune/AstraZeneca® , Sanofi®
HARMONIE, 2022-2023	NCT05437510	Astra-Zeneca®, Sanofi ®
MEDLEY, 2022	NCT03959488	MedImmune/AstraZeneca® , Sanofi®

Appendix 1.4. Follow-up of the RCTs

Author, year, country	Design and sample size and setting	Intervention and control	Timeframe and follow-up	Targeted population	Main characteristics *intervention group*	Main characteristics *control group*	Outcomes (intervention vs control) and efficacy (95%CI)
Dagan[29], 2024 *(follow-up MELODY trial: evaluation of the theoretical risk of antibody enhancement of infection or potential shift or the burden of the diseases to the second year of life)*	Follow-up of the participants to MELODY trial (second RSV season: 362 to 511 days post-dose) N = 2 911 (from the initial cohort of 3012): 1 944 nirsevimab/967 control)* 211 sites 31 countries ** 1 873/923 completed the follow-up at day 511*	Nirsevimab 50 mg (weight <5 kg) or 100 mg (weight ≥5 kg), or placebo No dose was administered prior the second RSV season	July, 23 2019-October, 22 2021 *(enrollment paused between March, 15 2020 to April, 9 2021)* Follow-up: 362 to 511 days post-dose (second RSV season)	Infants born at term or late preterm ≥ week 35 gestational age and ≤1 year (cf: MELODY trial)	/	/	• Medically attended# RSV-LRTI, % (n): 1.0% (19) vs 1.0% (10) • Medically attended# RSV-LRTI with hospitalisation, % (n): 0.2% (3) vs 0.3% (3) • Very severe medically attended** RSV-LRTI, % (n): 0.2% (3) vs 0.3% (3) • Medically attended# RSV-LRTI on any test result, % (n): 1.8% (35) vs 2.1% (20) • Medically attended# RSV-LRTI with hospitalisation on any test result, % (n): 0.5% (10) vs 0.6% (6)
Domachowske[30], 2023 (follow-up MEDLEY trial)	N = 262 (from the initial group of 310 participants with CLD or CHD): • N/N =180 • P/N= 40 • P/P= 42 N= nirsevimab	Before the second RSV season: -those from nirsevimab group (1st season) received 200 mg nirsevimab followed by 4 once-monthly	July, 28 2020-April, 30 2022 Follow-up: 360 days post RSV-season 2	Infants at risk for severe RSV restricted to those with heart, lung diseases	**Median age at the start of second RSV season, months (range):** • N/N: 16.7 (12.1-23.2) • P/N: 16.4 (12.5-22.3)	/	**AE occurring through ≥150 days post first dose of RSV season 2 (N/N vs P/N vs P/P)** : • ≥1 AE: 70% vs 72.5% vs 69.0% • ≥1 Treatment-related AE: 0% vs 0% vs 0% • ≥1 Grade 3 AE: 7.8% vs 10.0% vs 2.4% • ≥1 SAE: 2.2% vs 2.5% vs 0 % • Any AE with outcome of death: 0% vs 0% vs 0% • ≥1 AE of special interest: 0% vs 0% vs 0%

	P=placebo	doses of placebo **(N/N)** -those in the palivizumab group (1st season) were re-randomised 1:1 to either 200 mg nirsevimab followed by four once-monthly doses of placebo **(P/N)** or five once-monthly doses of palivizumab **(P/P)**			• P/P: 15.8 (12.5/19.9)		Efficacy against medically attended RSV-associated LRTI was extrapolated from pharmacokinetic data: nirsevimab concentration levels among infants and children aged ≤24 months with chronic lung or heart diseases who received 200 mg nirsevimab entering their second RSV season were comparable to levels known to be efficacious in preventing medically-attended RSV- LRTI.

*# Medically attended RSV-LRTI has been defined in Table 3. ** Children requiring oxygen supplementation or intravenous fluids for management of medically attended RSV-LRTI.*

Appendix 1.5. Assessment of the within study methodological quality (randomised controlled trials) using Risk of bias-2 tool (RoB-2)

Quality appraisal of Griffin *et al*, 2020[23]

Domain	RoB	Remarks
1: Randomisation process	Low	Participants were randomly assigned in a 2:1 ratio, with the use of a central system (i.e. an interactive web response system). A subject identification number is used to identify the subject during the screening process and throughout study participation. Stratification performed by hemisphere and age at randomisation (i.e. ≤3 months, <3 to ≤6 months, <6 months).
2: Deviations from the intended interventions	Low	Double-blinded trial. Nirsevimab and placebo are visually indistinguishable once in syringes. Neither the participant nor any of the investigator or site staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received. Intention-to-treat analysis performed.
3: Missing outcome data	Low	97.5% of participants completed day 151 efficacy follow-up. 94.2% of those assigned to nirsevimab and 93.8% of those assigned to placebo completed the 361-day follow-up.
4: Measurement of the outcome (medically attended RSV-LRTI through 150 days after drug/placebo)	Low	Case definition clearly described, and similarly used in both groups. Investigator or site staff who are involved in the clinical evaluation of the subjects are not aware of the assignment to experimental groups.
5. Selection of the reported result	Low	Outcomes clearly prespecified in the protocol.
Overall RoB	Low	

RoB: Risk of Bias, LRTI: low respiratory tract infection.

Quality appraisal of MELODY trial (Hammitt et al, 2022- and Muller et al, 2023)[24, 25]

Domain	RoB	Explanation
1: Randomisation process	Low	Participants were randomly assigned in a 2:1 ratio, with the use of a central system (i.e. an interactive web response system). A subject identification number is used to identify the subject during the screening process and throughout study participation. Stratification performed by hemisphere and age at randomisation (i.e. ≤3 months, <3 to ≤6 months, <6 months).

2: Deviations from the intended interventions	Low	Double-blinded trial. Nirsevimab and placebo are visually indistinguishable once in syringes (and not labelled to reveal treatment identity). Neither the participant nor any of the investigator or site staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received. Intention-to-treat analysis performed.
3: Missing outcome data	Low	93.9% of those assigned to nirsevimab and 95.5% of those assigned to placebo completed the day 151 efficacy follow-up. 2 994 participants were in the as-treated population reporting safety events at 360 days post dose.
4: Measurement of the outcome (medically attended RSV-LRTI through 150 days after drug/placebo)	Low	Case definition clearly described, and similarly used in both groups. Investigator or site staff who are involved in the clinical evaluation of the subjects are not aware of the assignment to experimental groups.
5: Selection of the reported result	Low	Outcomes were prespecified in the protocol.
Overall RoB	Low	

RoB: Risk of Bias; LRTI: low respiratory tract infection.

Quality appraisal of HARMONIE trial (Drysdale et al, 2023)[26, 27]

Domain	**RoB**	**Explanation**
1: Randomisation process	Low	Participants were randomly assigned in a 1:1 ratio, with the use of a central interactive response technology. A subject identification number is used. Stratification performed by country and age at randomisation (i.e. ≤3 months, <3 to ≤6 months, <6 months).
2: Deviations from the intended interventions	Low	Open-label study. Methods that decrease risk of bias were used: standardisation of questionnaires, narrowly-defined end-points, training of parents/legal representative about the reporting of efficacy and safety data and the use of systematic procedures to report efficacy and safety data. The decision of hospitalisation was made before the treating physician knew the result of the RSV testing.
3: Missing outcome data	Low	99.6% of those assigned to nirsevimab received it during the RSV season (further follow-up ongoing)
4: Measurement of the outcome (hospitalisation for RSV-related LRTI during the RSV season)	Low	Authors included methods to mitigate bias of the measure of the outcome (e.g. decision to hospitalise was made before the result of RSV testing was available). RSV testing is part of the routine practice for infants with LTRTI (parent were provided a card to give to the treating physician to encourage RSV testing if testing had not been performed and to facilitate the transfer of data to the trial sites).
5: Selection of the reported result	Low	Outcomes (and timeframe- RSV season) were prespecified in the protocol.
Overall RoB	Low	

RoB: Risk of Bias; LRTI: low respiratory tract infection.

Quality appraisal of MEDLEY trial (Domachowske et al, 2023)

Domain	RoB	Explanation
1: Randomisation process	Low	In RSV season 1, all participants (preterm and with chronic lung of heart diseases were randomised using a 2:1 ratio to either the nirsevimab or palivizumab arms. Within each cohort, the randomisation was stratified by hemisphere (northern, southern) and subject age at the time of season 1 randomisation (≤3 months, <3 to ≤6 months, <6 months). In RSV season 2, subjects with chronic lung or heart diseases only were randomised. Subjects who were randomised to the nirsevimab group in Season 1 remained in this group. Subjects who were randomised to the CLD/CHD group in Season 1 were re-randomised using a 1:1 ratio to either the nirevimab or palivizumab. Use of a central system (i.e. an interactive web response system). A subject identification number is used to identify the subject during the screening process and throughout study participation.
2: Deviations from the intended interventions	Low	Double-blinded trial. Commercially available saline was used as placebo. Syringe barrels were covered by the unblinded investigational product manager. Neither the subject/legal representative nor the investigator or any of the site staff who are involved in the treatment or clinical evaluation of the participants were aware of the treatment received.
3: Missing outcome data	Low	Follow-up to day 151 completed for 95.8% and follow-up to day 361 had been completed in 86.1% of those with CLD/CHD assigned to nirsevimab and 81.2% in those with CLD/CHD assigned to palivizumab. In season 2, overall 96% (252/262) completed the 151 days follow-up.
4: Measurement of the outcome ***(safety and pharmacokinetics of nirsevimab though the 360 days after drug administration)***	Low	Safety and tolerability of nirsevimab as assessed by the occurrence of all treatment-emergent adverse events, treatment-emergent serious adverse events, adverse event of special interest, and new onset chronic disease.
5: Selection of the reported result	Low	Adverse effects were defined in the protocol and coded by Medical Dictionary for Regulatory Activities.
Overall RoB	Low	

RoB: Risk of Bias; LRTI: low respiratory tract infection.

Appendix 1.6. Excluded studies due to possible overlap of data

Author, year, country (region)	Reason for exclusion	Design and sample size	Timeframe and observation time (days)	Age and characteristics *(immunized vs non-immunized)*	Source of information and settings of included populations	Outcome(s) by study group	Adjusted effectiveness *(methods, variables of adjustment)*
Lopez-Lacort[36] (2024) Spain (Valencia, Murcia)	Potential data overlap with Estrella-Porter *et al.* (region of Valencia)	Test negative case-control study N = 160	01 November 2023- 29 February 2024 120 days	Median age (IQR), months total cohort: 4.50 (3.0-6.0)	Consultation to a Network of primary care and pediatricians (MEDIPRIM) and vaccination register	**Primary care attendance for RSV disease:** • Nirsevimab: 33/120 • No nirsevimab: 11/19	**Effectiveness for primary care attendance for RSV disease (95%CI):** 75.8% (40.4-92.7) Bayesian logistic regression (random effect: primary care centre)
Andina-Martinez[33] (2024) Spain (multiregions)	Potential data overlap with the other studies conducted in Spain	Retrospective observational study N = 906 594; 608 for the cohort 2023-2024	Epidemic seasons for RSV (November-January) between 2018 and 2024	*Not mentioned*	Data extracted from 15 pediatric emergency departments in 9 Spanish regions	**Hospital admission for RSV-LRTI:** • Nirsevimab: 150/331 • No nirsevimab: 246/277	*Not mentioned*
Agüera[34] (2024) Spain Catalunya)	Potential data overlap with studies from Coma *et al.* and Andina-Martinez *et al*	Test negative case control study N = 234	November 2023-February 2024 (exact dates not mentioned)	Median (IQR), months: 3.6 (1.5-8.1) **Comorbidities (nirsevimab group vs no nirsevimab group):** • Prematurity (<36 weeks):28% vs 11% • Heart disease: 5% vs 6% • Lung disease: 4% vs 0%	Data extracted from hospital admissions in 3 centres	**Hospital admission for RSV-LRTI:** • Nirsevimab: 40/109 • No nirsevimab: 54/72	**Effectiveness (95%CI):** • **RSV-LRTI:** 81.0% (60.9-90.7) • **Severe disease (requiring non-invasive ventilation):** 85.6% (41.7-96.4%) Logistic regression ***Adjust:*** *age, weight, preexisting condition, month of admission, hospital*

Lopez-Lacort[35] (February 2024) Spain (Valencia, Murcia, Castilla y León)	Potential data overlap with Estrella-Porter *et al.* (region of Valencia)	Retropective cohort study N = 166	01 October 2023 – 10 January 2024 101 days	Among 95 infants positive for RSV, 73 aged 0-3 months	Infants hospitalised for RSV-LRTI (review of medical record and database of a hospital network at regional level-VAHNSI)	**RSV-LRTI hospitalisation:** • Nirsevimab: 56/115 • No nirsevimab: 39/51	**Effectiveness for RSV-LRTI (95%CI):** 84.4% (76.8-90.0) *Bayesian model (hospital as random effect)*

Appendix 1.7. Availability of nirsevimab and observation time in studies using real-world data

Authors	Date of birth of children eligible for nirsevimab during the immunisation campaign	Date of nirsevimab availability, or dates of immunisation campaign	Observation time of the study
Coma[46] *et al.*	April-September 2023	01 October 2023- 31 January 2024	01 October 2023- 31 January 2024
Assad[51] *et al.*	Born after 06 February 2023	15 September 2023 (due to early shortage, nirsevimab was preferentially administered to newborns)	15 October 2023- 10 December 2023
Lassoued[49] *et al.*	Born after 06 February 2023		15 September 2023- 01 February 2024
Carbajal[45] *et al.*	Born after 06 February 2023		14 October 2023- 29 September 2024
Barbas del Buey[52] *et al.*	01 April 2023 – 31 December 2023	01 October 2023- 31 March 2024	01 October 2023- 29 February 2024
NIRSEGAL study[43, 53]	Catch-up: 01 April 2023- 24 September 2023 Seasonal: 25 September 2023- 31 March 2024	25 September 2023- 31 March 2024	25 September 2023- 15 April 2024
Estrella Porter[48] *et al.*	01 April 2023- 30 September 2023	01 October 2023- 31 March 2024	01 October 2023- 09 January 2024
Paireau[54] *et al.*	After 06 February 2023	15 September 2023 (due to early shortage, nirsevimab was preferentially administered to newborns)	15 September 2023- 31 January 2024
Moline[44] *et al. (b)*	Age <8 months or born after 01 October 2023	August 2023	01 October 2023- 30 March 2024
Consolati[56] *et al.*	01 May 2023 -15 February 2024	20 December 2023	20 December 2023- 15 February 2024
Ezpeleta[40] *et al.*	01 October 2023-31 December 2023	01 October 2023- 31 January 2024	01 October 2023- 28 January 2024
Jeziorski[38] *et al.*	Born after 15 September 2023	15 September 2023 (maternity wards)	27 October 2023- 29 February 2024
Lefferts[42] *et al.*	<8 months age or birth during or entering in the first RSV season	16 October 2023- 30 April 2024	23 October 2023- 30 Juni 2024
Lenglart[47] *et al.*	Born after 6 February 2023	15 September 2023 (maternity wards)	01 October 2023- 29 February 2024
Chauvel[39] *et al.*	Born after 15 September 2023	15 September 2023- 31 December 2024	28 October 2023- 18 February 2024
Perramon Malavez[37] *et al.*	01 October 2023- 21 January 2024	October 2023	01 October 2023 – 31 January 2024
Nuñez[41] *et al.*	Catch-up: 01 April 2023- 30 September 2023 Seasonal: 01 October 2023- 31 March 2024	25 September 2023- 31 March 2024	01 October 2023- 31 March 2024

Appendix 1.8. Subgroup analysis of the assessment of the effectiveness of nirsevimab

Authors	Outcome of interest	Proportion of infants <3 months age in the study	Effectiveness <3 months (95%CI)	Effectiveness ≥3 months (95%CI)
Assad[51] *et al.*	Hospitalisation	46%	82.4% (69.3-89.9)	82.7% (52.8-93.7)
Carbajal[45] *et al.*	Hospitalisation	45% (≤3 months)	78% (62-88)	3-6 months: 88% (71-97) >6-12 months: 89% (72-97)
Lassoued[49] *et al.*	RSV bronchiolitis	10%	65.5% (-0.8-94.0)	≥3-6 months: 87.8% (66.9-95.5) >6 months: 82.0% (62.2-91.5)
Jeziorki[38] *et al.*	Hospitalisation	43.8%	76% (63-84)	90% (81 - 95)
Lenglart[47] *et al.*	Emergency department visit	62%	77.1% (52-89)	90.3% (62.5 - 97.5)

Appendix 1.9. Funding of studies using real-world data

Authors	Date Source(s) of funding
Coma[46] *et al.*	none
Assad[51] *et al.*	Grant (ANRS0420) from National Agency for AIDS Research-Emerging Infectious Diseases and the ATIP-Avenir partnership between INSERM and French National Centre for Scientific Research.
Lassoued[49] *et al.*	Association Clinique et Thérapeutique Infantile du Val de Marne, French Pediatrician Ambulatory Association, unrestricetd grants from GSK, MSD, Pfizer, and Sanofi
Carbajal[45] *et al.*	None
Barbas del Buey[52] *et al.*	None
NIRSEGAL study[43, 53]	Sanofi and Astra Zeneca
Estrella Porter *et al.*	Not mentioned
Paireau[54] *et al.*	Santé Publique France, Laboratoire d'Excellence Integrative Biology of Emerging Infectious Diseases program (Grant ANR-10-LABX-62-IBEID)
Moline[44] *et al. (b)*	UC Centre for Diseases Control and Prevention
Consolati[56] *et al.*	Azienda Usl Vale d'Aosta, 11100 Aosta, Italy (PED-01)
Ezpeleta[40] *et al.*	Instituto de Salud Carlos III, European Regional Development Fund (CM19/00154, CP22/00016, and INT21/00100)
Jeziorski[38] *et al.*	Sanofi Vaccine and Astra Zeneca
Carcione[50] *et al.*	None
Lefferts[42] *et al.*	Declaration of grants and support of authors, no particular funding mentioned
Lenglart[47] *et al.*	Sanofi and Astra Zeneca
Chauvel[39] *et al.*	Center of Excellence in Respiratory Pathogens (CERP), Lyon, France
Perramon Malavez[37] *et al.*	Grant 202134-30-31 funded by "La Fundació La Marató de TV3"
Nuñez[41] *et al.*	Institute of Health Carlos III

Appendix 1.10. Assessment of the within study methodological quality (studies on real world data) using SIGN tool

Quality assessment of observational cohort studies (SIGN tool - checklist 3)

Item	Wilkins[31] (2024)	Coma[46] (2024)	Barbas del Buey[52] (2024)	Ares-Gomez (2024), Mallah (2024)	Estrella-Porter[48] (2024)	Consolati[56] (2024)	Ezpeleta[40] (2024)	Chauvel[39] (2024)	Jeziorski[38] (2024)	Perramon-Malavez[37] (2025)
SECTION 1: INTERNAL VALIDITY										
1.1 The study addresses an appropriate and clearly focused question	Y	Y	Y	Y	Y	Y	Y	Y	CS	Y
Selection of subjects										
1.2 The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	Y	CS	Y	Y	CS	CS	CS	CS	Y	CS
1.3 The study indicates how many of the people asked to take part did so, in each of the groups being studied.	NA	NA	Y	Y	NA	Y	Y	NA	Y	NA
1.4 The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis	NA	Y	CS	Y	CS	N	N	CS	CS	CS
1.5 What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.	NA	NA	CS	98%	NA	CS	CS	NA	CS	NA
1.6 Comparison is made between full participants and those lost to follow up, by exposure status.	NA	NA	CS	CS	NA	N	N	NA	N	NA
Assessment										
1.7 The outcomes are clearly defined.	Y	Y	Y	Y	Y	CS	Y	CS	Y	Y
1.8 The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable	N	N	N	N	N	N	N	N	N	N

1.9 Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	Y	Y	Y	Y	Y	CS	Y	Y	Y	Y
1.10 The method of assessment of exposure is reliable.	Y	Y	Y	Y	Y	CS	Y	CS	CS	Y
1.11 Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	Y	Y	Y	Y	Y	CS	Y	CS	Y	Y
1.12 Exposure level or prognostic factor is assessed more than once.	NA	NA	N	N	NA	N	N	NA	CS	NA
Confounding										
1.13 The main potential confounders are identified and taken into account in the design and analysis.	N	N	Y	Y	N	N	N	N	CS	N
Statistical analysis										
1.14 Have confidence intervals been provided	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
SECTION 2: OVERALL ASSESSMENT OF THE STUDY										
2.1 How well was the study done to minimise the risk of bias or confounding.	Acceptable to high	Acceptable	Acceptable	High	Acceptable	Low	Acceptable	Low	Acceptable	Acceptable
2.2 Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	Y	Y	Y	Y	Y	CS	Y	CS	Y	Y
2.3 Are the results of this study directly applicable to the patient group targeted in this guideline?	Y	Y	Y	Y	Y	CS	Y	CS	Y	Y

Quality assessment of case control studies (SIGN- checklist 4)

Item	Assad[51] (2024)	Lassoued[49] (2024)	Carbajal[45] (2024)	Paireau[54] (2024)	Moline[55] (a) (2024)	Nuñez[41] (2025)	Lenglart[47] (2024)	Lefferts[42] (2024)	Moline[44] (2024) bis
SECTION 1: INTERNAL VALIDITY									
1.1 The study addresses an appropriate and clearly focused question	Y	Y	Y	Y	Y	Y	Y	Y	Y
Selection of subjects									
1.2 The cases and controls are taken from comparable populations.	Y	Y	Y	Y	Y	Y	Y	CS	Y
1.3 The same exclusion criteria are used for both cases and controls.	Y	Y	Y	Y	Y	Y	Y	Y	Y
1.4 What percentage of each group (cases and controls) participated in the study?	83% vs 91% -ratio 2:1	58% vs 56%	26% vs 74% (no matching)	53% vs 9,2%	58% vs 42%	CS	CS	4.2% vs 25%	47.3%/52.7%
1.5 Comparison is made between participants and non-participants to establish their similarities or differences.	Y	Y	N	N	CS	CS	N	N	Y
1.6 Cases are clearly defined and differentiated from controls.	Y	Y	CS	Y	Y	Y	Y	CS	Y
1.7 It is clearly established that controls are non-cases	Y	Y	Y	Y	Y	Y	Y	Y	Y
Assessment									
1.8 Measures will have been taken to prevent knowledge of primary exposure influencing cases ascertainment	N	N	NA	N	N	N	N	N	N
1.9 Exposure status is measured in a standard, valid and reliable way	Y	Y	Y	Y	Y	Y	Y	Y	Y
Confounders									
1.10 The main potential confounders are identified and taken into account in the design and analysis	Y	Y	N	Y	Y	Y	Y	Y	Y
Statistical analysis									
1.11 Confidence intervals are provided.	Y	Y	Y	Y	Y	Y	Y	Y	Y
SECTION 2: OVERALL ASSESSMENT OF THE STUDY									
2.1 How well was the study done to minimise the risk of bias or confounding.	High	High	Acceptable	Acceptable	Acceptable to high	High	Acceptable	Acceptable to low	High
2.2 Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	Y	Y	Y	Y	Y	Y	Y	Y	Y
2.3 Are the results of this study directly applicable to the patient group targeted in this guideline?	Y	Y	Y	Y	Y	Y	Y	Y	Y

Quality assessment of the cross sectional survey (CHERRIES tool[ddd])

Checklist	Explanation
Describe survey design	Described partially
IRB approval	Ethical approval obtained
Informed consent	Not mentioned
Data protection	Not clearly mentioned
Development and testing	Mentioned
Open versus closed survey	Open survey
Contact mode	Mentioned
Adverstising the survey	Not mentioned
Web/E-mail	Not mentioned
Context (description website in which the survey was posted.	Personal email
Mandatory/voluntary	Volontary
Incentives	No incentive
Time/Date	Mentioned
Randomisation of items questionnaires	No
Adaptative questionning	Not mentioned
Number of items	Not mentioned
Number of screens (pages)	Not mentioned
Completeness check	Not mentioned
Review step	Not mentioned
Unique site visitor	Not mentioned
View rate (ratio of unique survey visitors/unique site visitors)	Not mentioned
Participation rate	27%
Completion rate (ratio of users who finished the survey)	Not mentioned
Cookies used	Not mentioned
IP check	Not mentioned
Log file anbalysis	Not mentioned
Registration	Not mentioned
Handling of incomplete questionnaires	Not mentioned
Questionnaires submitted with an atypical timestamp	Not mentioned
Statistical correction	Not mentioned

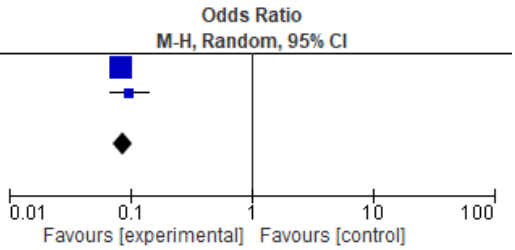
ddd https://www.equator-network.org/reporting-guidelines/improving-the-quality-of-web-surveys-the-checklist-for-reporting-results-of-internet-e-surveys-cherries/

Appendix 1.11. Meta-analysis: complementary and sensitivity analysis

Appendix 1.11.1. Effect of nirsevimab on RSV-associated hospitalisation: sensitivity analysis pooling the cohort studies with high sample sizes (follow-up <120 days)

Study or Subgroup	nirsevimab Events	nirsevimab Total	no nirsevimab Events	no nirsevimab Total	Weight	Odds Ratio M-H, Random, 95% CI
Barbas del Buey 2024	133	29684	376	7383	76.0%	0.08 [0.07, 0.10]
Coma 2024	52	23127	76	3398	24.0%	0.10 [0.07, 0.14]
Total (95% CI)		**52811**		**10781**	**100.0%**	**0.09 [0.07, 0.10]**
Total events	185		452			

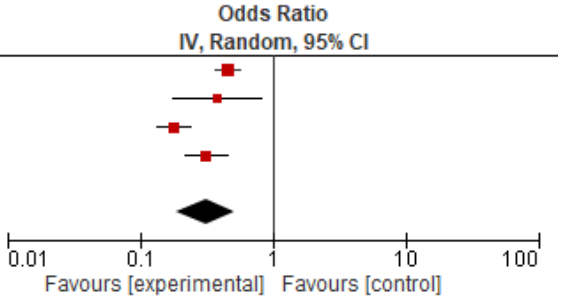
Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 1 (P = 0.44); I² = 0%
Test for overall effect: Z = 27.51 (P < 0.00001)



Appendix 1.11.2. Effectiveness of nirsevimab using the generic variance method on case-control studies (with follow-up <120 days)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Carbajal 2024	-0.769	0.11	28.6%	0.46 [0.37, 0.57]
Lefferts 2024	-0.958	0.39	18.0%	0.38 [0.18, 0.82]
Lenglart 2025	-1.71	0.15	27.4%	0.18 [0.13, 0.24]
Moline 2024	-1.155	0.19	26.0%	0.32 [0.22, 0.46]
Total (95% CI)			**100.0%**	**0.31 [0.19, 0.52]**

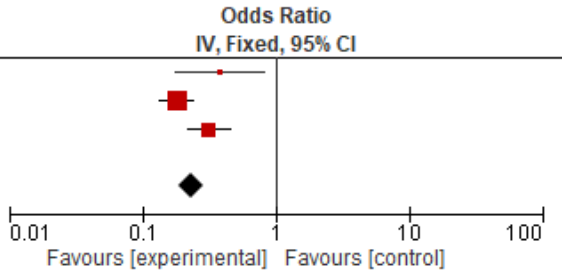
Heterogeneity: Tau² = 0.22; Chi² = 25.81, df = 3 (P < 0.0001); I² = 88%
Test for overall effect: Z = 4.47 (P < 0.00001)



Appendix 1.11.3. Effectiveness on nirsevimab using the generic variance method on case-control studies: sensitivity analysis pooling only case-control studies with similar adjustment

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Lefferts 2024	-0.958	0.39	8.4%	0.38 [0.18, 0.82]
Lenglart 2025	-1.71	0.15	56.5%	0.18 [0.13, 0.24]
Moline 2024	-1.155	0.19	35.2%	0.32 [0.22, 0.46]
Total (95% CI)			**100.0%**	**0.23 [0.19, 0.29]**

Heterogeneity: Chi² = 7.01, df = 2 (P = 0.03); I² = 71%
Test for overall effect: Z = 12.88 (P < 0.00001)

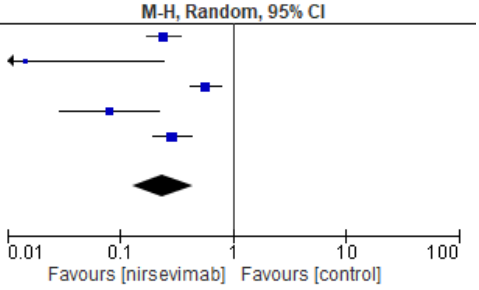


Appendix 1.11.4. Effectiveness of nirsevimab against hospitalisation for RSV LRTI (studies with follow-up <120 days)

For the outcome of RSV-associated hospitalisation with a follow-up duration of less than 120 days, 5 studies were included (comprising four cohort studies and one case-control study). These studies reported 395 hospitalisation events among immunised infants and 735 events among non-immunised infants. The pooled analysis, presented hereunder revealed a significant reduction in hospitalisation likelihood among those who received nirsevimab, with an odds ratio (OR) of 0.24 (95%CI: 0.13-0.44), corresponding to an effectiveness of 76% (95%CI: 66-87). This estimate was associated with substantial heterogeneity (I² = 86%). A sensitivity analysis, excluding the single case-control study, yielded a similar pooled estimate, with an effectiveness of 79% (95%CI: 49-91). Notably, this exclusion did not alter the level of heterogeneity (see Appendix 1.11.5).

Study or Subgroup	Nirsevimab Events	Nirsevimab Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Assad 2024	60	157	630	878	26.4%	0.24 [0.17, 0.35]
Consolati 2024	0	369	14	168	4.2%	0.01 [0.00, 0.24]
Estrella-Porter 2024	218	24223	49	3139	26.9%	0.57 [0.42, 0.78]
Ezpeleta 2024	8	1083	8	94	16.5%	0.08 [0.03, 0.22]
Perramon-Malavez 2025	109	14055	34	1286	26.0%	0.29 [0.19, 0.42]
Total (95% CI)		**39887**		**5565**	**100.0%**	**0.24 [0.13, 0.44]**
Total events	395		735			

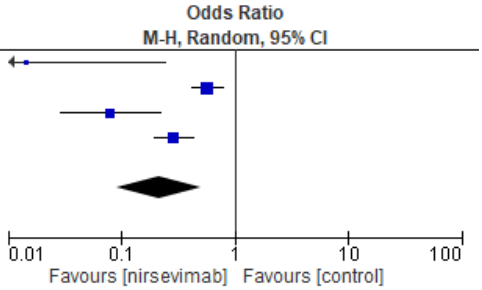
Heterogeneity: Tau² = 0.35; Chi² = 27.77, df = 4 (P < 0.0001); I² = 86%
Test for overall effect: Z = 4.53 (P < 0.00001)



Appendix 1.11.5. Effectiveness of nirsevimab on RSV-associated hospitalisation: analysis of cohort studies only (follow-up <120 days)

Study or Subgroup	nirsevimab Events	nirsevimab Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Consolati 2024	0	369	14	168	7.5%	0.01 [0.00, 0.24]
Estrella-Porter 2024	218	24223	49	3139	34.5%	0.57 [0.42, 0.78]
Ezpeleta 2024	8	1083	8	94	24.3%	0.08 [0.03, 0.22]
Perramon-Malavez 2025	109	14055	34	1286	33.7%	0.29 [0.19, 0.42]
Total (95% CI)		**39730**		**4687**	**100.0%**	**0.21 [0.09, 0.51]**
Total events	335		105			

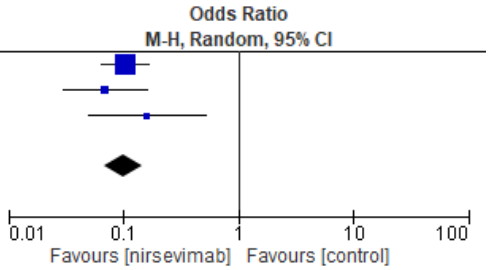
Heterogeneity: Tau² = 0.54; Chi² = 23.03, df = 3 (P < 0.0001); I² = 87%
Test for overall effect: Z = 3.49 (P = 0.0005)



Appendix 1.11.6. Effectiveness of nirsevimab on RSV-associated PICU admission: analysis of cohort studies only (follow-up <120 days)

Study or Subgroup	nirsevimab Events	nirsevimab Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Barbas del Buey 2024	24	29684	57	7383	67.2%	0.10 [0.06, 0.17]
Coma 2024	8	23127	17	3398	21.7%	0.07 [0.03, 0.16]
Jeziorski 2024	15	24	63	69	11.1%	0.16 [0.05, 0.51]
Total (95% CI)		**52835**		**10850**	**100.0%**	**0.10 [0.07, 0.15]**
Total events	47		137			

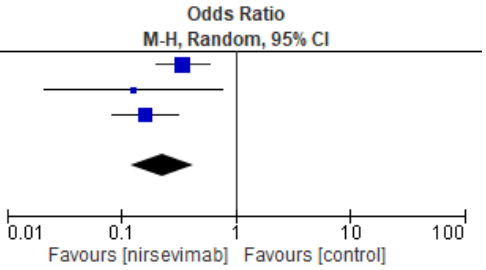
Heterogeneity: Tau² = 0.00; Chi² = 1.38, df = 2 (P = 0.50); I² = 0%
Test for overall effect: Z = 11.54 (P < 0.00001)



Appendix 1.11.7. Effectiveness of nirsevimab on RSV-associated PICU admission: analysis of studies with follow-up <120 days

Study or Subgroup	nirsevimab Events	nirsevimab Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Assad 2024	27	74	166	265	48.3%	0.34 [0.20, 0.58]
Ezpeleta 2024	3	1083	2	94	10.6%	0.13 [0.02, 0.77]
Perramon-Malavez 2025	25	14055	14	1286	41.1%	0.16 [0.08, 0.31]
Total (95% CI)		**15212**		**1645**	**100.0%**	**0.23 [0.12, 0.43]**
Total events	55		182			

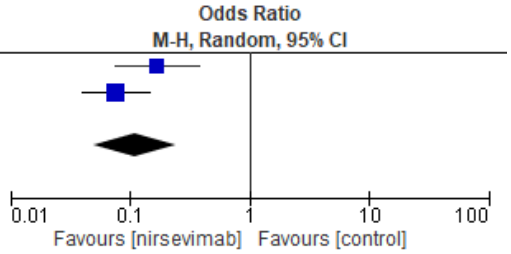
Heterogeneity: Tau² = 0.14; Chi² = 3.77, df = 2 (P = 0.15); I² = 47%
Test for overall effect: Z = 4.59 (P < 0.00001)



Appendix 1.11.8. Effectiveness of nirsevimab on primary care medically-attended RSV infection

Study or Subgroup	nirsevimab Events	nirsevimab Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Lefferts 2024	8	161	31	131	45.2%	0.17 [0.07, 0.38]
Moline 2024	10	765	126	851	54.8%	0.08 [0.04, 0.15]
Total (95% CI)		**926**		**982**	**100.0%**	**0.11 [0.05, 0.24]**
Total events	18		157			

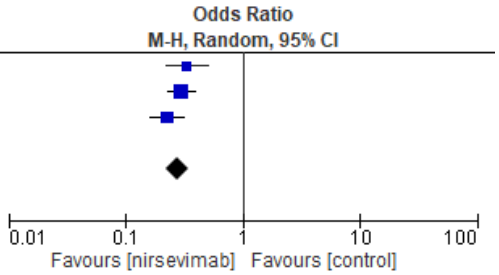
Heterogeneity: Tau² = 0.19; Chi² = 2.30, df = 1 (P = 0.13); I² = 57%
Test for overall effect: Z = 5.50 (P < 0.00001)



Appendix 1.11.9. Effectiveness of nirsevimab on the incidence of RSV infection

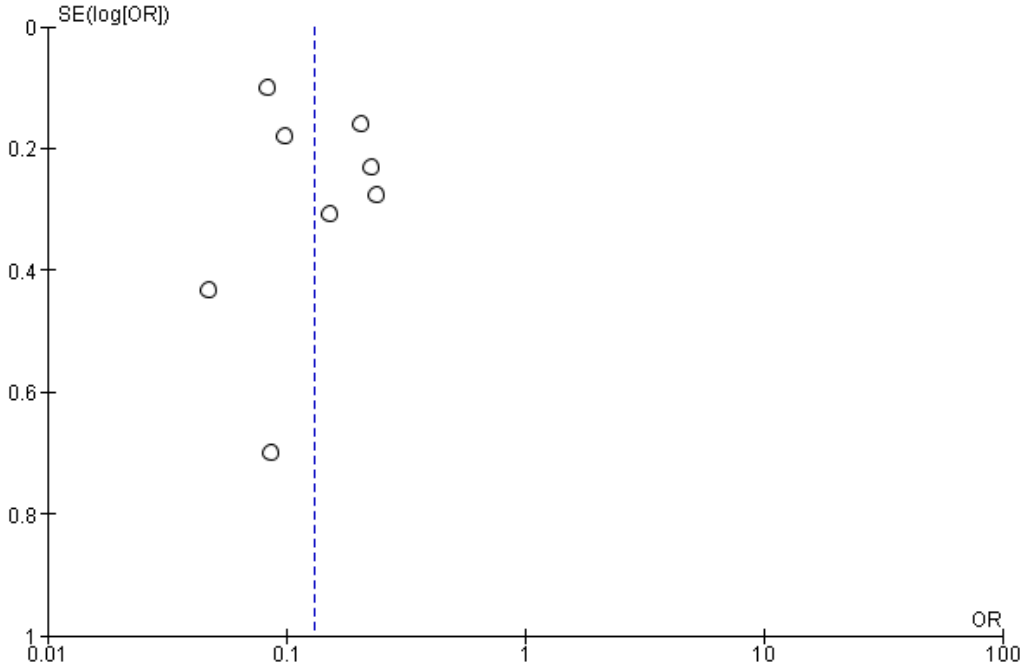
Study or Subgroup	nirsevimab Events	nirsevimab Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Coma 2024	71	23127	31	3398	22.4%	0.33 [0.22, 0.51]
Estrella-Porter 2024	168	24223	72	3139	43.7%	0.30 [0.23, 0.39]
Lassoued 2024	62	239	391	644	33.9%	0.23 [0.16, 0.32]
Total (95% CI)		**47589**		**7181**	**100.0%**	**0.28 [0.22, 0.35]**
Total events	301		494			

Heterogeneity: Tau² = 0.01; Chi² = 2.52, df = 2 (P = 0.28); I² = 21%
Test for overall effect: Z = 11.57 (P < 0.00001)



Appendix 1.12. Publication bias

Assessment of the publication bias for the pooled analysis of the association of nirsevimab with hospitalisation (studies with a follow-up <120 days)



APPENDIX 2. SYSTEMATIC REVIEW ON THE EFFICACY/EFFECTIVENESS OF ABRYSVO

Appendix 2.1. Search strategy

Appendix 2.1.1. Ovid Medline

Search MEDLINE OVID 25 October 2024		
1	abrysvo.ab,ti,kf.	38
2	STN 125769.ab,ti,kf.	0
3	STN 125768.ab,ti,kf.	0
4	RSVpreF.ab,ti,kf.	53
5	C5827885.ab,ti,kf.	0
6	"PF 06928316".ab,ti,kf.	0
7	1 or 2 or 3 or 4 or 5 or 6	82
Update February 17, 2025		
1	abrysvo.ab,ti,kf.	47
2	STN 125769.ab,ti,kf.	0
3	STN 125768.ab,ti,kf.	0
4	RSVpreF.ab,ti,kf.	57
5	C5827885.ab,ti,kf.	0
6	"PF 06928316".ab,ti,kf.	0
7	1 or 2 or 3 or 4 or 5 or 6	94
8	limit 7 to ed="20241024-20250217"	12

Appendix 2.1.2. Embase

Search MEDLINE OVID 25 October 2024		
#9	#8 NOT ('conference abstract'/it OR 'conference paper'/it OR 'conference review/it)	42
#8	#7 NOT [medline]/lim	56
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	121
#6	'c5827885': ab,ti	0
#5	'stn125 768': ab,ti	0
#4	'stn125769': ab,ti	0
#3	'rsvpref': ab,ti	63
#2	'abrysvo': ab,ti	34
#1	'pf 06928316'/exp	72
Update February 19, 2025		
#10	#8 NOT ('conference abstract'/it OR 'conference paper'/it OR 'conference review/it) AND [26-10-2024]/sd NOT [19-02-2025]/sd	11
#9	#8 NOT ('conference abstract'/it OR 'conference paper'/it OR 'conference review/it)	51
#8	#7 NOT [medline]/lim	78
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	163
#6	'c5827885': ab,ti	0
#5	'stn125 768': ab,ti	0
#4	'stn125769': ab,ti	0
#3	'pf 06928316'/exp	99
#2	'rsvpref': ab,ti	92
#1	'abrysvo': ab,ti	45

Appendix 2.1.3. Cochrane

Search COCHRANE 20 December 2024		
1	abrysvo:ab,ti	5
2	PF 06928316:ab,ti	3
3	STN 125769:ab,ti	0
4	STN 125768:ab,ti	0
5	C5827885:ab,ti	0
6	RSVpreF:ab,ti	42
Update February 17, 2025		
1	abrysvo:ab,ti	4
2	RSVpreF:ab,ti	43
3	STN 125769:ab,ti	0
4	STN 125768:ab,ti	0
5	C5827885:ab,ti	0
6	PF 06928316:ab,ti	3

Appendix 2.2. List of excluded studies

Author, year,	Reason(s) for exclusion
Ishiwada,2024	Outcome: modellisation study
Otsuki, 2024	Other: duplicate data (subset study of the MATISSE trial)
Lopez-Lacort, 2024	Outcome: modellisation study
Alvarez-Aldean, 2024	Outcome: modellisation study
Alami, 2024	Type of article: article under review

Appendix 2.3. MATISSE trial: preliminary results (Kampmann et al, 2023)

Author, year, country	Design and sample size and setting	Intervention and control	Timeframe and follow-up	Targeted population	Main characteristics *intervention group*	Main characteristics *control group*	Outcomes (intervention vs control) and efficacy (95%CI)
Kampmann[64], 2023 ***(interim analysis of the MATISSE trial)***	Phase 3 Randomised placebo controlled trial (ratio 1:1) N= 7 392 randomised and 7 358 received Abrysvo or placebo (3 682/3 676) Infants: 3 570/3 558 18 countries (both hemispheres)	Unadjuvanted RSVpreF vaccine Abrysvo IM 120 µg or placebo	Interim analysis: June, 17 2020 - September, 30 2022 (data on efficacy) and September, 2 2022 (data on safety)	**Maternal participants:** healthy pregnant women (≤49 aged); gestational age 24 to 36 weeks **Infant participants:** infants born to participants who received the investigational product at least 14 days before birth	**Median age of maternal participants** (range), years: 29 (16-45) **Gestation at injection**, median (range), weeks: 31.3 (24.0-36.6) **Gestational birth** (weeks), %: • 24 to <28: <0.1 • 28 to <34: 0.6 • 34 to <37: 5.0 • 37 to <42: 93.7 • ≥42: 0.6	**Median age of maternal participants** (range), years: 29 (14-47) **Gestation at injection**, median (range), weeks: 31.3 (24.0-36.9) **Gestational birth** (weeks), %: • 24 to <28: <0.1 • 28 to <34: 0.3 • 34 to <37: 4.4 • 37 to <42: 94.3 • ≥42: 0.8	**Primary outcome:** medically attended severe* RSV-associated LRTI, % (n) - efficacy: • Day 90: 0.2% (6) vs 0.9% (33) - **81.8% (99.5%CI: 40.6-96.3)** • Day 180: 0.5% (19) vs 1.8% (62) - **69.4% (97.58%CI: 44.3-84.1)** **Primary outcome:** medically attended* RSV-associated lower respiratory tract, % (n) - efficacy: • Day 90: 0.7% (24) vs 1.6% (56) - **57.1% (99.5%CI: 14.7-79.8)** • Day 180: 1.6% (57) vs 3.4% (117) - **51.3% (97.58%CI: 29.4-66.8)** **Secondary outcome: RSV-associated hospitalisation,** % (n) - efficacy: • Day 90: 0.3% (10) vs 0.9% (31) - **67.7 (99.17%CI: 15.9-89.5)** • Day 180: 0.5% (19) vs 1.3% (44) - **56.8 (99.17%CI: 10.1-80.7)** **Safety:** • Maternal AEs reported one month after vaccination: 13.8% vs 13.1% • Maternal serious AE though 6 months after injection: 1.8% vs 1.4% • Maternal AE of special interest: 2.7% vs 2.5% (premature delivery similar in both groups: 0.8% vs 0.6%) • Infant AEs within one month after birth: 37.1% vs 34.5% • Infant AE of special interest: 8.4% vs 7.2% (low birth weight, developmental delay, SARS-CoV2 positive, prematurity) • Death (reported within 24 months after birth), % (n): 0.1% (5) vs 0.3% (12)

** Severe medically attended RSV-associated LRTI and medically attended RSV-associated LRTI are defined in the report at Table 9. # Serious adverse events in four RSVpreF vaccine recipients (pain in an arm followed by bilateral lower-extremity pain, premature labor, systemic lupus erythematosus, and eclampsia — in one recipient each) and in one placebo recipient (premature placental separation) were assessed by the investigator as being related to the injection. AE: adverse event, N: number.*

Appendix 2.4. Assessment of the within study methodological quality

Appendix 2.4.1. Quality assessment of the MATISSE trial[61]

Domain	RoB	Remarks
1: Randomisation process	Low	Participants were randomly assigned in a 1:1 ratio, through the use of a web-based Interactive Response Technology (IRT) system. A subject identification number is used to identify the subject during the study.
2: Deviations from the intended interventions	Low	Double-blinded trial. The maternal participants, investigator, study coordinator, and all site staff were blinded. The infant evaluable efficacy population is the primary population for efficacy analyses (definition "All infant participants who are eligible, are born to the maternal participants who received the investigational product to which they were randomised at least 14 days prior to delivery, did not receive palivizumab or another monoclonal antibody targeting RSV, have no major protocol violations, and did not have transfusions of more than 20 mL/kg of any blood products at <180 days"). The analysis is repeated on the infant mITT (definition: "All infant participants who are born to vaccinated maternal participants").
3: Missing outcome data	Low	98.0% (7 159/7 307), 95.5% (6 977/7 307), and 86.7% (6 821/7 307) of children completed the 1-, 6-, and 12-month follow-up; 86.7% (3 299/3 803) completed the 24-month follow-up; and 90.5% (6 612/7 307) completed the study.
4: Measurement of the outcome (medically attended RSV-LRTI through 150 days after drug/placebo)	Low	Efficacy assessment (definition of LRTI, testing) clearly described, and similarly used in both groups. Outcome assessors not aware of the intervention received.
5: Selection of the reported result	Low	Outcomes clearly prespecified in the protocol. MATISSE was registered in ClinicalTrials.gov (number, NCT04424316) and EudraCT (number, 2019-002943-85)
Overall RoB	Low	

Appendix 2.4.2. Quality assessment of observational cohort studies (SIGN tool - checklist 3)

Item	Son[62] (2024)	Blauvelt[59] (2025)
SECTION 1: INTERNAL VALIDITY		
1.1 The study addresses an appropriate and clearly focused question	Y	Y
Selection of subjects		
1.2 The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	Y	Y
1.3 The study indicates how many of the people asked to take part did so, in each of the groups being studied.	NA	NA
1.4 The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis	NA	NA
1.5 What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.	NA	NA
1.6 Comparison is made between full participants and those lost to follow up, by exposure status.	NA	NA
Assessment		
1.7 The outcomes are clearly defined.	Y	Y
1.8 The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable	N	N
1.9 Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	Y	V
1.10 The method of assessment of exposure is reliable.	CS	CS
1.11 Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	Y	Y
1.12 Exposure level or prognostic factor is assessed more than once.	NA	NA
Confounding		
1.13 The main potential confounders are identified and taken into account in the design and analysis.	Y	Y
Statistical analysis		
1.14 Have confidence intervals been provided	Y	Y
SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1 How well was the study done to minimise the risk of bias or confounding.	Acceptable	Acceptable
2.2 Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	Y	Y
2.3 Are the results of this study directly applicable to the patient group targeted in this guideline?	Y	Y

APPENDIX 3. DESCRIPTION OF ICD CODES

Appendix 3.1. Respiratory syncytial virus

Description	ICD-9	ICD-10
respiratory syncytial virus	796	B974

Appendix 3.2. Upper Respiratory Tract Infections

Description	ICD-9	ICD-10
acute nasopharyngitis	460	J00
pharyngitis	462	J028, J029
- streptococcal pharyngitis		J020
tonsillitis	463	J0300, J038, J0380, J0381, J039, J0390, J0391
- streptococcal tonsillitis		J030
- acute recurrent streptococcal tonsillitis		J0301
laryngitis	46400, 46401	J040
tracheitis	46410, 46411	J0410, J0411
laryngotracheitis	46420, 46421	J042
Croup infection	4644	J050
epiglottitis	463, 46430, 46431	J051, J0510, J0511
laryngopharyngitis	4650	J060
sinusitis	4610, 4611, 4612, 4613, 4618, 4619	
supraglottitis	46450, 46451	
Unspecified	4659, 4658	J06, J068, J069

Appendix 3.3. Lower Respiratory Tract Infections

Description	ICD-9	ICD-10
Influenza	4870, 4871, 4878	J09, J09X, J09X1, J09X2, J09X3, J09X9, J100, J1000, J1001, J1008, J110, J1100, J1108, J101, J111, J108, J1081, J1082, J1083, J1089, J118, J1181, J1182, J1183, J1189
Pneumonia		
- adenoviral pneumonia	4800	J120
- respiratory syncytial virus pneumonia	4801	J121
- parainfluenza virus pneumonia	4802	J122
- sars-associated coronavirus / COVID-19	4803	J1281, J1282, U071, U09, U099, U099, U072, U08, U10
- Other viral pneumonia	4808, 4809	J123, J128, J1289, J129
- streptococcus	481, 48249, 48230, 48231, 48232, 48239	J13, J153, J154
- hemophilus influenzae	4822	J14
- klebsiella pneumoniae	4820	J150
- Pseudomonas	4821	J151
- staphylococcus	48240, 48241, 48249	J152, J1520, J1521, J15211, J15212, J1529

- escherichia coli	48282	J155
- gram-negative bacteria	48283	J156
- mycoplasma pneumoniae	4830	J157
- chlamydia	4831	J160
- Other or Unspecified	48289, 4829, 4838, 485, 514, 48281, 48284, 4841, 4843, 4845, 4846, 4847, 486	J158, J159, J168, J180, J181, J182, J188, J189
Bronchitis/bronchiolitis	46611, 4660, 46619	
- Coxsackievirus, rhinovirus, echovirus		J203, J206, J207
- respiratory syncytial virus pneumonia		J205, J210
- parainfluenza virus pneumonia		J204
- rhinovirus		J206
- Metapneumovirus		J211
- streptococcus		J202
- hemophilus influenzae		J201
- mycoplasma pneumoniae		J200
- Other or Unspecified		J208, J209, J218, J219
Unspecified	4848, 5198	J22, J40, J17

APPENDIX 4. LITERATURE REVIEW TO IDENTIFY THE PARAMETERS FOR THE ECONOMIC MODEL

Appendix 4.1. Methods

Appendix 4.1.1. Search strategy in PubMed (conducted on 29th October 2024 via PubMed)

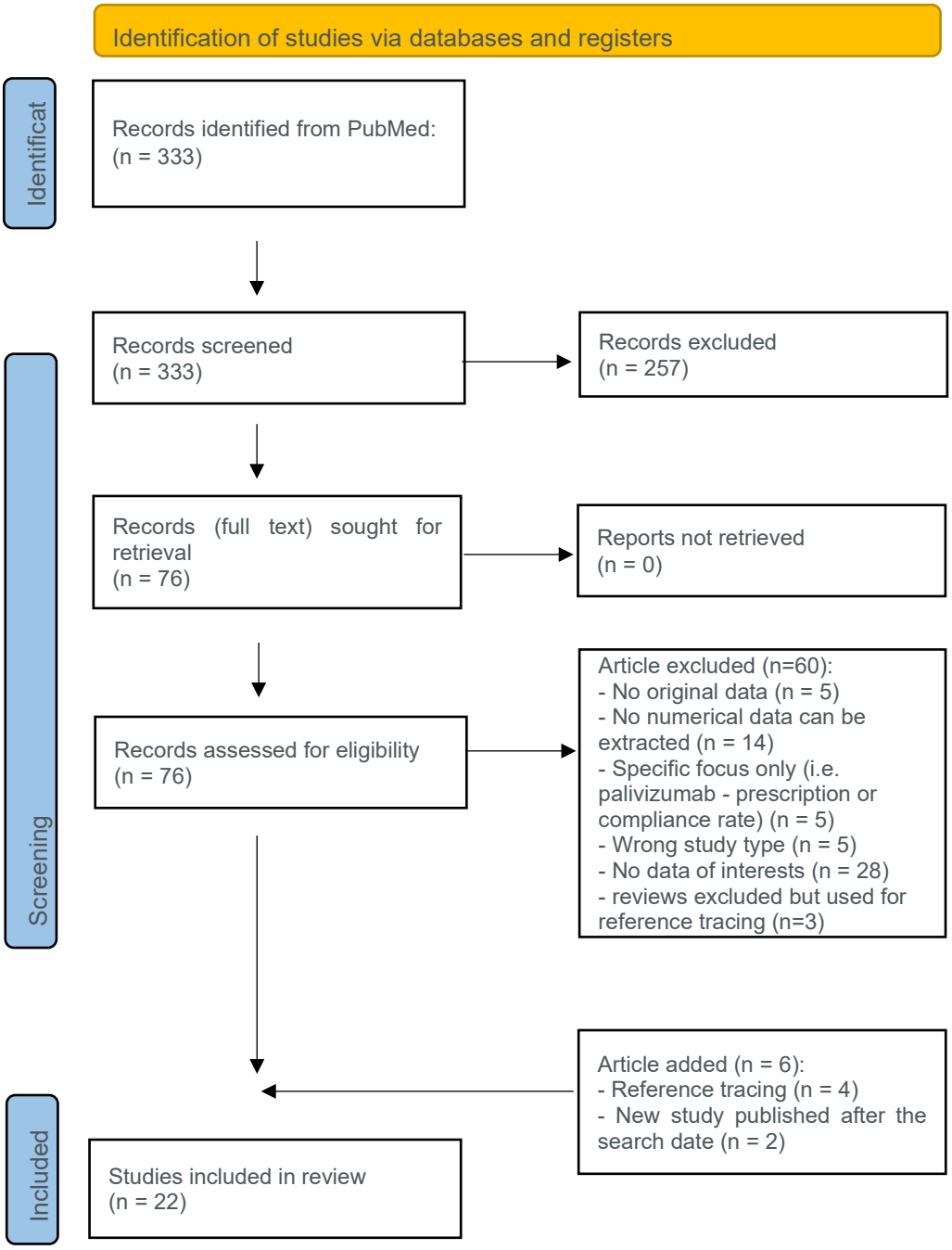
#	Keywords	Hits
1	respiratory syncytial virus [MeSH Terms] OR RSV [All Fields] OR orthopneumovirus [Title/Abstract]	21,677
2	pneumonia [Title/Abstract] OR bronchiolitis [Title/Abstract]	175,316
3	"disease burden" [Title/Abstract] OR "burden of disease" [Title/Abstract]	40,582
4	hospitalization [Title/Abstract] OR hospitalisation [Title/Abstract] OR "hospital admission"[Title/Abstract] OR incidence[Title/Abstract] OR morbidity[Title/Abstract] OR mortality[Title/Abstract] OR case-fatality[Title/Abstract] OR "case fatality"[Title/Abstract] OR mortality[Title/Abstract] OR death[Title/Abstract]	2,933,114
5	costs [Title/Abstract] OR "cost of illness"[Title/Abstract] OR cost-effectiveness [Title/Abstract] OR cost-utility [Title/Abstract] OR cost-benefit [Title/Abstract] OR "economic analysis" [Title/Abstract] OR "economic evaluation"[Title/Abstract] OR productivity [Title/Abstract]	441,088
6	“health care utilisation” [Title/Abstract] OR “health care utilization” [Title/Abstract] OR “resource use” [Title/Abstract]	22,901
7	quality of life [MeSH Terms]	295,761
8	Belgium [Text Word] OR Brussels [Text Word] OR Flanders [Text Word] OR Wallonia [Text Word] OR Europe [Text Word] OR European[Text Word]	34,832
9	France [Text Word] OR French [Text Word] OR Germany [Text Word] OR German [Text Word] OR Luxembourg [Text Word] OR Netherlands [Text Word] OR Dutch [Text Word]	655,895
10	"Child, Preschool"[MeSH Terms] OR "infant"[MeSH Terms] OR "infant, newborn"[MeSH Terms] OR "neonat*"[Title/Abstract] OR "baby"[Title/Abstract] OR "babies"[Title/Abstract] OR "toddler*"[Title/Abstract]	1,955,748
11	#1 OR #2	193,273
12	#3 OR #4 OR #5 OR #6 OR #7	3,561,962
13	#8 OR #9	995,480
14	#11 AND #12 AND #13 AND #10	704
15	Publication date: from 2014/1/1 - date	333

Appendix 4.1.2. Inclusion and exclusion criteria

	Inclusion	Exclusion
Population	Children <5 years of age in Belgium and neighbouring countries Multi-country studies that included Belgium	≥5 years of age Studies in non-European countries European countries with very different health care system as Belgium (i.e. the UK)
Intervention	No intervention, Palivizumab, RSV maternal vaccine (Abrysvo®), nirsevimab, clesrovimab	
Comparison	with or without RSV preventive strategies or treatments	
Outcome	RSV incidence or rate or ratio: • symptomatic infection rate • asymptomatic infection rate • medically attended rate • non-medically attended rate • hospitalisation rate • intensive care admission rate or probability • mortality rate or in-hospital case fatality ratio • outpatient visit rate • primary care visit rate unit cost and health care resource use Health-related quality of life data which can be converted into quality-adjusted life-years (QALY)	Non-RSV disease: Studies with a focus on pneumococcal diseases, influenza, bacterial infections, streptococcal infections, COVID-19, antibiotic resistance Studies without quantification/data. Studies that identify risk factors Health-related quality of life studies of which the data do not allow conversion into quality-adjusted life-years (QALY)
Study types	Epidemiological studies: • prospective • retrospective Modelling studies: • dynamic transmission model • static model • time series analysis Economic evaluations reporting original epidemiological, cost or resource use data: • cost or cost of illness • cost-effectiveness • cost utility • budget impact Health-related quality of life studies	Study protocols, commentaries, editorial letters, prevalence studies, safety studies, environmental studies, effectiveness studies, genome studies Health-related quality of life studies which cannot be converted into quality-adjusted life-year (QALY) Study will be excluded, but subject to reference tracing: • study reference costs from other studies • systematic reviews (without pooling the data)
Language	English, French, Dutch, German	Other language

Appendix 4.2. Results

Appendix 4.2.1. PRISMA flow diagram



Appendix 4.2.2. Data extraction

For studies conducted in Belgium or multi-country studies including Belgian patients, the data extraction table is presented in Table 58 and Table 59. For studies conducted in the neighbouring countries of Belgium, we extracted epidemiology (Table 60), costs (Table 61), and resource use data (Table 62) exclusively from non-hospital settings, along with mortality data (Table 63), to bridge data gaps for the cost-effectiveness analysis in Belgium. Health-related quality of life studies in both hospital and non-hospital settings were eligible to extract utilities / QALY (Table 61).

Table 58 – Studies conducted in Belgium: hospitalisation rate

Author	Year	Country	Study type	Study period	Cases definition	Age	Setting	Sample size	Hospitalisation incidence rate	Funding
Del Riccio[75]	2023	29 European countries including Belgium	Regression modelling based on data from the Netherlands, Norway, Finland, Denmark, France, England and Scotland	Registries data from 2006-2018	ICD-9 and ICD-10 coded	<5y	Hospitalisation	NA	Hospitalisation rate per 1000 population per year: mean (95%CI): 0-2m: 68.6 (58.8-78.4) 3-5m: 36.3 (30.9-41.7) 6-11m: 15.9 (13.1-18.7) 12-35m: 4.8 (3.8-5.9) 35-59m: 1.2 (0.9-1.4)	IHI funding, mixed: public and private partnership (RESCEU)
Bouckaert[6]	2023	Belgium	Retrospective national hospitalisation data analysis	2017-2018	ICD-10-coded	<5y	Hospitalisation (B-HDDS)	0-28 days: N=965 29 days -<1y: N=7081 1-4y: N=2499 0-4y: N=10545	Hospital episode per 1000 population: 0-1y: 68.3 1-4y: 5.0 0-4y: 17.2 (Death in hospital: 0-28 days: N=0 29 days-<1y: N=4 1-4y: N=1 0-4y: N=5)	Public funding (KCE)

IHI: Innovative Health Initiative, m: month, y: year, ICD: international Classification of Diseases, RESCEU: REspiratory Syncytial virus Consortium in Europe, KCE: Belgian health care knowledge centre.

Table 59 – Studies conducted in Belgium: direct cost and resource used

Author	Year	Country	Study type	Study period	Cases definition	Age	Setting	Sample size	Characteristics	Direct cost or healthcare utilisation	Funding
Tilmanne[8]	2025	Belgium	Retrospective cohort study	01/01/2018 – 31/12/2019	ICD-10-coded	<3 y	16 hospitals	N=2176	Hospital characteristics RSV as primary diagnosis: 88.3% (N=1921) RSV as secondary diagnosis: 11.7% (N=255) ED admission: 90.1% (N=1960) PICU admission: 4.4% (N=96) hCFR: 0.1% (N=1) Readmission: 53% (N=1153) Transfer to another hospital: 3.8% (N=83) Non-invasive ventilation: 5.1% (N=110) LoS: median [p25-p75] 3.7 days [2.2-5.4]	Cost in € year 2019, reported in median [25th and 75th percentile] Hospital perspective: €2924 [1919-4404] Health insurance perspective: €2221 [1796-2852] By diagnosis* Primary: €3078 [2045-4557]/€2274 [1840-2918] Secondary: €1962 [1548-3082]/€1882 [1564-2320] By age* 0-1y: €2973 [1916-4645]/€2287 [1183-2959] 1-2y: €2833 [1944-4393]/€2124 [1749-2729] 2-3y: €2951 [1900-3975]/€2139 [1840-2638] By ED admission* No: €2792 [1888-4491]/€2113[1539-2804] Yes: €2945 [1922-4386]/€2232[1818-2867] By PICU admission* No: €2834 [1892-2011]/€2184 [1780-2763] Yes: €7295 [5340-10181]/€4364 [3740-5725] By re-admission* No: €2973 [1946-4735]/€2301 [1835-3105] Yes: €2898 [1913-4352]/€2195[1781-2772]	Public funding
Hak[77]	2025	5 European countries, including Belgium	Prospective study	2020-2023	PCR confirmed	<5 y	Primary care: In Belgium, 6 sites in Flanders, paediatrician centers based in hospital	N=182 RSV+ (out of 446 total tested)		Healthcare utilisation: Primary care visit: mean: 2.5 (95%CI: 2.2-2.9) % ED visit: 32.4% (95%CI: 24.8-40.8) Hospitalisation: 43.7% (35.4-52.2%) Visit to another doctor: 4.2% (1.6-8.9%) Paramedical care visits: 6.3% (2.9-11.7%) Any prescribed medication: 31.7% (24.1-40.0%) Antibiotics: 12.7% (7.7-19.3%) Bronchodilators: 28.9% (21.6-37.1%) Corticosteroid inhalers: 12.4% (10.2-14.9%) Systemic corticosteroids: 9.4% (7.5-11.6%) Any over-the-counter medication: 51.4% (42.9-60.0) Paracetamol: 38.7% (30.7-47.3%) Nonsteroidal anti-inflammatory drugs: 17.6% (11.7-24.9%) Nasal spray: 37.9% (29.8-46.4%) Cough syrup: 3.5% (1.2-8.0%) Daycare/school absence: mean: 9.6 days (7.9-11.3) Parental work absence: 4.1 days (3.3-5.0)	Private funding (Sanofi and AstraZeneca)

*ICD: international Classification of Diseases, y: year, hCFR: in hospital case fatality ratio, ED: emergency department, PICU: paediatric intensive care unit, RESCEU: REspiratory Syncytial virus Consortium in Europe, KCE: Belgium health care knowledge centre * Hospital/Health insurance perspectives.*

Table 60 – Studies conducted outside of Belgium: epidemiology data from non-hospital setting (grey area: articles from reference tracing)

Author	Year	Country	Study type	Study period	Cases definition	Age	Setting	Sample size	Epidemiological data		Funding
Wildenbeest[3]	2023	Finland, England, Scotland, Spain, the Netherlands	Prospective, multi-center, observational cohort study (RESCEU)	01/07/2017-31/07/2020 But analysis period 01/09/2017-30/11/2019 (due to COVID-19 pandemic)	PCR-confirmed	≤1y	Community	Total birth cohort N=9154 Active RSV surveillance in a nested cohort of total birth cohort N=993 (included in the analysis) RSV+: 249	Medically attended RSV-associated ARI (MA) rate per 1000 infant-months: mean (95%CI) **Overall (5 countries)** <3m: 11.69 (8.34-16.38) 3-5m: 15.21 (11.28-20.52) 6-11m: 10.77 (8.36-13.88) <12m: 12.11 (10.24-23.1)	RSV-associated ARI rate per 1000 infant-months: mean (95%CI) **Overall (5 countries)** <3m: 17.55 (13.34-23.1) 3-5m: 31.69 (25.76-39.98) 6-11m: 22.81 (19.16-27.17) <12m: 23.70 (21.02-26.73)	IHI (RESCEU)
									Scotland: <3m: 4.95 (1.60-15.35) 3-5m: 19.10 (10.63-34.32) 6-11m: 11.47 (6.62-19.87) <12m: 11.75 (8.06-17.12)	**Scotland:** <3m: 11.70 (5.58-24.56) 3-5m: 44.82 (30.18-66.56) 6-11m: 24.77 (16.78-36.56) <12m: 26.52 (20.54-34.25)	
									England: <3m: 8.61 (3.58-20.71) 3-5m: 17.00 (8.89-32.54) 6-11m: 5.04 (2.09-12.10) <12m: 8.98 (5.69-14.18)	**England:** <3m: 13.31 (6.44-27.51) 3-5m: 34.07 (21.68-53.55) 6-11m: 12.99 (7.63-22.1) <12m: 18.39 (13.4-25.23)	
									Spain: <3m: 20.11 (11.37-35.55) 3-5m: 22.22 (12.92-38.24) 6-11m: 8.93 (4.80-16.61) <12m: 15.09 (10.82-21.06)	**Spain:** <3m: 27.46 (16.81-44.88) 3-5m: 37.28 (24.56-56.59) 6-11m: 20.58 (13.77-30.75) <12m: 26.49 (20.63-43.03)	
									Finland: <3m: 3.34 (0.84-13.55) 3-5m: 3.35 (0.84-13.41) 6-11m: 8.24 (4.37-15.52) <12m: 5.79 (3.40-9.85)	**Finland:** <3m: 3.34 (0.84-13.35) 3-5m: 8.38 (3.49-20.14) 6-11m: 11.78 (6.98-19.89) <12m: 8.81 (5.74-13.51)	
									The Netherlands: <3m: 21.93 (12.46-38.57) 3-5m: 14.27 (7.14-28.54) 6-11m: 20.28 (13.43-30.64) <12m: 19.20 (14.21-25.93)	**The Netherlands:** <3m: 32.63 (20.57-51.77) 3-5m: 33.90 (21.62-53.15) 6-11m: 44.48 (33.62-58.85) <12m: 38.89 (31.49-48.02)	
Krauer et al.[167]	2024	Germany	Dynamic transmission model	2015-2019	Lab-confirmed	all age group	Sentinel surveillance from primary care setting	NA	Fig 2 C: total weekly outpatient cases in all age-group: Highest number 2015-16: 19 (~Feb) 2016-17: 43 (Jan) 2017-18: 27 (Jan) 2018-19 38 (Jan) Fig 2 D: Distribution of cases by age group (primary care) 0-1y: 35%		Public funding

									2-4y: 24%	
Dolk[168]	2021	The Netherlands	Regression analysis of GP surveillance data	2003-2014	PCR confirmed	All age, including 0-4 years	Lab-confirmed	NA	RSV-attributable GP consultation: 0-4y: N=16345 Average rate: 1763 per 100 000	Private: AstraZeneca
Van Boven[169]	2020	The Netherlands	Dynamic transmission model using surveillance data	2015-2017	Linked with RSV virological data	All age, including <5y	Nivel primary care database	NA	RSV infection: Median (2.5%-97.5% posterior quantiles) **Probability of GP consultation**: <1y: 0.23 (0.21-0.25) 1-4y: 0.19 (0.17-0.21) **Probability of hospitalisation:** <1y: 0.014 (0.013-0.015) 1-4y: 0.014 (0.013-0.017)	IHI funding (RESCEU)
Muñoz-Quiles[108]	2016	Spain	Database	2009-2012	Bronchiolitis, ICD-coded	<2y	Outpatient	N=41,479	Outpatient incidence rate of bronchiolitis per 100 population 0-5m: 3.2 (95%CI: 3.1-3.3) 6-11m: 0.4 (0.3-0.4) 12-17m: 0.09 (0.06-0.11) 18-23m: 0.05 (0.03-0.07) 0-23m: 1.2 (1.2-1.3)	Private funding (AbbVie)
Barbieri[107]	2023	Italy	Paediatric primary care database	2012-2019	ICD-coded RSV-bronchiolitis	<24 month	Outpatient	Bronchiolitis episode N=7956	RSV-bronchiolitis rate per 1000 population (95%CI) <30 days: 8.83 (6.06-11.61) 31-60d: 12.74 (10.00-15.48) 61-90d: 10.67 (8.22-13.12) 4m: 8.5 (6.33-10.66) 5m: 3.42 (2.05-4.79) 6m: 3.82 (2.38-5.27) 7m: 2.68 (1.47-3.88) 8m:1.96 (0.94-2.99) 9m:1.4 (0.53-2.26) 10m: 0.83 (0.17-1.5) 11m: 1.38 (0.53-2.24) 12m: 0.59 (0.07-1.11) 13-24m: 0.22 (0.12-0.31)	Private: Sanofi
Reyes Domínguez[170]	2022	Spain	Database regression analysis	01/2016-06/2021	Lab-confirmed RSV	0-14y including 0- 24m	ED	sampling	ED rate per 1000 population 0-24m: 53.4	Public funding
Thomas[109]	2021	Finland	prospective cohort study	2017/2018 (1 RSV season)	RTI with PRC-confirmed RSV	<3m	Outpatient	N=408 RSV+: N=134	Outpatient rate per 1000 population 0-3m: 328.4 (275.2-389.0)	IHI (RESCEU)
Heikkinen[110]	2017	Finland	Cohort study	2000-2002 (2 RSV seasons)	Pneumonia with PCR-confirmed RSV	<13y	Outpatient	<3y: N=184	Outpatient rate per 1000 population (95%CI) 2001-2001 season / 2001-2002 season <1y: 167(141-219) / 360 (213-569) 1y: 160 (111-222) / 369 (237-549) 2y: 196 (142-263) / 379 (288-490)	Private: Novavax

ARI: acute respiratory illness, CI: confidence interval, ED: emergency department, IHI: Innovative Health Initiative, MA: medically-attended, HC: health care, RSV: Respiratory Syncytial Virus, PCR: Polymerase Chain Reaction, PICU: paediatric intensive care unit, RESCEU: REspiratory Syncytial virus Consortium in EUrope, m: month, y: year, RTI: respiratory tract infection.

Table 61 – Studies conducted outside of Belgium: costs data from non-hospitalisation setting and health-related quality of life data

Author	Year	Country	Study type	Study period	Cases definition	Age	Setting	Sample size	Cost	Health related Quality of life	Funding
Mao[79]	2023	Same as Wildenbeest	Same as Wildenbeest	07/2017-11/2019	Same as Wildenbeest	≤1y	Community	RSV episodes N=265 Cost data: N=256 Hospitalised: N=18 AMB: N=116 Non-MA: 120	Cost in € year 2021 value Direct cost from HC payer/societal perspectives. Pooled: Mean: €399.5 (95%CI: 242.3-584.2)/€494.3 (317.7-696.1)	Qaulity of life-day (QALD) loss Mean (95%CI) **Infants / Caregiver** Pooled: 1.9 (1.7-2.1) / 0.1 (0-0.2)	IHI (RESCEU)
									By resource use: Hospitalisation cost mean: €4587.9 (3085-6229)/€5094.9 (3507-6894) AMB cost mean: €167.8 (129.9-202.9)/€254.7 (197.9-318.2) nonMA cost mean: €1.8 (1.4-2.3)/ €44.2 (17.13-80.98)	By resource use: AMB: 2.3 (2.0-2.6) / 0.2 (0-0.2) Non-MA: 1.3 (1.1-1.6) / -0.1 (-0.3-0.1) Hospitalised: 3.7 (3.3-4.3)/1.2 (30.8-1.7) By caregivers: mother: 1.9 (1.6-2.1) / 0.1 (-0.1-0.2) father: 2.0 (1.4-2.6) / 0.1 (-0.2-0.4)	
									Finland: €317.7 (103.1-692.7) / €395.1 (145.5-777.6)	Finland: 2.0 (1.5-2.6) / -0.5 (-1.2-0.1)	
									The Netherlands: €335.4(116.8-660.3)/€445.5 (197.7-801.6)	The Netherlands: 1.6 (1.2-2.0) / 0 (-0.2-0.2)	
									Spain: €803.7 (322.2-1460.4)/€912.9 (383.4-1588.1)	Spain: 2.3 (1.9-2.7) / 0.2 (0-0.3)	
									UK: €201.4 (66.7-383.1)/€275.6 (115.3-482.3)	UK: 1.8 (1.5-2.0) / 0.2 (0.1-0.4)	
Alchikh[171]	2024	Germany (Berlin)	Cohort study from a prospective surveillance study in Berlin	12/2009-03/2014	ILI with PCR confirmed RSV	<18 years, but stratified by 0-5y	Hospital, ICU, ED and outpatient	Outpatient N=112	Cost in € (year unclear, likely 2024, it stated the unit cost was updated from 2015) Direct cost 0-5y: cost per episode DRGs related total (Direct +Non-Direct Medical Cost): €85 Summary of Individual Items: €95.17 Indirect cost: €340.20 Total of individual Items: €435.37		Public funding
Butel[172]	2021	France	Cost study using	10/2012 - 04/2014 (2 bronchiolitis seasons)	1st moderate or severe bronchiolitis episode (with PCR)	Age 6 weeks to 12	24 French pediatric EDs	Bronchiolitis: N=777 RSV+: N=674	Cost in € year 2018 Mean cost HC system/ social perspectives: ambulatory care (85%): €108 / €240 hospitalisation (15%): €2041/€3199		Public funding

						mon ths					
Garcia-Marcos [173]	2014	Spain	Prospective observational study (10 ED)	2010-2011	episodes of wheezing /bronchiolitis	<24 months	ED	N=644 RSV test performed: N=374 (56.3%) Sample size for RSV+ unknown	RSV+ (including €12.8 per test) Mean direct cost: €240.7 (SD=117.4) Mean indirect cost: €45.8 (SD=60.3) Year of value unclear		Private: Abbott

IHI: Innovative Health Initiative, m: month, y: year, RESCEU: REspiratory Syncytial virus Consortium in Europe, QALD: quality adjusted life-day, AMB: ambulatory care, ARI: acute respiratory illness.

Table 62 – Studies conducted outside of Belgium: resource use from non-hospitalisation setting (grey area: articles from reference tracing)

Author	Year	Country	Study type	Study period	Cases definition	Age	Setting	Sample size	Health care resource use	Funding
Hak et al. [80]	2024	Same as Wildenbeest	Same as Wildenbeest	07/2017-12/2019	Same as Wildenbeest	≤1y	Community	Non-MA: n=97 MA: n=102 (including 9 hospitalised) Non-MA: n=97 Spain: n=18 Scotland: n=26 England: n=13 Finland: n=7 The Netherlands: n=3	Overall: non-MA vs. MA [q25-q75] Parental Work Absenteeism: 25.8% vs. 37.5%: Median duration (day): 1 [1.0-4.25] vs. 4 [1.0 - 4] Use of any medication: 52.6% vs. 81.2% Finland Parental work absenteeism: 28.6% Use of any medication: 57.1% The Netherlands Parental work absenteeism: 25.8% Use of any medication: 33.3% Spain Parental work absenteeism: 41.2% Use of any medication: 61.1% England Parental work absenteeism: 30.8% Use of any medication: 61.5% Scotland Parental work absenteeism: 12.0% Use of any medication: 65.4%	IHI (RESCEU)
Dolk [168]	2021	The Netherlands	Regression analysis of GP surveillance data	2003-2014	PCR confirmed	All age, including 0-4 years	Lab-confirmed	NA	RSV-attributable GP consultation rate : 1763 per 100 000 0-4y: N=16345	Public funding

Heikkinen[110]	2017	Finland	Cohort study	2000-2002 (2 RSV seasons)	Pneumonia with PCR-confirmed RSV	<13y	Outpatient	<3y: N=184	Parental Work Absenteeism / Children's absence Mean duration: 2.6 days (SD=1.5) /3.0 days (SD=1.6)	Private: Novavax

IHI: Innovative Health Initiative, m: month, y: year, RESCEU: REspiratory Syncytial virus Consortium in Europe, MA: medically-attended.

Table 63 – Studies conducted outside of Belgium: mortality data

Author	Year	Country	Study type	Study period	Cases definition	Age	Setting	Sample size	Motality rate or in-hopital case fatality ratio	Funding
Lade et al.[174]	2024	Germany	Retrospective health claims analysis	01/01/2013-31/12/2019	ICD-10-coded data in hospitalisation setting	≤24 m	Statutory Health Insurance (SHI) data	1-12m: N=5565 13-24m: N=2131	Mortality rate per 1,000 person year (number of deaths over 5 years) 0-12m: 0.08 (N=14) 13-24m: 0.04 (N=6) 0-24m: 0.06 (N=20)	Private: Pfizer
Wick[175]	2023	Germany	Retrospective national hospitalisation data analysis	2019-2022	ICD-10-coded	≤2y	Hospital	Hospitalisation: N=98,220	In-hospital mortality (hCFR): 2019 / 2020 / 2021 / 2022 <1y: N=1 (0.005%) / N=2 (0.02%) / N=6 (0.03%) / N=4 (0.02%) 1-2y: N=2 (0.03%) / N=2 (0.05%) / N=6 (0.03%) / N=4 (0.02%) 0-2y: N=3 (0.01%) / N=4 (0.03%) / N=7 (0.02%) / N=10 (0.04%)	Public funding
Linssen[176]	2021	The Netherlands	Retrospective PICU registry analysis	2003-2016	PCR confirmed	0-24 m	PICU	N=2161 0-3m: N=1697 4-12m: N=359 13-24m: N=105	Death: N= 37 0-3m: 0.9%(N=16) 4-12m: 3.6% (N=13) 13-24m: 7.6% (N=8)	IHI funding (RESCEU)
Blanken[106]	2018	The Netherlands	Trial-based evaluations but the mortality data was based on registries	2003-2008	RSV-coded (with RSV confirmation)	0-3 year	PICU	N=1099	Deaths: total N=16 (over 6 years) Annual number: 2.3 children per year Estimated mortality rate: 0.00122% per year (population base)	Public funding

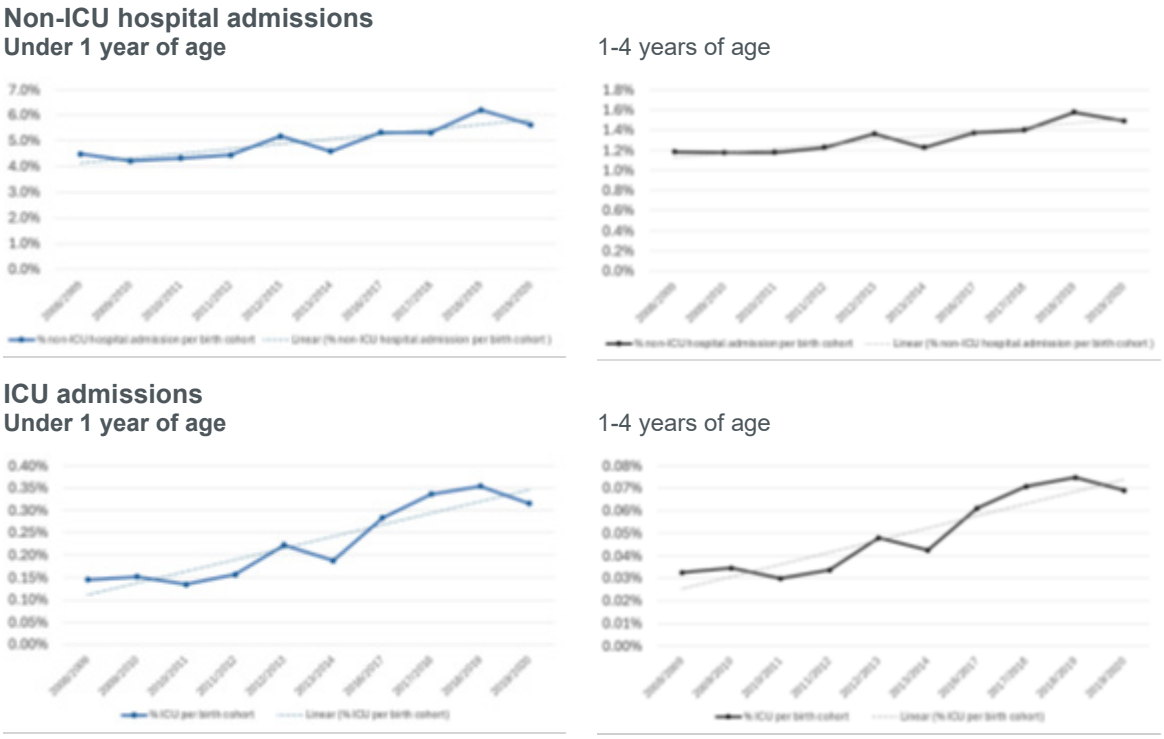
CI: confidence interval, ED: emergency department, IHI: Innovative Health Initiative, m: month, MA: medically-attended, HC: health care, OP: outpatient, RSV: Respiratory Syncytial Virus, PCR: Polymerase Chain Reaction, PICU: pediatric intensive care unit, QALD: quality adjusted life-days, RESCEU: REspiratory Syncytial virus Consortium in EUrope, y: year.

APPENDIX 5. COST-EFFECTIVENESS ANALYSIS: METHODS

Appendix 5.1. RSV-ICD coded hospitalisation data over 10 seasons

Figure 43 illustrates that an increasing trend was observed in non-ICU and ICU hospital admissions as a percentage of the birth cohort. The rise in non-ICU admissions was steady over time, while ICU admissions showed a steeper increase, particularly from the 2016/2017 season onwards.

Figure 43 – Percentage of non-ICU (top panels) and ICU admissions (bottom panels) for <1 y olds (left panels) and 1-4 y olds (right panels) relative to birth cohort size



Source: TCT data.TCT data is unavailable in calendar year 2015 due to technical errors. ICU: intensive care unit.

For the base case of our cost-effectiveness analysis, we used the average number of non-ICU and ICU admissions from the most recent 4 pre-COVID-19 RSV seasons (Table 30), while the 10-season annual average (Table 64) was used in scenario analysis.

Table 64 – Average number of RSV-ICD-coded non-ICU and ICU admissions in children <5 years by calendar month prior to the COVID-19 pandemic (summed over RSV seasons 2008/2009-2013/2014 and 2016/2017-2019/2020*, divided by 10 (number of seasons) and rounded to nearest integer)

Age	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC
Non-ICU hospital admissions												
0 month	94	32	18	9	4	3	2	5	15	93	338	380
1-11 month	657	243	136	58	33	19	12	8	43	247	1313	2057
1 year	7	10	9	5	5	4	3	4	11	99	461	581
2 years	123	43	23	9	5	3	2	1	6	38	179	191
3 years	40	15	8	2	1	1	0	0	2	23	95	83
4 years	12	6	3	2	1	0	0	0	2	6	23	23
ICU admissions												
0 month	12	6	3	1	0	0	0	1	2	8	29	45
1-11 months	24	9	5	2	0	1	0	0	1	10	48	72
1 year	0	0	0	0	0	0	0	0	0	1	6	10
2 years	2	1	0	0	0	0	0	0	0	1	2	2
3 years	1	0	0	0	0	0	0	0	0	0	2	1
4 years	1	0	0	0	0	0	0	0	0	0	0	1

*Source: TCT data. * TCT data is unavailable in calendar year 2015 due to technical errors. ICU: intensive care unit,*

Appendix 5.2. Healthcare practitioners in Belgium

Appendix 5.2.1. Proportion of accredited versus non-accredited practitioners

In Belgium, accreditation means that a health professional meets several criteria for continuing professional development, demonstrating a commitment to quality of care. With such accreditation, a health professional receives a higher fee for certain services, such as consultations, with no change in patient co-payment.

The RIZIV-INAMI Reports on Health Professionals[177] show the percentage of accreditation for each health profession (measured in full-time equivalents). In 2023, the percentages of accredited paediatricians[88] and GPs[178] were 94% and 95%, respectively.

Taking into account the percentage of accredited and non-accredited professionals, the average cost of a consultation with a paediatrician and a GP is shown in Table 65. The cost of a consultation with a paediatrician is estimated at €50.99, of which €12 is paid by the patient and €38.99 by the NIHDI. The cost of a consultation with a GP is estimated at €32.52, of which €6 is paid by the patient and €26.52 by the NIHDI.

Table 65 – General practitioners and paediatrician consultation costs

Nomenclature code	Label FR	Label NL	Cost (01/01/2025)
Paediatrician			
102071	Consultation au cabinet par un médecin spécialiste en pédiatrie, y compris un rapport écrit éventuel au médecin traitant	Raadpleging in de spreekkamer door een artsspecialist in de kindergeneeskunde, inclusief een eventueel schriftelijk verslag aan de behandelende arts	Honoraria: €44.97 Patient: €12 NIHDI: €32.97
102572	Consultation au cabinet par un médecin spécialiste en pédiatrie **accrédité**, y compris un rapport écrit éventuel au médecin traitant	Raadpleging in de spreekkamer door een **geaccrediteerde** artsspecialist in de kindergeneeskunde, inclusief een eventueel schriftelijk verslag aan de behandelende arts	Honoraria: €51.37 Patient: €12 NIHDI: €39.37
% accredited paediatricians (in FTE, 2023): 94%			
Average cost of a consultation with a paediatrician			Honoraria: €50.99 Patient: €12 NIHDI: €38.99
General Practitioner			
101032	Consultation au cabinet par un médecin généraliste	Raadpleging in de spreekkamer door een huisarts	Honoraria: €26.50 Patient: €6 NIHDI: €20.50
101076	Consultation au cabinet par un médecin généraliste **accrédité**	Raadpleging in de spreekkamer door een **geaccrediteerde** huisarts	Honoraria: €32.84 Patient: €6 NIHDI: €26.84
% accredited GPs (in FTE, 2023): 95%			
Average cost of a consultation with a GP			Honoraria: €32.52 Patient: €6 NIHDI: €26.52

FTE: full-time equivalent, GP: general practitioner, NIHDI: National Institute for Health and Disability Insurance.

APPENDIX 6. COST-EFFECTIVENESS ANALYSIS: SCENARIO ANALYSIS ON COVERAGE

Appendix 6.1. Impact of both interventions on RSV disease and economic burden with 70% coverage

Table 66 reports the RSV-related disease and economic burden under the standard of care, as well as following the implementation of the five RSV immunisation strategies with 70% coverage from HCP perspective. Table 67 presents the RSV-related disease and economic burden averted by each immunisation strategy, along with the corresponding intervention costs (based on list prices and 70% coverage), compared to a 'no intervention' scenario in children under 5 years of age.

Table 66 – Scenario analysis: disease and economic burden of standard care and 5 RSV strategies at 70% coverage in children <5 years from the HCP perspective (Mean [95%CrI])

	No intervention	MV	MV: Sep-Mar	mAb	mAb: Oct-Mar	mAb: Oct-Mar + catch-up
Coverage	*NA*	*70%*	*70%*	*70%*	*70%*	*70%*
Undiscounted cases						
Non-MA episodes	40,481 [16,594 ; 88,731]	38,611 [15,691 ; 84,799]	39,395 [16,193 ; 86,568]	37,340 [14,961 ; 82,709]	39,351 [16,013 ; 86,625]	36,419 [14,477 ; 80,800]
Outpatient episodes	66,249 [23,654 ; 145,314]	61,980 [22,722 ; 136,746]	63,414 [23,066 ; 139,464]	59,928 [21,429 ; 132,588]	63,505 [22,717 ; 139,847]	58,592 [20,970 ; 129,578]
Hospitalisations (non-ICU)	8,638	6,939 [5,897 ; 7,917]	7,246 [6,545 ; 8,010]	5,921 [5,674 ; 6,239]	7,110 [6,971 ; 7,289]	5,479 [5,192 ; 5,849]
ICU admissions	428	265 [219 ; 338]	288 [255 ; 348]	248 [232 ; 269]	303 [292 ; 318]	231 [213 ; 254]
Total cases	115,796 [49,314 ; 243,111]	107,795 [44,529 ; 229,800]	110,343 [46,059 ; 234,390]	103,437 [42,296 ; 221,805]	110,269 [45,993 ; 234,079]	100,721 [40,852 ; 216,481]
Deaths	5.0	3.6 [3.2 ; 4.3]	3.9 [3.6 ; 4.4]	3.4 [3.3 ; 3.6]	4.0 [4.0 ; 4.2]	3.2 [3.0 ; 3.4]
Life years lost	411	296 [258 ; 349]	318 [292 ; 359]	277 [265 ; 293]	329 [322 ; 339]	258 [245 ; 276]
Discounted QALYs (rate 1.5%)						
QALY losses due to non-MA episodes	132 [53 ; 286]	126 [50 ; 272]	128 [51 ; 277]	121 [48 ; 266]	128 [51 ; 279]	118 [47 ; 259]
QALY losses due to outpatient episodes	380 [137 ; 828]	355 [127 ; 781]	363 [131 ; 797]	343 [123 ; 757]	364 [131 ; 796]	335 [121 ; 742]
QALY losses due to hospitalisations	84 [72 ; 97]	68 [55 ; 84]	71 [59 ; 85]	58 [49 ; 67]	69 [59 ; 81]	53 [45 ; 63]
QALY losses due to ICU admissions	4.2 [3.6 ; 4.8]	2.6 [2.0 ; 3.4]	2.8 [2.3 ; 3.5]	2.4 [2.0 ; 2.9]	3.0 [2.5 ; 3.5]	2.3 [1.9 ; 2.7]
QALY losses due to deaths	205	147 [128 ; 174]	158 [145 ; 179]	138 [131 ; 145]	164 [160 ; 169]	128 [121 ; 137]
Total discounted QALY losses	805 [471 ; 1,421]	699 [362 ; 1,314]	723 [388 ; 1,342]	662 [353 ; 1,238]	728 [404 ; 1,328]	636 [336 ; 1,204]
Discounted cost (€'000) (rate 3%)						
Direct cost due to non-MA episodes	170 [70 ; 372]	162 [66 ; 354]	165 [68 ; 362]	156 [63 ; 345]	165 [67 ; 362]	152 [61 ; 337]
Direct cost due to outpatient episodes	6,031 [2,130 ; 13,370]	5,578 [1,993 ; 12,407]	5,730 [2,035 ; 12,748]	5,360 [1,902 ; 11,943]	5,740 [2,028 ; 12,765]	5,219 [1,856 ; 11,601]
Direct cost due to hospitalisations	29,888 [29,725 ; 30,065]	23,749 [19,991 ; 27,335]	24,856 [22,284 ; 27,663]	20,068 [19,166 ; 21,230]	24,364 [23,824 ; 25,026]	18,474 [17,435 ; 19,834]
Direct cost due to ICU admissions	6,251 [6,001 ; 6,502]	3,924 [3,265 ; 4,999]	4,258 [3,738 ; 5,142]	3,687 [3,411 ; 4,026]	4,471 [4,226 ; 4,753]	3,444 [3,153 ; 3,805]
Total discounted treatment cost	42,340 [37,926 ; 50,309]	33,413 [25,315 ; 45,095]	35,009 [28,125 ; 45,915]	29,271 [24,542 ; 37,544]	34,740 [30,145 ; 42,906]	27,289 [22,505 ; 35,577]
Intervention costs (list price*)	NA	14,151	8,255	59,155	29,578	59,155

** The cost of the intervention includes the cost per dose of the product (valued at list price), excluding delivery costs. QALY: quality-adjusted life-year, non-MA: non-medically attended, ICU: intensive care unit, CrI: credible interval, MV: year-round maternal vaccine, MV: Sep-Mar: seasonal maternal vaccine from September to March, mAb: year-round nirsevimab, mAb: Oct-Mar: seasonal mAb strategy from October to March, mAb: Oct-Mar + catch-up: seasonal mAb combined with a catch-up strategy.*

Table 67 – Scenario analysis: disease and economic burden averted in children <5 years at 70% coverage compared to 'no intervention' from the HCP perspective (Mean [95%CrI])

	MV	MV: Sep-Mar	mAb	mAb: Oct-Mar	mAb: Oct-Mar + catch-up
Coverage	*70%*	*70%*	*70%*	*70%*	*70%*
Undiscounted cases averted					
Non-MA episodes	1,870 [561 ; 3,968]	1,086 [340 ; 2,270]	3,141 [1,562 ; 5,999]	1,130 [599 ; 2,094]	4,062 [2,009 ; 7,875]
Outpatient episodes	4,269 [1,186 ; 9,762]	2,835 [788 ; 6,455]	6,321 [2,294 ; 12,962]	2,744 [949 ; 5,826]	7,657 [2,764 ; 15,790]
Hospitalisations (non-ICU)	1,699 [721 ; 2,742]	1,393 [628 ; 2,094]	2,718 [2,399 ; 2,965]	1,529 [1,350 ; 1,668]	3,159 [2,789 ; 3,446]
ICU admissions	163 [89 ; 208]	139 [80 ; 173]	179 [158 ; 196]	124 [110 ; 136]	196 [173 ; 214]
Total cases	8,001 [3,397 ; 15,581]	5,453 [2,491 ; 10,109]	12,359 [6,909 ; 21,846]	5,527 [3,259 ; 9,702]	15,074 [8,324 ; 27,078]
Deaths	1.4 [0.8 ; 1.9]	1.1 [0.6 ; 1.4]	1.6 [1.4 ; 1.8]	1.0 [0.9 ; 1.1]	1.9 [1.6 ; 2.0]
Life-years lost	116 [62 ; 153]	93 [52 ; 120]	134 [119 ; 146]	82 [72 ; 89]	153 [135 ; 167]
Discounted QALYs gained (rate 1.5%)					
QALYs gained due to non-MA episodes	6.3 [1.8 ; 13.5]	3.6 [1.1 ; 7.9]	10.5 [5.0 ; 20.5]	3.8 [1.9 ; 7.3]	13.6 [6.4 ; 26.7]
QALYs gained due to outpatient episodes	25 [6.8 ; 58]	17 [4.6 ; 39]	37 [13.5 ; 79]	16 [5.6 ; 35]	45 [16.2 ; 96]
QALYs gained due to hospitalisations	17 [6.9 ; 28]	14 [6.2 ; 21]	27 [22.0 ; 31]	15 [12.4 ; 18]	31 [25.5 ; 37]
QALYs gained due to ICU admission	1.6 [0.9 ; 2.2]	1.4 [0.8 ; 1.8]	1.8 [1.4 ; 2.1]	1.2 [1.0 ; 1.4]	1.9 [1.6 ; 2.3]
QALYs gained due to deaths	58 [31 ; 76]	47 [26 ; 60]	67 [59 ; 73]	41 [36 ; 45]	76 [67 ; 83]
Total discounted QALYs gained	107 [70 ; 153]	82 [54 ; 113]	143 [113 ; 193]	77 [63 ; 99]	168 [131 ; 230]
Discounted treatment costs saved (€ '000) (rate 3%)					
Direct cost saved due to non-MA episodes	8.3 [2.5 ; 17.6]	4.8 [1.5 ; 10.1]	13.9 [6.9 ; 26.6]	5.0 [2.6 ; 9.3]	18.0 [8.9 ; 34.9]
Direct cost saved due to outpatient episodes	453 [123 ; 1,084]	301 [85 ; 716]	671 [247 ; 1,472]	291 [103 ; 656]	812 [299 ; 1,801]
Direct cost saved due to hospitalisations	6,139 [2,605 ; 9,893]	5,032 [2,271 ; 7,575]	9,820 [8,663 ; 10,701]	5,524 [4,873 ; 6,020]	11,414 [10,069 ; 12,438]
Direct cost saved due to ICU admissions	2,327 [1,277 ; 2,976]	1,993 [1,141 ; 2,487]	2,564 [2,265 ; 2,832]	1,780 [1,573 ; 1,966]	2,807 [2,480 ; 3,100]
Total treatment cost averted	8,928 [5,225 ; 12,724]	7,330 [4,458 ; 9,945]	13,068 [11,505 ; 14,362]	7,600 [6,719 ; 8,314]	15,051 [13,232 ; 16,578]
Intervention and incremental costs (€ '000)					
Intervention costs (list price*)	14,151	8,255	59,155	29,578	59,155
Incremental costs	5,222.8 [1,427 ; 8,926]	924.7 [-1,691 ; 3,797]	46,086.9 [44,793 ; 47,650]	21,977.4 [21,264 ; 22,859]	44,104.3 [42,577 ; 45,923]

*Negative incremental costs indicate savings. * The cost of the intervention includes the cost per dose of the product (valued at list price), excluding delivery costs. CrI: credible interval, QALY: quality-adjusted life year, non-MA: non-medically attended, ICU: intensive care unit, MV: year-round maternal vaccine, MV: Sep-Mar: seasonal maternal vaccine from September to March, mAb: year-round nirsevimab, mAb: Oct-Mar: seasonal mAb strategy from October to March, mAb: Oct-Mar + catch-up: seasonal mAb combined with a catch-up strategy.*

Appendix 6.2. Impact of maternal vaccine on RSV disease and economic burden with 90% coverage for MV

Table 68 – Scenario analysis: disease and economic burden of standard care and MV strategies at 90% coverage in children <5 years from the HCP perspective (Mean [95%CrI])

	No intervention	MV	MV: Sep-Mar
Coverage	*NA*	*90%*	*90%*
Undiscounted cases			
Non-MA episodes	40,481 [16,594 ; 88,731]	38,076 [15,315 ; 83,663]	39,085 [15,961 ; 85,951]
Outpatient episodes	66,249 [23,654 ; 145,314]	60,761 [22,236 ; 133,609]	62,604 [22,900 ; 137,804]
Hospitalisations (non-ICU)	8,638	6,454 [5,113 ; 7,711]	6,848 [5,946 ; 7,831]
ICU admissions	428	218 [160 ; 313]	248 [205 ; 325]
Total cases	115,796 [49,314 ; 243,111]	105,509 [42,824 ; 225,296]	108,785 [45,012 ; 231,911]
Deaths	5.0	3.2 [2.6 ; 4.1]	3.6 [3.2 ; 4.2]
Life years lost	411	263 [214 ; 331]	291 [258 ; 344]
Discounted QALYs (rate 1.5%)			
QALY losses due to non-MA episodes	132 [53 ; 286]	124 [49 ; 269]	127 [50 ; 275]
QALY losses due to outpatient episodes	380 [137 ; 828]	347 [125 ; 764]	358 [129 ; 787]
QALY losses due to hospitalisations	84 [72 ; 97]	63 [48 ; 81]	67 [54 ; 82]
QALY losses due to ICU admission	4.2 [3.6 ; 4.8]	2.1 [1.5 ; 3.1]	2.4 [1.9 ; 3.3]
QALY losses due to deaths	205	130 [106 ; 165]	145 [128 ; 171]
Total discounted QALY losses	805 [471 ; 1,421]	666 [329 ; 1,282]	699 [363 ; 1,318]
Discounted cost (€'000) (rate 3%)			
Direct cost due to non-MA episodes	170 [70 ; 372]	159 [64 ; 349]	164 [67 ; 359]
Direct cost due to outpatient episodes	6,031 [2,130 ; 13,370]	5,448 [1,950 ; 12,187]	5,644 [2,012 ; 12,506]
Direct cost due to hospitalisations	29,888 [29,725 ; 30,065]	21,995 [17,158 ; 26,591]	23,419 [20,119 ; 26,994]
Direct cost due to ICU admissions	6,251 [6,001 ; 6,502]	3,259 [2,432 ; 4,609]	3,689 [3,052 ; 4,795]
Total discounted treatment cost	42,340 [37,926 ; 50,309]	30,861 [21,604 ; 43,736]	32,916 [25,250 ; 44,654]
Intervention costs (list price*)	NA	18,194	10,613

** The cost of the intervention includes the cost per dose of the product (valued at list price), excluding delivery costs. QALY: quality-adjusted life-year, non-MA: non-medically attended, ICU: intensive care unit, CrI: credible interval, MV: year-round maternal vaccine, MV: Sep-Mar: seasonal maternal vaccine from September to March.*

Table 69 – Scenario analysis: disease and economic burden averted by MV strategies at 90% coverage in children <5 years compared to 'no intervention' from the HCP perspective (Mean [95%CrI])

	MV	MV: Sep-Mar
Coverage	*90%*	*90%*
Undiscounted cases averted		
Non-MA episodes	2,404 [721 ; 5,101]	1,396 [437 ; 2,919]
Outpatient episodes	5,488 [1,525 ; 12,551]	3,645 [1,014 ; 8,299]
Hospitalisations (non-ICU)	2,185 [927 ; 3,525]	1,790 [807 ; 2,692]
ICU admissions	209 [115 ; 267]	179 [102 ; 222]
Total cases	10,286 [4,367 ; 20,033]	7,011 [3,203 ; 12,997]
Deaths	1.8 [1.0 ; 2.4]	1.5 [0.8 ; 1.9]
Life-years lost	149 [80 ; 197]	120 [67 ; 154]
Discounted QALYs gained (rate 1.5%)		
QALYs gained due to non-MA episodes	8.1 [2.3 ; 17.4]	4.7 [1.4 ; 10.2]
QALYs gained due to outpatient episodes	32 [8.7 ; 75]	21 [5.9 ; 50]
QALYs gained due to hospitalisations	21 [8.9 ; 35]	18 [8.0 ; 28]
QALYs gained due to ICU admissions	2.1 [1.1 ; 2.8]	1.8 [1.0 ; 2.3]
QALYs gained due to deaths	74 [40 ; 98]	60 [33 ; 77]
Total discounted QALYs gained	138 [89 ; 197]	105 [69 ; 145]
Discounted treatment costs saved (€'000) (rate 3%)		
Direct cost saved due to non-MA episodes	10.7 [3.2 ; 23]	6.2 [1.9 ; 13]
Direct cost saved due to outpatient episodes	583 [159 ; 1,394]	387 [109 ; 920]
Direct cost saved due to hospitalisations	7,893 [3,349 ; 12,720]	6,469 [2,920 ; 9,739]
Direct cost saved due to ICU admissions	2,992 [1,642 ; 3,827]	2,562 [1,467 ; 3,198]
Total treatment cost averted	11,479 [6,718 ; 16,360]	9,424 [5,732 ; 12,787]
Intervention and incremental costs (€'000)		
Intervention costs (list price*)	18,194	10,613
Incremental costs	6,715.0 [1,834 ; 11,476]	1,188.9 [-2,174 ; 4,881]

*Negative incremental costs indicate savings. * The cost of the intervention includes the cost per dose of the product (valued at list price), excluding delivery costs. CrI: credible interval, QALY: quality-adjusted life year, non-MA: non-medically attended, ICU: intensive care unit, MV: year-round maternal vaccine, MV: Sep-Mar: seasonal maternal vaccine from September to March.*

APPENDIX 7. COST-EFFECTIVENESS ANALYSIS: TWO-WAY THRESHOLD ANALYSES OF INTERVENTIONS' COST FOR EACH SCENARIO

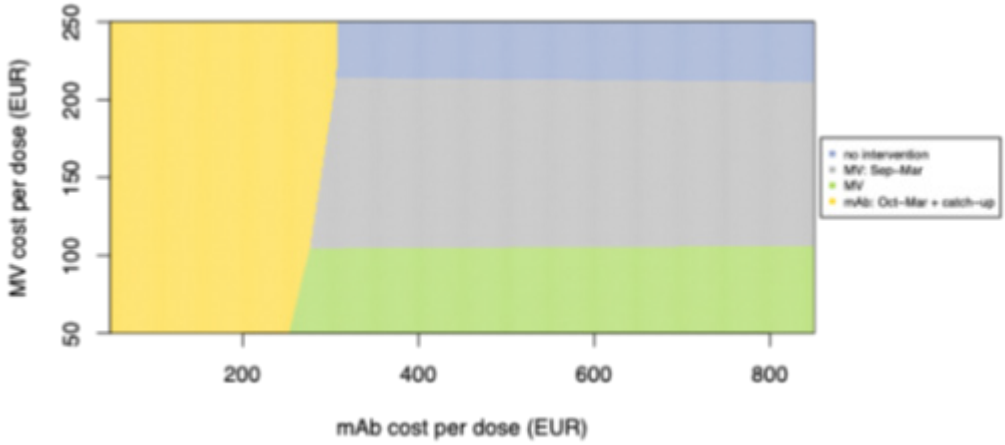
A list of scenario analyses is provided in Table 55, with overall results presented in Figure 41 and Figure 42. This section presents the cost threshold analysis for each scenario. The costs per dose should be interpreted to include both purchase and delivery costs.

Appendix 7.1. Cost-effectiveness from the societal perspective

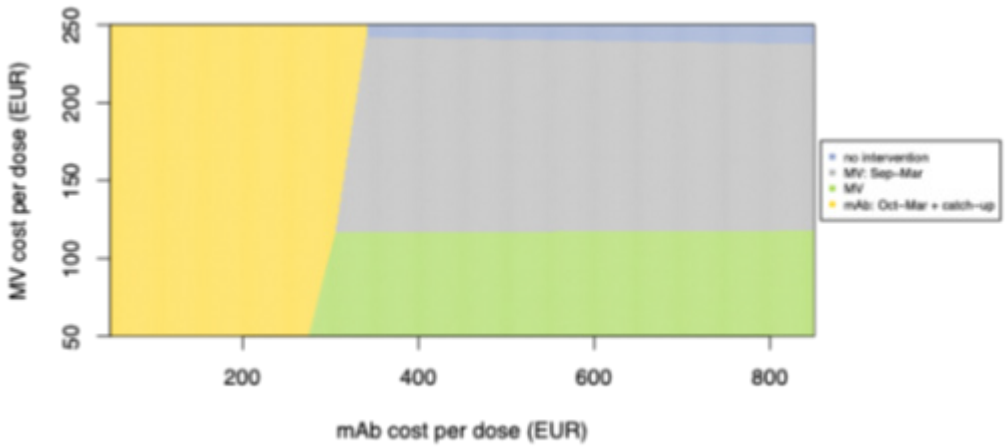
The seasonal mAb strategy is never the optimal choice, indicating it is dominated by MV and seasonal mAb plus catch-up strategies.

Figure 44 – Intervention cost threshold analysis from the societal perspective

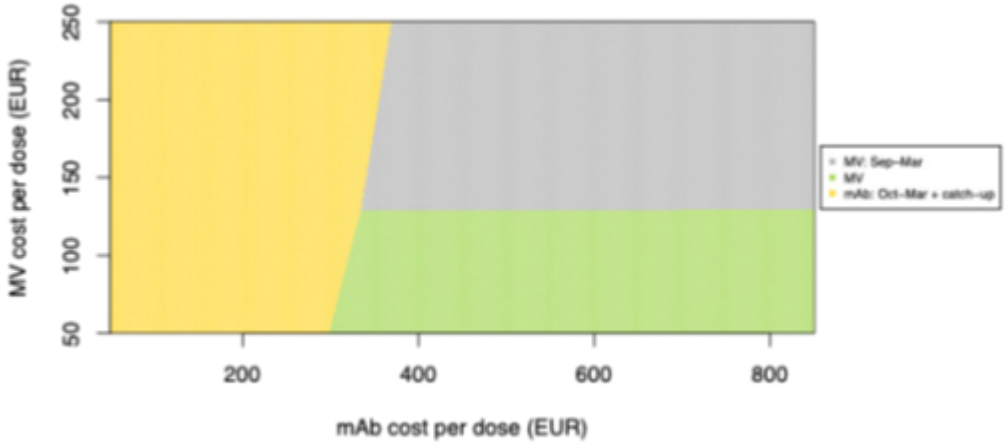
Willingness to pay: €20,000 per QALY gained



Willingness to pay: €35,000 per QALY gained



Willingness to pay: €50,000 per QALY gained



EUR: euro, HCP: health care payers', QALY: quality-adjusted life-year, MV: year-round maternal vaccine, MV: Sep-Mar: seasonal maternal vaccine from September to March, mAb: Oct-Mar + catch-up: seasonal mAb combined with a catch-up strategy.

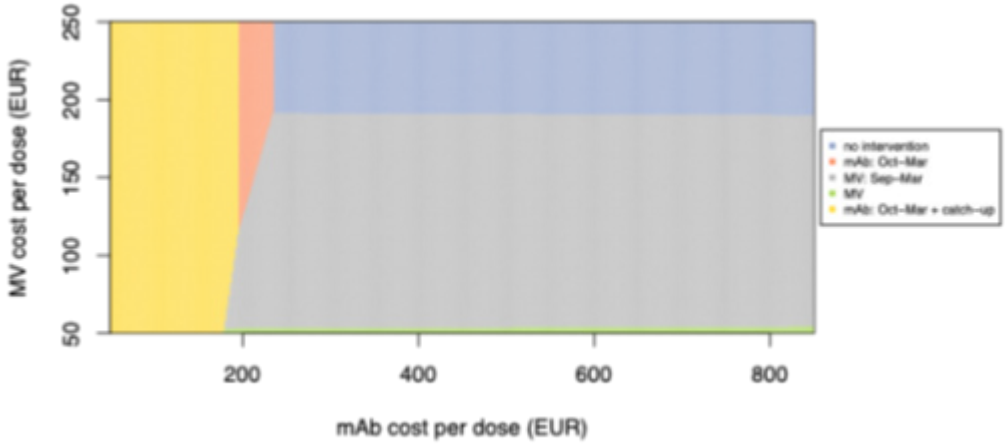
Appendix 7.2. Hospitalisation data-related scenarios

When using the 10-season average data for non-ICU and ICU admissions, the seasonal mAb strategy (colour in orange) could be the optimal strategy under all three WTP values. The area where this strategy was preferred was larger at the lower WTP value of €20,000 and narrower at the higher WTP value of €50,000. For example, at a WTP of €35,000 per QALY gained, the seasonal mAb strategy would be preferred, if the mAb costed between €210 to €230 per dose and the MV costed more than €150 per dose (Figure 45, middle plot).

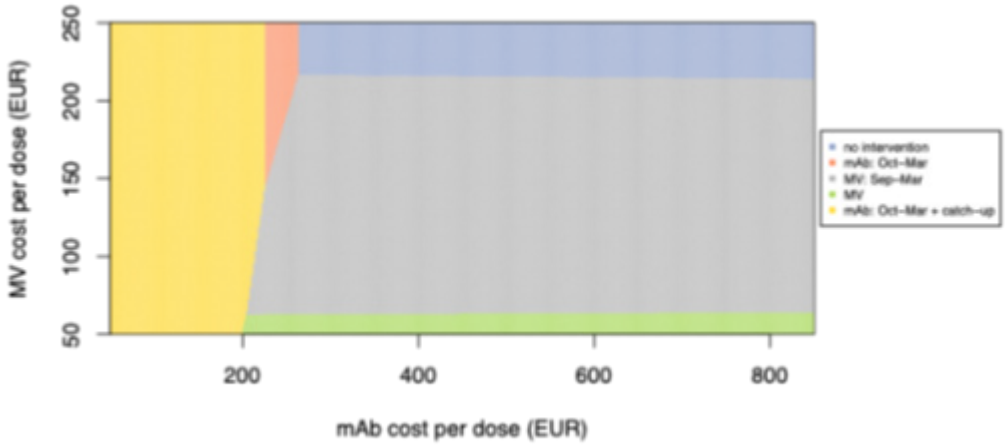
Compared to the base case, the colour pattern shifted left and downwards when using only the primary diagnosis code to select hospitalisations (Figure 46), as well as using season 2023/2024 age distribution data among the 1-11-month age-group (Figure 47). When combining primary (only) ICD diagnostic codes with the 2023/2024 season BELSARI-NET data for the distribution of children aged 1–11 months (Figure 48), the colour pattern shifted further left and downwards.

Figure 45 – Intervention cost threshold analysis from HCP perspective: scenario of using average 10 seasons TCT hospital admissions data

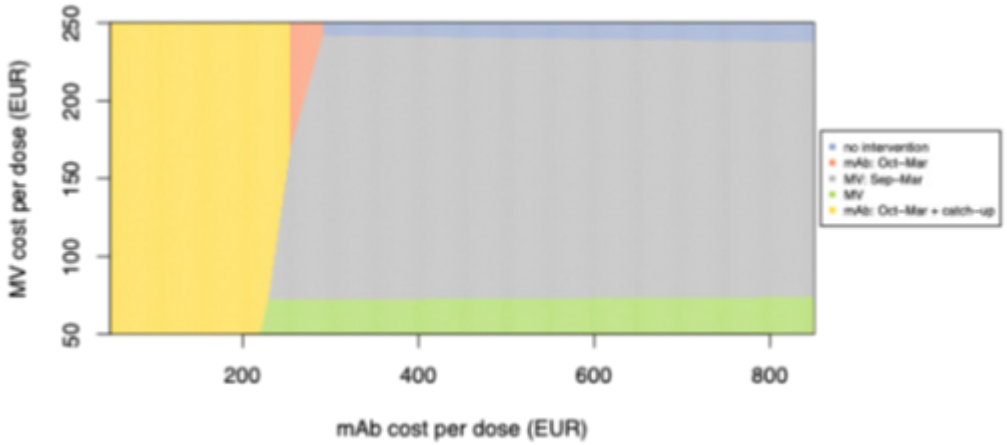
Willingness to pay: €20,000 per QALY gained



Willingness to pay: €35,000 per QALY gained



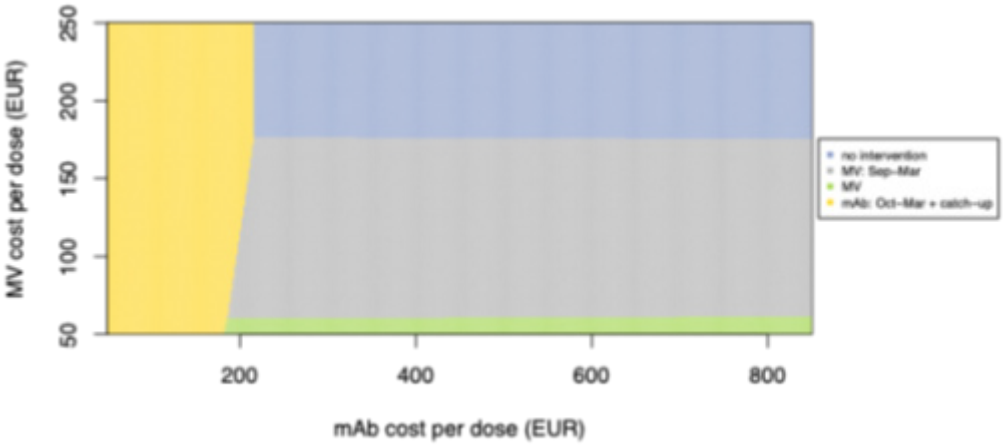
Willingness to pay: €50,000 per QALY gained



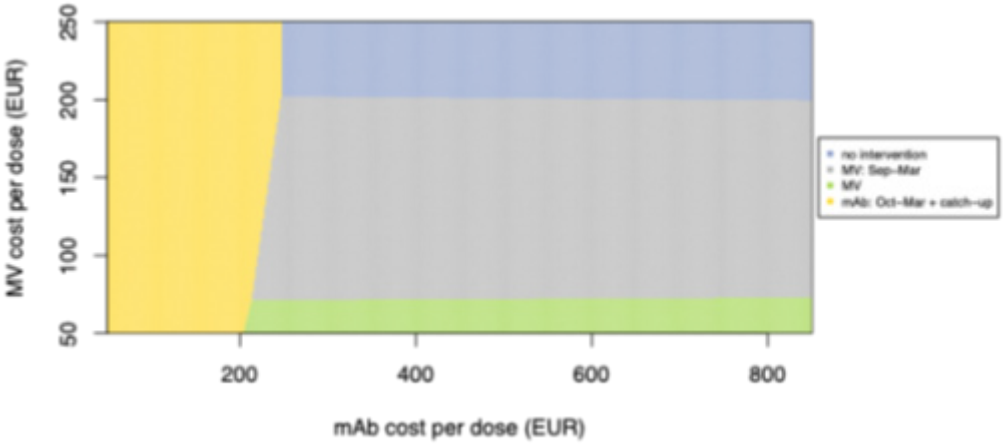
EUR: euro, HCP: health care payers', QALY: quality-adjusted life-year, MV: year-round maternal vaccine, MV: Sept-Mar: seasonal maternal vaccine from September to March, mAb: Oct-Mar: seasonal mAb strategy from October to March, mAb: Oct-Mar + catch-up: seasonal mAb combined with a catch-up strategy.

Figure 46 – Intervention cost threshold analysis from HCP perspective: scenario of using only the primary diagnosis ICD-code to select hospitalisations

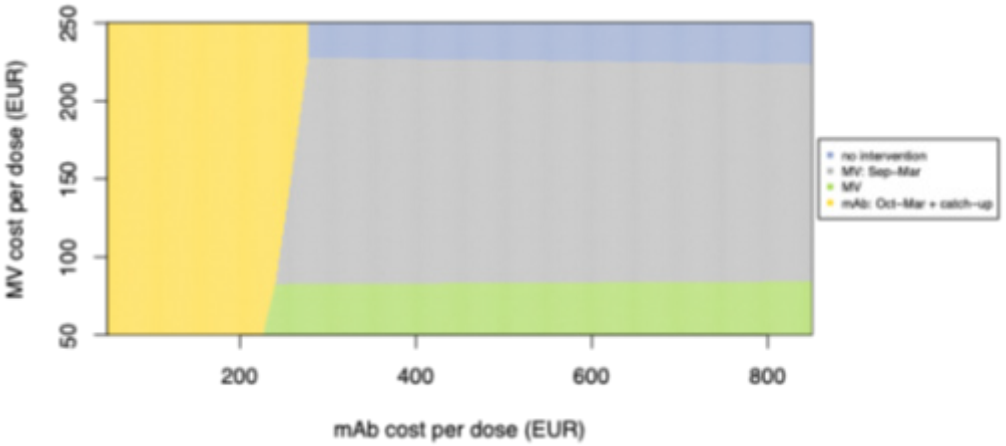
Willingness to pay: €20,000 per QALY gained



Willingness to pay: €35,000 per QALY gained



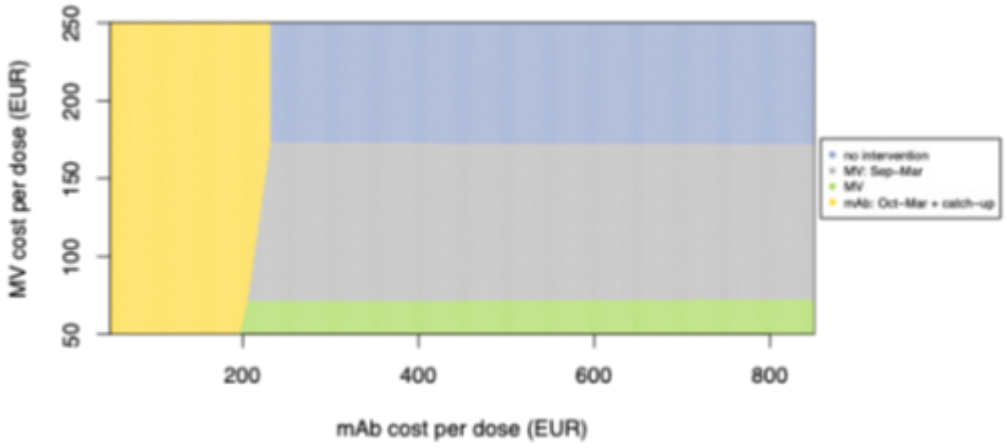
Willingness to pay: €50,000 per QALY gained



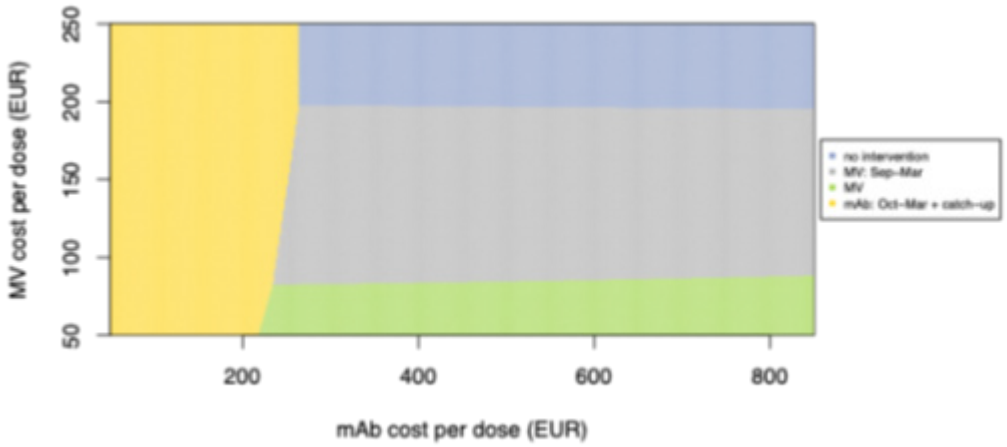
EUR: euro, HCP: health care payers', QALY: quality-adjusted life-year, MV: year-round maternal vaccine, MV: Sep-Mar: seasonal maternal vaccine from September to March, mAb: Oct-Mar + catch-up: seasonal mAb combined with a catch-up strategy.

Figure 47 – Intervention cost threshold analysis from HCP perspective: scenario of using season 2023/2024 age distribution data among the 1-11-month age-group

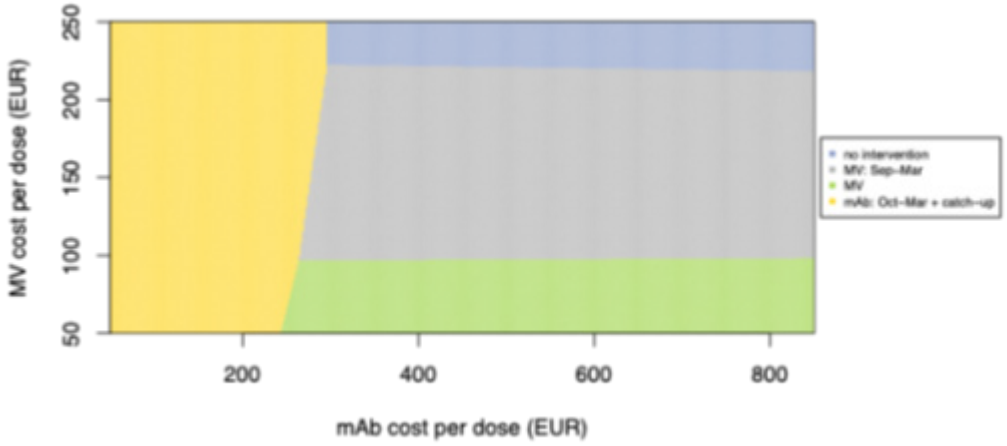
Willingness to pay: €20,000 per QALY gained



Willingness to pay: €35,000 per QALY gained



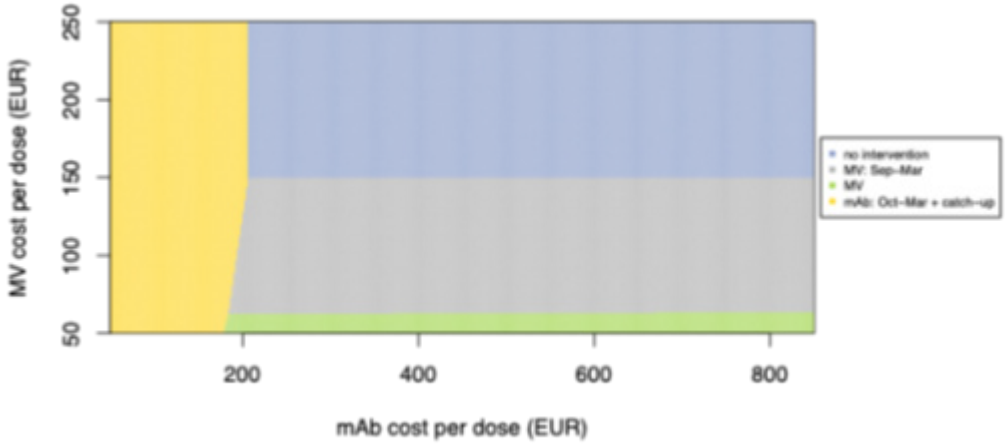
Willingness to pay: €50,000 per QALY gained



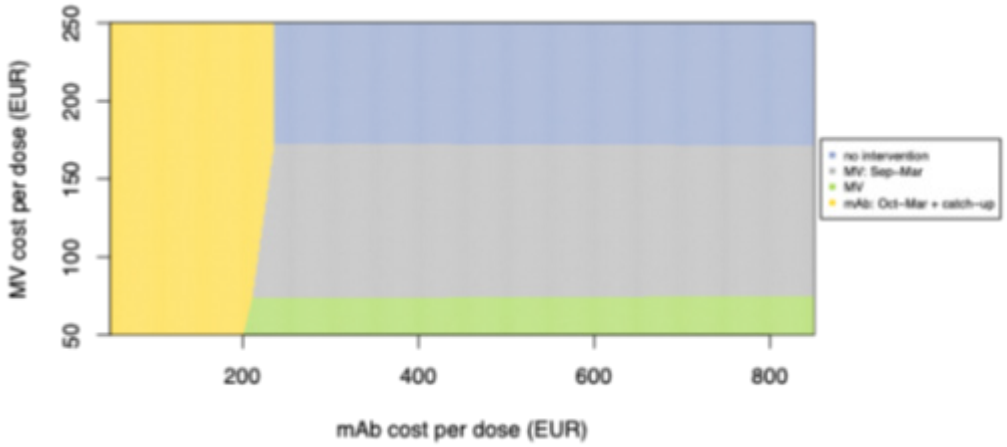
EUR: euro, HCP: health care payers', QALY: quality-adjusted life-year, MV: year-round maternal vaccine, MV: Sep-Mar: seasonal maternal vaccine from September to March, mAb: Oct-Mar: seasonal mAb strategy from October to March, mAb: Oct-Mar + catch-up: seasonal mAb combined with a catch-up strategy.

Figure 48 – Intervention cost threshold analysis from HCP perspective: scenario of using season 2023/2024 age distribution data among the 1-11-month age-group and only the primary diagnosis code to select hospitalisations

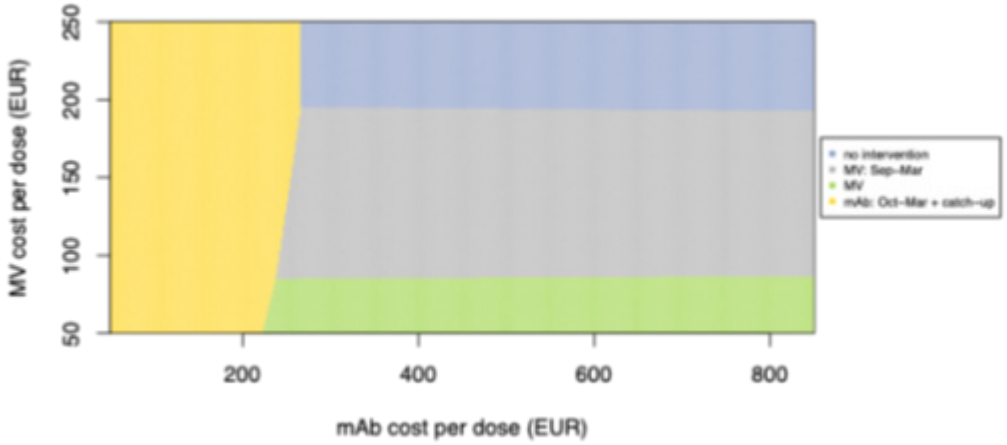
Willingness to pay: €20,000 per QALY gained



Willingness to pay: €35,000 per QALY gained



Willingness to pay: €50,000 per QALY gained



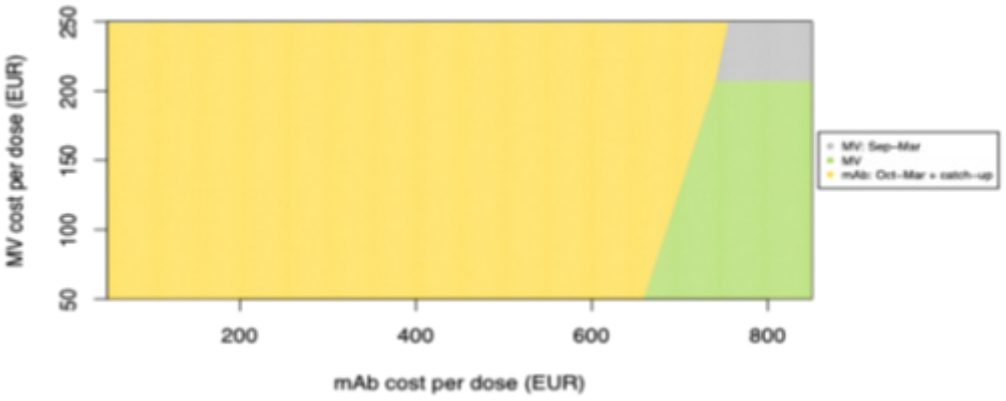
EUR: euro, HCP: health care payers', QALY: quality-adjusted life-year, MV: year-round maternal vaccine, MV: Sep-Mar: seasonal maternal vaccine from September to March, mAb: mAb: Oct-Mar + catch-up: seasonal mAb combined with a catch-up strategy.

Appendix 7.3. Inclusion of recurrent wheezing and asthma

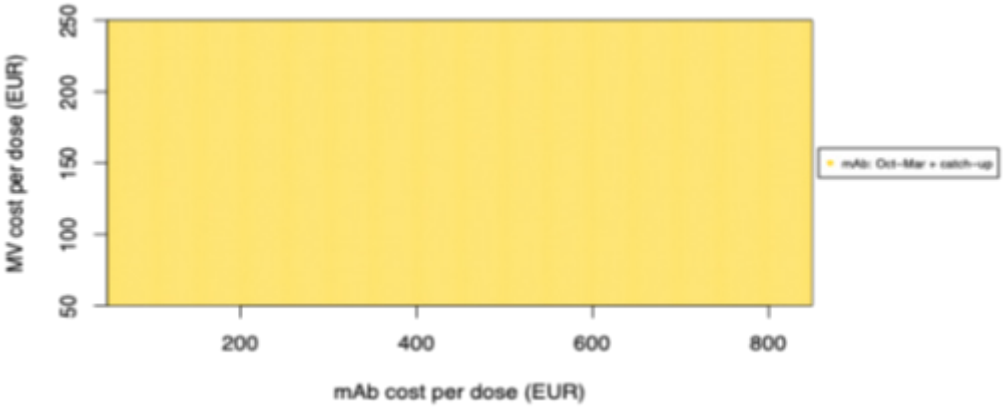
Including our recurrent wheezing and asthma scenarios led to substantial changes in the overall results, rendering seasonal mAb with catch-up cost-effective at much higher intervention costs per dose. The causality and quantification of this effect are both debated.

Figure 49 – Intervention cost threshold analysis from HCP perspective: inclusion of recurrent wheezing and asthma up to 3 years

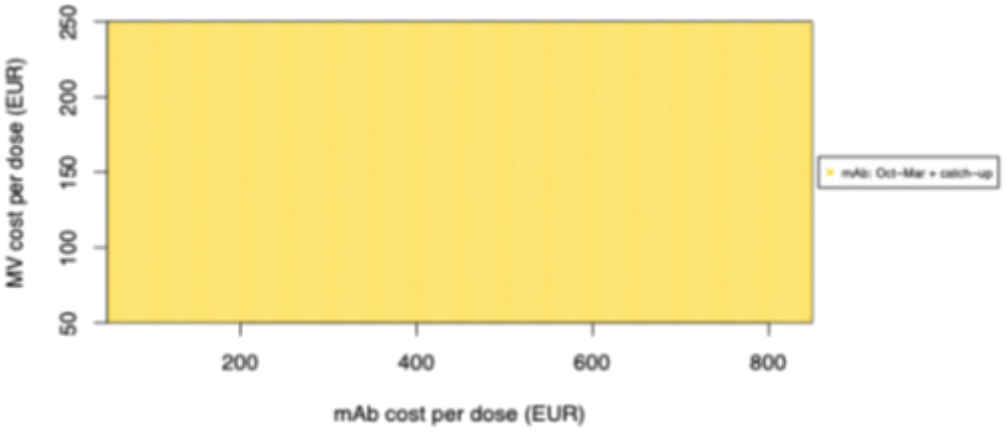
Willingness to pay: €20,000 per QALY gained



Willingness to pay: €35,000 per QALY gained



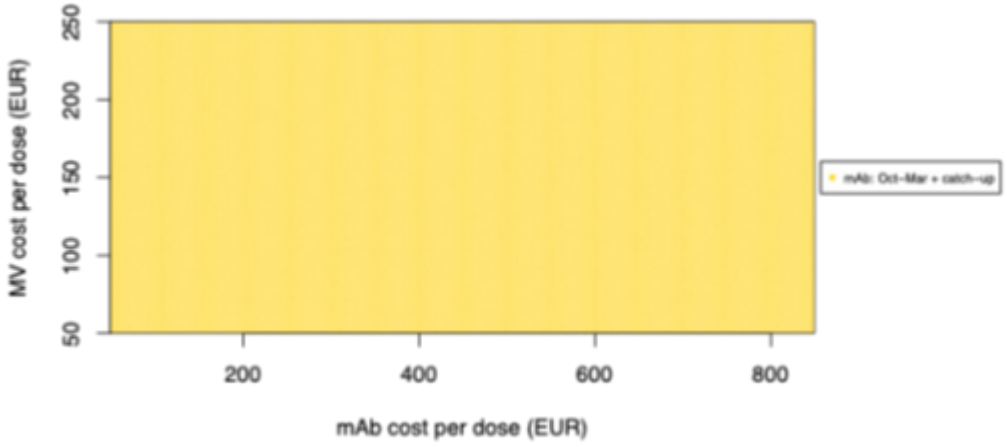
Willingness to pay: €50,000 per QALY gained



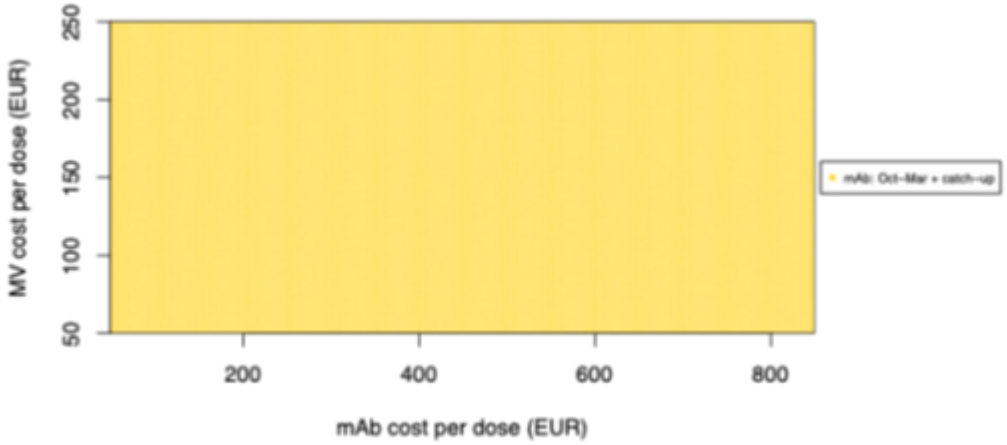
EUR: euro, HCP: health care payers', QALY: quality-adjusted life-year, MV: year-round maternal vaccine, MV: Sep-Mar: seasonal maternal vaccine from September to March, mAb: Oct-Mar + catch-up: seasonal mAb combined with a catch-up strategy.

Figure 50 – Intervention cost threshold analysis from HCP perspective: inclusion of recurrent wheezing and asthma up to 13 years

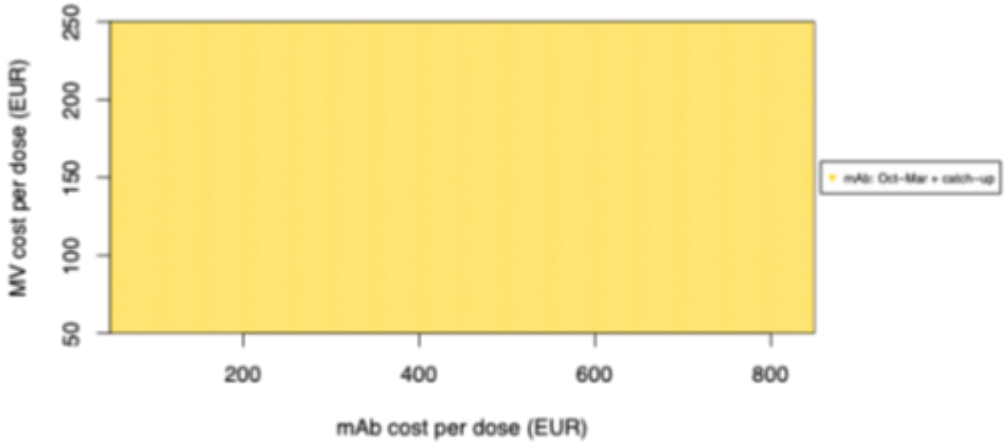
Willingness to pay: €20,000 per QALY gained



Willingness to pay: €35,000 per QALY gained



Willingness to pay: €50,000 per QALY gained



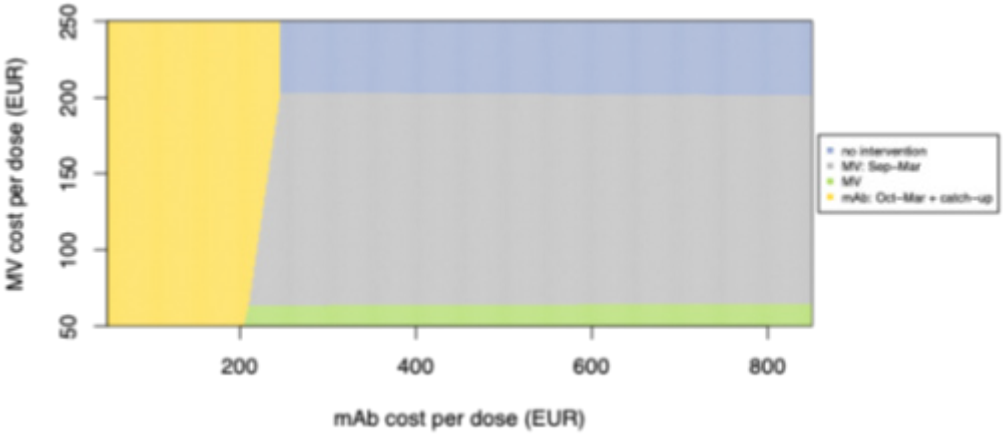
EUR: euro, HCP: health care payers', QALY: quality-adjusted life-year, mAb: Oct-Mar + catch-up: seasonal mAb combined with a catch-up strategy.

Appendix 7.4. RSV-related outpatient incidence rate

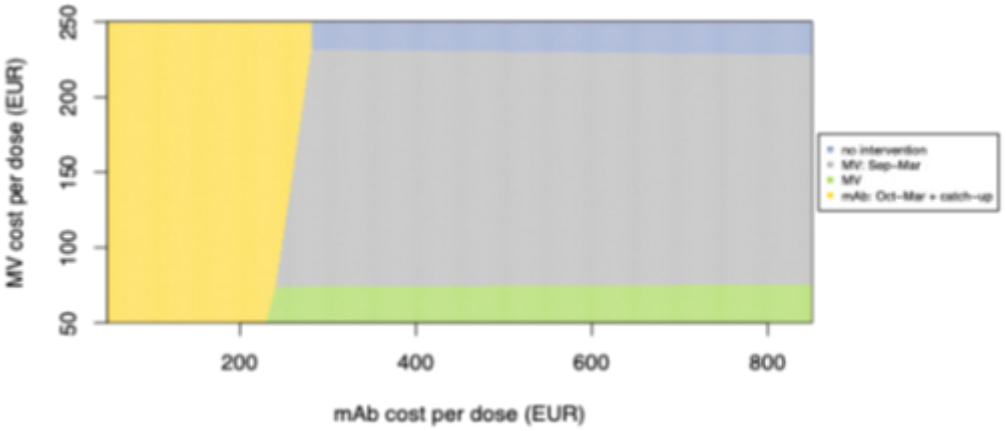
In the scenario analysis using the Dutch outpatient and pooled incidence rate, the results were comparable to the base case analysis.

Figure 51 – Intervention cost threshold analysis from HCP perspective: using the outpatient incidence rate from the Netherlands

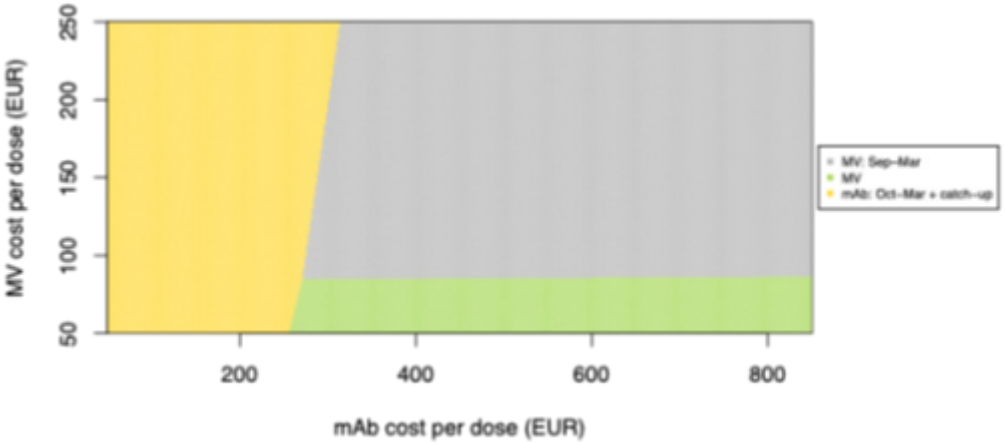
Willingness to pay: €20,000 per QALY gained



Willingness to pay: €35,000 per QALY gained



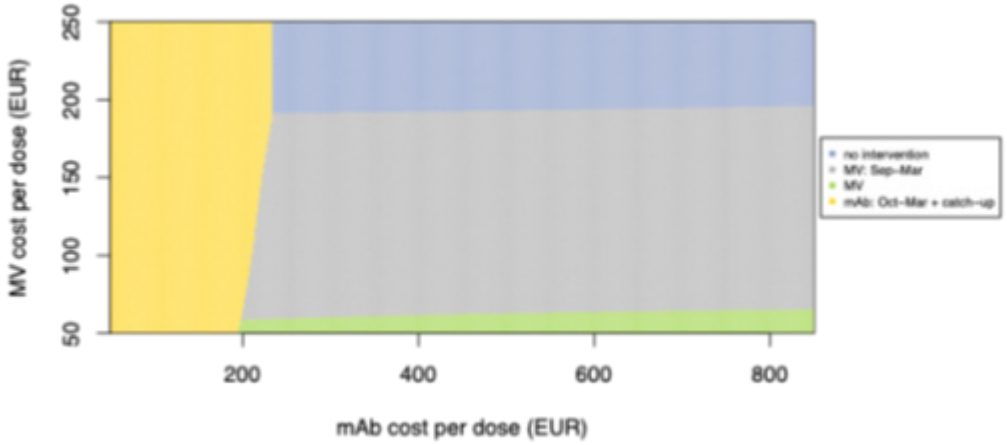
Willingness to pay: €50,000 per QALY gained



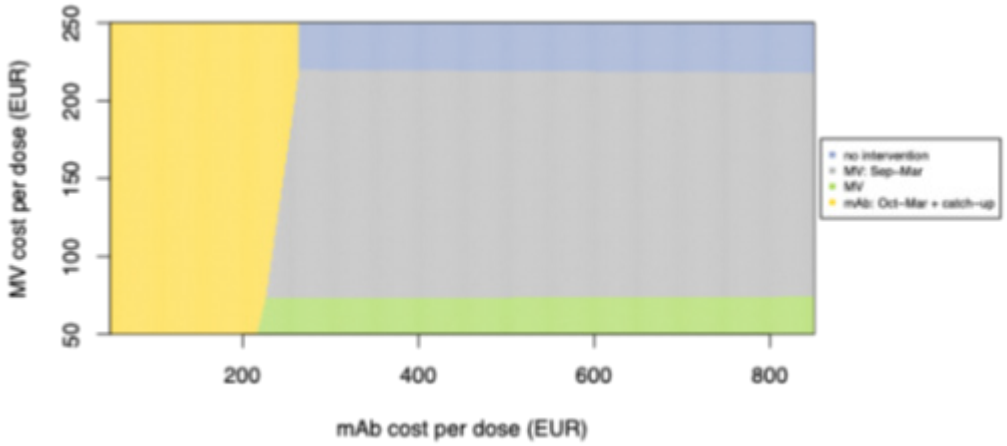
EUR: euro, HCP: health care payers', QALY: quality-adjusted life-year, MV: year-round maternal vaccine, MV: Sep-Mar: seasonal maternal vaccine from September to March, mAb: Oct-Mar + catch-up: seasonal mAb combined with a catch-up strategy.

Figure 52 – Intervention cost threshold analysis from HCP perspective: using the pooled (5 countries) outpatient incidence rates

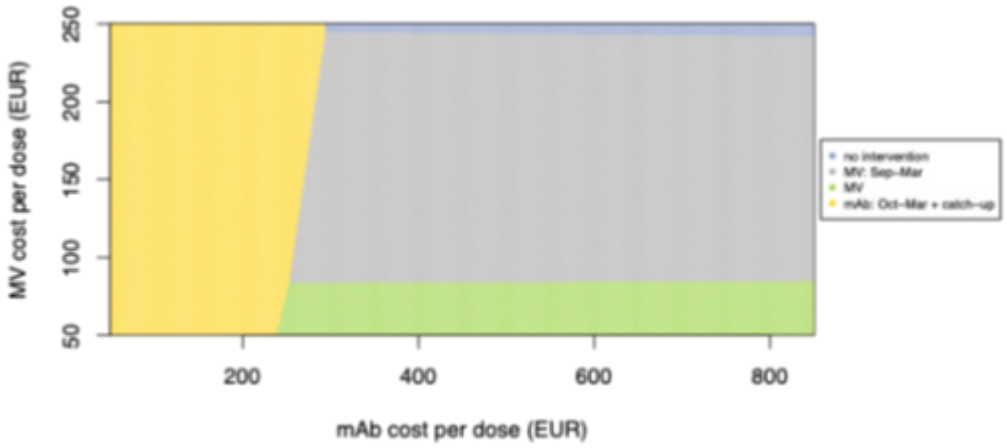
Willingness to pay: €20,000 per QALY gained



Willingness to pay: €35,000 per QALY gained



Willingness to pay: €50,000 per QALY gained



EUR: euro, HCP: health care payers', QALY: quality-adjusted life-year, MV: year-round maternal vaccine, MV: Sep-Mar: seasonal maternal vaccine from September to March, mAb: Oct-Mar: seasonal mAb strategy from October to March, mAb: Oct-Mar + catch-up: seasonal mAb combined with a catch-up strategy.

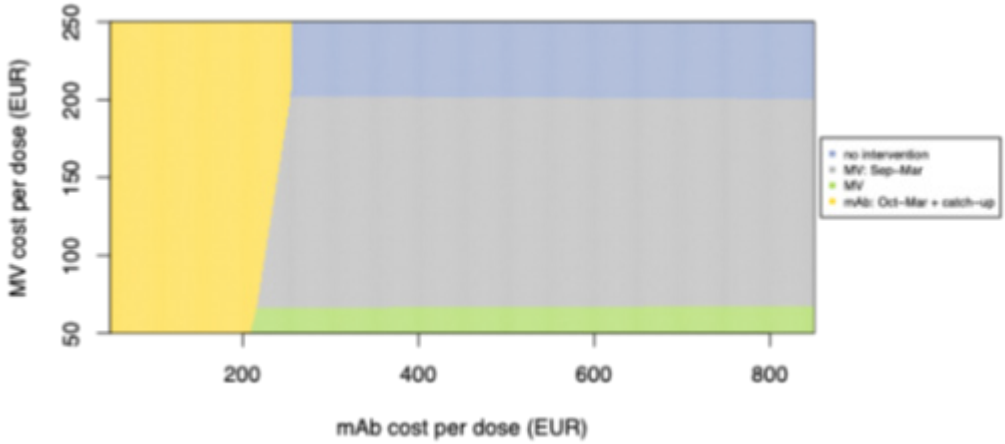
Appendix 7.5. Efficacy and effectiveness of RSV interventions

In the scenario with constant mAb efficacy over 6 months, the colour pattern shifted slightly to the right, whereas in the scenario with waning over 5 months, it shifted to the left (Figure 53 and Figure 54).

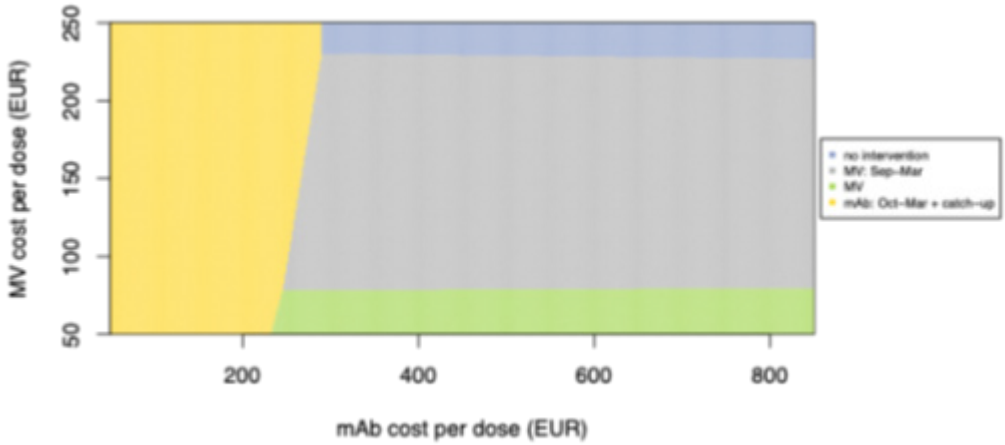
When assuming that both interventions provided no protection against RSV non-MA episodes, the results were comparable to the base case, whereas assuming no efficacy against RSV-related deaths for either intervention, the colour pattern shifted slightly to left and down (Figure 55 and Figure 56).

Figure 53 – Intervention cost threshold analysis from HCP perspective: effectiveness data of nirsevimab using RWE studies (6 months constant)

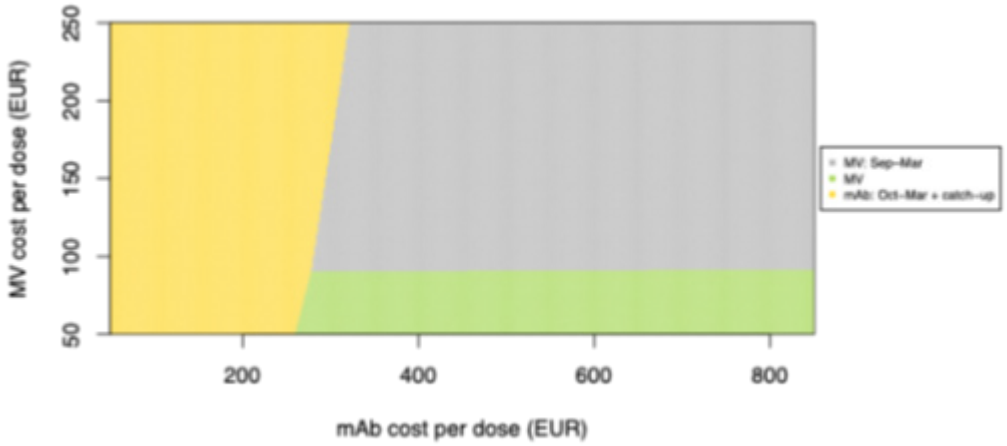
Willingness to pay: €20,000 per QALY gained



Willingness to pay: €35,000 per QALY gained



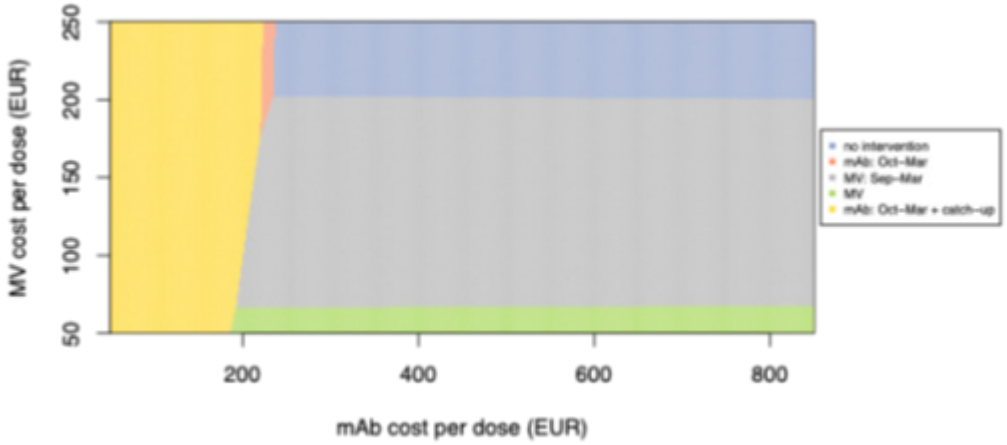
Willingness to pay: €50,000 per QALY gained



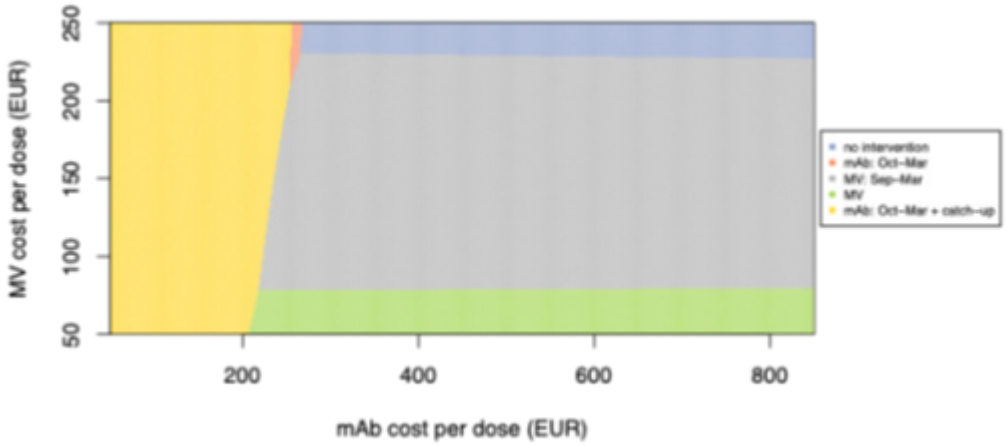
EUR: euro, HCP: health care payers', QALY: quality-adjusted life-year, MV: year-round maternal vaccine, MV: Sep-Mar: seasonal maternal vaccine from September to March, mAb: Oct-Mar: seasonal mAb strategy from October to March, mAb: Oct-Mar + catch-up: seasonal mAb combined with a catch-up strategy.

Figure 54 – Intervention cost threshold analysis from HCP perspective: effectiveness data of nirsevimab using a test-negative case-control study (waning over 5 months)

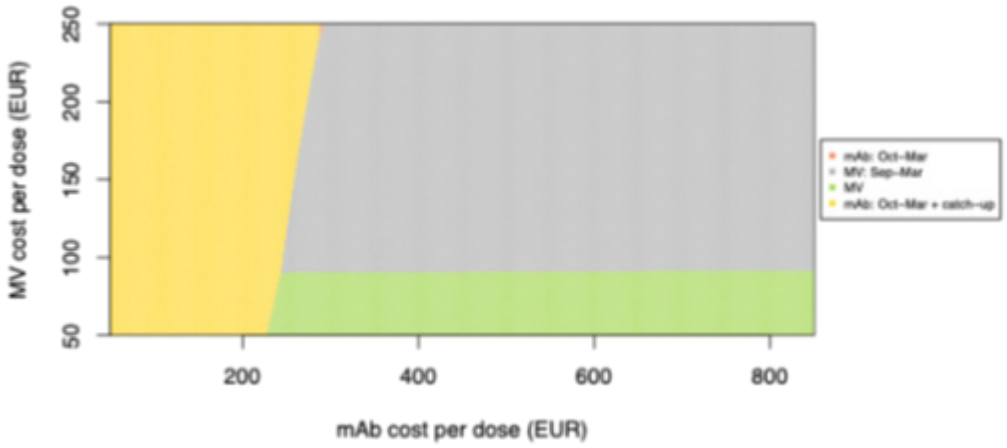
Willingness to pay: €20,000 per QALY gained



Willingness to pay: €35,000 per QALY gained



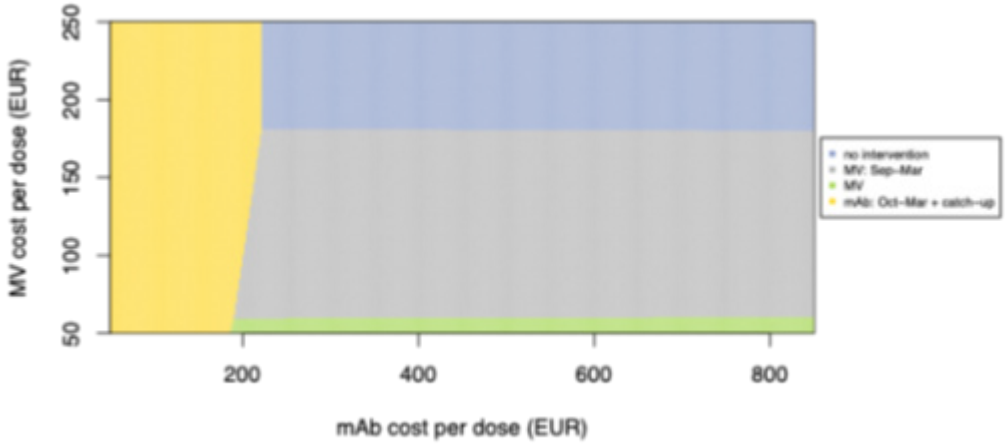
Willingness to pay: €50,000 per QALY gained



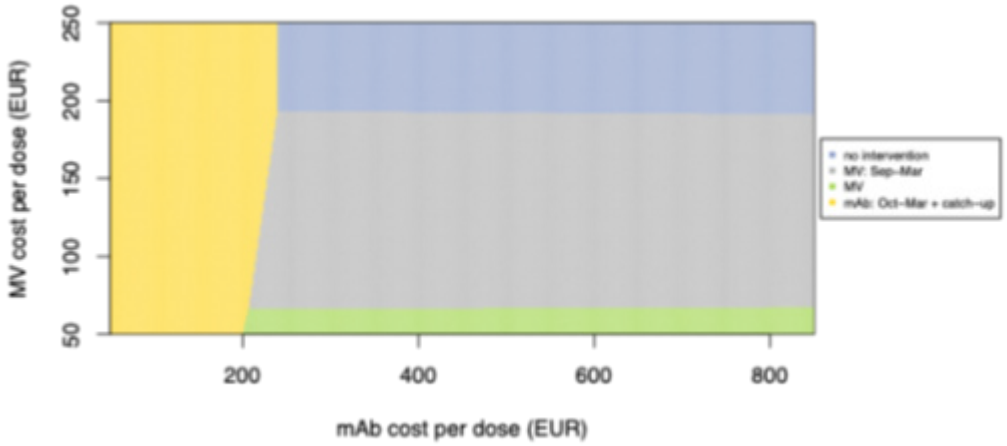
EUR: euro, HCP: health care payers', QALY: quality-adjusted life-year, MV: year-round maternal vaccine, MV: Sept-Mar: seasonal maternal vaccine from September to March, mAb: Oct-Mar: seasonal mAb strategy from October to March, mAb: Oct-Mar + catch-up: seasonal mAb combined with a catch-up strategy.

Figure 55 – Intervention cost threshold analysis from HCP perspective: both interventions have no protection against RSV mortality

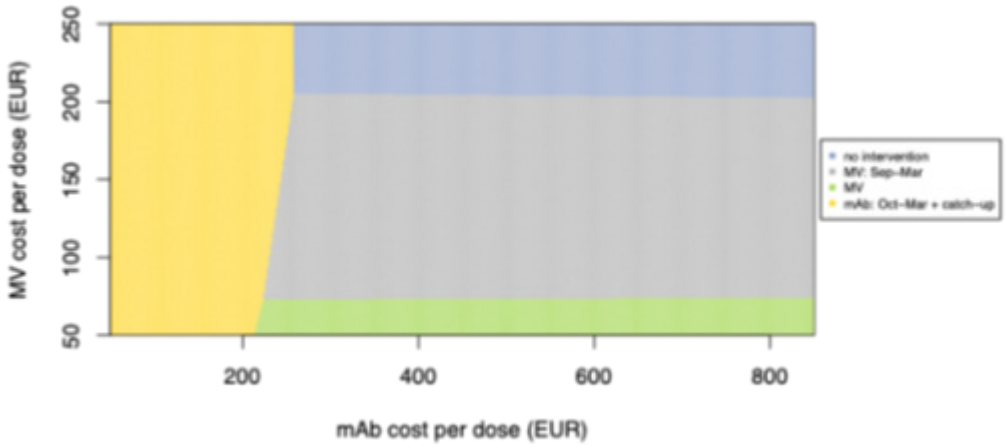
Willingness to pay: €20,000 per QALY gained



Willingness to pay: €35,000 per QALY gained



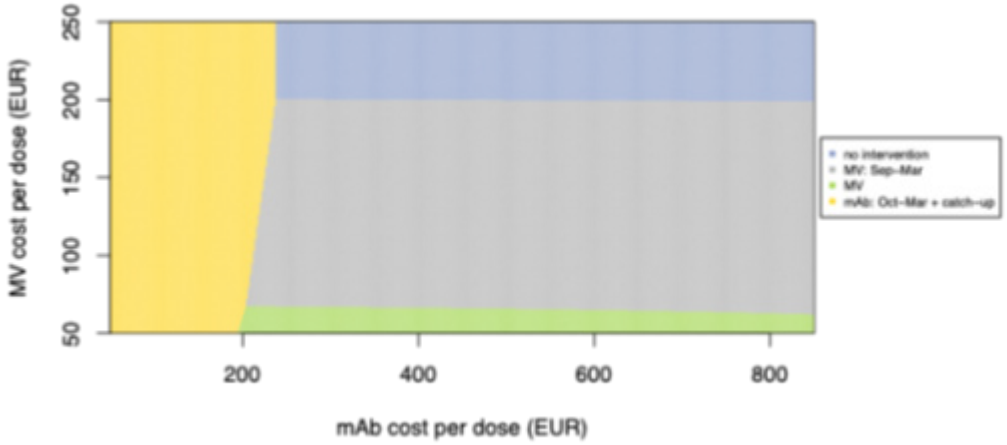
Willingness to pay: €50,000 per QALY gained



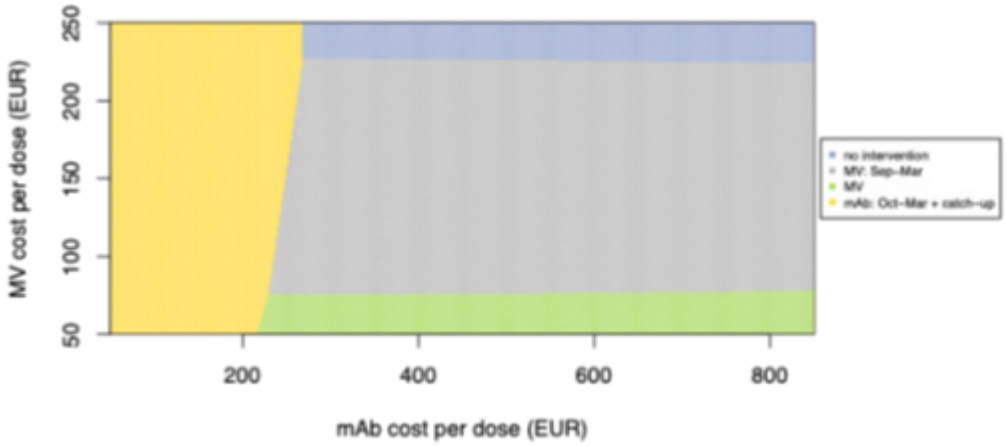
EUR: euro, HCP: health care payers', QALY: quality-adjusted life-year, MV: year-round maternal vaccine, MV: Sept-Mar: seasonal maternal vaccine from September to March, mAb: Oct-Mar + catch-up: seasonal mAb combined with a catch-up strategy.

Figure 56 – Intervention cost threshold analysis from HCP perspective: both interventions have no protection against RSV non-MA episodes

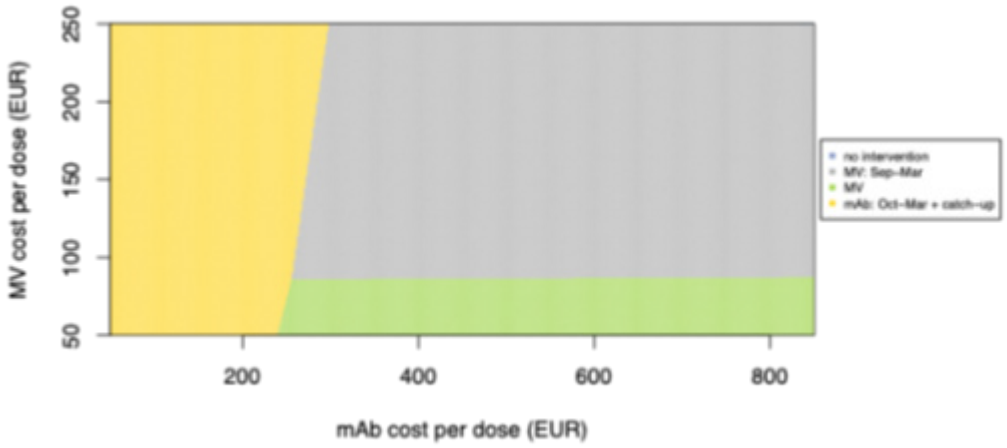
Willingness to pay: €20,000 per QALY gained



Willingness to pay: €35,000 per QALY gained



Willingness to pay: €50,000 per QALY gained



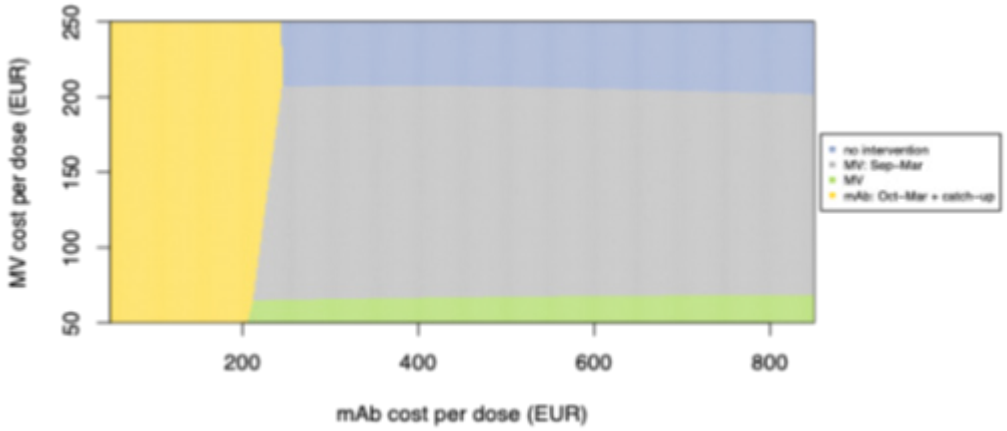
EUR: euro, HCP: health care payers', QALY: quality-adjusted life-year, MV: year-round maternal vaccine, MV: Sept-Mar: seasonal maternal vaccine from September to March, mAb: Oct-Mar: seasonal mAb strategy from October to March, mAb: Oct-Mar + catch-up: seasonal mAb combined with a catch-up strategy.

Appendix 7.6. Inclusion of parental QALY losses

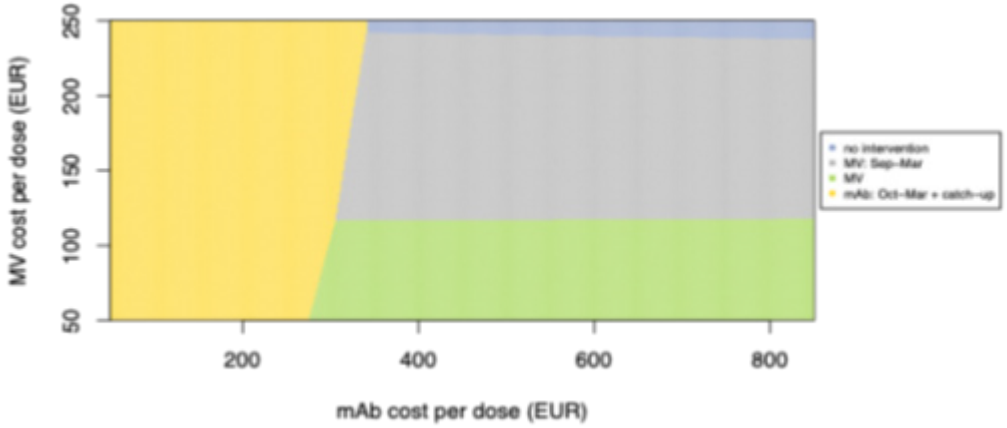
The additional inclusion of parental QALY losses had limited effect over and above the baseline's parental evaluation of the child's quality life, showing comparable results to the baseline.

Figure 57 – Intervention cost threshold analysis from HCP perspective: inclusion of parental QALY losses per RSV episode

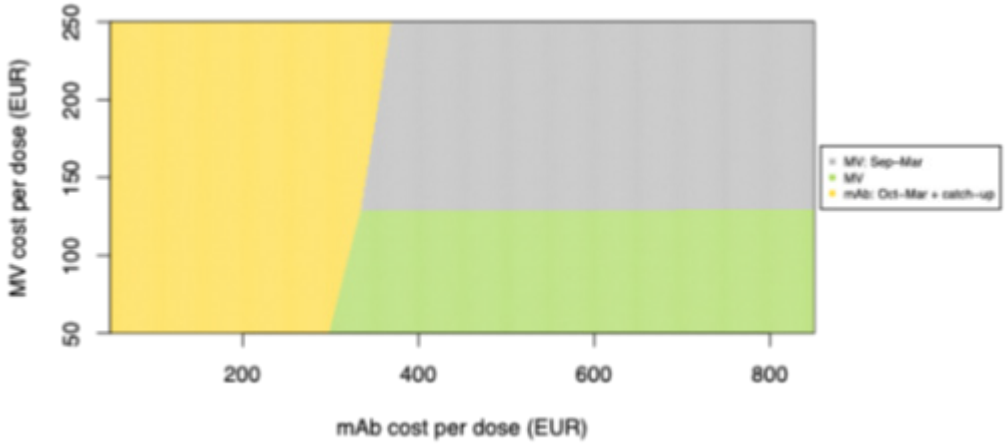
Willingness to pay: €20,000 per QALY gained



Willingness to pay: €35,000 per QALY gained



Willingness to pay: €50,000 per QALY gained



EUR: euro, HCP: health care payers', QALY: quality-adjusted life-year, MV: year-round maternal vaccine, MV: Sept-Mar: seasonal maternal vaccine from September to March, mAb: Oct-Mar + catch-up: seasonal mAb combined with a catch-up strategy.