Infect Dis Ther
https://doi.org/10.1007/s40121-024-00975-6

ORIGINAL RESEARCH

Cost-effectiveness Analysis of Maternal Immunization with RSVpreF Vaccine for the Prevention of Respiratory Syncytial Virus Among Infants in Spain

Javier Álvarez Aldean · Irene Rivero Calle · Rosa Rodríguez Fernández · Susana Aceituno Mata · Alba Bellmunt · Miriam Prades · Amy W. Law · Alejandra López-Ibáñez de Aldecoa · Cristina Méndez · María L. García Somoza · Javier Soto · Virginia Lozano

Received: February 7, 2024 / Accepted: April 8, 2024

ABSTRACT

Introduction: Respiratory syncytial virus (RSV) is the leading cause of acute lower respiratory infections (ALRI) in children under one year of age. In high-income countries, RSV infections cause a significant overload of care every winter, imposing a significant burden to the healthcare system, which has made the development of prevention strategies a major global health priority. In this context, a new bivalent RSV prefusion F protein-based vaccine (RSVpreF) has recently been approved. The objective of this study was to evaluate the cost-effectiveness of vaccinating pregnant women with the RSVpreF vaccine to prevent RSV in infants from the Spanish National Healthcare System (NHS) perspective.

Methods: A hypothetical cohort framework and a Markov-type process were used to estimate clinical outcomes, costs, quality-adjusted life years (QALY) and cost-per-QALY gained (willingness-to-pay threshold: €25,000/QALY) for newborn infants born to RSV-vaccinated versus unvaccinated mothers over an RSV season. The base case analysis was performed from the NHS perspective including direct costs (€2023) and applying a discount of 3% to future costs and outcomes. To evaluate the robustness of the model, several scenarios, and deterministic and probabilistic analyses were carried out. All the parameters and assumptions were validated by a panel of experts.

Results: The results of the study showed that year-round maternal vaccination program with 70% coverage is a dominant option compared to no intervention, resulting in direct cost savings of €1.8 million each year, with an increase of 551 QALYs. Maternal vaccination could prevent 38% of hospital admissions, 23% of emergency room visits, 19% of primary care visits, and

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40121-024-00975-6.

J. Álvarez Aldean
Hospital Costa del Sol, Marbella, Málaga, Spain

I. Rivero Calle
Hospital Clínico Universitario de Santiago de Compostela, A Coruña, Spain

R. Rodríguez Fernández
Hospital Gregorio Marañón, Madrid, Spain

S. Aceituno Mata · A. Bellmunt (✉) · M. Prades
Market Access, Outcomes'10 S.L.,
Castellón de La Plana, Castellón, Spain
e-mail: abellmunt@outcomes10.com

A. W. Law
Pfizer, Inc., New York, USA

A. López-Ibáñez de Aldecoa · C. Méndez · M. L. García Somoza · V. Lozano
Pfizer S.L.U, Alcobendas, Madrid, Spain

J. Soto
Former Pfizer S.L.U Employee, Madrid, Spain

Published online: 11 May 2024

34% of deaths due to RSV. All scenario analyses showed consistent results, and according to the probabilistic sensitivity analysis (PSA), the probability of maternal vaccination being cost-effective versus no intervention was 99%.
Conclusions: From the Spanish NHS perspective, maternal vaccination with bivalent RSVpreF is a dominant alternative compared with a non-prevention strategy.

Keywords: Cost-effectiveness; Maternal immunization; Respiratory syncytial virus (RSV); RSVpreF vaccine; Spain

Key Summary Points

Why carry out this study?

Respiratory syncytial virus (RSV) disease is associated with an important public health impact and substantial economic burden, which has made the development of RSV prevention strategies a major global health priority.

In this study, the cost-effectiveness of the immunization of pregnant women with the new bivalent RSV prefusion F protein-based (RSVpreF) vaccine was evaluated in Spain.

What was learned from the study?

Maternal immunization with RSVpreF vaccine was dominant versus no intervention from the Spanish National Healthcare System perspective, demonstrating its value as an RSV preventive strategy.

Maintaining high levels of vaccination coverage is important to ensure that as many cases as possible are prevented.

INTRODUCTION

Respiratory syncytial virus (RSV) is the leading cause of acute lower respiratory infections (ALRI) in children under 1 year of age, mainly those related to bronchiolitis and pneumonia. All infants are at risk of acquiring an RSV infection with severe complications, which are unpredictable and cause hospitalization [1]. In particular, about 1–2% of bronchiolitis are severe enough to require hospital admission, and of these, about 10–20% require care in intensive care units (ICU) [2, 3]. Worldwide, RSV is the second leading cause of death in children under 1 year of age. While RSV mortality in developed countries is lower relative to developing countries, high-risk infants with comorbidities experience higher rates of mortality. In Spain, mortality rates of 1.47 deaths per 100,000 in children aged < 5 years and 3.40 deaths per 100,000 in children aged < 2 years have been reported, with an average of 30 deaths per year [4]. An observational study in Spain recently found an in-hospital case fatality rate of 0.14% [1].

In high-income countries like Spain, RSV infections cause a significant overload of care every winter, both in primary care services and in hospitals, imposing a significant burden to the healthcare system. In 2019, in Spain, the annual cost of hospitalizations due to RSV in children was €44.8 million, and infants aged < 6 months accounted for almost 60% of these costs [5]. Consequently, RSV disease is associated with an important public health impact and substantial economic burden, which has made the development of RSV prevention strategies a major global health priority [6, 7].

In this context, a new bivalent RSV prefusion F protein-based vaccine (RSVpreF) has recently been approved by the European Medicines Agency (EMA) [8] and reimbursed in Spain. This new strategy aims to prevent RSV-associated illness in infants in the first 6 months of life by active immunization of pregnant women between 24 and 36 weeks gestational age, providing passive protection of the newborn through transplacental antibody transfer [8]. The efficacy, safety, and immunogenicity of RSVpreF in infants born to people vaccinated during pregnancy has been evaluated in a placebo-controlled phase III clinical trial (MATernal Immunization Study for Safety and Efficacy [MATISSE]) [9]. In this study, RSVpreF efficacy against severe medically attended ALRI due to RSV was 81.8% (99.5% confidence interval [CI] 40.6–96.3) through the first 90 days of life and

69.4% (97.6% CI 44.3–84.1) over the 6-month follow-up period. Against RSV-related medically attended ALRI, vaccine efficacy was 57.1% (99.5% CI 128 14.7–79.8) through the first 90 days of life and 51.3% (97.6% CI 29.4–66.8) over the 6-month follow-up period [9].

While the efficacy and safety of RSVpreF vaccine have been demonstrated based on MATISSE, public health discussions should also consider if maternal vaccination against RSV is an efficient allocation of resources. This study has been used to inform healthcare national authorities in order to evaluate the efficiency of vaccinating pregnant women with the RSVpreF vaccine for an RSV immunization program against the standard of care on that moment, which was no intervention, by performing a cost-effectiveness analysis from the Spanish National Healthcare System (NHS) perspective.

METHODS

Model Structure

A hypothetical cohort framework (deterministic) and a Markov-type process were used to depict clinical outcomes and costs related to RSV infections in newborn infants from birth to 1 year of age (Fig. 1).

The model population was initially characterized based on gestational age at birth (weeks of gestational age; wGA). Infants were assumed to be protected against RSV due to maternal vaccination (which occurred before model entry) or were assumed to have received no intervention. Infants born to vaccinated and unvaccinated mothers fell into one of the following health states: uninfected or infected, based on RSV infection rates and vaccine effectiveness if the mother had been vaccinated. RSV cases requiring medical care were stratified by care setting (hospital, emergency department or primary care). Hospitalized patients had a certain probability of dying from the disease.

Expected outcomes were evaluated at the end of each monthly cycle through the 1-year modeling horizon, based on age, wGA at birth, disease/fatality rates (which may vary by age, wGA at birth, and calendar month), and mother's vaccination status. The model compared the reduction in RSV-medically attended cases (hospitalizations, emergency room visits and primary care visits) and RSV-related deaths versus no intervention, the corresponding life years (LYs), quality-adjusted life years (QALYs) gained, and cost savings. An incremental cost-effectiveness ratio (ICER) was calculated, and a €25,000/QALY willingness-to-pay (WTP) threshold was set to evaluate the cost-effectiveness of maternal vaccination versus no intervention [10].

The base-case analysis reflected the NHS perspective following Spanish cost-effectiveness recommendations and included only direct medical costs (€2023). All costs and outcomes were calculated for an entire RSV season, except for QALY loss due to premature RSV-related death, which was calculated over the lifetime of the cohort and discounted at 3% per year, according to the

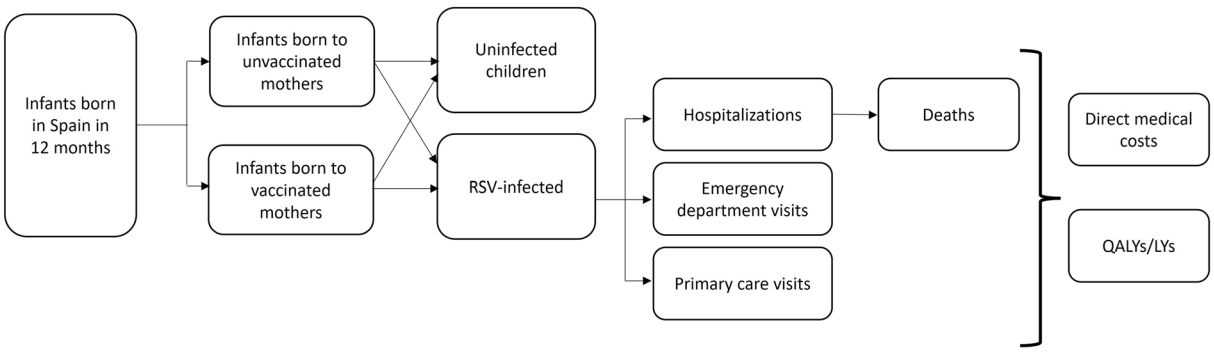

Fig. 1 Schematic of the health-economic model. *LYs* life years, *QALYs* quality-adjusted life years, *RSV* respiratory syncytial virus

local recommendations for economic evaluation of health technologies [11, 12]. All data inputs were validated by a panel including three Spanish pediatrician experts in RSV management.

The model was based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Population

The model population included liveborn infants (n = 360,633) born to 355,250 women during a 1-year period. Data were taken from the Spanish Statistics National Institute for the year 2019 [13]. Specifically, data for 2019 were used to avoid the COVID-19 pandemic influencing the epidemiology estimate, since the number of cases and the seasonality of RSV were modified during this period [14].

Liveborn infants were characterized by term status and were distributed as follows: 92.9% were born at ≥ 37 wGA (full term), 6.0% were born at 32–36 wGA (late preterm), 0.8% were born at 28–31 wGA (early preterm) and 0.3% were born at ≤ 27 wGA (extreme preterm). Births were also distributed by calendar month according to Spanish data for 2019 [14].

Disease Incidence

Annual incidence rates of RSV by month of age and by care setting (i.e., hospital, emergency department, and primary care) were obtained from the retrospective observational study BARI (Burden of Acute Respiratory Infections) conducted in Spain (Table 1) [15]. The authors of the BARI study estimated RSV incidence considering both RSV-specific ICD-10 codes and unspecified ALRI cases, based on evidence that this broader definition improves sensitivity without sacrificing specificity [15].

Age-specific relative rates of RSV by term status were applied based on the study by Rha 2020., which reported cases by gestational age at birth and chronologic age at infection (Supplementary Material Table S1) [16]. Rates of RSV were allocated across calendar months using data from ISCIII (Carlos III Health Institute; Supplementary Material Table S2) [17].

Table 1 Incidence rates for RSV (per 1000) by care setting and age

Months of age	Hospital [15]	Emergency department [15]	Primary care [15]
< 1 months	137.9	124.1	124.1
1 to < 2 months	164.3	166.3	168.3
2 to < 3 months	94.3	101.4	102.9
3 to < 6 months	56.9	76.3	98.4
6 to < 12 months	34.9	85.5	146.0

Vaccination Strategy and Effectiveness

Maternal immunization was implemented as a year-round program, in line with the strategy in the MATISSE trial. The vaccination coverage was estimated to be 70%, calculated as an intermediate value between the coverage observed in 2022 in pregnant women against Tdap (86%) and the coverage in pregnant women for influenza (53%), according to the Spanish Vaccination Information System of the Ministry of Health [18].

The distribution of RSVpreF administration by fetal wGA was based on a US observational study on maternal Tdap [19] and adjusted according to approved indication (administration between weeks 24 and 36 of gestation) [8] (Table 2).

Setting-specific vaccine effectiveness (VE) estimates were derived using the cumulative efficacy data (at 90, 120, 150, and 180 days) for the co-primary endpoints from MATISSE [9]. Efficacy against severe RSV-positive medically attended ALRI was used as a proxy for VE against RSV cases requiring hospitalization, and efficacy against RSV-positive medically attended ALRI was used as a proxy for VE against RSV cases treated in the emergency department or primary care setting. For full-term infants, VE by single month of age was derived by fitting a line to the cumulative efficacy datapoints

Table 2 Distribution of pregnant women by fetal wGA at the time of vaccination

wGA	24	25	26	27	28	29	30	31	32	33	34	35	36
Distribution of vaccination	0.6%	0.8%	1.8%	6.5%	20.7%	18.5%	13.4%	10.1%	9.3%	6.7%	4.8%	3.8%	3.2%

wGA weeks of gestational age

from MATISSE and deriving marginal monthly estimates through age 5 to < 6 months. VE was then assumed to wane linearly to 0% by age 9 to < 10 months (Fig. 2).

MATISSE was not powered to provide estimates of efficacy among preterm infants; therefore, VE for late preterm infants was assumed to be 83.3% of corresponding values for full-term infants based on an ongoing observational seroepidemiology study of naturally acquired RSV antibody transplacental transfer [20]. In this study (n = 300 mother-infants), the transplacental transfer neutralizing antibody titer ratio (GMT CMR) was evaluated for RSV A/B. GMR was reported to be 1.2 among full-term infants and 1.0 among infants born at 32 to < 37 wGA (1.0/1.2 = 83.3%). VE among early and extreme preterm infants was assumed to be 0% (Fig. 2). For infants born < 2 weeks after maternal administration of RSVpreF, irrespective of term status, VE was conservatively assumed to be 0%, as early delivery was associated with low transfer [8].

Utilities

Lacking robust estimates of healthy infant utility values, utility was assumed to be 1 for infants without RSV. For infants who experience RSV, utility value during the period of illness (14 days, irrespective of care setting) was 0.59 for infants treated in hospital and 0.84 for infants treated in outpatient settings based on Roy 2013 [21]. QALY loss was thus estimated to be 0.0157 for infants who are hospitalized and 0.0061 for outpatient cases [21]. QALY losses were assumed to be invariant by term status.

Utility values for persons aged ≥ 1 year (i.e., for use in quantifying the lifetime impact of RSV) were based on the reference population norms of the Spanish population obtained using the EQ-5D-5L instrument [22]. For children aged 1–15 years, utility values were estimated by linearly interpolating between values for children aged < 1 year and > 15 years.

Mortality

Both infant mortality due to general causes and mortality due to RSV were considered to calculate the mortality of the population included in the model. The infant mortality rate in the general population was obtained from the data published by the Spanish Statistics National Institute for deaths in children under 1 year of age for 2019 [13] (Supplementary Material Table S3). These rates were then adjusted by applying a relative risk (RR) of age-specific infant mortality by subgroup of wGA at birth: RR of 6.3 for late preterm, 42.0 for early preterm, and 144.0 for extreme preterm infants [23].

The RSV-associated mortality was based on the mean in-hospital case-fatality rate of 0.14% observed in the BARI study [1]. This rate was adjusted by applying a RR of 12.9 for preterm infants (irrespective of wGA subgroup) [1]. Due to the absence of data, infants with RSV treated in the outpatient setting were conservatively assumed not to be at risk of disease-related death.

Costs

In the base-case analysis from the NHS perspective, only the direct medical costs of vaccination and disease events were considered (Table 3). The cost of an episode requiring hospitalization was extracted from an observational study employing Spanish Minimum Basic Data Set (MBDS) [5], while the cost for both emergency department and primary care events were extracted from the BARI study [15], which does

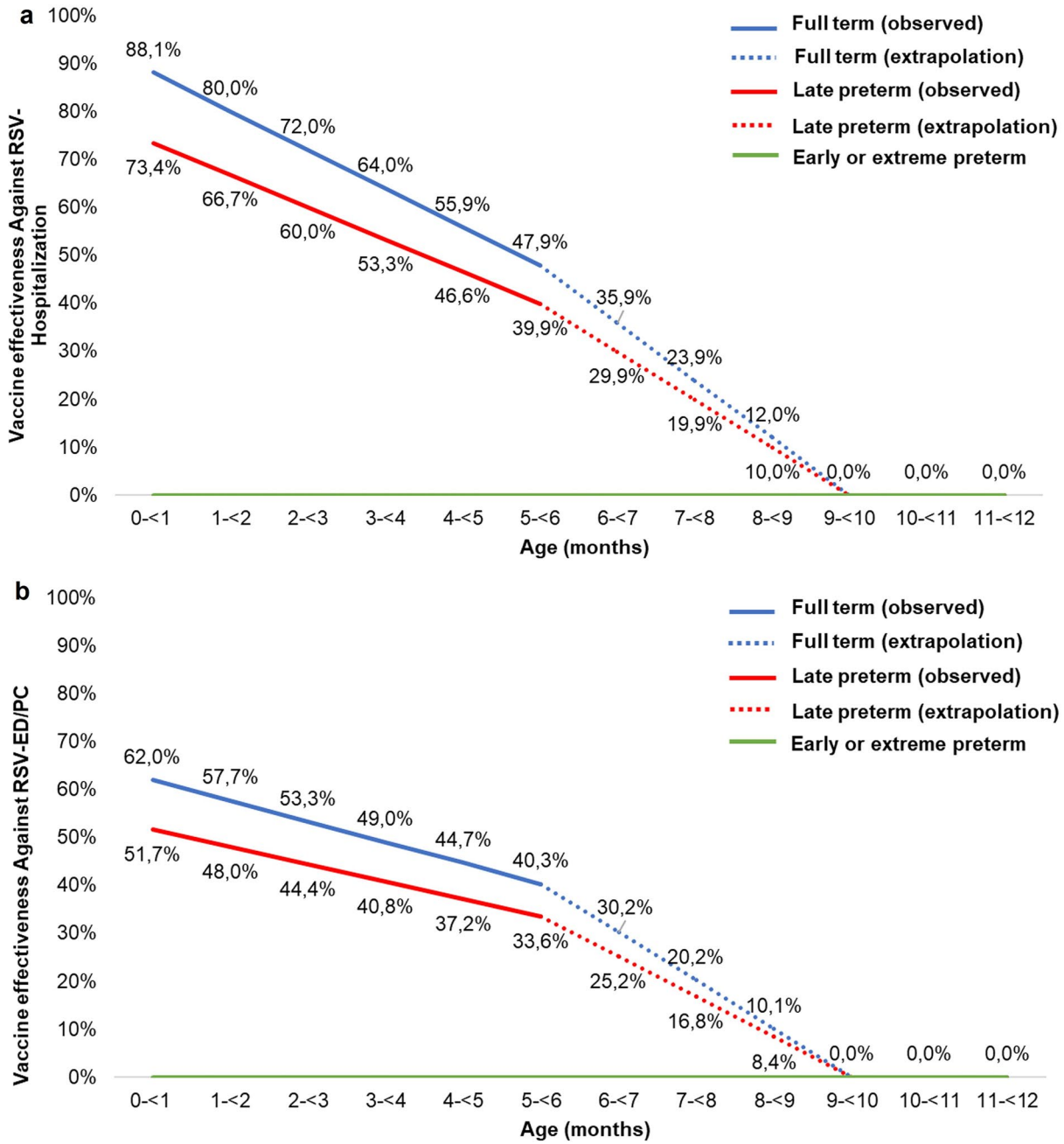

Fig. 2 Vaccine effectiveness against **a** RSV-LRTI requiring hospitalization for infants born ≥ 2 weeks after administration of maternal vaccine; **b** RSV-LRTI treated in ED or PC for infants born ≥ 2 weeks after administration of maternal vaccine. *ED* emergency department, *PC* primary care, *RSV* respiratory syncytial virus

not distinguish by wGA at birth, so the same cost for each subgroup was assumed.

For the vaccine, the list price was obtained from the Spanish Official College of Pharmacists database and discounted by a 7.5% according to the RDL 8/2010 national law decree [24]. A 6€ cost of administration was considered per

Table 3 Direct medical costs

Cost type	Subgroup of interest				References
	Full term (≥ 37 wGA)	Late preterm (32–36 wGA)	Early preterm (28–31 wGA)	Extreme preterm (≤ 27 wGA)	
Cost of intervention					
Maternal vaccine	€166.5				BotPlus [24]
Administration	€6.0				Soneira et al. [25]
Cost of RSV hospitalization (per episode, by age)					
< 1 months	€4435	€7766	€10,084	€46,155	
1 to < 2 months	€3679	€7156	€9132	€29,536	Law et al. [5]
2 to < 6 months	€3396	€7026	€6100	€9865	
6 to < 12 months	€3441	€3441	€3441	€3441	
Cost of RSV ED encounter (per episode, by age)					Martinón-Torres et al. [15]
< 1 months	€408	€408	€408	€408	
1 to < 2 months	€461	€461	€461	€461	
2 to < 6 months	€502	€502	€502	€502	
6 to < 12 months	€547	€547	€547	€547	
Cost of RSV PC encounter (per episode, by age)					
< 1 months	€455	€455	€455	€455	Martinón-Torres et al. [15]
1 to < 2 months	€551	€551	€551	€551	
2 to < 6 months	€587	€587	€587	€587	
6 to < 12 months	€547	€547	€547	€547	

ED emergency department, *PC* primary care, *wGA* weeks of gestational age

injection [25]. All costs were adjusted to 2023 prices [26].

Sensitivity Analysis

To assess the robustness of the results, two sensitivity analyses were performed: a one-way deterministic sensitivity analysis (DSA) to determine which variable had the greatest impact on cost-effectiveness results individually, and a probabilistic sensitivity analysis (PSA), which assessed the level of uncertainty of the variables in combination within the model. DSA was performed by varying disease incidence, vaccine effectiveness, mortality, utilities, and costs by ± 25%. Finally, results were compared to the base-case in a tornado diagram. The PSA was performed using Monte Carlo simulation with 1000 iterations, each selecting the input parameter values from a specified probability distribution. Supplementary Material Table S4 reports the variables included in the PSA, the form of distribution used for sampling and the parameters of the distribution.

Alternative Scenarios

The base-case analysis was modified to evaluate the impact of reduced vaccine coverage to account for the variability in vaccination uptake across the different Spanish regions, considering a reduced vaccine coverage of 50%. Moreover, we performed an alternative scenario assuming vaccine effectiveness to wane linearly to 0% by age 12 months, to test the assumption of no vaccine effect beyond 10 months.

Additionally, alternative scenarios with different cost assumptions and from the societal perspective were performed. Given that vaccine administration may occur during a routine pre-natal obstetric appointment or be co-administered with another vaccine at the same visit, an alternative scenario with a lower cost of administration (€1.43) was considered. A scenario with an alternative vaccine price was also conducted to assess the variability in costs between different regions, decreasing the vaccine price in the base-case by 5%. In addition, a €21,000/QALY WTP threshold was set as an alternative scenario.

To build the alternative scenario from the societal perspective, the non-healthcare indirect cost of caregiver productivity loss due to an RSV-hospitalization event was estimated, assuming that infants with an RSV infection would receive care throughout the duration of illness from one parent. The cost was calculated considering the mean cost of a lost day of work (€185.76 [27]) together with the probability that both parents are working and one needs to take time off (59% × 59% = 35%) [28, 29]; and assuming conservatively that the number of workdays lost due to RSV was the same as the average hospitalization length of stay per RSV event considering people work 5 days a week on average (i.e., work loss was estimated by multiplying episode length by 5/7). Considering that in Spain the length of maternity leave is 16 weeks, caregiver work loss days were considered only for infants ≥ 5 months, estimated as 1.9 in children 3 to < 6 months and 3.4 in children 6 to < 12 months.

RESULTS

Base-Case Analysis

Incremental costs and outcomes are shown in Table 4. The model estimated year-round maternal vaccination program with 70% coverage against RSV could prevent 38% of hospital admissions ($n = 8872$), 23% of emergency room visits ($n = 7632$), and 19% of primary care visits ($n = 8969$) each year. Furthermore, vaccination could prevent 34% of RSV-related deaths ($n = 11$) per year. Regarding life years gained, vaccination with RSVpreF would result in 327 additional LYs and 551 additional QALYs to the entire cohort compared to no vaccination.

From a direct medical perspective, maternal vaccination against RSV resulted in a net savings of €1.8 million versus no intervention, mainly due to the reduction in the medical care costs (€44.13 million) (Table 4), resulting in a dominant strategy (more effective and less expensive) when compared to no intervention in the Spanish NHS setting.

Sensitivity Analysis

Sensitivity analyses confirmed the robustness of the results. Results from DSA are shown in Table 5. The only variations to the parameters that affected the outcomes were the 25% decrease in the effectiveness of maternal vaccine, in the incidence of RSV hospitalization and in the cost of hospitalizations, and the 25% increase in the cost of maternal vaccine. However, maternal immunization with RSVpreF remained cost-effective at a WTP of €25,000/QALY in all cases.

The PSA, including a total of 1000 simulations, showed that 99% of iterations fell below the WTP threshold of €25,000/QALY, meaning maternal immunization was cost-effective in 99% of iterations. In addition, as 63% of all iterations fell within the southeast quadrant, maternal immunization was dominant 63% of the time (Fig. 3).

Table 4 Base-case analysis results

	Maternal vaccine	No intervention	Δ
Clinical outcomes (events)			
RSV hospitalization	14,431	23,303	− 8872
RSV ED encounter	26,231	33,863	− 7632
RSV primary care encounter	37,684	46,653	− 8969
No. of RSV-related deaths	22	32	− 11[a]
Life years (discounted)	10,961,910	10,961,583	327
QALYs (discounted)	10,529,537	10,528,986	551
Economic outcomes (€M)			
Medical care	88.63	132.76	− 44.13
Hospitalization	55.38	91.08	− 35.70
Emergency department	13.10	16.69	− 3.59
Primary care	20.15	24.99	− 4.84
Maternal vaccination	42.32	0.00	42.32
Total: cost of medical care + cost of vaccination	130.96	132.76	− 1.80
ICER			
Cost per LY			Dominant
Cost per QALY			Dominant

ED emergency department, *LY* life years, *M* million, *PC* primary care, *QALY* quality-adjusted life years, *RSV* respiratory syncytial virus

[a]The difference in the number of deaths averted does not correspond to the subtraction of the integer values (32–22), but to the rounding of the subtraction between two decimal values (32.3–21.5)

Scenario Analysis

The results of the scenario analysis for reduced coverage of maternal vaccination are shown in Table 6. Reducing vaccination coverage from 70 to 50% would result in a decrease in RSV cases prevented, avoiding up to 27% of hospital admissions ($n = 6337$) due to RSV, 16% of emergency room visits ($n = 5451$), and 14% of primary care visits ($n = 6406$) each year. Furthermore, vaccination with 50% uptake could prevent up to 25% of RSV-related deaths per year ($n = 8$). However, maternal immunization would still be dominant compared to no intervention.

When administration cost, or the price of the vaccine, were reduced, savings compared to no intervention increased from €1.8 M in the base case to €2.9 M for the scenario with an administration cost of €1.43 and to €3.9 M for the scenario with lower vaccine price (€158.2). On the other hand, at a WTP threshold of €21,000/QALY, maternal immunization had a 98.6% probability of being a cost-effective alternative for RSV prevention compared to no intervention, very similar to the 99.0% for the €25,000/QALY WTP threshold of the base case. When

Table 5 Deterministic sensitivity analyses

Parameter	Percent over base case	ICER
Effectiveness of maternal vaccine	+ 25%	Dominant
	− 25%	€22,349
Incidence of RSV hospitalization	+ 25%	Dominant
	− 25%	€16,265
Cost of maternal vaccine	+ 25%	Dominant
	− 25%	€15,274
Cost of RSV hospitalization	+ 25%	Dominant
	− 25%	€12,936
Incidence of RSV ED encounters	± 25%	Dominant
Incidence of RSV PC encounters	± 25%	Dominant
General infant mortality	± 25%	Dominant
Case fatality due to RSV-hospitalization	± 25%	Dominant
Cost of RSV ED encounters	± 25%	Dominant
Cost of RSV PC encounters	± 25%	Dominant
Health infant utility	± 25%	Dominant
Disutility values	± 25%	Dominant

ED emergency department, *ICER* incremental cost-effectiveness ratio, *PC* primary care, *RSV* respiratory syncytial virus

including indirect costs in the analysis (societal perspective), savings increased from €1.8 M to €2.1 M. Maternal immunization remained dominant in all scenarios analyzed (Table 7).

DISCUSSION

Our model suggests that maternal vaccination with RSVpreF would be a cost-effective option that could bring savings to the Spanish NHS when compared to no intervention.

Several studies have been published on the cost-effectiveness of maternal vaccination with RSVpreF (none of them in Spain). Compared to no intervention, the cost-effectiveness of immunization during pregnancy ranged from dominant (more effective and less costly) to €200,000 per QALY gained, depending on the modeled region, efficacy, pricing, and severity of the RSV season. Researchers from the European Respiratory Syncytial Virus Consortium in Europe (RESCEU) programme conducted a multi-country analysis in six European countries (Denmark, England, Finland, Italy, The Netherlands, and Scotland). This analysis found that RSVpreF maternal vaccination was dominant from the Finnish NHS perspective and cost-effective from the Scottish NHS perspective (€28,600/QALY) considering a WTP of £20–30,000 (€23–34,500) per QALY gained, compared to no-intervention [30]. Another evaluation was taken from the Norwegian NHS perspective [31]. In this analysis, maternal immunization was considered not to be cost-effective when compared to no intervention (~€118,000/QALY). However, these analyses did not incorporate deaths avoided due to RSV prevention strategies because of very low rates of RSV-related deaths in high-income countries [30, 31]. This may underestimate the cost-effectiveness of RSVpreF should a portion of these deaths be avoided in clinical practice.

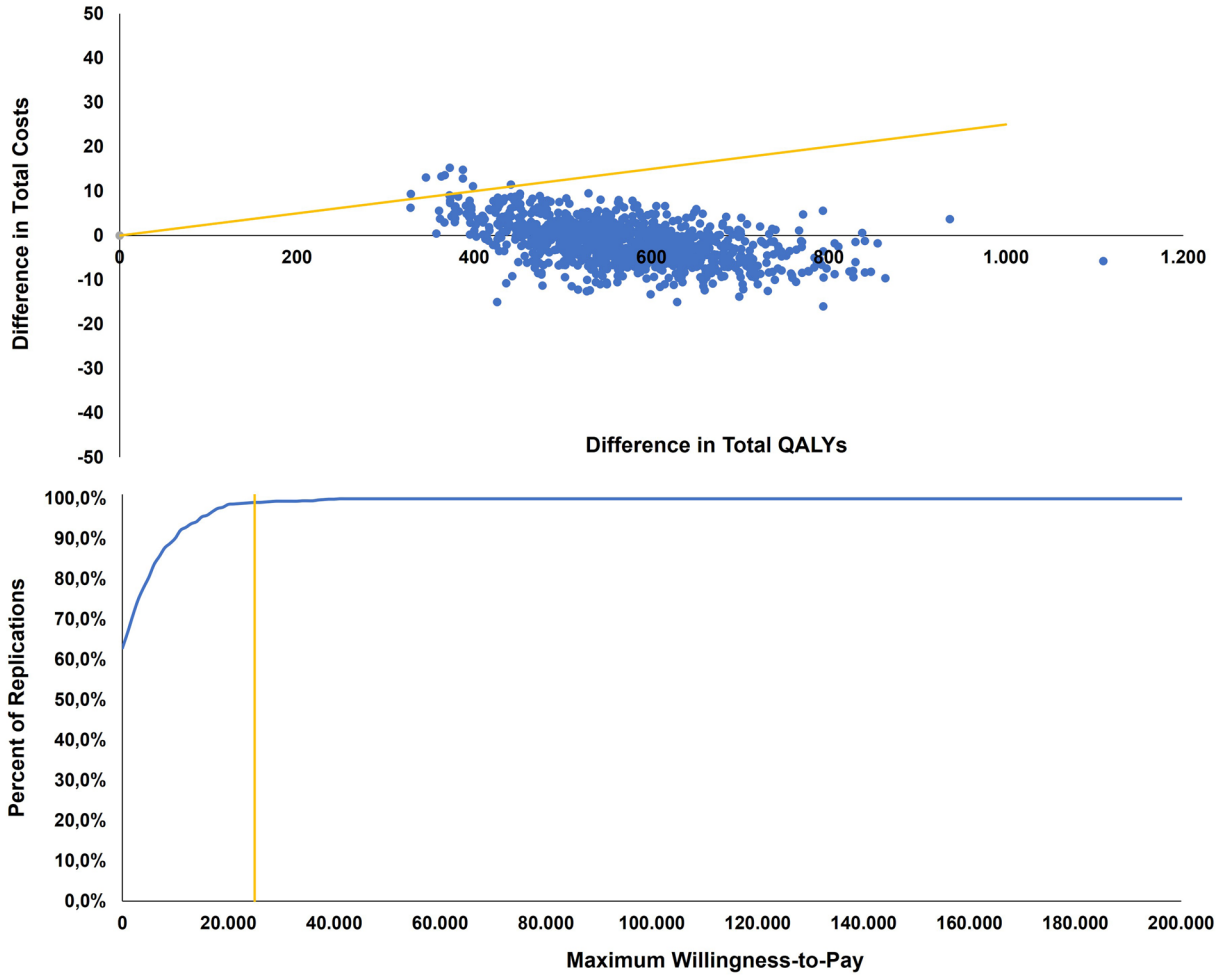

Fig. 3 Probabilistic sensitivity analysis, **a** scatterplot; **b** cost-effectiveness acceptability curve. *QALYs* quality-adjusted life years, *WTP* willingness-to-pay

Furthermore, data from the MATISSE trial were not published at the time of these analyses, so the authors assumed the World Health Organization (WHO) preferred product characteristics, 70% efficacy and 4-month protection. Higher efficacy rates have been reported from the MATISSE trial, especially in younger infants, which in turn are those with higher rates of RSV infection. As such, the efficacy inputs used in the previously mentioned studies may not be reflective of the efficacy of RSVpreF in preventing severe RSV outcomes in very young infants. Another study from the Canadian Immunisation Research Network (CIRN) found that maternal immunization was cost-effective at the WTP threshold of $50,000 per QALY gained at a maximum vaccine price of $160 (€146) from a healthcare perspective or $200 (€183) from a societal perspective [32]. Finally, another study published by RESCEU applied the same parameters and data for a hypothetical cohort of 100,000 births in five different models (three static and two dynamic), and interventions were compared against non-immunization [33]. The three static models estimated comparable medically attended cases averted by maternal vaccination versus no intervention (1.019–1.073 cases), saving ~€1 million medical and €0.3 million nonmedical costs while gaining 4–5 discounted quality-adjusted life years (QALYs) annually in < 1-year-olds, being a dominant intervention [33].

Table 6 Alternative scenario with 50% vaccination coverage

	Maternal vaccine	No intervention	Δ
Clinical outcomes (events)			
RSV hospitalization	16,966	23,303	− 6337
RSV ED encounter	28,412	33,863	− 5451
RSV primary care encounter	40,247	46,653	− 6406
No. of RSV-related deaths	25	32	− 8[a]
Life years (discounted)	10,961,910	10,961,583	233
QALYs (discounted)	10,529,537	10,528,986	393
Economic outcomes (€M)			
Medical care	101.24	132.76	− 31.52
Hospitalization	65.51	91.08	− 25.50
Emergency department	14.13	16.69	− 2.56
Primary care	21.54	24.99	− 3.45
Maternal vaccination	30.23	0.00	30.23
Total: cost of medical care + cost of vaccination	131.47	132.76	− 1.29
ICER			
Cost per LY			Dominant
Cost per QALY			Dominant

ED emergency department, *LY* life years, *M* million, *PC* primary care, *QALY* quality-adjusted life years, *RSV* respiratory syncytial virus

[a]The difference in the number of deaths averted does not correspond to the subtraction of the integer values (32–25), but to the rounding of the subtraction between two decimal values (32.3–24.6)

It should be noted that, in all studies, published ICERs have been calculated versus no intervention and none of them have carried out a cost-effectiveness analysis of maternal vaccination versus the approved monoclonal antibodies nirsevimab and palivizumab. This is mainly due to the absence of indirect comparisons and the limitations encountered when comparing both strategies due to the different clinical endpoints and populations included, as in the case of palivizumab, only used in high risk and/or extreme preterm infants.

A study evaluating maternal vaccination's impact on the prevention of RSV cases in the UK and Wales has been recently published. The results of this study are very much aligned with the results we obtained from the pharmacoeconomic study carried out for our NHS. In the UK study, a year-round maternal vaccination program with 60% coverage would reduce hospitalizations by 32%; in our study, with a 70% coverage, maternal vaccination would reduce hospitalizations by almost 40%. However, unlike our analysis, the UK study uses a dynamic transmission model that allows investigators also to estimate the benefit of vaccination in pregnant women, which they estimate at 20% of cases averted [34].

When assessing the impact of the reduction in vaccination coverage, we see a decrease in RSV

Table 7 Alternative scenarios analyses

Parameter	Scenario value	Base case value	ICER	Cost-effective (%)
Base case	–	–	Dominant	99.0
Vaccine uptake	50%	70%	Dominant	98.1
Linear waning of VE until	12 months	10 months	Dominant	99.0
Administration cost	€1.43	€6	Dominant	98.1
Vaccine price	€158.2	€166.5	Dominant	99.6
WTP threshold	€21.000/QALY	€25.000/QALY	Dominant	98.6
Perspective	Societal perspective	NHS perspective	Dominant	98.7

ICER incremental cost-effectiveness ratio, *QALY* quality-adjusted life years, *VE* vaccine effectiveness, *WTP* willingness-to-pay

cases avoided. Specifically, reducing vaccination coverage from 70 to 50% could avoid 2535 fewer hospitalizations, 2181 fewer emergency department visits, and 2563 fewer primary care visits. Moreover, savings in medical care would decrease from 44.1 to 31.5 million euros, annually. These findings highlight the importance of achieving higher levels of vaccination coverage in order to have a greater impact on reducing the burden of disease, both clinically and economically.

The present study has some limitations to be considered when interpreting the results. Firstly, while initial VE and waning through age 6 months were based on data from MATISSE, assumptions for VE waning during the months thereafter (i.e., ages 6 to < 10 months) were informed by evidence on the kinetics and decay of maternal transferred antibodies following natural infection and vaccination [35–37]. Secondly, while we assumed vaccine provided some protection against RSV among late preterm infants (based on an ongoing observational seroepidemiology study of naturally acquired RSV antibody transplacental transfer [20]), we conservatively assumed that VE among early and extreme preterm infants would be 0%. Thirdly, in the model we assumed homogeneity in both disease incidence and vaccine uptake across all the Spanish territory, therefore, not reflecting the possible inequalities that may occur as a result of social and geographical particularities in certain populations. To address this aspect, the RSV incidence was obtained from a study including two Spanish regions, which would account for variability between regions, and variations of ± 25% in disease incidence rates were analyzed in sensitivity analysis, which showed that vaccine would still be cost-effective in a worst-case scenario. Moreover, a reduced vaccine uptake of 50% was also evaluated in an alternative scenario, demonstrating that vaccine would still be dominant. In addition, a literature review was performed to obtain the model inputs to be adapted to the Spanish environment and when not available, assumptions or data adjustments had to be made. Sensitivity analyses mitigated the uncertainty around the magnitude of the model key parameters, and expert opinion confirmed the totality of the assumptions.

There are also several assumptions and limitations which may confer a conservative bias to our model. For example, our model does not capture the potential direct effects of immunization on RSV among vaccinated pregnant people since vaccine efficacy among pregnant women was not an outcome in MATISSE. However, the recent study previously mentioned that did include health benefits for pregnant women as an outcome showed that the benefit accounted for 20% of the population-level health burden averted [34]. In this regard, a recent systematic

review also summarizes the evidence about the RSV burden among pregnant women, and up to 10.7% of women with respiratory infections tested positive for RSV. Those RSV-positive pregnant women had higher odds of preterm delivery (OR 3.6 [1.3; 10.3]) [38]. Moreover, we use a static model that does not account for the potential indirect impact of maternal vaccination on other populations (e.g., other susceptible individuals who may reside in the same household as the infant). Nevertheless, as Pitman et al. 2012 [38] indicated, static models are acceptable when their projections suggest that an intervention is cost-effective, and dynamic effects would further enhance this (e.g., via prevention of secondary cases). In addition, due to the lack of data, there are also a number of potential short- and long-term sequelae of RSV that were not captured in this model as secondary bacterial infections, subsequent respiratory infections, recurrent wheezing, worsening of chronic lung disease among preterm infants, exacerbation of congenital heart disease, and asthma.

CONCLUSIONS

In conclusion, the results of this economic evaluation suggest that, in Spain, maternal vaccination with bivalent RSVpreF could avoid a high number of hospitalizations, emergency room visits and primary care visits, while generating savings for the NHS, being a more efficient strategy (dominant) when compared to a non-prevention strategy.

Author Contributions. Amy Law, Alejandra López-Ibáñez de Aldecoa, Virginia Lozano, Cristina Méndez, María L. García Somoza, Alba Bellmunt, and Miriam Prades contributed to the work. Javier Álvarez Aldeán, Irene Rivero Calle, and Rosa Rodríguez-Fernández validated the parameters and provided data about local management of patients. Alba Bellmunt and Miriam Prades performed the analysis. All authors participated in the interpretation of the results. The first draft of the manuscript was primarily written by Alba Bellmunt and Virginia Lozano, and all authors provided comments and revision on subsequent versions of the manuscript. All authors reviewed and approved the final manuscript.

Funding. This study, including the journal's Rapid Service Fee, was supported by Pfizer, S.L.U., Madrid, Spain.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Conflict of Interest. This work was sponsored by Pfizer, S.L.U., Spain. Susana Aceituno Mata, Alba Bellmunt and Miriam Prades are employees of Outcomes'10, which received funding from Pfizer for the development of the study and this manuscript. Amy W. Law, Alejandra López-Ibáñez de Aldecoa, Cristina Méndez, María L. García Somoza, and Virginia Lozano are employees of Pfizer and may hold Pfizer stock. Javier Soto is a former employee of Pfizer and may hold Pfizer stock. Javier Álvarez Aldeán has collaborated in teaching activities funded by AstraZeneca, GlaxoSmithKline, MSD, Pfizer, Sanofi and Seqirus; has participated as an investigator in clinical trials for GlaxoSmithKline and Sanofi; and has participated as a consultant in Advisory Boards for AstraZeneca, GlaxoSmithKline, MSD, Pfizer and Sanofi. Irene Rivero Calle has received speaking fees from MSD, GSK, Sanofi and Pfizer; scholarships/research grants from Sanofi Pasteur, MSD, Novartis and Pfizer; consulting fees for Pfizer, MSD and Sanofi; has participated as a subinvestigator in clinical trials of vaccines from Ablynx, Abbot, Seqirus, Sanofi Pasteur MSD, Sanofi Pasteur, Cubist, Wyeth, Merck, Pfizer, Roche, Regeneron, Jansen, Medimmune, Novavax, Novartis and GSK with the funds paid to her institution; and belongs to the Board of Directors of the CAV-AEP. Rosa Rodríguez-Fernández has received fees for lectures from AbbVie, Pfizer, Merck, Astra-Zeneca and Sanofi and fees for participation in Advisory Boards from AbbVie, Sanofi, and Pfizer.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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