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Cost-effectiveness of monoclonal antibody and maternal immunization against respiratory syncytial virus (RSV) in infants: evaluation for six European countries

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ABSTRACT

Background: Respiratory syncytial virus (RSV) imposes a substantial burden on pediatric hospital capacity in Europe. Promising prophylactic interventions against RSV including monoclonal antibodies (mAb) and maternal immunizations (MI) are close to licensure. Therefore, we aimed to evaluate the costeffectiveness of potential mAb and MI interventions against RSV in infants, for six European countries.

Methods: We used a static cohort model to compare costs and health effects of four intervention programs to no program and to each other: year-round MI, year-round mAb, seasonal mAb (October to April), and seasonal mAb plus a catch-up program in October. Input parameters were obtained from national registries and literature. Influential input parameters were identified with the expected value of partial perfect information and extensive scenario analyses (including the impact of interventions on wheezing and asthma).

Results: From the health care payer perspective, and at a price of €50 per dose (mAb and MI), seasonal mAb plus catch-up was cost-saving in Scotland, and cost-effective for willingness-to-pay (WTP) values ≥€20,000 (England, Finland) or €30,000 (Denmark) per quality adjusted life-year (QALY) gained for all scenarios considered, except when using ICD-10 based hospitalization data. For the Netherlands, seasonal mAb was preferred (WTP value: €30,000-€90,000) for most scenarios. For Veneto region (Italy), either seasonal mAb with or without catch-up or MI was preferred, depending on the scenario and WTP value. From a full societal perspective (including leisure time lost), the seasonal mAb plus catch-up program was cost-saving for all countries except the Netherlands.

Conclusion: The choice between a MI or mAb program depends on the level and duration of protection, price, availability, and feasibility of such programs, which should be based on the latest available evidence. Future research should focus on measuring accurately age-specific RSV-attributable hospitalizations in very young children.

1. Introduction

Respiratory syncytial virus (RSV) is a major cause of acute lower respiratory tract infections (LRTI) in infants. A global meta-analysis estimated 6.6 million RSV episodes, 1.4 million RSV-associated hospital admissions, and 45.7 thousand RSV-attributable deaths in infants under six months of age in 2019 [1]. In Europe, a multi-country, multi-season database analysis demonstrated that the average RSV-ICD-10-coded hospitalization rates ranged from 20.5 to 22.3 per 1000 children under one year of age in Scotland, Finland, and Denmark, and from 8.6 to 11.7 per 1000 children in the Netherlands and Italy [2].

Currently, there is only one marketed RSV prophylactic intervention available in Europe: palivizumab, which is indicated only for high-risk children and requires monthly injections throughout the RSV season [3]. Its list price varies from €356 in England to €955 in Finland per 0.5 mL dose [4,5], and the high price limits its clinical use, so there is still a large remaining disease burden.

In 2021, a long-lasting single-dose RSV monoclonal antibody (mAb) nirsevimab achieved its phase 3 primary endpoint and received market authorization from The European Medicines Agency [6]. It showed protection against RSV-associated LRTI for five months. Alternatively, RSV maternal immunization (MI) candidates, which would protect both the immunized pregnant women, and later their infants through placental transfer of antibodies, are also under development. Overall, a maternal vaccine announced top-line results of the phase 3 trial and one other mAb are undergoing phase 3 trial, they are likely to become available in the next few years.

Since RSV is highly seasonal in Europe, and mAb and MI would offer durations of protection less than a year, different programmatic choices can be considered [6]. Three RSV prevention programs are often evaluated, namely: year-round, seasonal (immunizing only during the RSV season), and catch-up (immunizing infants, who were born before RSV season, at the start of the RSV season).

Cost-effectiveness analysis is commonly used to facilitate decision making in Europe, especially when considering introducing a new RSV immunization program. There has been an increasing number of RSV cost-effectiveness analyses published during the last few years [7–14]. Overall, seasonal MI and mAb programs with or without catch-up had more favorable cost-effectiveness ratios compared to year-round programs, but the cost-effectiveness price per full schedule varied from 500 Norwegian Krone (~€50) to 1,065 Canadian dollars (~€718) under country-specific willingness-to-pay (WTP) thresholds. As part of the RESCEU international consortium (REspiratory Syncytial virus Consortium in EUrope, https://resc-eu.org), new evidence on RSV disease burden in Europe has emerged, requiring new health economic evaluations of interventions against RSV. For instance, RSV hospitalizations have recently been estimated based on laboratory data using time series analysis, resulting in substantially higher RSV hospitalization rates than based on RSV-coded data for all European countries considered [15].

The objective of our analysis is to evaluate the costeffectiveness of year-round RSV MI and mAb programs, as well as a seasonal RSV mAb program, and a seasonal mAb plus catchup program using the most recent country-specific data for six European countries: Denmark, Finland, England, Scotland, Italy, and the Netherlands. As such, it presents the first multi-country analysis of RSV prevention programs in infants in a high-income setting.

2. Methods

2.1. Cost-effectiveness model

A previously published static cohort model (Multi-Country Model Application for RSV Cost-Effectiveness poLicy: MCMARCEL Li et al. 2020 and 2022 [9,10]; Fig. 1) was used to estimate RSV disease and economic burden in children under five years of age, and to evaluate the cost-effectiveness of RSV interventions per country (for Italy, only for the Veneto region, see further). The model accounts for costs and quality-adjusted life-years (QALYs) loss due to RSV cases in the primary care and hospitalization setting. The model does not account for symptomatic RSV cases not seeking professional medical care, nor for RSV cases requiring only a hospital outpatient or emergency department visit, because limited data was available for most of the countries considered. In scenario analyses, we further assessed the RSV-related mortality by assuming that RSV mortality only occurs in hospitalized infants, given good health care accessibility in the countries considered and assuming only severe cases would die due to RSV.

Four programs were compared to no program and to each other in a full incremental analysis (Supplementary Table 1): (a) year-round MI program in the third trimester of pregnancy (‘year-round MI’), (b) mAb administered at birth throughout the year (‘year-round mAb’), (c) mAb administered at birth during the RSV season from October to April (‘seasonal mAb’) and (d) seasonal mAb plus a catch-up program in October to protect children born in May to (including) September. Seasonal MI

programs were not considered given the associated practical implications. Targeted immunization programs were not considered given the difficulty to define specific target groups (e.g., high-risk infants).

Cost-effectiveness was evaluated from the health care payer perspective (HCP: including only direct costs for RSV treatment and RSV intervention), partial societal perspective (all direct costs + productivity loss due to workdays off from paid employment for caring for a child with RSV and for receiving an RSV intervention), and full societal perspective (all direct costs + economic cost of total time (including leisure time) lost due to caring for a child with RSV and for receiving an RSV intervention). See section 2.2 for details on how productivity loss and total time lost were estimated for each country.

Discount rates for costs and effects were based on local pharmacoeconomic guidelines [16], i.e., 3.5/3.5% for Denmark, England and Scotland, 3/3% for Finland and Italy and 4/1.5% for the Netherlands. All costs were first inflated to 2021 using consumer price indices (all sectors), and those reported in local currency were converted to euro using the annual exchange rates of 2021. Health benefits were measured as Quality-Adjusted Life-Years (QALYs) gained.

Parametric uncertainty was accounted for with probabilistic sensitivity analysis (PSA) [17,18]. Uncertainties underlying potentially influential input parameter choices were explored in scenario analyses (see further).

[Figure 1]

2.2. Model input parameters and assumptions

Supplementary Table 15 gives an overview of all input parameters, and Supplementary section 1.4 provides details on how each input parameter was obtained.

Average annual number of RSV hospitalizations by age in months and by calendar month were sourced from a time series analysis for all countries but Italy [15]. Scotland and Finland had the highest and the Netherlands the lowest estimated RSV hospitalization rate for infants 0–5 months of age. For Italy, only RSV International Classifications of Diseases (ICD-9-CM)-coded hospitalizations were available for the Veneto region [2]. The RSV-ICD-10-coded hospitalizations for Denmark, Finland, the Netherlands, England, and Scotland (Reeves et al. [2]) were consistently lower than the estimates based on time series analysis (23–80% lower, Supplementary Table 2). Therefore, for base case analysis of Veneto region (Italy), we used the RSV-ICD-9CM-coded hospitalizations multiplied by 1.9, 2.3, and 2.5 for age 0–2 months, 3–5 months, and 6–11 months, respectively. These multiplication factors were derived from the average ratio of underestimation of RSV-coded hospitalizations [2] compared to RSV-estimated hospitalizations based on the five other countries [15]. In scenario analysis, we also used RSV-coded hospitalizations for all six countries (see Supplementary section 1.5.1).

We obtained age-specific number of RSV-related primary care episodes, by assuming on average five RSV primary care episodes for each RSV hospitalization for age 0–5 months, and 12.5 primary care episodes for each RSV hospitalization for age 6–59 months (refer to Li et al. 2022 [9]). This assumption is supported by data that became recently available for Italy, the Netherlands, the UK, Spain and Finland (details see Supplementary section 1.4.2) [19].

It is uncertain whether mortality of children with RSV can be prevented by mAb and MI. Children who died with RSV as (one of the) cause(s) of death, often suffered from severe comorbidities that would likely lead to premature death without RSV infection. Therefore, we assumed no RSV mortality can be prevented in the base case analysis. Given the uncertainty around this assumption, we also did a scenario analysis assuming RSV mortality can be prevented, with RSV mortality rates based on data from Denmark and Scotland. In Denmark, 29 death certificates for deaths that occurred in

children under two years of age during the years 2000–2016 contained an ICD-10 RSV code (i.e., mortality rate of 63 per 100,000 RSV hospitalizations per year, see Appendix 1.4.3). In Scotland, 10 RSV-related deaths were identified in children under two years of age during the years 2010–2016,[2] resulting in a mortality rate of 69 per 100,000 RSV hospitalizations per year. In Finland, the number of RSV-related deaths extracted for the years 2000–2018 was too small to be shared due to the European Union's General Data Protection Regulation. No empirical mortality data were available for England, the Netherlands, and the Veneto region (Italy). Hence, in addition to the base case without mortality, we show in scenario analysis the other extreme of the available evidence by assuming for Finland, England, the Netherlands, and the Veneto Region (Italy), the same mortality rate as in Scotland (i.e., the country with the highest RSV mortality rate given hospitalization for infants aged 0–5 months).

Country-specific costs were obtained for hospitalizations, including intensive care unit (ICU) admissions, primary care visits, and mAb and MI administration costs (Supplementary Table 15 and Supplementary section 1.4.4). For the partial societal perspective, productivity loss was obtained by multiplying the number of workdays off due to RSV illness and the time of receiving the intervention, by the average country-specific gross earnings per day. The number of workdays off was assumed to be equal to the length of hospitalization for hospitalized children, and to be between 0 and 4.3 days for primary care cases (see Supplementary section 1.4.4). For the full societal perspective, we calculated the costs of total time lost due to RSV illness (whether for work, leisure, or other activities) as the duration of illness in days multiplied by the average country-specific gross earnings per day (see Supplementary section 1.4.4).

We assumed €50 per dose for both mAb and MI intervention procurement cost in the base case analysis (indicatively based on the list price of rotavirus vaccine). Due to the absence of pricing information from manufacturers, we varied this assumption in a two-way price sensitivity analysis considering 25 combinations of prices between €10 and €100 per dose (indicatively based on the list prices of measles-mumps-rubella and meningococcal B vaccines). The administration costs of mAb and MI were varied by country depending on the national/regional childhood/maternal vaccination schedule (Supplementary section 1.4.4). We also assumed an annual implementation costs of €300,000 per program for scenario analysis.

Efficacy and duration of protection for mAb were based on a recently published randomized controlled trial (RCT) of nirsevimab in healthy late-preterm and term infants [6]. The primary and secondary endpoints of this phase 3 trial were medically attended RSV-associated LRTI and hospitalization for RSV-associated LRTI through five months after a single injection of nirsevimab, where the authors reported efficacy rates of 74.5% (95% CI: 49.6 to 87.1) and 62.1% (95% CI: -8.6 to 86.8) against the two endpoints, respectively [6]. The MI candidate ResVax showed significant protection against RSV-related LRTI hospitalization but failed to meet its primary endpoint in 2019 [20]. However, other MI candidates are undergoing phase 3 trials, so we assumed the World Health Organization (WHO) preferred product characteristics (PPC), 70% efficacy and 4-month protection, for MI [21]. In scenario analysis, we based MI efficacy on the preliminary phase 3 trial results of a bivalent RSV prefusion F protein–based (RSVpreF) vaccine, i.e. 51.3% [29.4–66.8] against any medically attended RSV-associated LRTI and 69.4% [44.3 – 84.1] against medically attended severe RSV associated LRTI with a 6-month duration of protection [22]. Immunization coverages for both mAb and MI were assumed to be 90%, but impact on burden assuming 60% coverage for MI (based on maternal pertussis vaccine coverage) is also shown in scenario analysis. We assumed complete protection starting from administration and lasting for four (MI) and five (mAb) months [6,21].

[2] children with respiratory tract infections (RTI) ICD-10 code in primary or the first three secondary causes of death and who got an RSV positive lab result within one month before the death date.

We assumed average QALY loss to be 0.0102 [95% confidence interval (CI): 0.0089–0.0117] for an RSV hospitalization and 0.0063 [0.0055–0.0070] for an RSV-related primary care visit, based on a prospective multi-country infant cohort study (Mao et al. [23]). Given the challenges associated with valuing QALY in infants using economic evaluation [24], we explored a scenario assuming average QALY loss estimates based on Hodgson and colleagues [8].

Currently, it is still uncertain to what extent these RSV interventions can have an impact on potential long-term consequences of RSV (i.e., recurrent wheeze and asthma), if any. In the base case, we assume there is no impact, but we explore the burden of recurrent wheeze and asthma as a consequence of RSV hospitalization in the first year of life in scenario analyses (Supplementary section 1.5.2).

2.3. Model outcome

To identify the cost-effective programs, we applied the concepts of (extended) dominance and the incremental cost-effectiveness ratio (ICER) [18,25]. First, we removed the strongly dominated programs, i.e., programs that are on average more costly and less effective than any other program. Second, we calculated the expected ICER for the remaining programs as the ratio of expected incremental costs divided by expected incremental effects of each non-strongly dominated program compared to its next most effective alternative. Third, we removed extendedly dominated programs, i.e., programs with an expected ICER greater than the next most effective alternative. The remaining non-dominated programs form the cost-effectiveness frontier and, hence, are preferred over all other programs for a particular range of WTP values (depending on their expected ICER).

In addition, and completely equivalent, we identified cost-effective programs based on the net loss framework, i.e., for a given WTP value the cost-effective program is the program with the lowest expected net loss (this is also equivalent to the program with the highest expected net monetary benefit) [25,26]. The results are presented as net loss curves, which also show the decision uncertainty surrounding the cost-effective options (i.e., the expected value of perfect information (EVPI)) [18,26]. The higher the EVPI, the more uncertain we are about the cost-effective option, hence, the higher the potential value in obtaining more evidence to inform the decision.

To identify the input parameters that contribute most to decision uncertainty, we obtained the expected value of partial perfect information for each uncertain input parameter separately (i.e., EVPPI). Parameters with the highest EVPPI are most influential. EVPI and EVPPI only account for uncertainty included in the PSA. In addition, cost-effectiveness results are obtained for different scenarios in which one or two input parameter values are changed to explore their impact on the results (i.e., one- and two-way sensitivity analysis).

All analyses were done in R version 4.1.2.

3. Results

3.1. RSV disease and economic burden

Supplementary Table 16 reports the overall RSV disease and economic burden for the six countries. The estimated annual RSV-related disease burden in children under the age of five ranged from 8,197 cases and 1,109 hospitalizations in Veneto region (Italy) to 317,228 cases and 35,644 hospitalizations in England. The corresponding treatment costs ranged from €2,835,133 to €95,536,644 with most of these costs (93% and 88%, respectively) due to RSV hospitalization. From a full societal perspective, the model estimated more costs due to RSV-related time lost than RSV-related treatment costs for all countries.

3.2. Averted RSV disease and economic burden, and intervention costs

In all countries, the seasonal mAb plus catch-up program averted the highest RSV disease burden (Supplementary Table 17). The discounted total RSV cases and hospital admissions averted using this strategy ranged from 2,828 cases and 441 hospitalizations in Veneto region (Italy) to 69,896 cases and 10,295 hospitalizations in England. The mAb plus catch-up program also resulted in the most discounted QALY gained varying from 19 in Veneto region (Italy) to 478 in England. The intervention costs of mAb plus catch-up ranged from €1,730,949 in Veneto region (Italy) to €32,021,870 in England.

3.3. Cost-effectiveness of RSV interventions

From the HCP perspective, and under the base case assumptions, the cost-effective programs for Denmark, England, Veneto region (Italy), and the Netherlands were either no program, seasonal mAb, or seasonal mAb with catch-up, depending on the WTP value. Seasonal mAb was preferred for WTP values from €4,444 (England), €9,129 (Denmark), €23,814 (Veneto region) and €21,187 per QALY gained (the Netherlands), seasonal mAb with catch-up was preferred for WTP values from €8,864 (England), €24,664 (Denmark), €42,245 (Veneto region) and €130,308 per QALY gained (the Netherlands), and no program was preferred for lower WTP values. For Finland, seasonal mAb with catch-up was cost-effective from €13,373 per QALY gained, and for lower WTP values seasonal mAb without catch-up was preferred. For Scotland, seasonal mAb with catch-up was preferred over all other programs for the range of WTP values considered (Fig. 2).

[Figure 2]

These results depended strongly on the following aspects: 1) the assumed intervention procurement price, 2) the assumed intervention administration cost, 3) the perspective, and – most of all - 4) the type of data used to inform RSV-related hospitalizations (ICD-10-coded counts or estimates based on time series analysis).

(1) The price combinations of mAb and MI at which different programs were cost-effective from the HCP perspective, depended on the country, the WTP value and MI efficacy. Using base case MI efficacy, year-round MI became cost-effective over all other programs when priced at least 50% lower than mAb for the price range we considered. When mAb was priced at >€75 and MI >€50 per dose, either 'no program' or a seasonal mAb program with or without catch-up became preferred over all other programs, for all countries (Fig. 3 using Finland as an example, and Supplementary Fig. 4 and Fig. 12b).

[Figure 3]

(2) Only for the Netherlands and the Veneto region (Italy), the administration cost for mAb at catch-up was assumed to be higher than for mAb at birth (€30 vs €14 for the Netherlands, and €12 vs €8 for the Veneto region). Especially for the Netherlands, this resulted in the seasonal mAb with catch-up program being preferred at a much higher WTP value (€130,308 per QALY gained) than the WTP value at which the seasonal mAb without catch-up was preferred (€21,187 per QALY gained), from the HCP perspective under base case assumptions.

(3) From the full societal perspective and under base case assumptions, seasonal mAb plus catch-up dominated all other programs for all countries except for the Netherlands, regardless of the probabilistic uncertainty accounted for (Fig. 2; Supplementary Fig. 3). For the Netherlands, seasonal mAb without catch-up dominated all other programs from the full societal perspective. For each country, except the Netherlands, the results from the HCP perspective and partial

societal perspective were similar (Fig. 2). Note that the Netherlands was the only country for which paid workdays lost due to caring for a child under six months with RSV was considered from the partial societal perspective, due to the short maternity leave (three months).

(4) From the HCP perspective, and when using ICD-coded RSV hospitalizations (scenario) instead of estimates based on time series analysis (base case), none of the intervention programs was cost-effective for England, the Veneto region (Italy), and the Netherlands for all WTP values considered. For Finland and Denmark, the WTP value at which the seasonal mAb program with catch-up became preferred increased substantially (Denmark: from €24,664 to €77,000; Finland: from €13,373 to €50,000 per QALY gained). In Scotland, the mAb program plus catch-up no longer dominated the other programs but became costeffective for WTP values from €40,000 per QALY gained (Fig. 2; Supplementary Fig. 6).

It is worth noting that using phase 3 MI efficacy with 6-month duration of protection does not substantially change the costeffectiveness results, because the additional RSV episodes averted in children aged 4–5 months due to longer protection (6 instead of 4 months) is offset by the lower number of ambulatory episodes averted in infants aged 0–3 months due to lower assumed efficacy (51.3% instead of 70%) (Fig. 2; Supplementary Fig. 13).

From the uncertainties accounted for in PSA, the uncertainty around the average ratio of RSV hospitalized versus primary care cases in the age group 0–5 months was most influential (i.e., highest EVPPI, Supplementary Fig. 5). Uncertainty around MI efficacy was most influential for the scenario using MI phase 2b efficacy (Fig. 2 and Supplementary Fig. 12c). Scenario analyses further showed that uncertainty about the impact of the intervention programs on recurrent wheezing and asthma, the interventions' implementation cost, RSV health-related quality of life (HRQoL), and mortality impacted the results to a lesser extent (Fig. 2 and Supplementary Figs. 7–11).

4. Discussion

This is the first multi-country analysis that assessed the cost-effectiveness of various RSV MI and mAb programs in Europe using country-specific data. Under base case assumptions, from all considered analytical perspectives (HCP, partial, and full societal perspectives), and for all six countries, year-round MI and year-round mAb programs were consistently dominated by 'no program' or seasonal mAb program, with or without catch-up. However, from the HCP perspective, large between-country differences were found regarding the minimum WTP value at which seasonal mAb and seasonal mAb plus catch-up became preferred. For the Netherlands, seasonal mAb became cost-effective at WTP value >€21,187 per QALY gained and seasonal mAb plus catch-up at WTP value >€130,308 per QALY gained. In contrast, for Scotland, seasonal mAb plus catch-up dominated all other programs from the HCP perspective.

These differences in cost-effectiveness results reflect country-specific differences in RSV disease burden and health care system organization, as well as in data collection and assumptions. The Netherlands had the lowest estimated RSV hospitalization rate for infants under six months based on the time series analysis and the highest administration cost per dose of all countries (€30 for MI and mAb catch-up and €14 for mAb at birth). In the Netherlands, a separate visit to the youth health center was assumed to be necessary for MI and mAb catch-up programs. According to current Dutch vaccination practice, the number of jointly administered immunizations is limited to two, hence the MI program is unlikely to be added to the visit for pertussis and influenza vaccination during pregnancy. For the mAb catch-up program, no regular check-up visits for infants under six months exists in October in the Netherlands. Scotland and Finland had the highest RSV hospitalization rates for infants under six months. Furthermore, for Finland, we used the lowest administration cost per dose (€2.10 for MI and mAb), accounting only for the time needed to administer one additional

vaccine during a regular check-up visit. Additionally, primary care costs ranged from €27 per pediatrician visit in Italy to €87 per general practitioner visit in Finland, however, primary care costs contributed little to the overall RSV-related treatment costs. Better documentation of the country-specific disease burden would be helpful to reduce uncertainty about the different policy choices between the countries.

Our results were comparable with previously published cost-effectiveness analyses in Europe. Hodgson and colleagues estimated the threshold price for seasonal mAb programs (October to February) in England to be £90 and £40 without and with catch-up, respectively, from a HCP's perspective and using the WTP threshold of £20,000 per QALY gained [8]. Our analysis in England showed results slightly more in favor of the seasonal mAb program (October to April) with catch-up, i.e., it was cost-effective (WTP value <€20,000) at the price of €50 per dose. We used lower mAb efficacy values based on the phase 3 RCT results (i.e., 62% vs. 78% in the phase 2b RCT) and did not account for the burden of disease among children not seeking medical care, but our hospital admission rate was higher (i.e., 90.4 per 1000 infants 0–2 months of age) than Hodgson et al.'s estimate (30, 70, and 50 admissions per 1000 infants aged 0, 1, and 2 months, respectively). A Norwegian analysis that assumed €50 per mAb dose concluded that the RSV seasonal mAb program with catchup was not cost-effective from a HCP's perspective using only ICD-10 hospitalization codes if WTP value was <€100,000 per QALY gained [9]. Our sensitivity analysis using ICD-10 hospitalization codes showed that the seasonal mAb program with catch-up only became cost-effective in Denmark if WTP value was >€77,000 per QALY gained. However, when using the hospitalization estimates from the latest time series analysis (base case), the seasonal mAb program with catch-up was the preferred strategy for WTP value >€24,664 per QALY gained.

Despite large efforts to collect country-specific data, there are still large data gaps and uncertainties around the RSV-related burden in Europe. Our analysis highlighted the impact of using different data sources to inform RSV hospitalization rates and QALY. Time series analysis estimated 1.3 (Denmark) up to 3 (England) times more RSV-attributable hospitalizations than the RSV-ICD-10 coded rates for infants aged 0–2 months, and a 1.7 (Denmark) up to 4 (England) times higher number for the 3–5 months age group [2,15]. As RSV clinical symptoms are very similar to many other respiratory virus infections, the RSV-ICD-10-coded hospitalization rate might be less reliable without laboratory-confirmed data. On the other hand, the time series analysis included only a limited number of pathogens (influenza A, B, and RSV) that could cause respiratory infections, as such potentially overestimating the association with RSV [15].

The average QALY loss per RSV episode in children estimated by Mao and colleagues was more than double the estimate by Hodgson and colleagues (e.g., 0.0102 [0.0089, 0.0117] per hospitalized RSV episode versus 0.0039 [0.0002, 0.0123] per medically attended RSV episode, of which 84% were hospitalized) [23,28]. The advantages and disadvantages of these two studies are discussed elsewhere [23], but in general, measuring QALY loss in very young children is challenging. Our study showed that the type of data used to inform RSV hospital admission and QALY can have a strong influence on the cost-effectiveness of RSV intervention programs. Hence, it remains essential to assess the best methods to accurately estimate age-specific RSV-related hospitalizations and QALY in young children, and consequently account for any associated uncertainty, as was noted previously for economic evaluations of rotavirus vaccination [29].

Cost-effectiveness results can be sensitive to the assumed mAb and MI level and duration of protection and should be updated when new/comprehensive RCT data are available. However, when assuming phase 3 MI efficacy with 6 months duration of protection, seasonal mAb with or without catch-up remains preferred for all countries for WTP values > €25,000 per QALY gained. Notably, we used average efficacy over the duration of protection considered (all-or-nothing protection) and did not consider waning given the lack of clinical data. An exponential or linear decay of intervention's efficacy would likely lead to more favorable cost-effectiveness results for both interventions

compared to no intervention, because of the higher efficacy for the first months after vaccination at the age when the burden is highest (age 0–2 months) and increasingly lower efficacy when children get older (and when RSV burden is lower, i.e., age 3–5 months). Longer and detailed follow-up efficacy data are needed to account accurately for the benefit of the interventions, with potential impact over multiple seasons [21]. Furthermore, we assumed optimistically that newborns would receive the same protection from MI, irrespective of their gestational age. Despite this potential overestimation of the benefits of MI for preterm infants, year-round MI was dominated by the mAb programs in base case analysis. Therefore, this assumption has limited influence on our findings.

Our study has several strengths. It used the most recent country-specific data to populate the model under each country's setting according to the local pharmacoeconomic guidelines, thus providing policy makers of these countries with relevant information. Moreover, both partial and full societal perspectives were used. In five of the six countries, the duration of maternity leave is equal or longer than five months, and therefore, RSV in infants may rarely cause work absenteeism for one of their parents, and thus hardly impede caregiver productive time for society. However, parents' usual activities during a period of maternity leave would be interrupted, and this is accounted for under the full societal perspective we presented separately. From a full societal perspective, the seasonal mAb catch-up program was dominant in five of the six countries. Finally, extensive sensitivity analyses were performed using a wide range of WTP thresholds for each country, to increase the usefulness of these analyses to decision makers.

There are also several limitations in our study. Firstly, we used a static model, in which herd immunity was not accounted for. However, since the duration of protection was relatively short for both MI and mAb, this should have a limited impact on our results [30]. Secondly, our analysis used an average RSV season, although the timing and peak of the seasons varied over time in all countries, and some countries had biennial peaks. We also used pre-COVID-19 data, and the RSV season had shifted in 2020 and 2021 in several European countries [31]. Therefore, continued surveillance remains important to monitor seasonality changes over time, and to establish whether the RSV seasons revert to pre-COVID-19 patterns. Moreover, RSV-associated otitis media was not included in our analysis, which might lead to an underestimation of the impact of RSV prevention strategies [32]. Finally, our study used ‘‘no program” as a baseline comparator versus universal strategies aiming to protect all children, and not just high-risk children. Hence, we ignored that a long-lasting single-dose mAb could replace the existing monthly costs for palivizumab in high-risk children, either as a targeted immunization program or as part of a universal program. Clinical guidelines on palivizumab use are not standardized across the six countries under analysis [2]. Given the high price of palivizumab, the net costs of mAb program implementation might be lower than we assumed, especially over a longer time span. However, in a full cost-effectiveness analysis such as ours, when all programs are not only compared to ‘‘no program” but also to each other, the selection of the preferred strategy would not depend heavily on cost offsets versus a strongly dominated option (such as ‘‘no program”). The inclusion of an extra cost-offset from comparisons with ‘‘no program” would render the ‘‘no program” option even more dominated by the other options, but it is unlikely to impact the choice between seasonal, year-round mAb or catchup mAb for all children.

5. Conclusion

The results of this study can inform decision making in six European countries on the implementation of RSV intervention programs in infants. It shows that year-round MI can become cost-effective if the price per dose is at least 50% lower than mAb and/or if higher protection is assumed. When mAb and MI are equally priced, seasonal mAb with or without catch-up is preferred over year-round MI and mAb programs. The choice between no program, seasonal mAb, or seasonal mAb plus catch-up programs depends on the country, the WTP value, the perspective taken and

several key input parameters. Our study highlights the importance of developing methods to accurately measure age-specific RSV-related hospitalizations and QALY loss in very young children, as well as the need for better RSV-related disease and economic burden estimates.

6. RESCEU Investigators

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8. Data availability

Almost all the data analysed and generated during this study are included in this published article and its supplementary material files. Formal requests for additional data can be made to the corresponding author (XL) or the senior author (JB and PB).

9. Ethics

The work presented in the article has been carried out in an ethical way. No Ethics committee approval is needed.

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: 'PB reports grants from Respiratory Syncytial Virus Consortium in Europe (RESCEU), Innovative Medicines Initiative 2 of the European Commission, Joint Undertaking under grant agreement No 116,019 during the conduct of the study; and grants from Pfizer, GSK, Merck and European Commission IMI project PROMISE, outside the submitted work, but

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Appendix A. Supplementary material

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Tables and figures

Figure 1. A schematic representation of the RSV health outcomes considered in the model. [&]Included in scenario analysis.

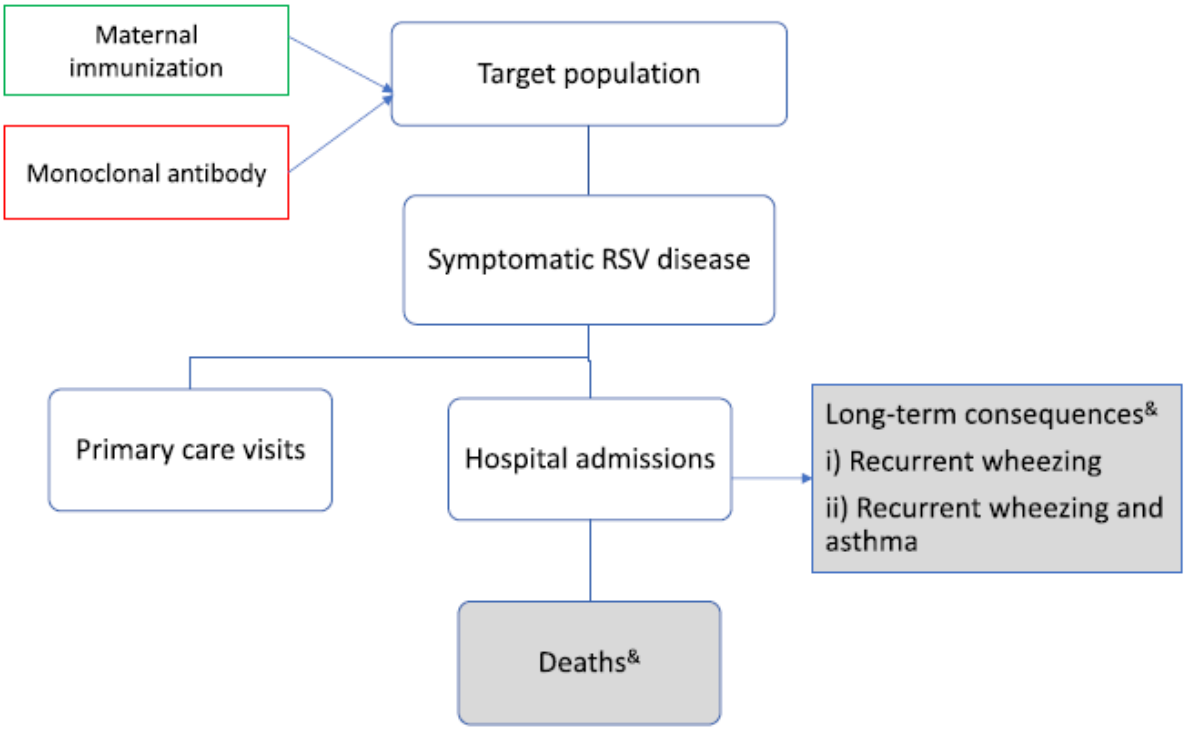

Figure 2. Preferred strategy in terms of cost-effectiveness for preventing respiratory syncytial virus (RSV) in infants for a range of willingness-to-pay (WTP) values. Preferred strategy is the strategy with the lowest expected net loss when compared to the other strategies considered. Strategies compared were (1) no program, (2) year-round MI, (3) year-round mAb, (4) seasonal mAb, and (5) seasonal mAb + catch-up. Base case refers to the parameter values used in base case analysis. Price per dose assumed €50 for mAb use in infants and maternal vaccination. HCP: health care payer

Figure 3. Cost-effective program for different prices of maternal vaccination and mAb, for five willingness-to-pay (WTP) values (from €10 to €100,000 per QALY gained), example of Finland. Year-around MI, year-round mAb, seasonal mAb program, and seasonal mAb with a catch-up program were compared to no program and to each other. The size of the squares is relative to the degree of decision uncertainty (as expressed by EVPI [27]). The larger the square, the more certain that this is the cost-effective strategy.