BMC Infectious Diseases

RESEARCH

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Modelling the potential clinical and economic impact of universal immunisation with nirsevimab versus standard of practice for protecting all neonates and infants in their first respiratory syncytial virus season in Spain

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Abstract

Background Respiratory syncytial virus (RSV) is associated with substantial morbidity among infants. This study modelled the potential public health and economic impact of nirsevimab, a long-acting monoclonal antibody, as an immunoprophylactic strategy for all infants in Spain in their first RSV season.

Methods A static decision-analytic model of the Spanish birth cohort during its first RSV season was developed to estimate the impact of nirsevimab on RSV-related health events and costs versus the standard of practice (SoP). Spain-specific costs and epidemiological data were used as model inputs. Modelled outcomes included RSV-related outpatient visits, emerging room (ER) visits, hospitalisations – including pediatric intensive care unit (PICU) admission, mechanical ventilation, and inpatient mortality.

Results Under the current SoP, RSV caused 151,741 primary care visits, 38,798 ER visits, 12,889 hospitalisations, 1,412 PICU admissions, and 16 deaths over a single season, representing a cost of €71.8 million from a healthcare payer perspective. Universal immunisation of all infants with nirsevimab was expected to prevent 97,157 primary care visits (64.0% reduction), 24,789 ER visits (63.9%), 8,185 hospitalisations (63.5%), 869 PICU admissions (61.5%), and 9 inpatient deaths (52.6%), saving €47.8 million (62.4%) in healthcare costs.

Conclusions These results suggest that immunisation with nirsevimab of all infants experiencing their first RSV season in Spain is likely to prevent thousands of RSV-related health events and save considerable costs versus the current SoP.

Keywords Hospitalisation, Immunisation, Infant, Nirsevimab, Public health, Respiratory syncytial viruses, Respiratory tract infections, Spain

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Background

Respiratory syncytial virus (RSV) is a leading cause of medically attended lower respiratory tract infection (MA-LRTI) in young children, especially infants in their first year of life [1, 2]. Approximately 90% of infants under 24 months will suffer at least one RSV infection [3, 4], leading to RSV making up a considerable proportion of all primary care visits, emergency room (ER) visits, and hospitalisations for this age group [5, 6]. While preterm infants and children with underlying medical conditions are at higher risk of severe RSV, more than 90% of hospitalisations, medical visits, and costs are for otherwise healthy infants [6, 7]. In Spain, up to 62% of RSV hospitalisations among children under 5 years are for infants < 12 months [8]. Other estimates show this equates to 1.8–4.0% of infants being hospitalised with RSV-associated LRTI within their first year of life [9–11]. An estimated 6.5% of hospitalised cases in Spain are admitted to pediatric intensive care unit (PICU), although this percentage is higher among the youngest infants and those with comorbidities [12, 13].

Palivizumab, a humanised monoclonal antibody against RSV F glycoprotein, is the only approved prophylactic intervention for RSV and has been used in Spain as the standard of practice (SoP) for those patients eligible since 2002 [14]. However, its use is restricted to a limited infant population – defined as those with hemodynamically significant congenital heart disease, chronic lung disease, or born prematurely [15, 16]. Term infants, who represent the majority of Spanish RSV hospitalisations [7] and PICU admissions [17], are not eligible for palivizumab and typically receive only supportive care for RSV MA-LRTI. These limited prophylaxis and treatment options in infants coupled with high RSV incidence constitute an unmet medical need and a considerable public health burden. Because of that impact, the World Health Organization recognises the need to bring strategies to prevent RSV in all infants [13].

Nirsevimab is a human antibody indicated for the prevention of RSV LRTI in neonates and infants during their first RSV season [18]. It has a rapid onset of protection, and an extended half-life that allows for at least 5 months protection [18–20]. In phase 2b and phase 3 studies, nirsevimab administered as a single injection significantly reduced RSV-associated LRTIs and hospitalisations in preterm and term infants [19, 21, 22]. So far, public health and economic outcomes have not been evaluated for a universal prophylactic antibody strategy against RSV in young infants during their first RSV season in Spain. Previous economic evaluations of palivizumab in the Spanish context focused on high-risk and preterm newborns [15, 23–25]. This study aims to assess the potential public health and economic impact of a universal passive immunisation strategy with nirsevimab versus the current SoP for all Spanish neonates and infants experiencing their first RSV season and can help decision makers to evaluate the introduction of nirsevimab in the national immunisation calendar.

Methods

Model overview

A static decision analytic model was developed that tracks the new-born Spanish neonate and infant cohort (by month of birth) during their first RSV season considering the different possible RSV-related health outcomes and their associated costs (Fig. 1). A full description of the model has been previously published [26].

The model systematically combined empirical data on epidemiology, prophylaxis efficacy, and number of health events with unit costs based on published literature and tariff prices in Spain [27]. The RSV season was defined as the five-month period from November to March, with a peak in December, in line with epidemiological data from Spain [10, 28–30], although the model also accounted for RSV circulation outside of the typical five-month season. All infants entered the model susceptible to an RSV MALRTI, with risks changing during the year depending

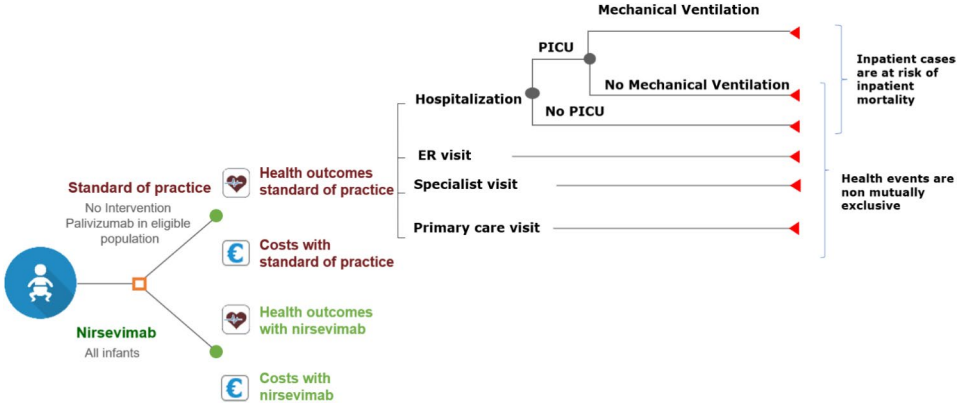

Fig. 1 Model structure. *Abbreviations* ER, emergency room; PICU, pediatric intensive care unit

on age, infant subpopulation, and the density of RSV circulation over the season.

The base case was analysed from a healthcare payer perspective, with a societal perspective reported separately. Outcomes included inpatient hospitalisations (including PICU and mechanical ventilation [MV]), emergency room (ER) visits, primary care visits, specialist visits, inpatient deaths, and the costs associated with these events. The time horizon was the first RSV season for all resources except for premature deaths which was considered lifetime. This time horizon was selected to capture the costs and resources associated with RSV infection, considering the typical duration of the infection period. The assessment of the impact of prophylaxis measures relied on their uptake rate, efficacy, and the potential extent of population coverage. The economic impact of nirsevimab versus SoP was calculated as the reduction in RSV MA-LRTIs and the associated healthcare resource costs saved. A 3% discount rate was used throughout the analysis in accordance with national guidelines [31].

Target population and immunisation strategies

The current SoP in Spain is to administer up to five monthly doses of palivizumab to premature infants (variable indications among regions and hospital guidelines based on scientific recommendations) or those with chronic lung disease or congenital heart disease as per the Spanish association of Neonatology recommendations during their first RSV season (November to March) [28, 32, 33]; prophylaxis is not available for the rest of the newborn population.

In the model, infants were stratified into three subpopulations to account for the SoP, with different individual risks of RSV-related MA-LRTI, and in order to correspond with groups assessed in the nirsevimab clinical trials [19, 21, 34, 35]: palivizumab-eligible infants; preterm infants not eligible for palivizumab as per recommendations, defined as those born at 29 to 34 weeks and 6 days gestational age; and late preterm and term infants not eligible for palivizumab as per recommendations, defined as infants born at or after 35 weeks gestational age.

The model compared two immunisation strategies. Strategy 1: the current SoP for each subpopulation, consisting of monthly administrations of palivizumab in the eligible population during the RSV season (up to five doses) and no prophylaxis for non-eligible preterm and term infants; strategy 2: universal immunisation with nirsevimab (single dose) in all infants. Both strategies employed a seasonal-based approach in which prophylaxis was administered at the beginning of or during the infants' first RSV season (Fig. 2). Immunisation began at the start of the season (i.e., November) for infants born from April to October (i.e., outside of the RSV season); and at birth for those born within the season. The modelling of strategy 2 assumed a 5-month duration of protection with no residual efficacy beyond 5 months. Both strategies assumed immediate onset of protection after dosing.

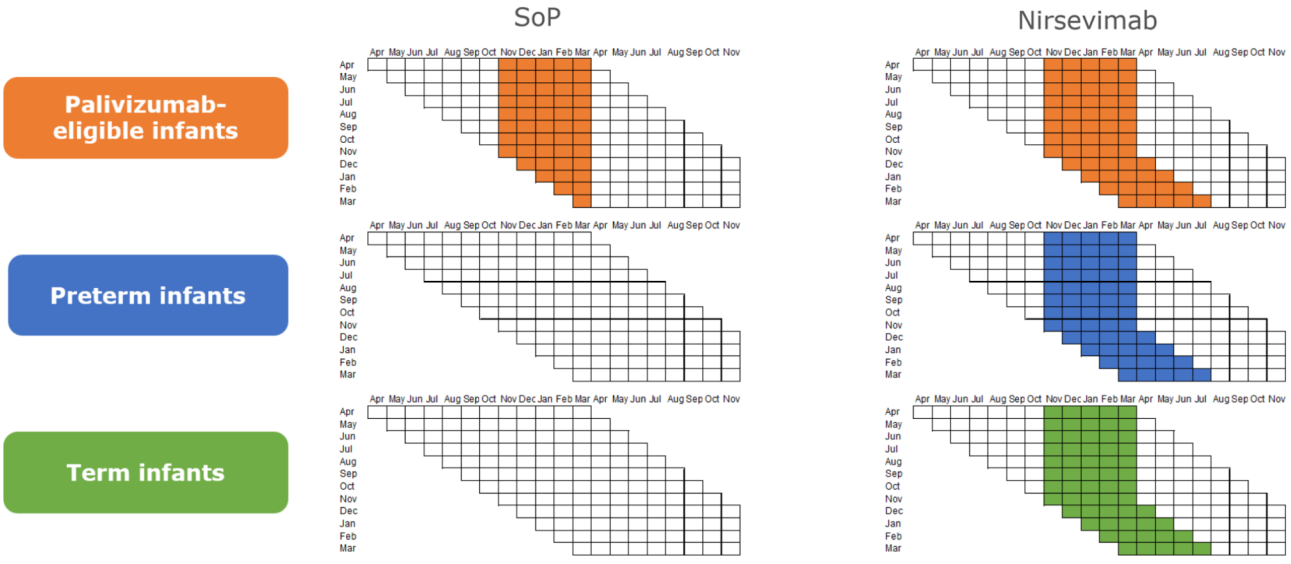

Fig. 2 Immunisation strategies. Standard of practice (SoP) in Spain is to administer palivizumab monthly, for up to 5 doses, to eligible infants during their first respiratory syncytial virus (RSV) season (November to March; left panel) [32] and to provide supportive care for preterm and term infants not eligible for palivizumab. A strategy using a single dose of nirsevimab for all infants during their first RSV season was investigated (right panel). Shaded months indicate protection from RSV from immunisation with palivizumab or nirsevimab. A 5-month duration of protection from a single nirsevimab injection was assumed based on the duration of protection evaluated in the pivotal study [18]

Model inputs

Model parameters and their associated base-case estimates are listed in Table 1 and Table S2. Spanish sources were used wherever possible to obtain input data. Two consensus meetings were conducted with a panel of multidisciplinary experts knowledgeable in RSV disease and its burden in Spain (authors JAA, RGP, and JJP) to determine or validate input data.

Demographic inputs were sourced from the Spanish National Institute of Statistics [36]. RSV MA-LRTI seasonality and incidence inputs were obtained from the Burden of Acute Respiratory Infections (BARI) study [30]. The BARI study used three different definitions of RSV determined by the international classification of diseases-10 (ICD-10; Table S1). In this analysis, RSV was defined as RSV and/or acute bronchiolitis (ICD-10 J12.1, J20.5, and all J21 codes except J21.1). This definition was selected based on the results of a German study showing that the most restrictive definition (RSV-specific codes) and the RSV and/or acute bronchiolitis definition both have equivalent sensitivity and specificity, and the most restrictive definition might underestimate the number of cases [37]. This approach has also been supported and used by Spanish experts in national studies [30]. Scenario analyses were conducted to explore how model outputs were affected by the more restrictive definition of RSV.

RSV-related event rates were obtained from published literature. Risk of health events by age are provided in Table S2. Inputs related to inpatient hospitalization were informed by retrospective studies for palivizumab-eligible and preterm infants [9] and for term infants [10]. PICU rates in palivizumab-eligible and term infants were informed by Viguria et al. [12], and in preterm infants by Sanchez-Luna et al. [15]. MV rates were sourced from Hervás et al. 2012 [38]. Inpatient mortality rates for each of the three sub-populations were sourced from Sanchez Luna et al. [7].

The risk of outpatient visits, including ER, PC, and specialist visits, were informed by the BARI study [30]. The BARI study reported the mean number of visits per infant and the incidence of RSV visits per setting, which were combined to inform the model. Due to a lack of granular data, rates of MV, ER visits, specialist visits, and PC visits were equal across each subpopulation.

Nirsevimab efficacy against RSV MA-LRTIs in term infants and preterm infants not eligible for palivizumab was determined from pre-specified pooled efficacy data from the pivotal phase 2b and phase 3 studies (pooled efficacy, 79.5% [95% confidence interval, 65.9—87.7%]) [35]. For palivizumab-eligible infants, nirsevimab efficacy was assumed non-inferior to that of palivizumab based on the results achieved in the pivotal phase 2/3 trial (MEDLEY) [34] and because palivizumab effectiveness is indirectly included in the model through the epidemiological input data. Nirsevimab uptake was assumed similar to that for primary series vaccinations in infants included in the national immunisation program in 2020 [39] since it is likely to follow a programmatic approach to implementation.

Cost inputs were obtained from the BARI study [30], published literature, and tariffs from the national eSalud database [27] (Table 1). Costs were updated to 2023 where necessary. Direct costs related to the first season were not discounted; long-term productivity costs due to premature death were discounted at 3% per annum, in line with the Spanish recommendations [31].

The societal perspective was reported separately from the third-party payer base case analysis. Societal perspective parameters were based on or calculated from Spanish data, although caregiver workdays lost were assumed the same as for published data from the US [40, 41] due to the lack of literature from Spain in this regard (Table 1).

Analysis

The model evaluated the disease burden for all infants based on the SoP in terms of healthcare resource utilisation (number of inpatient hospitalisations, PICU, mechanical ventilations, ER, specialist and primary care visits), deaths, and direct medical costs. The model was then used to estimate the expected numbers of these events and associated costs that could be avoided through a universal nirsevimab immunisation strategy during the infants' first RSV season. The results were presented from a full birth cohort perspective, with detailed results based on health events and related costs per subgroup (i.e., palivizumab eligible, preterm, and term infants) and by month of birth.

Scenario analyses were conducted to assess how the model outputs were impacted by a more restrictive case definition of RSV (ICD-10 codes J12.1, J20.5, and J21.0 only), higher and lower nirsevimab efficacy estimates (87.7%—65.9% [35]), a longer (6-month) RSV season (October to March), and the impact of different RSV-related mortality rates reported in the literature. Additionally, a deterministic sensitivity analysis (DSA) was conducted by varying key model parameters to test their impact on healthcare costs. Variability in parameters used to inform the DSA is presented in Table 1.

Results

Base case analysis

Under SoP, the model estimated the MA-LRTI burden comprised 224,530 health events, with 151,741 primary care visits, 38,798 ER visits, 21,102 specialist visits, 12,889 hospitalisations (incl. PICU and MV), and 16 deaths due to RSV in Spain over one season, amounting to €71.8 million in annual healthcare costs (Fig. 3; Table 2, and Table S3). Of the hospitalisations, 1,412 involved admissions

Table 1 Model inputs

Input	Palivizumab-eligible infants (< 29 wGA or with CLD/CHD)	Preterm infants (29 to 34 weeks and 6 days GA)	Term infants (≥ 35 wGA)
Demographic and epidemiologic inputs			
Birth Cohort (for year 2020)	337,380 [36]		
Population size, n (%)	4,791 (1.42%) [42]	10,965 (3.25%) [42]	321,624 (95.3%)
Seasonality of RSV	November to March incidence data [28, 30]		
Burden of disease[a]			
Inpatient hospitalisation	7.55% [9] (6.75 – 8.45%)[b] [9]	7.55% [9] (6.75 – 8.45%)[b] [9]	3.82% [10] (3.72 – 3.93%)[b] [10]
PICU (conditional on inpatient hospitalisation)	17.1% [12] (12.12 – 22.17%)[c] [12]	17.8% [15] (14.24 – 21.36%)[d]	4.98% [12] (4.24 – 5.72%)[c] [12]
Mechanical ventilation (conditional on PICU)	2.7% for each subpopulation [38] (2.16 – 3.24%)[d]		
Primary care visits	48.0% for each subpopulation [30] (28.8 – 124.0%)[e] [30]		
Specialist visits	6.87% for each subpopulation [30] (3.89 – 19.0%)[e] [30]		
ER visits	12.4% for each subpopulation [30] (7.44 – 31.3%)[e] [30]		
In-hospital mortality	0.95% [7] (0.764 – 1.13%)[c]	0.95% [7] (0.764 – 1.13%)[c]	0.051% [7] (0.048 – 0.054%)[c]
Nirsevimab profile			
Efficacy	Non-inferiority to palivizumab: 0%[f]	79.5%[g] [35] (65.9 – 87.7%)[b] [35]	79.5%[g] [35] (65.9 – 87.7%)[b] [35]
Duration of protection	5 months	5 months	5 months
Uptake	100.0%	97.6% [39]	97.6% [39]
Palivizumab profile			
Duration of protection	1 month [43]	–	–
Uptake	100% [42]	–	–
Costs[h]			
Inpatient hospitalisation	€5,953 [30] (€4,762 – €7,143)[d]	€5,953 [30] (€4,762 – €7,143)[d]	€2,518 [30] (€2,015 –€3,022)[d]
PICU[i]	€13,971 [15, 27] (€11,177 – €16,766)[d]	€13,971 [15, 27] (€11,177 – €16,766)[d]	€11,157 [27, 44] (€8,926 – €13,388)[d]
Mechanical ventilation[j]	€16,489 [27, 44] (€13,191 – €19,787)[d]	€16,489 [27, 44] (€13,191 – €19,787)[d]	€ 13,315 [27, 44] (€10,652 – €15,978)[d]

Table 1 (continued)

Input	Palivizumab-eligible infants (< 29 wGA or with CLD/CHD)	Preterm infants (29 to 34 weeks and 6 days GA)	Term infants (≥ 35 wGA)
Primary care visits	€74.97 E-Salud tariffs 2020 [27] (€60 – €90)[d]		
Specialist visits	€147.09 E-Salud tariffs 2018 [27] (€118 – €177)[d]		
ER visits	€212.34 E-Salud tariffs 2022 [27] (€170 – €255)[d]		
Productivity cost parameters (for sensitivity analysis)			
Labor force rate	59.1% [45]		
Unemployment rate	14.6% [45]		
Average hourly wage	€15.75 [46]		
Average annual income	€16,105.82[k]		
Lifetime lost earnings due to infant RSV death	€273,966.49[l]		
Caregiver lost days of work – inpatient setting	3.4 days [40]		
Caregiver lost days of work – outpatient setting	1.3 days [41][m]		

Deterministic sensitivity analysis (DSA) ranges are shown in parentheses. Abbreviations: CHD, congenital heart disease; CLD, chronic lung disease; ER, emergency room; PICU, pediatric intensive care unit; RSV, respiratory syncytial virus; wGA, weeks gestational age

[a] Values described in the table are an average of the risk of health events by month of age that are provided in Table S2

[b] Average range for DSA lower and upper bounds is based on the confidence interval provided by the source

[c] 95% confidence level computed using the standard deviation, derived from the data provided by the source

[d] DSA range computed by applying a margin of 20% to the values obtained from the source

[e] The lower bound for the DSA relies on the RSV-specific BARI distribution, while the higher bound is determined by the distribution of both RSV and ALRI

[f] Nirsevimab efficacy was assumed non-inferior to that of palivizumab based on the results achieved in the pivotal phase 2/3 trial (MEDLEY) [34] and because palivizumab effectiveness is indirectly included in the model through the epidemiological input data

[g] Pooled efficacy based on reduction in MA-RSV LRTIs from double-blind randomised control trials of term and preterm infant

[h] All costs are inflated to 2023 prices and come from autonomous regions' tariffs and available literature

[i] PICU costs are computed as the daily PICU cost multiplied by the mean length of stay. The mean length of stay is 5 days for preterm and palivizumab-eligible population [15], and 4 days [44] in term infants

[j] Mechanical ventilation costs are computed as the summation of PICU costs and the costs computed from the mean length of stay in MV [44] and daily cost of MV use [27]

[k] Calculated based on average hourly wage, 8 h per workday, 253 workdays per year, labour force rate of 59.14%, and unemployment rate of 14.57%

[l] Calculated for all individuals aged > 15 years, assuming a retirement age of 65 years

[m] Rotavirus study

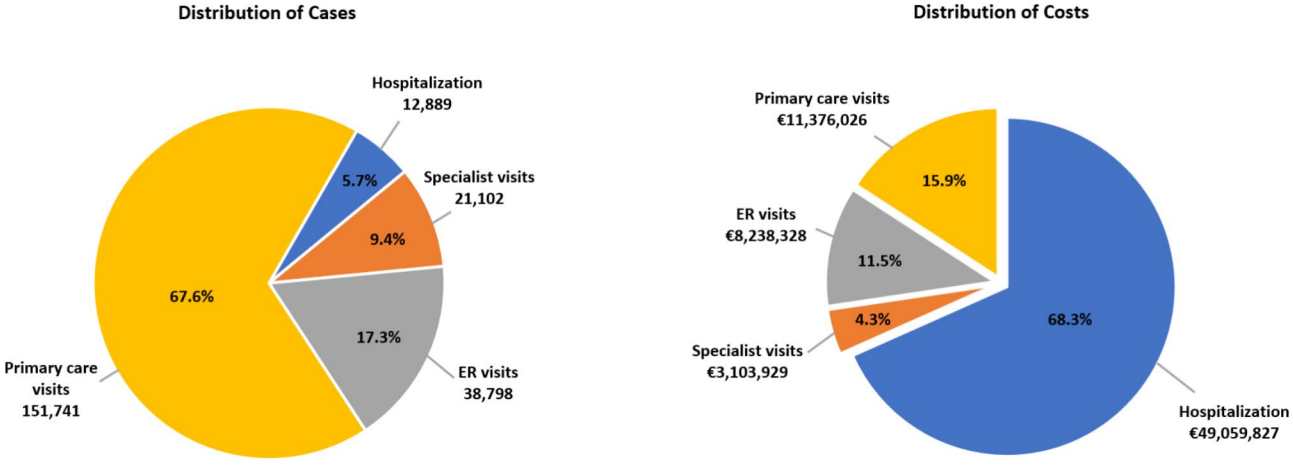

Fig. 3 Current RSV burden over the first RSV season. Hospitalisation costs include PICU and MV cases. Numbers are rounded to the nearest digit. *Abbreviations* ER, emergency room; MV, mechanical ventilation; PICU, pediatric intensive care unit; RSV, respiratory syncytial virus

Table 2 Base case results

Outcome	Palivizumab-eligible infants			Preterm infants			Term infants		
	Current SoP	Nirsevimab	Difference, n (%)	Current SoP	Nirsevimab	Difference, n (%)	Current SoP	Nirsevimab	Difference, n (%)
Health event (% per subgroup)									
Primary care visits	2,155	2,155	0 (0)	4,932	1,729	-3,203 (-65)	144,655	50,701	-93,954 (-65)
% per subgroup	1.42	3.95		3.25	3.17		95.33	92.89	
Specialist visits	300	300	0 (0)	686	244	-442 (-64)	20,117	7148	-12,969 (-64)
% per subgroup	1.42	3.90		3.25	3.17		95.33	92.94	
ER visits	551	551	0 (0)	1,261	444	-817 (-65)	36,986	13,014	-23,972 (-65)
% per subgroup	1.42	3.93		3.25	3.17		95.33	92.90	
Inpatient hospitalisations (incl. PICU and MV)	334	334	0 (0)	765	266	-500 (-65)	11,790	4,104	-7,686 (-65)
% per subgroup	2.59	7.11		5.94	5.65		91.47	87.25	
PICU admissions (incl. MV)	66	66	0 (0)	157	54	-102 (-65)	1,189	423	-767 (-64)
% per subgroup	4.70	12.21		11.11	10.02		84.20	77.77	
MV	9	9	0 (0)	21	7	-13 (-65)	318	111	-208 (-65)
% per subgroup	2.59	7.11		5.94	5.65		91.47	87.25	
Inpatient deaths	3	3	0 (0)	7	3	-5 (-65)	6	2	-4 (-65)
% per subgroup	19.32	40.79		44.22	32.40		36.47	26.80	
Costs									
Primary care visits	€ 161,540	€ 161,540	0 (0)	€369,721	€129,586	-€240,135 (-65)	€10,844,766	€3,801,056	-€7,043,710 (-65)
Specialist visits	€ 44,076	€ 44,076	0 (0)	€100,878	€35,842	-€65,035 (-64)	€2,958,976	€1,051,338	-€1,907,637 (-64)
ER visits	€ 116,984	€ 116,984	0 (0)	€267,746	€94,213	-€173,533 (-65)	€7,853,598	€2,763,482	-€5,090,116 (-65)
Inpatient hospitalisations	€ 1,595,185	€ 1,595,185	0 (0)	€3,620,891	€1,256,740	-€2,364,151 (-65)	€26,695,621	€9,270,642	-€17,424,978 (-65)
PICU admissions	€ 800,547	€ 800,547	0 (0)	€1,902,790	€660,421	-€1,242,369 (-65)	€9,716,858	€3,478,321	-€6,238,537 (-64)
MV	€ 148,831	€ 148,831	0 (0)	€340,635	€118,228	-€222,407 (-65)	€4,238,470	€1,475,344	-€2,763,126 (-65)
Total healthcare costs	€ 2,867,162	€ 2,867,162	0 (0)	€6,602,660	€2,295,030	-€4,307,631 (-65)	€62,308,288	€21,840,184	-€40,468,105 (-65)
Societal perspective outcomes									
Productivity loss due to premature death	€ 870,072	€ 870,072	0 (0)	€1,991,362	€691,162	-€1,300,199 (-65)	€1,642,295	€571,657	-€1,070,638 (-65)
Caregiver productivity loss	€ 375,824	€ 375,824	0 (0)	€860,161	€301,309	-€558,852 (-65)	€22,531,501	€7,904,319	-€14,627,182 (-65)

Numbers are rounded to the nearest digit

Abbreviations PICU, pediatric intensive care unit; ER, emergency room; MV, mechanical ventilation; SoP, standard of practice

to a PICU and 348 required mechanical ventilation. Primary care visits represented almost three-quarters of the MA-LRTI burden (68%) but only 16% of total healthcare payer costs. While hospitalisations represented less than 6% of the MA-LRTI burden over one season, the associated costs amounted to €49 million (including PICU and MV cost), representing more than two-thirds (68.3%) of the annual economic burden.

Most RSV-related hospitalisations (97.4%) and deaths (80.7%) were estimated to occur among term infants and preterm infants not eligible for palivizumab – i.e., the population for which no prevention is currently available (Table 2). Similarly, more than 95% of costs occurred in term and preterm infants not eligible for palivizumab. The model showed that 41% of RSV MA-LRTIs and RSV-related hospitalisations occur in infants born within the projected 5-month RSV season (November to March)

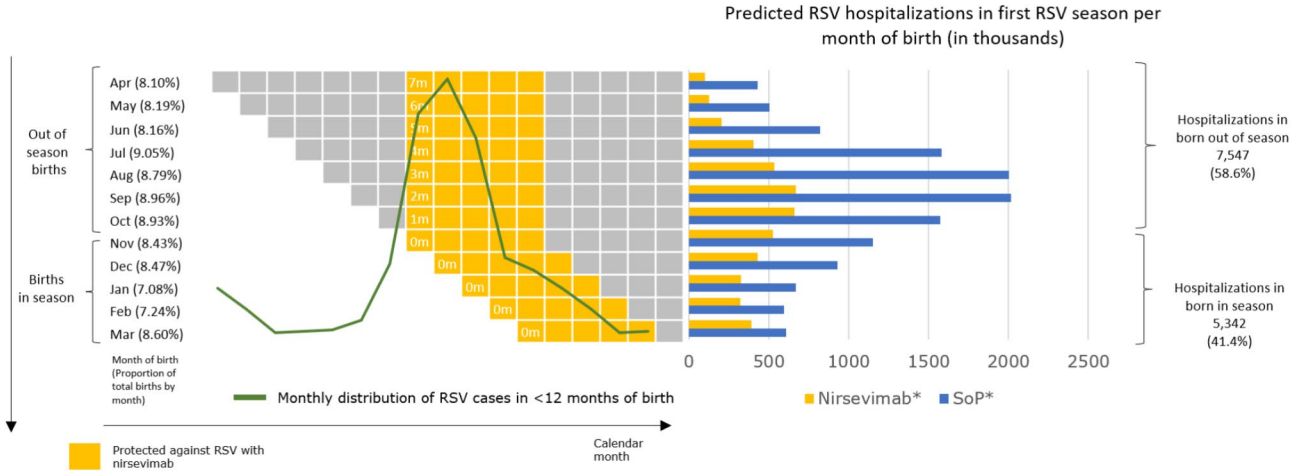

Fig. 4 Modelled RSV burden in infants born within and outside of the RSV season. Burden shown under two scenarios: all infants immunised during RSV season with nirsevimab and high-risk infants immunised according to SoP. Hospitalisations include intensive care unit and mechanical ventilation cases. Nirsevimab describes strategy 2 (single dose of nirsevimab for all infants). SoP describes strategy 1 (palivizumab only for palivizumab subpopulation and no prophylaxis for the rest). Numbers are rounded to the nearest digit. Abbreviations: RSV, respiratory syncytial virus; SoP, standard of practice

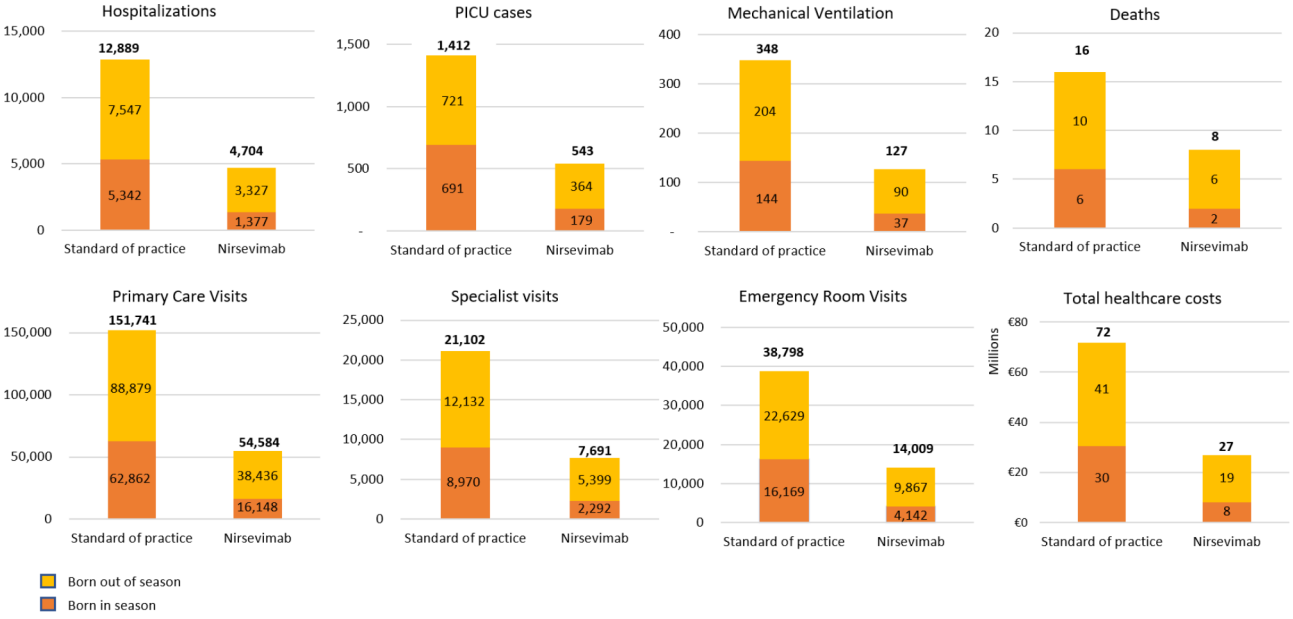

Fig. 5 Modelled impact of nirsevimab immunisation. Hospitalisations include intensive care unit and mechanical ventilation cases. Numbers are rounded to the nearest digit. *Abbreviation* PICU, pediatric intensive care unit

and 59% in those born outside of the season (Fig. 4, Table S4, and Table S5).

Applying 97.6% nirsevimab uptake (in line with the primary vaccination series in Spain), the model estimated nirsevimab immunisation would avoid 8,185 hospitalisations (incl. PICU and MV), 869 intensive care cases (incl. MV), 13,411 specialist visits, 221 MV cases, 24,789 ER visits, 97,157 primary care visits, and 9 deaths over one season; equivalent to a ~ 64% reduction in the number of these events versus the SoP (Table S3, Table 2, and Fig. 5). The switch to universal immunisation with nirsevimab would save €44.8 million in direct healthcare costs (excluding the cost of prophylaxis) – primarily from hospitalisation, PICU, and MV cost savings, which accounted for 67.5% of the total direct healthcare costs saved. Results from a societal perspective suggested that €15.2 million of caregiver productivity loss and €2.4 million of productivity loss due to premature death would be saved with a universal nirsevimab program in Spain (Table 2 and Table S3).

Scenario analysis

The model was moderately sensitive to changes in nirsevimab efficacy, although even the low efficacy estimate

(65.9% for preterm non-palivizumab eligible and term) still prevented more than half of hospitalisations and outpatient visits (Fig. 6). Narrowing the definition of RSV to specific ICD-10 codes resulted in a slightly higher proportion of nirsevimab-prevented outpatient visits versus those prevented in the base case (~68.4% vs. ~64.0% of combined primary care, ER, and specialist visits prevented under SoP (Fig. 6) and healthcare cost savings (~66.4% vs.~62.4%; Table S6 and Table 2). Combining the RSV-specific definition with the low efficacy estimate continued to avert ~56% of hospitalisations and outpatient visits (Fig. 6). Modelling a six-month RSV season (October–March) with a 6-month duration of protection provided by nirsevimab [20] averted ~9.4% more health events than in the base case (November–March). The proportion of deaths prevented through universal nirsevimab immunization was moderately sensitive to the variation in RSV mortality rates from available literature, ranging between 49.3% of deaths prevented (when applying a 2.33% in-hospital mortality among palivizumab-eligible and preterm infants) and 57.9% (when applying a 0.15% inpatient mortality rate among term infants).

Sensitivity analysis

In the DSA, only seven parameters influenced the model results (Fig. 7). The most significant drivers on healthcare costs are the RSV risk by age for term infants, treatment costs in the term infant population and the variance in the distribution of RSV infection by month. Variability in the risk of health events by subpopulation was assessed using published confidence intervals, a 20% variation, or alternative distributions based on the BARI study [30] for outpatient care. Detailed estimates for the upper and lowers bounds are presented in Table 1. Varying the risk of health events for term infants resulted in a variation in costs of −16% and 39% compared to the base case. Based on an assumed variability of 20% in RSV treatment costs in term infant population, healthcare costs varied by −18% and 18% compared to the base case. To inform variability in the distribution of RSV infections by month, alternate definitions of RSV cases based on the BARI study [30] were used. Using a restrictive definition of RSV diagnosis (RSV only) resulted in an increase of 8% in total healthcare costs. Similarly, using a broader definition including RSV and ALRI, resulted in a 24% decrease in the total costs. Finally, shortening the RSV season to 4 months decreased healthcare costs by 24%, and prolonging the season to 6 months increased healthcare costs by 6%.

Discussion

Under the current SoP, the model estimated 12,889 infants are hospitalised in Spain due to RSV during their first RSV season – roughly 38 in every 1000. This estimate lies within the range of expected hospitalizations as reported by other studies conducted in Spain (2.48 – 4.6%) [10, 11, 30, 49]. These hospitalisations represented most of the annual economic burden of RSV in Spain,

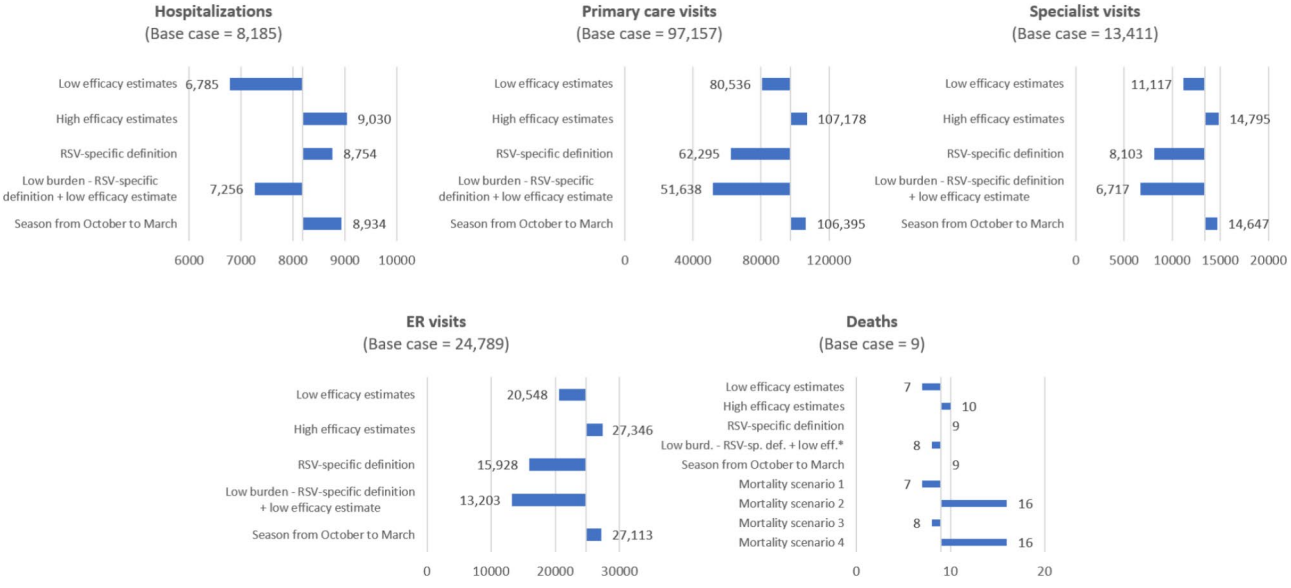

Fig. 6 Scenario analysis results – health events averted. Low efficacy estimate = 65.9% nirsevimab efficacy (1st dose) among preterm and term infants. High efficacy estimate = 87.7% nirsevimab efficacy (1st dose) among preterm and term. RSV Specific definition = Monthly probability of RSV infections 0.33–29.94%; specialist visits: 0.02-0.97%; ER visits: 0.44–21.21%; GP visits: 0.96–81.1%. Mortality scenario 1 = 0.53% inpatient mortality among palivizumab-eligible and preterm infants [47]; mortality scenario 2 = 2.33% inpatient mortality among palivizumab-eligible and preterm infants [15]; mortality scenario 3 = 1.00% inpatient mortality in palivizumab-eligible infants and 0.80% inpatient mortality in other preterm infants [30]; mortality scenario 4 = 0.15% inpatient mortality among term infants [48]. Numbers are rounded to the nearest digit. Abbreviations: ER, emergency room; RSV, respiratory syncytial virus

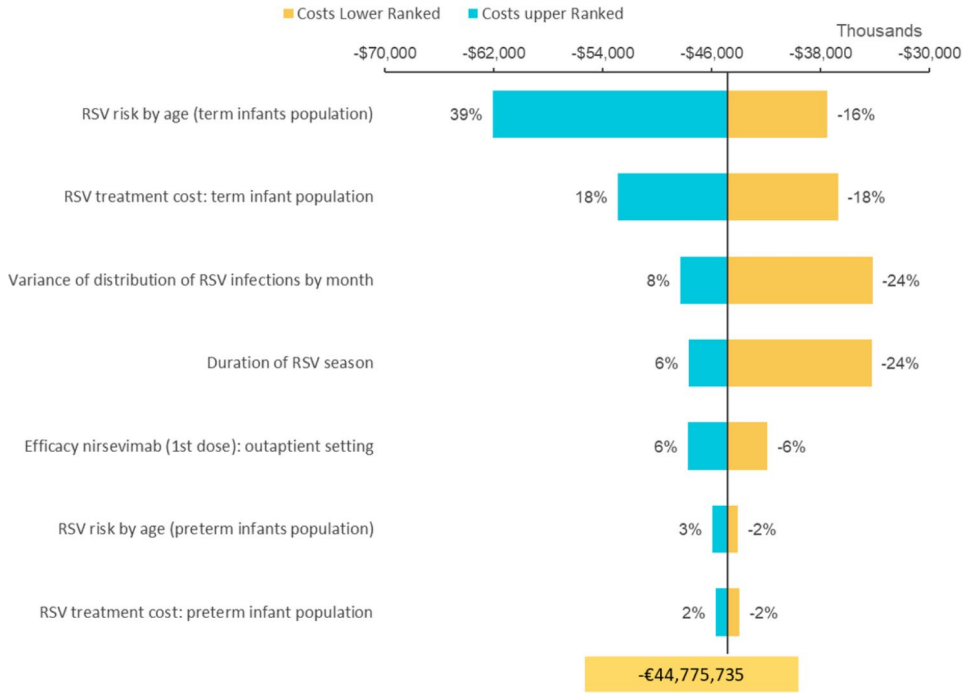

Fig. 7 Deterministic sensitivity analysis. Tornado plot shows healthcare costs averted

and moreover, over 90% of the hospitalised infants were otherwise healthy and born at term. The model suggested that ~63% of these hospitalisations, other health visits, and related costs could be saved annually through a switch to universal and seasonal immunisation with nirsevimab of all Spanish infants in their first RSV season. The model also estimated 16 inpatient deaths annually, in line with published data [10, 48]. Switching to universal nirsevimab was estimated to halve the number of inpatient deaths to 8 per year. Overall, the model predicted the nirsevimab immunisation strategy to save €44.8 million in healthcare costs, €15.2 million of caregiver productivity loss, and €2.4 million of productivity loss due to premature death annually.

The RSV season was defined in the model as the five-month period from November to March in line with epidemiological data from Spain (pre-coronavirus disease 2019 [COVID-19] pandemic) [10, 28, 29]. This also aligns with the five-month protection window for nirsevimab, although this is likely a conservative estimate given that preliminary results suggest nirsevimab protection could last beyond this timeframe [19, 50]. A scenario analysis of a six-month RSV season in Spain – from October to March – resulted in a small (9.4%) increase in averted RSV-related health events. The results from this study are consistent with those from a similar analysis in the US birth cohort, which modelled a six-month RSV season [26]. Similar to the Spanish estimates, the results from this US model showed that most RSV MA-LRTIs and associated costs were incurred by infants born outside of the Spanish RSV season [26]. Infants born out of season, especially those born in the 4 months preceding it, are exposed to the full RSV season when they are at their youngest and are highly susceptible to severe RSV. Infants born within the season however are exposed to the virus for a shorter duration in their first months of life – especially those born after the RSV peak. This pattern of distribution for hospitalisations among infants born outside the RSV season has been observed in real-world evidence studies in France [51] and the UK [52].

Nirsevimab efficacy against RSV MA-LRTIs in infants not eligible for palivizumab was determined from prespecified pooled efficacy data from the pivotal phase 2b and phase 3 studies [35]. Pooling provided a more precise point estimate for nirsevimab efficacy than that achieved for individual study populations, and was justified by: the mechanism of action of nirsevimab being the same regardless of gestational age at birth; the source efficacy studies being double-blinded, placebo-controlled, large pivotal trials allowing for direct comparisons with a robust control group; the source studies having similar eligibility criteria and the same surveillance, case assessment, and case definitions.

In palivizumab-eligible infants, nirsevimab was assumed to be non-inferior to palivizumab based on the pharmacokinetics and the descriptive efficacy endpoints established in the MEDLEY study [34]. Extrapolation was used to determine efficacy in the population included in MEDLEY. This approach is considered acceptable and is in accordance with the pediatric investigation plan [18,

34, 35]. Also, in the palivizumab-eligible population, the analysis did not estimate additional avoided cases that would result from the expected higher nirsevimab uptake, as a conservative assumption of 100% uptake was made for both nirsevimab and palivizumab. As a matter of fact, based on data from a recent pooled analysis of randomised controlled trials and considering the mechanism of action of nirsevimab, an efficacy of 79.5% could have been considered across all subpopulations [35].

Our findings align with those from alternative models evaluating the impact of immunisation products on RSV MA-LRTIs in countries with similar RSV seasonality to Spain [53–56]. The results were robust, showing low sensitivity to variation in nirsevimab efficacy, mortality rates, and the case definition of RSV. Reductions in hospitalisations, outpatient visits, and associated costs are consistent with those in a study using the same model in a US infant population [26]: based on a 71% uptake rate in term and preterm infants and an 80% uptake rate in palivizumab-eligible infants, the use of nirsevimab to immunise all infants decreased RSV MA-LRTIs in the annual US birth cohort by 55% and reduced associated medical costs and RSV-related deaths by a similar margin.

This study was the first model to cover all infants in Spain over their first RSV season – including otherwise healthy term infants – which expands on earlier cost-effectiveness analyses that focused only on the Spanish infant population at higher risk including palivizumab-eligible infants [15, 23–25]. A key strength of the model was its ability to stratify estimates by age at the time of infection and by infant subpopulation, which allowed the population to be disaggregated to identify optimal strategies with the greatest public health impact.

The model was limited by a lack of data on preterm and palivizumab-eligible infants in Spain and variability in cost estimates from available literature. To address this, conservative estimates were used based on available literature and expert validation. The mortality rate in healthy term infants (0.051%) might also be overestimated, since this value was taken from a retrospective study of the Spanish National Health Service hospital discharge register, in which comorbidities were not registered [7]. We conducted sensitivity analyses to address the variability in reported in-hospital RSV mortality rates across different infant risk populations in Spain. These analyses suggested our results were not substantially impacted by the different rates applied. A further limitation to our study was that the model did not consider long-term sequelae of RSV, such as asthma and recurrent wheezing, which may result in additional health resource use and productivity losses [28, 57]. Moreover, the model did not consider findings from the HARMONIE study [58], in which nirsevimab efficacy in preventing RSV hospitalisations reached 83.2%. Regarding the vaccination coverage for RSV in Spain, the model assumed it to be that of primary vaccinations although uncertainties may arise due to implementation challenges. Finally, while the traditional seasonality of RSV infections is likely to continue, the potential for sporadic cases outside the expected timeframe should not be disregarded. In this sense, nirsevimab is currently the only approach capable of preventing potential peaks outside the RSV season.

Conclusions

Our findings add to evidence that most RSV MA-LRTI and inpatient deaths in Spain occur in otherwise healthy infants for whom no prevention is currently available. Immunisation with nirsevimab for all infants experiencing their first RSV season would extend protection to the whole annual birth cohort. The model results show this strategy would reduce the health and economic burden from this population by almost two-thirds versus the current SoP in Spain. Given the substantial incidence of RSV in Spain, all-infant prophylaxis with nirsevimab is likely to be discussed. The findings from this study should allow public health decision-makers to examine the impact of this strategy in the Spanish pediatric healthcare program to prevent RSV-attributed MA-LRTIs.

Abbreviations

ER	Emergency room
PICU	Pediatric intensive care unit
MA-LRTI	Medically attended lower respiratory tract infection
MV	Mechanical ventilation
RCT	Randomised clinical trial
RSV	Respiratory syncytial virus
SoP	Standard of practice

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-024-09642-0.

Supplementary Material 1

Acknowledgements

The authors thank Jonathan Pitt, PhD of Evidera-PPD, a Thermo Fisher company, for medical writing, which was funded by Sanofi and AstraZeneca and provided in accordance with Good Publication Practice guidelines.

Author contributions

RGP, JJP, GD, AK, JR, PK, AS, JLL-B, MB, and JAA were responsible for the conceptualisation of the study. GD, JR, PK, and AS supervised the study, and GD, AK, JR, PK, AS, JLLB, and MB were responsible for project administration. PK, AS, and SdB were responsible for methodology and visualisation. PK and SdB were responsible for formal data analysis and software. SdB was responsible for data curation. JR wrote the original draft, and RGP, JJP, GD, AK, JR, JLLB, MB, and JAA edited and reviewed the manuscript.

Funding

This study was funded by Sanofi and AstraZeneca.

Data availability

The data used during this study are available from the following public repositories: Instituto Nacional de Estadística (2021). Birth and Fertility, Birth-

rate Indicators, National results. https://www.ine.es/en/. Ministerio de Sanidad (2020). Coberturas de primovacunación y dosis de recuerdo con vacuna hexavalente. Comunidades autónomas, año 2020. https://vacunasaep.org/sites/vacunasaep.org/files/minsanidad_coberturas-vacunales-2020-todas-las-tablas.pdf Instituto Nacional de Estadística (2021). Encuesta de poblacion activa. EPA. Cuarto trimestre 2021. https://www.ine.es/dyngs/INEbase/es/operacion.htm?c=Estadistica_C&cid=1254736176918&menu=ultiDatos&idp=1254735976595 Instituto Nacional de Estadística (2021). Salario por hora por tipo de jornada y periodo. https://www.ine.es/jaxiT3/Datos.htm?t=10885. The remaining inputs were informed by published literature as cited and by the following database: eSalud (2023). Barcelona: Oblikue Consulting, S.L. 2007. http://www.oblikue.com/bddcostes/. The data generated or analysed during this study are available from the corresponding author, JLLB, upon request.

Declarations

Ethics approval and consent to participate

The study was based on publicly accessible anonymised databases (see 'Availability of data and materials' for full list of repositories), and thus is exempt from ethical compliance.

Consent for publication

Not applicable.

Competing interests

RGP reports grants/honorarium from Sanofi, Merck, Pfizer, Moderna, Seqirus and GSK. JJP reports grants/personal fees from Sanofi. GD, AK, JLLB, and MB are employees of Sanofi and may hold shares and/or stock options in the company. JR, PK, AS, and SdB are employed by Evidera, a part of Thermo Fisher Scientific that receives funding for research from Sanofi. JAA reports grants/honorarium from Sanofi, Merck, Pfizer, GSK, and AstraZeneca.

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Received: 12 December 2023 / Accepted: 23 July 2024
Published online: 06 September 2024

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