# Cost-effectiveness of respiratory syncytial virus preventive interventions in children: a model comparison study

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**Abstract**

**Objective**: Model-based cost-effectiveness analyses on maternal vaccine (MV) and monoclonal antibody (mAb) interventions against respiratory syncytial virus (RSV) use context-specific data and produce varied results. Through model comparison, we aim to characterise RSV cost-effectiveness models and examine drivers for their outputs.

**Methods**: We compared three static and two dynamic models using a common input parameter set for a hypothetical birth cohort of 100,000 infants. Year-round and seasonal programmes were evaluated for MV and mAb interventions, using available evidence during the study period (e.g., phase 3 MV and phase 2b mAb efficacy).

**Results**: Three static models estimated comparable medically-attended (MA) cases averted versus no intervention (MV: 1,019-1,073, mAb: 5,075-5,481), with the year-round MV directly saving ~€1 million medical and €0.3 million non-medical costs, while gaining 4-5 discounted Quality-adjusted life years (QALYs) annually in <1-year-olds, and mAb resulting in €4 million medical and €1.5 million non-medical cost savings, and 21-25 discounted QALYs gained. In contrast, both dynamic models estimated fewer MA cases averted (MV: 402-752, mAb: 3,362-4,622); one showed an age shift of RSV cases, whereas the other one reported many non-MA symptomatic cases averted, especially by MV (2014). These differences can be explained by model types, assumptions on non-MA burden and interventions' effectiveness over time.

**Conclusions**: Our static and dynamic models produced overall similar hospitalisation and death estimates, but also important differences, especially in non-MA cases averted. Despite the small QALY decrement per non-MA case, their larger number makes them influential for the costs per QALY gained of RSV interventions.

**Keywords**: RSV, model comparison, cost-utility analysis, high-income country, maternal vaccine, monoclonal antibody, year-round programme, seasonal, catch-up

# 1 Introduction

Respiratory syncytial virus (RSV) is one of the leading causes of acute lower respiratory infections (ALRI) in children. A global systematic review estimated 3.3 million RSV-associated ALRI episodes and 3.6 million hospital admissions in 2019 among children < 5 years [1]. To date, there is only one licensed RSV prophylaxis, palivizumab, which is licensed to be administrated monthly throughout the RSV season to provide protection against severe disease among high-risk infants (i.e., bronchopulmonary dysplasia) [2]. The high price of palivizumab has resulted in limited clinical use based on recommendation and uptake [3]. Multiple RSV prophylactic interventions are under development and have shown promising progress. For instance, a single-dose long-lasting monoclonal antibody (mAb), nirsevimab, achieved its phase 3 primary endpoint in 2021, and it is under accelerated assessment by regulatory agencies [4]. Furthermore, two maternal vaccine (MV) candidates and another mAb are in phase 3 trials, with results expected in 2023-2024 [5-7].

Once the new RSV prophylactic interventions are licensed, policy makers will decide if they will use them in new RSV preventive strategies. In many countries, cost-effectiveness analyses (CEA) have been used to inform decision making when considering new immunisation programmes [8]. Alongside the RSV interventions' development, there is an increasing number of RSV cost-effectiveness models published in the literature, including both static and dynamic models [9, 10]. However, these models can produce varied outcomes. For example, in England, a static model estimated the cost-effective price for a mAb seasonal programme at birth from October to January to be £183 per course [11], but a dynamic model estimated the price to be £90 per dose for a single-dose mAb seasonal programme from October to February [12]. Whereas variations in model results are typically discussed as stemming from the use of different data, assumptions, health economic concepts and model structures, multi-model comparisons allow gaining valuable insights into some of the more complex drivers of model outcome differences, by holding data, assumptions and health economic concepts largely constant across models [8, 13, 14].

This study aims to compare the outcomes of different available model-based analytical approaches designed to estimate the cost-effectiveness of RSV prevention in infancy and pregnancy using a standardised set of input parameters. Our objectives are: 1) to understand the impact of model structure and parameterisation on model outcomes; 2) to investigate the robustness of model results to variations in assumptions; and 3) to generate insights for future RSV modelling efforts.

# 2 Methods

This section summarises our methods in accordance with guidelines for multi-model comparisons [13]. Details are available in Supplement 1 and 2 method sections.

## Model selection and procedure

In January 2017, an open invitation was sent through the REspiratory Syncytial virus Consortium in EUrope (RESCEU) network, which includes both academic institutions and pharmaceutical companies, to gauge interest in joining a model comparison workgroup. In May 2017, a workshop was organised to establish the framework for analysis and confirm interest. Between 2017 and 2020, as individual models were developed and refined independently, a common input dataset was compiled by the academic lead partner, University of Antwerp (UA). Formal model comparison was initiated in November 2020 with the presentation of the model structures and discussion of the common input dataset. Inclusion of models was based solely on the interest and ability to join. Finally, the five models that were able to join the comparison were three static models developed by UA, Novavax (NV) and Sanofi Pasteur (SPS: Sanofi Pasteur static model) and two dynamic models developed by Sanofi Pasteur and EPIMOD (SPD: Sanofi Pasteur dynamic) and London School of Hygiene & Tropical Medicine (LSHTM). The model structures are presented in *Supplement 1: Figure 1-5*. Each group independently produced model results and UA performed internal consistency checks.

## Health economic framework

We decided to adapt all models to a hypothetical country setting where the RSV season starts in October and ends in April, in line with pre-COVID-19 RSV seasons in Europe. The target population for the interventions were pregnant women and infants, allowing both MV and mAb to be evaluated. Quality-

adjusted life years (QALYs) were used to calculate the incremental cost-effectiveness ratio (ICER) [15]. Both healthcare payer's perspective (including direct medical costs only) and societal perspective (including both direct medical and non-medical costs) were employed. An annual discount rate of 3% was used for both cost and health outcomes [8, 16].

### Model input and output

The standardised input parameters were based on available data sourced from European countries and approved by all modelling groups (*Supplement 1: Table 1*). To model RSV transmission, dynamic models used additional input parameters and assumptions, e.g., regarding RSV asymptomatic and non-medically-attended (non-MA) symptomatic cases (Table 1 and *Supplement 1: Table 3*), and used bespoke fitting and calibration methods (*Supplement 2*) as well as assumptions of waning efficacy. Specific sensitivity analyses around key parameters were agreed upon using identical ranges across models (*Supplement 1: Table 4-5*).

A common output template was discussed and agreed upon. Each group produced the following set of outputs for children < 5 years: primary care visits, hospital outpatient visits, hospitalisations (non-ICU and ICU), deaths, QALYs, medical costs, and non-medical costs without and with the following RSV preventive programmes:

1) **Year-round programmes** of MV for pregnant women with 67% coverage (based on maternal pertussis vaccine coverage in England) and mAb for infants at birth with 94% coverage (based on infant rotavirus vaccine coverage) [17]
2) **Seasonal programmes** of MV with 44% coverage (based on seasonal maternal influenza vaccine coverage) and mAb with 94% coverage protecting infants at birth during October to April
3) **Seasonal programme with a catch-up** of seasonal mAb uptake plus a mAb catch-up programme with 94% coverage where infants < 6 months born outside of the season (May to September) would be administered mAb in the beginning of the RSV season (October)

The outcomes were analysed for each intervention versus no intervention. Extensive scenario and sensitivity analyses were performed to explore the drivers of different model outcomes (*Supplement 1: Table 4-5)*. Before comparing model results, a group discussion was organised to formulate expected differences in model outcomes, conditional on the model structures and key assumptions (summary in Table 1 and full details in *Supplement 1: Table 2*)

### Model runs

Two test runs were performed for a limited set of scenarios to check the clarity of the common input and output templates. The final run outputs were provided by each group to UA. The model outputs were locked and unblinded for a final group discussion in March 2022. Any changes made were recorded systematically and no change was made after these model outputs were shared (details in *Supplement 1: section 1.6-1.8)*.

## 3 Results

We describe outcomes and their drivers, distinguishing: 1) within-static model, 2) within-dynamic model, and 3) between static and dynamic model differences.

### Estimated (baseline) disease burden without intervention

Using a hypothetical annual birth cohort of 100,000 infants, the estimated RSV-associated disease burden per model is reported in *Supplement 1: Table* 6-7. Overall, the three static models reported similar medical-attended (MA) cases per year in children < 1 year: 14,361 RSV primary care visits (all three models), ranging from 2,125 to 2,142 non-intensive care unit (non-ICU) hospitalisations and 0.82-0.83 deaths. The dynamic models estimated 12,016-12,743 primary care visits, 1,890-1,869 non-ICU hospitalisations and 0.74-0.83 deaths. The small within-static and within-dynamic model differences were likely caused by different ways of handling the hospitalisation rates (see Table). However, the dynamic models estimated approximately 10-16% fewer MA cases compared to the static models.

**Table 1: overview of main differences in this model comparison (a simplified version of Supplement 1: Table 2)**

| | UA | NV | SPS | SPD | LSHTM |
|---|---|---|---|---|---|
| | **Static models** | | | **Dynamic models** | |
| **Model type and population structure** | Stochastic, multi-cohort | Deterministic, decision tree | Deterministic, multi-cohort | Deterministic, compartmental (SIRS) population | Deterministic, compartmental (SEIRS), population |
| **Model time stratification** | Monthly (cycle) | Not applicable (decision tree) | Monthly (cycle) | 0.5 day | Daily |
| **Rate of medically-attended[#] cases (e.g., inpatients, provided by calendar month and age in month)** | Applied directly by type, calendar month and age in month | Group by births within and outside of RSV season | Estimated number of cases by incidence rate per calendar month, then re - distributed cases across the RSV season | Used primary care cases for model calibration | Used hospitalisation cases for model calibration |
| **RSV-related deaths** | Independent from hospital admissions | A direct proportion of hospital admissions | Independent from hospital admissions | Independent from hospital admissions | Independent from hospital admissions |
| **Non-medically[#] attended symptomatic infections** | Not considered | Not considered | Not considered | An age-dependent proportion of the infections are considered as symptomatic (based on literature values): 0-5m: 50% and 6-11m: 40%<br>Symptomatic RSV infections are split into cases with and without medical attendance to fit age-specific probabilities: range from 100% (0m) to 64% (11m) | Symptomatic infections compartment in the model structure, which is further split into medically attended and non-medical attended to fit age-specific probabilities range from 40% (5m) to 10% 10% (10m) |
| **Asymptomatic[#] infections** | Not considered | Not considered | Not considered | The complement of the symptomatic infections on the total infections. Assuming no difference in infectiousness between asymptomatic and symptomatic infections. | Asymptomatic compartment in model structure, with lower assumed infectiousness than the symptomatic compartment; 9% (0-11m) of infections are assumed to be asymptomatic. |
| **Time horizon** | 1 year | 1 year | 1 year | Steady state over 10 years | 10 years |

| | | | | | |
|---|---|---|---|---|---|
| **Age group** | 0-4 years | Under 1 year | Under 1 year | All age groups were considered in transmission, but only health outcomes for 0–4-year-olds were reported | All age groups were considered in transmission, but only health outcomes for 0–4-year-olds were reported |
| **Discounting** | Discrete, annually | Discrete, annually | Discrete, annually | Continuous using an exponential function | Discrete, monthly |
| **QALY losses due to death** | Life expectancy without quality adjustment | Quality-adjusted life expectancy | Life expectancy without quality adjustment | Quality-adjusted life expectancy | Life expectancy without quality adjustment |
| **Protection: efficacy reported in supplement 1 and duration: 3 months for MV [38] and 5 months for mAb [37]** | All or nothing with a stepwise function for duration | All or nothing with a stepwise function for duration<br>mAb: weighted the vaccine efficacy in 3-5 months age group to approximate 5-month protection* | All or nothing with a stepwise function for duration | MV: all-or-nothing with an exponential decline function for individuals moving out of the "protected" compartment over time (90 days (median 62 days)<br>mAb: all-or-nothing with a stepwise function for 150 days (individuals moving out of the protected compartment after 5 months) | both MV and mAb: all-or-nothing with an exponential decline function for individuals moving out of the "protected" compartment over time:<br>MV: 90 days (median 62 days)<br>mAb: 150 days (median 103 days) |
| **Default disease burden output** | By calendar month | By within season birth and year-round burden | By calendar month | By calendar month | By calendar month |

# Note that the static and dynamic models used the same data and assumptions for medically-attended symptomatic cases, which is therefore not shown in this table (for details see supplement 1). * NV model had pre-defined age groups of 0-2 months, 3-5 months, and 6-11 months. Therefore, when modelling mAb, 5-month protection was reduced in age group 3-5 months by one-thirds of the original efficacy. Abbreviations: UA: University of Antwerp model, SPS: Sanofi Pasteur static model, SPD: Sanofi Pasteur dynamic model, LSHTM: London School of Hygiene & Tropical Medicine model, RSV: respiratory syncytial virus, MV: maternal vaccine, mAb: monoclonal antibody.

The estimated number of non-ICU hospitalisations among children <1 year (Figure 1) illustrates that during January and February, the dynamic models estimated similar numbers of non-ICU hospitalisations compared to the static models. However, both dynamic models did not sufficiently capture the pre- and post-peak RSV hospitalisations (i.e., >20% lower in December, >30% lower in March).

Both dynamic models estimated ~13% of all RSV infections would be MA cases in children < 5 years. However, large differences occurred within dynamic models when estimating non-MA symptomatic and asymptomatic RSV infections (*Supplement 1: Table 7*). The SPD model estimated fewer non-MA symptomatic infections (~14,000) versus the LSHTM model (~155,000), but more asymptomatic infections (~161,000 vs. ~30,000 in the LSHTM model). Approximately 95% (SPD model) and 90% (LSHTM model) of these infections were in children <6 months. The differences were likely due to the assumptions on the proportion of non-MA symptomatic versus asymptomatic infections (SPD: 50%

infections at age of 0-5 months and 40% at 6-11 months at 40% were asymptomatic vs. LSHTM 0-11 months at 9%).

The estimated RSV-associated discounted costs and QALYs are presented in *Supplement 1: Table 7* over a 10-year period. In children < 1 year, the static models reported approximately €72-75 million direct medical costs and €34-36 million indirect costs, whereas the dynamic models estimated direct costs of €64-71 million and indirect costs of €29 million. All models consistently reported that more than 70% of costs occur in children < 6 months.

The static models estimated approximately 482 to 566 discounted QALYs lost due to RSV episodes and 202-222 discounted QALYs lost due to premature deaths among children <1 year. The LSHTM model had the highest QALY losses due to RSV episodes because it attributed QALY losses to non-MA symptomatic RSV infections. Non-MA symptomatic infections accounted for 76% of all symptomatic infections, and they lead to 71% of the total discounted QALY losses for RSV in children < 1 year. The SPD model reported the lowest QALY losses due to RSV episodes because it estimated lower incidences for both MA and non-MA symptomatic infections. It also reported the lowest QALY losses due to RSV-deaths because these were based on quality-adjusted life expectancy and were discounted continuously using an exponential function.

### RSV disease burden averted with intervention

#### Year-round programmes of maternal vaccine and monoclonal antibody

For year-round programmes, the static models estimated similar nominal and relative reductions of MA cases averted (Figure 2 and *Supplement 1: Table 10*). The SPS model estimated more primary care visits and hospitalisations averted, because it assumed that 20% of preterm infants would be protected by antibody transfer from their vaccinated mothers, whereas the other models assumed preterm infants would not be protected by MV.

In contrast to the static models, both dynamic models assumed MV protection wanes and therefore estimated a relatively smaller disease burden averted in 0–2-month-olds. Both models showed herd immunity reducing cases in the 3-5 months and 6-11 months age groups. The SPD model showed an age-shift increasing infections in children >1 year. By contrast, the LSHTM model's herd effects reduced infections further in children >1 year (*Supplement 1: Table 11*), because it accounted for reduced transmissibility through MV of both infants and mothers.

Important differences between the dynamic models were observed for mAb. The SPD model estimated proportionately more disease averted in the 3-5 months age-group when assuming no waning of mAb protection (59% vs. 23% non-ICU hospitalisations and 44% vs. 22% primary care cases in SPD vs. LSHTM model, respectively). An age-shift in infections towards the 24-59 months age-group was also observed in the SPD model (*Supplement 1: Table 11*). The LSHTM model showed RSV cases were prevented in all age-groups < 5 years, which can be explained by the assumed longer duration of protection of mAb (median: 103 days) and its impact on transmission. Given the same level of individual protection, herd immunity is estimated smaller for mAb than for MV because the common social contact matrix used in both dynamic models assumed young infants to have fewer social contacts than their mothers.

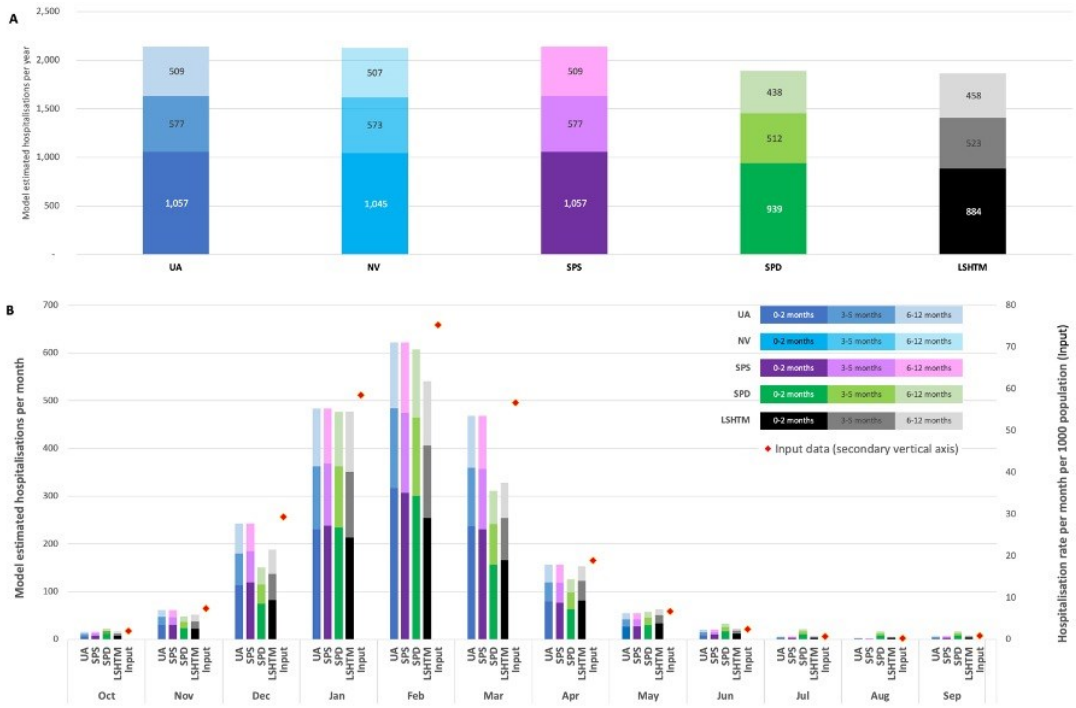


**Figure 1. RSV non-ICU hospitalizations in children ,1 year of age: (A) (top panel) yearly total by age group. (B) (bottom panel) RSV hospitalization rate by calendar month and the monthly total of the non-ICU hospitalizations.**

The results in Table 2 show the three static models reported that MV would annually avert €1 million direct medical costs and €0.3 million non-medical costs and gain 4-5 QALYs versus no intervention, with ICERs exceeding €290,000 per QALY gained from both perspectives. The mAb would avert €4 million direct medical costs and €1.5 million non-medical costs while gaining 21-25 QALYs, with ICERs at ~€60,000-70,000 per QALY gained from a healthcare payer's perspective. From a societal perspective, the UA and SPS models estimated ICERs of €11,658 and €1,635 per QALY gained, respectively. The higher ICER in the UA model is likely caused by its lower estimate of direct medical costs averted (and due to its probabilistic approach). The NV model found mAb to be dominant, because it estimated that more non-medical costs would be averted.

Both dynamic models reported the discounted ICERs over a 10-year period (Table 2). For the MV year-round programme, the SPD model projected approximately 2-fold fewer direct medical costs averted and 10-fold fewer QALYs gained versus the LSHTM model for three main reasons. First, the SPD model focused on the MV protection passed to infants but did not consider direct or indirect protection from vaccinating mothers, which led to fewer MA cases and deaths averted than the LSHTM model. Second, the SPD model used a single efficacy (39%) against all infections regardless of severity, hence it predicted lower hospitalisation costs averted versus the LSHTM model that applied a higher efficacy (44%) against hospitalisations. Third, differences in the model approaches on non-MA symptomatic infections resulted in further differences in QALY losses averted. For example, in children<5 years, the SPD model reported 18 additional non-MA symptomatic infections due to the age-shift in one year at steady state, whereas the LSHTM model estimated ~2,800 non-MA symptomatic infections averted on average per year. Consequently, for the MV year-round programme, the ICERs estimated by the SPD model and the LSHTM model were vastly different from both perspectives.

For mAb year-round programme, the SPD model reported a higher ICER for the healthcare payer versus the LSHTM model, because the SPD model assumed 5-month protection without waning for mAb while the LSHTM model assumed exponential waning, which led to ~20% more MA cases and deaths averted by the SPD model versus the LSHTM model. Nevertheless, the SPD model still estimated less than 400 non-MA symptomatic infections averted (vs. ~11,000 infections averted in LSHTM model). The

dynamic model ICERs are also presented without QALY impact of non-MA cases to improve comparability with the static models (*Supplement 1: Table 10*).

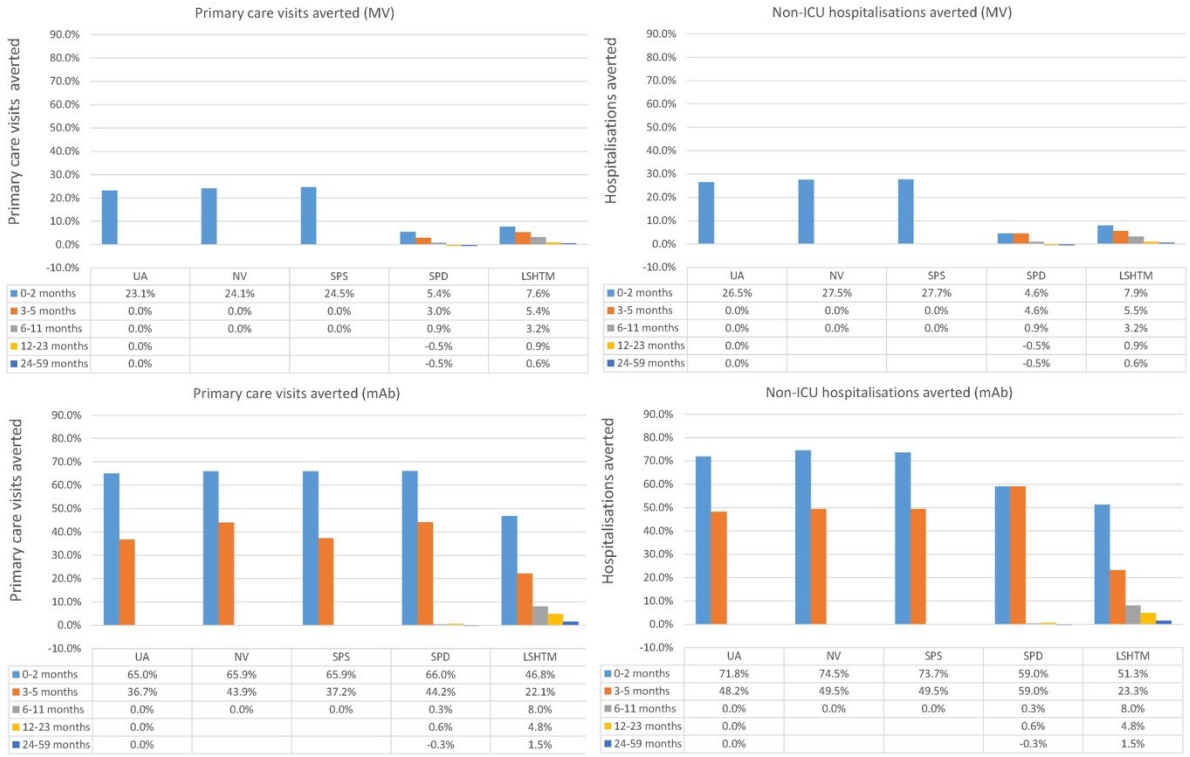


**Figure 2. Year-round programs: model-based primary care visits (left column) and non-ICU hospitalizations (right column) averted by MV (top row) and mAb (bottom row) as a percentage of the disease burden estimates without any intervention.**

### Seasonal MV and mAb programmes without catch-up

Although the seasonal and year-round programme evaluations gave broadly similar results (*Supplement 1: Figure 7 and Table 11*), all models reported 3% and 10% fewer hospitalisations averted with seasonal versus year-round MV and mAb, respectively. Since seasonal programmes immunise disproportionately fewer new-borns (during 7/12 months), all models estimated ICERs more in favour of seasonal programmes versus the year-round programmes from both perspectives.

### mAb seasonal programme with catch-up

Four models could explore mAb with catch-up programme, which can offer better protection during the RSV season for children who were born before the season (not eligible for the seasonal programme) and had their protection waned by the time of the RSV season (within a year-round programme). From the societal perspective, the LSHTM model estimated an ICER < €17,000 per QALY gained, whereas the other three models found dominance of catch-up over no intervention (Figure 3 and *Supplement 1. Table 14-16*).

### Sensitivity analyses

One-way sensitivity analyses were performed to identify the key drivers impacting ICERs from a societal perspective for year-round programmes. The analyses were conducted separately for MV and mAb (*Supplement 1. Figure 8-9*). Overall, the five top-ranked influential parameters were similar between models (Table 3). All models were sensitive to the intervention's efficacy, duration of protection, cost per dose, and severity of the season. QALY losses per RSV episode was influential for MV, while the length of hospital stay was more influential for mAB.

**Table 2: year-round programs: QALYs gained, incremental costs, and incremental cost-effectiveness ratios for MV or mAb versus current practice, from the health care payer's and societal perspectives (discount rate 3% per year, MV: €37.5 per dose and €8.32 delivery cost, mAb: €50 per dose and €5 delivery cost)**

| | QALY gained | Direct medical costs | Intervention costs [a] | Direct costs | **ICER per QALY gained (payer)** | Non-medical cost | Total costs | **ICER per QALY gained (societal)** |
|---|---|---|---|---|---|---|---|---|
| MV (67% coverage) | | | | | | | | |
| UA^ | 5 | -€ 1,060,110 | € 3,056,897 | € 1,996,787 | **€ 402,349** | -€ 344,403 | € 1,652,384 | **€ 332,952** |
| NV ^ | 4 | -€ 1,125,880 | € 3,056,897 | € 1,931,017 | **€ 463,979** | -€ 367,396 | € 1,563,621 | **€ 375,702** |
| SPS ^ | 5 | -€ 1,140,816 | € 3,047,500 | € 1,906,684 | **€ 366,437** | -€ 357,838 | € 1,548,846 | **€ 297,665** |
| SPD* | 11 | -€ 2,383,575 | € 24,800,671 | € 22,417,095 | **€ 1,973,816** | -€ 823,597 | € 21,593,498 | **€ 1,901,299** |
| LSHTM* | 109 | -€ 4,158,218 | € 23,677,256 | € 19,519,038 | **€ 178,322** | -€ 1,757,456 | € 17,761,583 | **€ 162,266** |
| mAb (94% coverage) | | | | | | | | |
| UA^ | 24 | -€ 3,944,424 | € 5,682,080 | € 1,737,656 | **€ 71,522** | -€ 1,454,427 | € 283,229 | **€ 11,658** |
| NV^ | 21 | -€ 4,196,864 | € 5,682,080 | € 1,485,216 | **€ 69,419** | -€ 1,635,871 | -€ 150,655 | **Dominant** |
| SPS^ | 25 | -€ 4,169,736 | € 5,682,080 | € 1,512,344 | **€ 61,626** | -€ 1,472,226 | € 40,118 | **€ 1,635** |
| SPD* | 163 | -€ 31,071,021 | € 47,561,842 | € 16,490,821 | **€ 101,282** | -€ 10,901,641 | € 5,589,180 | **€ 34,327** |
| LSHTM * | 447 | -€ 22,150,079 | € 46,382,850 | € 24,232,770 | **€ 54,272** | -€ 8,513,684 | € 15,719,086 | **€ 35,205** |

*Table footnote: * Cumulative value over 10 years. ^ ICERs are calculated for children under age 1 year. [a] intervention costs includes cost of intervention, delivery costs, and implementation costs. UA: University of Antwerp model, NV: Novavax model, SPS: Sanofi Pasteur static model, SPD: Sanofi Pasteur dynamic model, LSHTM: London School of Hygiene & Tropical Medicine model, QALY: quality-adjusted life year, MV: maternal vaccine, mAb: monoclonal antibody.*

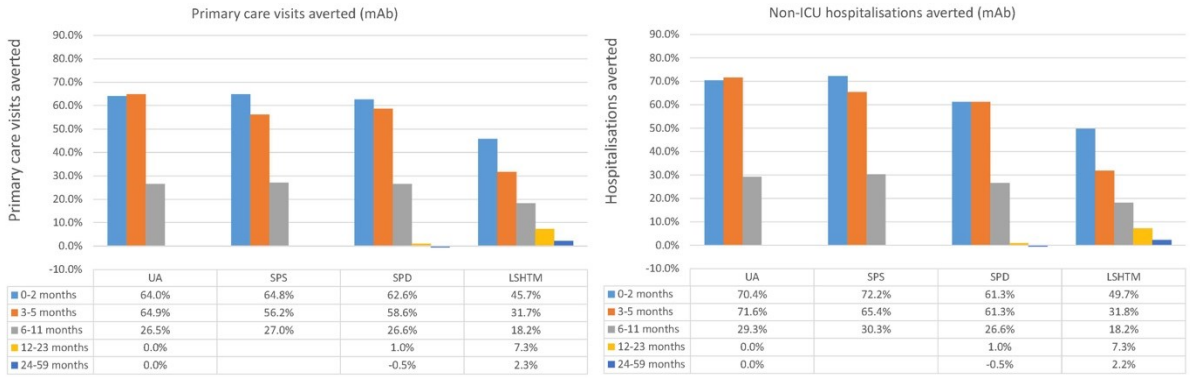


**Figure 3. Seasonal program with catch-up: model-based primary care visits and non-ICU hospitalizations averted by MV and mAb**

**Table 3: Top 10 ranking: drivers for ICER in the one-way sensitivity analysis for year-round programmes and the societal perspective**

| Rank | UA | NV | SPS | SPD | LSHTM |
|---|---|---|---|---|---|
| MV | | | | | |
| 1st | **Efficacy MV** | **Efficacy MV** | **Efficacy MV** | **Duration of protection MV** | **Efficacy MV** |
| 2nd | **QALY loss medical (including hospital) care** | **Strong/weak season§** | **QALY loss medical (including hospital) care** | **Efficacy MV** | **Duration of protection MV** |
| 3rd | **Duration of protection MV** | **QALY loss medical (including hospital) care** | **MV cost per dose** | **QALY loss medical (including hospital) care** | **MV cost per dose** |
| 4th | **Strong/weak season§** | **Duration of protection MV** | **Strong/weak season§** | **MV cost per dose** | **QALY loss medical (including hospital) care** |
| 5th | **MV cost per dose** | **MV cost per dose** | **LoS (days) hospital** | **Strong/weak season§** | **Strong/weak season§** |
| 6th | Hospital admission rate | LoS (days) hospital | **Duration of protection MV** | LoS (days) hospital | LoS (days) hospital |
| 7th | Cost per admission day | Hospital admission rate | Sick leave (days) outpatient | Cost per dose delivery | Cost per admission day |
| 8th | Fixed implementation costs | Cost per admission day | Cost per admission day | Mortality rate | Cost per dose delivery |
| 9th | Paid work per day | Paid work per day | Hospital admission rate | Cost per admission day | Hospital admission rate |
| 10th | Sick leave (days) outpatient | Fixed implementation costs | Paid work per day | Paid work per day | Paid work per day |
| Rank | UA | NV | SPS | SPD | LSHTM |
| mAb | | | | | |
| 1st | **LoS (days) hospital** | **LoS (days) hospital** | **LoS (days) hospital** | **Duration of protection mAb** | **Strong/weak season§** |
| 2nd | **Strong/weak season§** | **Strong/weak season§** | **Strong/weak season§** | **LoS (days) hospital** | **mAb cost per dose** |
| 3rd | **mAb cost per dose** | **mAb cost per dose** | **mAb cost per dose** | **Strong/weak season§** | **LoS (days) hospital** |
| 4th | **Efficacy mAb** | **Efficacy mAb** | **Efficacy mAb** | **mAb cost per dose** | **Efficacy mAb** |
| 5th | **Duration of protection mAb** | **Duration of protection mAb** | Sick leave (days) outpatient | **Efficacy mAb** | **Duration of protection mAb** |
| 6th | Hospital admission rate | Cost per admission day | **Duration of protection mAb** | QALY loss medical (including hospital) care | QALY loss medical (including hospital) care |
| 7th | Cost per admission day | Paid work per day | Cost per admission day | Cost per admission day | Cost per admission day |
| 8th | Paid work per day | Hospital admission rate | Paid work per day | Paid work per day | Hospital admission rate |
| 9th | Sick leave (days) outpatient | Sick leave (days) outpatient | Hospital admission rate | Hospital admission rate | Paid work per day |
| 10th | Fixed implementation costs | QALY loss medical (including hospital) care | Cost per dose delivery | Cost per dose delivery | Cost per dose delivery |

§ severity of the season: strong season measured by 50% high hospitalisation rate, and weak season measured by 50% lower hospitalisation rate based on Norwegian data over 9 seasons. Abbreviations: UA: University of Antwerp model, NV: Novavax model, SPS: Sanofi Pasteur static model, SPD: Sanofi Pasteur dynamic model, LSHTM: London School of Hygiene & Tropical Medicine model, LoS: length of stay, QALY: quality adjusted life-year MV: maternal vaccine, mAb: monoclonal antibody.

## 4 Discussion

We compared five independently developed models furnished with a common dataset to evaluate the cost-effectiveness of year-round, seasonal, and catch-up RSV programmes with MV and mAb interventions. Using a hypothetical birth cohort of 100,000, all models projected ~12-14,000 primary care visits, 2,000 hospitalisations and less than one death annually among children <1 year without any interventions. Overall, dynamic models estimated 10-16% fewer MA cases versus static models mainly because they did not sufficiently capture the pre- and post-peak number of RSV hospitalisations. This can be explained by the fitting approaches that traded off capturing the timing and height of the peak burden, resulting in a final model fit that captured the peak burden better than the burden two months before and one month after the peak.

The models produced qualitatively similar cost-effectiveness results, apart from one model (SPD), which estimated markedly different incremental QALYs gained and ICERs of MV from both perspectives. This difference relates mainly to the SPD model's distinct approach to estimate non-MA symptomatic infections, the proportion of asymptomatic infections, and the exclusion of indirect effects arising from vaccinated mothers. The static models did not consider non-MA symptomatic infections, while the dynamic LSHTM model estimated large numbers of non-MA symptomatic infections, to each of which a QALY loss was assigned. Compared to the LSHTM model, the SPD model estimated 11-fold fewer non-MA symptomatic cases and 5-fold more asymptomatic infections to which no QALY loss was assigned. The absence of age-specific incidence data on asymptomatic and symptomatic non-MA RSV infections in children (< 5 years) required making different model assumptions in this aspect, which had a large impact on the preventable disease burden and cost-effectiveness results. To overcome this, community-based observational studies investigating the age-specific proportions of asymptomatic and non-MA symptomatic RSV infections to all RSV infections would be useful. Moreover, wastewater-based epidemiological surveillance might be used as a complementary source of information to detect broad changes in RSV infection trends in the community [18, 19]. Transparency of model structure and assumptions is essential, as well as sensitivity analysis on assumptions for which strong evidence is missing.

Since dynamic models account for herd immunity, they may be expected to generate more optimistic outcomes compared to static models. However, this is not always true due to age-specific mechanisms [8]. Here, the dynamic models estimated fewer MA cases averted in the younger age-groups (0-2 months, 3-5 months) than the static models mainly due to the calibration dynamic models require, in order to capture the pre-intervention age distribution of cases, and the different approaches to model waning of protective effects. The static models assumed full protection for MV (3-month) and mAb (5-month), after which protection fell to 0%. Both dynamic models included exponential waning for MV and either exponential waning or an all-or-nothing step function for mAb. A systematic review reported that 7 out of 9 identified static RSV models applied an all-or-nothing duration of protection [9], with the remaining two implementing exponential or linear waning [20, 21]. Four out of 5 reviewed dynamic models considered waning of vaccine-induced and infection-induced immunity [22-27]. The exploration of different waning assumptions for these RSV interventions is recommended.

The WHO guidelines for economic evaluation of immunisation programmes recommend that a static model is justifiable if i) strong evidence suggest the eligible target groups are not epidemiologically influential for transmission; and ii) a formal model comparison demonstrates that the static and dynamic models would lead to equivalent cost-effectiveness results [8]. Although households as a whole are pivotal in the general transmission dynamics of close-contact infections such as RSV, the role of infants <6 months as infectors seems limited, as they are most likely to be infected through a within-household contact (e.g., via an older sibling or their parents), with relatively few opportunities to passing the infection on to others outside the household [28]. Infants' mixing patterns are generally also non-assortative, setting them apart from any other age group and implying that infant to infant transmission should be rare [29]. In summary, the community impact on RSV transmission by reducing infants' infectivity (such as through mAb) likely remains limited compared to reducing older children's infectivity. Our study showed no substantial difference in MA cases averted between static and dynamic models when applying 5-month mAb protection. Moreover, studies in the Netherlands, Australia and Kenya showed that MV had limited indirect impact at 50% coverage [24, 25, 30] .

Four additional cost-effectiveness models of RSV interventions in non-high-risk infants were published after our comparison started: two deterministic static models for China [31] and 131 low- and middle-income countries [32], one stochastic static model for Mali [33], and one agent-based dynamic model for Nunavik, Canada [34]. These models assumed all-or-nothing protection without waning for both MV and mAb, and they all assumed that all symptomatic RSV cases would be medically-attended. Furthermore, none of these recent CEA explicitly modelled asymptomatic RSV infections.

Our study has several strengths. To our knowledge, this is the first model comparison including both static and dynamic RSV cost-effectiveness models, where each model was independently developed and calibrated. Standardised input parameters were provided to focus on the intrinsic differences across models. Baral and colleagues conducted an RSV model comparison including two static models that

evaluated the year-round MV impact for 73 Gavi-eligible countries [35], without assessing the cost-effectiveness of MV. Similarly, they concluded that the within-static model differences were mainly explained by model structures, interpretation of input data, and assumptions. Our model comparison provided additional insights on benefits and limitations of choices between dynamic and static models. Furthermore, we aim through this early and hypothetical assessment to inform future developments of RSV models for policy making. We note that the NV model was primarily designed for MV and does not account for a catch-up scenario; the SPD model was designed primarily for mAb, and it has less flexibility for MV options inducing protective direct and indirect effects from mothers. It is essential for future models that they can study these interventions simultaneously.

We also recognise a few limitations. First, the comparison included only models of RESCEU network participants. However, this entailed including the only RSV cost-effectiveness models (UA and LSHTM) for infants published before the formal start of this comparison, one dynamic (SPD) and one static model (SPS) published in 2022[12, 36-38], and one unpublished model from industry (NV). Second, the cost-effectiveness of RSV interventions was evaluated for a hypothetical population, therefore our comparison cannot directly inform decision making for a specific country, given that this was not the purpose of this study. Third, given that the dynamic models are differently structured, the RSV transmission parameters, calibration methods (i.e., methods of fitting, number of free parameters), and associated assumptions regarding mAb protection were not fully standardised between the two dynamic models. However, there was sufficient harmonisation of input and conceptual approach to assess and explain the underlying reasons for the differences in results observed. Fourth, we did not involve policy makers, although they were made aware of RESCEU plans and activities. Fifth, efficacy values of phase 3 mAb (in late-preterm and term infants) and phase 2b MV were not used because the data were released after the end of our final run [4, 39]. However, the effectiveness of any approved interventions should be monitored by post-marketing surveillance studies in both pre- and full-term infants. Moreover, the MV and mAb interventions were not explicitly compared head-to-head, because the policy implications of the application itself, using a plausible but hypothetical data set, was not the aim of our study. The results for MV compared to those of mAb are driven mainly by the efficacy and duration of protection being reported inferior for MV versus mAb, using available evidence during the study period [40, 41]. For in-depth comparisons we refer to individual model applications for specific countries and/or regions. We also did not consider replacing palivizumab by a single-dose mAb in this hypothetical setting. Lastly, probabilistic sensitivity analyses (PSA) were not feasible in some of the included models. This has limited impact on our findings as our aim was not to examine the uncertainty within a given model, but to investigate the differences between models. Nevertheless, PSA should be considered for models used for policy, and future model comparisons should try to involve the assessment of uncertainty in the comparison.

## 5 Conclusion

When conducting a model-based RSV CEA, seasonal (by calendar month or week) and catch-up programmes are best considered at the early stages of model design, especially for modelling mAb in a country with a clear seasonal RSV pattern. This formal model comparison suggests that both static and dynamic models could produce similar output for mAb, because the community impact on RSV transmission by reducing infants' infectivity through mAb likely remains limited. However, there were important differences between static and dynamic models, and within dynamic models, especially regarding non-MA symptomatic RSV burden and waning of mAb and MV protection. The impact of uncertainty around these two aspects should be explored when evaluating RSV interventions. The dynamic models also showed herd immunity in children < 6 months, especially for MV, as well as a potential age-shift. This needs to be considered and weighted in the choice of static versus dynamic models, depending on the intervention under study.

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**Conflict of Interest Disclosures**

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