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Cost-utility analysis of the use of the 20-valent anti-pneumococcal vaccine (PCV20) in adults older than 60 years in Spain

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ABSTRACT

Background and objectives: A cost-utility analysis was conducted to assess the efficiency of implementing a PCV20 vaccination strategy in the Spanish adult population older than 60 years, for the prevention of non-bacteremic pneumococcal pneumonia (NBP) and invasive pneumococcal disease (IPD).
Methods: A Markov model, with annual cycles and a time horizon of 10 years was used. The analysis population was stratified by age and risk groups. The comparator was the sequential vaccination with the 15-valent pneumococcal conjugate vaccine (PCV15) followed by one dose of the pneumococcal polysaccharide vaccine (PPV23). The base case analysis was performed from the National Healthcare System (NHS) perspective including direct costs (€2018) and applying a discount of 3% to future costs and outcomes. Alternative scenarios explored a shorter time horizon (5 years), the societal perspective and other available vaccination strategies. All the parameters and assumptions were validated by a panel of experts. To evaluate the robustness of the model, deterministic and probabilistic sensitivity analyses (PSA) were carried out.
Results: The results of the study showed that the vaccination strategy with PCV20 is a dominant option compared to the sequential regimen (PCV15 + PPSV23), resulting in direct cost savings of €85.7 M over 10 years, with a small increase in quality-adjusted life years (QALYs). PCV20 vaccination avoided 2,161 cases of IPD, 19,470 of NBP and 3,396 deaths and according to the PSA, the probability of PCV20 being cost-effective compared to a sequential regimen (PCV15 + PPSV23) was 100%.
Conclusions/Recommendations: In the Spanish adult population older than 60 years, the vaccination strategy with one dose of PCV20 is more effective and less expensive (dominant) than vaccination with a sequential schedule with PCV15 and PPSV23.

1. Introduction

Pneumococcal disease (PD), a term referring to diseases caused by the gram-positive bacteria *Streptococcus pneumoniae*, can be further categorized into invasive (IPD) or non-invasive. Non-invasive PD in adults is mainly due to community-acquired pneumonia (CAP), while IPD refers to cases where there is a confirmation of *S. pneumoniae* infection in an isolation from a sterile site. IPD has a lower incidence when compared to CAP but considerably increased mortality [1].

In Spain, PD accounts for a substantial clinical and economic burden in the adult population, causing 10,842 annual hospitalizations, 87.65% of them in adults 45 years old and older [2]. Additionally, PD has been reported to generate total annual healthcare costs of €59.51 M in adults over 45 years old [3]. Of those, 84.6% (€50.36 M) were due to

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hospitalizations while primary care costs amounted to €5.57 M. Besides, *S. pneumoniae* was shown to be responsible for 44.4% of total direct medical costs generated by the most relevant vaccines-preventable infectious diseases in adults [3].

In 2001, the pneumococcal polysaccharide vaccine against 23 serotypes (PPSV23) was the first pneumococcal vaccine introduced in Spain [4]. However, PPSV23 has shown limitations in preventing non-bacteremic pneumonia (NBP) and limited effectiveness against IPD. After several years of routine use, it was shown unable to control the epidemiology of specific and unique serotypes contained in the vaccine, possibly due to the different immune response elicited in comparison to PCVs [5–8].

After the PPSV23 introduction, new technologies were developed leading to the emergence of conjugate vaccines. Since 2010, the pneumococcal conjugate vaccine 13-valent (PCV13) has been progressively included in several regional immunization programs (IPs) in Spain [9,10]. Importantly, PCV13 has demonstrated efficacy against both CAP and IPD for vaccine serotypes [11] and has been reported to be effective against CAP hospitalization in older adults including chronic and immunocompromised patients [12,13].

Two newly licensed conjugated vaccines approved in 2022, pneumococcal vaccine 15-valent (PCV15) and 20-valent (PCV20), have been developed aiming to protect against increasingly incident serotypes not included in PCV13 [4]. On one hand, PCV15 includes 2 additional serotypes over PCV13 and has been recommended to be used sequentially with PPSV23 [14]. On the other hand, PCV20, a vaccine developed using the same technology as PCV13 including seven additional serotypes, has been estimated to cover 62% of IPD cases and 23.9% of hospitalized all-cause CAP cases [8,15] in Spain (Supplementary Material 1).

PCV20 has already been introduced in the IPs of some Spanish regions, such as Catalonia, Murcia, and Castilla y Leon [16–18]. Additionally, the Spanish Society of Preventive Medicine, Public Health and Health Management (SEMPSPGS) recommends a single dose of PCV20 for adults 60 years and older, preferentially over sequential vaccination schedules [19]. Similarly, the NeumoExperts Prevention group (NEP) has recently published a practical vaccination guide to prevent CAP in the year 2023. In this guide, NEP considers that a single dose of PCV20 would facilitate compliance with the vaccine strategy and would avoid interference with future PCVs. Additionally, NEP recommends the vaccination against *S. pneumoniae* for all adults ≥ 60 years old and patients belonging to risk groups, regardless of the vaccine strategy used [5].

Considering the complex landscape of IPs recommendations and the promising new vaccines available, this study aims to evaluate the efficiency of vaccinating adults over 60 years old in Spain with a single dose of PCV20 by performing a cost-effectiveness and cost-utility analysis from the National Healthcare System (NHS) perspective.

2. Methods

2.1. Methodology and structure

A hypothetical cohort framework (deterministic) and a Markov-type process were used to depict expected lifetime risks, consequences, costs of IPD and all-cause non-bacteremic pneumonia (NBP) and the expected impact of anti-pneumococcal vaccination, in Spanish adults of 60 years and older. The model methodology and structure were described in earlier publications [20,21].

The model population was initially characterized based on age and risk profile and was evaluated at the end of each one-year cycle. (Fig. 1). Transition probabilities were estimated according to the incidence and case-fatalities, the type of vaccine received, serotype coverage and vaccine effectiveness, as well as the vaccination coverage rate (VCR) in Spain. It was assumed that patients would not transit between health states, hence would remain in the risk group assigned at baseline throughout modeling horizon.

Expected outcomes were evaluated for each subject in the model population at the end of each cycle, from model entry through the end of the 10-year modelling horizon. The model compared the reduction in the number of cases and deaths due to IPD and all-cause NBP for each vaccination strategy, the corresponding life years (LYs), quality-adjusted life years (QALYs) gained and cost savings. An incremental cost-effectiveness ratio (ICER) was calculated by dividing the difference in total costs (incremental cost) by the difference in QALYs of the compared vaccination strategies. A €25,000/QALY willingness-to-pay threshold was set to evaluate the cost-effectiveness of one alternative compared to the other [22].

The base-case analysis reflected the NHS perspective following Spanish cost-effectiveness recommendations [23] and included only direct medical costs (€2018). As per the guideline recommendations for economic evaluations a 3% annual discount was applied to account for the future value of costs and events [23].

To mitigate the uncertainty around the modelled parameters we performed a deterministic sensitivity analysis (DSA) varying vaccine

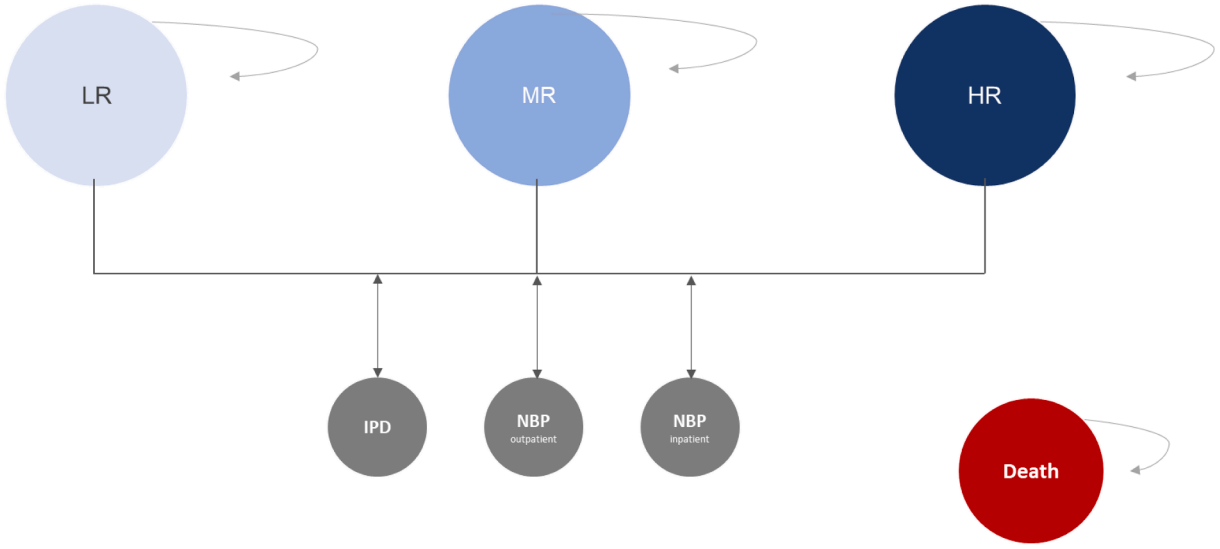


Fig. 1. Markov model structure HR: high risk; LR: low risk; MR: moderate risk; IPD: invasive pneumococcal disease; NBP: non-bacteremic pneumococcal pneumonia.

coverage, discount rate, efficacy, incidence, mortality, utility, and costs by +/-25%. A probabilistic sensitivity analysis (PSA), based on a Monte-Carlo simulation with 1,000 iterations was also performed for the base case and alternative scenarios.

2.2. Model inputs

All model inputs, together with the assumptions and results of the analysis, were validated by a panel of experts in health economics, vaccinology, infectious diseases, and Public Health.

2.2.1. Base case analysis

2.2.1.1. Population. Population estimates were based on national figures from the Spanish National Statistical Institute [24]. The risk of developing PD was determined according to age group. For age groups 60–64 and 65–74 the risk profile was determined using the publication of Ochoa-Gondar et al., an epidemiological study evaluating risk profile for pneumococcal vaccination recommendations in the general population over 50 years old using primary care database records [25]. The age groups of 75–84 and 85+ were estimated using a real-world data study carried out with a database of clinical records representative of all the Spanish territory [26].

2.2.1.2. Disease incidence. For the analysis, we considered IPD (bacteremia and meningitis) and NBP (stratified by the setting of care: inpatient and outpatient). The model considers all-cause NBP rather than pneumococcal pneumonia due to the scarce published epidemiological evidence available. Age-specific incidence estimates for IPD and inpatient NBP were obtained from the National Health System's Hospital Discharge Records Database (CMBD) [27] *(*Table 1*)*. To estimate the incidence of outpatient NBP, we used a real-world retrospective study of adults diagnosed with CAP attending primary care in Spain, that used data from the Computerized Database for Pharmacoepidemiological Studies in Primary Care (BIFAP) *(*Table 1*)* [28]. All incidence rates were adjusted per risk and age group [26].

2.2.1.3. Vaccination strategy. The population was assumed to be vaccinated at model entry. In the base case analysis, we compared the vaccination of the Spanish population 60 years and older with either a single dose of PCV20 or a sequential vaccination of PCV15 followed by PPSV23. Several scenario analyses were analysed to assess the benefits of PCV20 compared to other available vaccination strategies in Spain and different populations (see *Alternative Scenarios* section).

2.2.1.4. Vaccination coverage. To estimate the vaccination coverage expected for both conjugate vaccines, data were obtained from the real-world study performed by Rejas et al. [26] and assumed that 17% of the population who receive PCV15 would also receive PPSV23 to complete the vaccination scheme [29] *(*Table 2*)*.

2.2.1.5. Vaccine serotype coverage. The fraction of disease attributable to vaccine serotypes for IPD and NBP used in the model was also retrieved from Spanish epidemiologic studies and remained constant during the modelled 10-year horizon *(*Table 2*)* [8,15,30]. Replacement of serotypes over time was assumed; meaning no reduction in total disease throughout the modelled horizon was considered.

2.2.1.6. Vaccine effectiveness. Vaccine effectiveness (VE) for the conjugated vaccines was estimated using PCV13 efficacy data from the CAPITA clinical trial, while PPSV23 effectiveness was estimated using a real-world analysis developed in the UK [20,25] *(*Table 3*)*. For PCV vaccines, VE against IPD and NBP vaccine serotypes was considered stable during the first 5 years following vaccination [11] and thereafter assumed to wane annually at a rate of 5% during years 6 to 10 [31].

For PPSV23, VE against IPD was assumed to wane across all age and risk groups after year 1, with a linear decline to 76.2% of initial effectiveness by year 5, and a linear decline to no efficacy by year 10 [32]. In the base case analysis, the VE of PPSV23 against NBP vaccine serotypes

Table 1
Estimates of population size, incidence of events, mortality, case-fatality, and direct costs.

AGE GROUP	*18–49 YEARS*			*50–64 YEARS*			*65–74 YEARS*			*75–84 YEARS*			*85–99 YEARS*		
Risk profile	LR	MR	HR	LR	MR	HR	LR	MR	HR	LR	MR	HR	LR	MR	HR
Population [25,26]	76.7%	20.2%	3.1%	58.2%	36.7%	5.1%	45.3%	42.4%	12.3%	40.8%	35.4%	23.8%	39.4%	33.2%	27.4%
Annual disease incidence (per-100,000)															
Menigitis [27]	0.2	0.7	3.0	0.9	1.5	3.7	1.4	2.8	4.8	1.3	2.1	4.2	0.8	1.6	2.4
Bacteremia [27]	2.0	5.9	27.3	7.5	12.3	30.4	10.6	21.0	36.4	19.2	30.4	60.5	32.2	63.7	97.2
NBP (inpatient) [27]	41.5	122.5	563.9	165.1	269.8	667.6	392.1	776.0	1,334.4	939.0	1,448.7	2,964.4	1,857.6	3,663.0	5,587.2
NBP (outpatient) [28]	197.3	260.2	271.3	266.2	323.0	337.9	427.7	492.4	531.0	647.1	700.2	803.3	1,096.1	1,203.2	1,230.9
Annual mortality (per-100)/% case-fatality at 30 days															
Meningitis [26]	3.0	7.6	16.5	1.3	4.4	18.8	2.1	5.9	27.8	7.5	17.7	31.3	40.2	46.5	60.9
Bacteremia [26]	2.7	6.8	14.8	2.0	7.0	29.7	3.1	8.5	30.8	7.6	18.0	31.9	24.7	28.5	37.4
NBP (inpatient) [26]	0.1	1.8	2.6	0.5	2.3	7.4	1.6	4.4	20.8	4.5	10.6	18.8	22.6	26.1	34.2
NBP (outpatient) [24]	0.1	0.1	0.01	0.5	0.7	0.9	1.3	1.8	2.0	3.7	5.1	6.2	13.1	19.3	22.6
Direct medical costs of events (per-case, in thousands) (€)															
Menigitis [27]	11.8	11.8	11.8	12.4	12.4	12.4	14.0	14.0	14.0	13.6	13.6	13.6	10.3	10.3	10.3
Bacteremia [27]	4.1	4.1	4.1	5.0	5.0	5.0	4.9	4.9	4.9	4.5	4.5	4.5	4.1	4.1	4.1
NBP (inpatient) [26]	3.3	3.8	3.7	3.4	3.7	4.2	3.4	4.4	4.4	3.8	4.6	4.6	3.6	4.0	4.3
NBP (outpatient) [26]	0.4	0.5	0.6	0.4	0.5	0.7	0.5	0.6	0.7	0.5	0.7	0.8	0.6	0.6	0.7

ICD codes bacteremia: R78.81, B95.3, K65.9, A40.3: M00.1-M00.19, J13* (divided between bacteremia and pneumococcal CAP in-hospital).
ICD codes meningitis: G00.1.
ICD codes pneumococcal CAP in-hospital: J10.0 – J10.1, J11-J12, J14-J18; J13* (divided between bacteremia and pneumococcal CAP in-hospital;16.6% for IPD y el 83.4% NBP).
Due to lack of data, general population mortality by risk group was adjusted by applying a relative risk (RR) of 1.5 for moderate risk and 2.0 for high risk.
HR: high risk; LR: low risk; MR: moderate risk; NBP: all-cause non-bacteremic pneumococcal pneumonia.

Table 2
Vaccination coverage rates and vaccine serotype coverage (%).

	Vaccination coverage [26,29]			Fraction of disease attributable to vaccine serotypes							
	Risk profile			PCV13		PCV15		PCV20		PPSV23	
Age group	LR	MR	HR	IPD [8]	NBP [30,31]	IPD [8]	NBP [30,31]	IPD [8]	NBP [30,31]	IPD [8]	NBP [30,31]
18–49	0.0%	0.0%	0.0%	25.0%	13.0%	31.0%	13.0%	62.0%	29.0%	70.0%	24.0%
50–64	1.3%	15.1%	59.1%	25.0%	13.0%	31.0%	13.0%	62.0%	29.0%	70.0%	24.0%
65–74	6.6%	31.1%	48.3%	25.0%	14.0%	31.0%	16.0%	62.0%	22.0%	70.0%	24.0%
75–84	35.6%	46.1%	66.9%	25.0%	14.0%	31.0%	16.0%	62.0%	22.0%	70.0%	24.0%
85–99	69.5%	60.7%	77.0%	25.0%	14.0%	31.0%	16.0%	62.0%	22.0%	70.0%	24.0%

IPD: invasive pneumococcal disease; HR: high risk; LR: low risk; MR: moderate risk; NBP: non-bacteremic pneumococcal pneumonia; PCV13: pneumococcal conjugate vaccine 13-valent; PCV15: pneumococcal conjugate vaccine 15-valent; PCV20: pneumococcal conjugate vaccine 20-valent; PPSV23: pneumococcal polysaccharide vaccine 23-valent.

was assumed to be zero based on various published sources, and consistent with base-case assumptions employed in several economic studies [33–37].

2.2.1.7. Quality of life. The quality of life of the subjects was estimated based on the utilities of the general population [38] (without disease) to which the loss of quality of life (disutility) caused by an event of PD was subtracted (0.0709 for IPD and inpatient NBP and 0.0045 for outpatient NBP) [31].

2.2.1.8. Mortality. Mortality from IPD and NBP, as well as from general causes, is assumed to depend upon age and risk profile. IPD and hospitalized NBP annual mortality rates were estimated based on the general Spanish population mortality and adjusted with the disease case fatality rate at 30 days, calculated from the Spanish RAE-CMBD and adjusted per risk group [26,27] (Table 1). It was assumed that patients with outpatient NBP have the same mortality rate as the general population.

2.2.1.9. Costs. In the base case analysis and from the NHS perspective, only the direct medical costs of vaccination and disease events (Table 1) were considered. The cost of an IPD event was extracted from Rejas et al. while the cost for both hospitalized and ambulatory NBP events were extracted and adjusted by age and risk group from the CMBD [26,27].

For vaccines, the ex-factory price was obtained from the Spanish National Pharmacology database [39] and discounted by a 7.5% according to the RDL8/2010 national law decree (€45.23 PCV13; €55.50 PCV15; €49.76 PCV20; PPSV23 €14.29). For all vaccines, a 6€ cost of administration was considered per injection [40]. All costs were expressed in €2018 since it was assumed that PD epidemiology will progressively regain similar pre-pandemic trends.

Table 3
Vaccine effectiveness (%).

Years since vaccination / Risk profile	Year 1–5		Year 10	
	LR/MR (%)	HR (%)	LR/MR (%)	HR (%)
PCV vs VT-IPD [11,31]				
18–49	81.5%	65.2%	63.1%	50.5%
50–64	79.2%	63.3%	61.2%	49.0%
65–74	75.0%	60.0%	58.0%	46.4%
75–84	75.0%	60.0%	58.0%	46.4%
85–99	75.0%	60.0%	58.0%	46.4%
PCV vs VT-NBP [11,31]				
18–49	55.6%	44.5%	43.0%	34.4%
50–64	51.3%	41.1%	39.7%	31.8%
65–74	45.0%	36.0%	34.8%	27.9%
75–84	45.0%	36.0%	34.8%	27.9%
85–99	45.0%	36.0%	34.8%	27.9%

Years since vaccination / Risk profile	Year 1			Year 5		
	LR (%)	MR (%)	HR (%)	LR (%)	MR (%)	HR (%)
PPSV23 vs VT-IPD [33–37]						
18–49	59.1%	32.8%	17.1%	45.1%	25.0%	13.0%
50–64	58.3%	32.3%	16.8%	44.4%	24.6%	12.8%
65–74	55.7%	30.9%	16.1%	42.5%	23.5%	12.2%
75–84	50.8%	28.1%	14.6%	38.7%	28.1%	14.6%
85–99	37.9%	20.5%	10.6%	28.9%	15.6%	8.1%

IPD: invasive pneumococcal disease; HR: high risk; LR: low risk; MR: moderate risk; NBP: non-bacteremic pneumococcal pneumonia; PCV15: pneumococcal conjugate vaccine 15-valent; PCV20: pneumococcal conjugate vaccine 20-valent; PPSV23: pneumococcal polysaccharide vaccine 23-valent; VT-IPD: vaccine-type invasive pneumococcal disease; VT-NBP: vaccine-type non-bacteremic pneumonia.
The vaccine efficacy was derived for all age groups by adapting a logarithmic curve to the values for people aged 65–74 years, 75–84 years, and 85–99 years, and then estimating the age-specific values across the three risk groups using relative risks from Djennad et al. (40) and the population sizes.

2.2.2. Alternative scenarios

To account for the variability in vaccination recommendations across the Spanish autonomous regions, alternative scenarios were carried out considering different vaccine comparisons (PPSV23, PCV13 + PPSV23, PCV13), with different age and risk groups. Age recommendation scenarios included $\geq$ 60 and $\geq$ 65 years old, while high risk analyses included adults over 18 years old. Additionally, the base case analysis (population $\geq$ 60) was modified to evaluate the impact of a shorter time horizon (5 years), alternative vaccine prices and to explore the societal perspective.

To build the alternative scenario from the societal perspective, the non-healthcare indirect cost of work absenteeism due to a PD event was considered, exclusively for the population younger than 65 years. For NBP, this cost was estimated using the real-world CAP-specific study of Rejas et al. [26] For IPD, due to a lack of published data, the cost was calculated considering the mean cost of a lost day of work [€138.53 [26]] together with the proportion of active Spanish population within the specific age group [24]; and assuming conservatively that the number of workdays lost due to IPD was the same as the average

Table 4
Days of work loss due to pneumococcal disease.

Risk/Age group		Meningitis [24,26,27]	Bacteremia [24,26,27]	Inpatient NBP [24,26]	Outpatient NBP [24,26]
LR	**18–49**	16.1	8.1	22.9	19.1
	50–64	17.1	10.1	24.8	19.4
MR	**18–49**	16.1	8.1	22.3	20.5
	50–64	17.1	10.1	22.4	17.9
HR	**18–49**	16.1	8.1	22.7	17.2
	50–64	17.1	10.1	26.7	15.6

HR: high risk; LR: low risk; MR: moderate risk; NBP: non-bacteremic pneumococcal pneumonia.
Given the lack of published data for IPD, the number of sick days leave was assumed to be similar to the mean hospitalization length of stay, resulting in an underestimated value when compared to NBP.

hospitalization length of stay per IPD event (Table 4). Other indirect costs were not included in the model, due to a lack of robust data availability in Spain.

3. Results

3.1. Base case analysis

The model estimated that, on a 10-years horizon, vaccination with a single dose of PCV20 could prevent 2,161 additional IPD cases (2,044 bacteremia, 117 meningitis) when compared to the sequential vaccination with PCV15 and PPSV23. Overall, it prevented 19,470 additional NBP cases, of which 29.26% (5,700) were hospitalized. Furthermore, the use of PCV20 progressively reduced deaths related to PD, adding up to a total of 3,396 deaths avoided (Table 5).

In the Spanish NHS setting, vaccination with a single PCV20 dose saved up to €85.7 M cost, mainly (€64.6 M) due to the reduction in the cost of pneumococcal disease events (Table 5).

Regarding life years gained during a 10-years horizon, vaccination with a single PCV20 dose added more than 8,907 LYs (5,870 QALYs) to the entire cohort, compared to vaccination with PCV15 + PPSV23 and 0.0008 LYs (0.0005 QALYs) per patient (Table 5).

Overall, from the NHS perspective, the vaccination strategy with a single dose of PCV20 resulted in a dominant vaccination strategy (Table 6).

3.2. Scenario analysis

When including indirect costs into the analysis (societal perspective) a 4.1% increase in savings (−€3.9 M) was observed and PCV20 remained dominant (Table 7). PCV20 was dominant to PCV15 + PPSV23 even 5 years after vaccination, albeit clinical effectiveness and savings were lower. Furthermore, PCV20 remained dominant regardless of the age-risk profile, with higher benefits for the elderly and higher-risk populations (Table 7).

The cost-effectiveness of PCV20 compared to different vaccination strategies was also assessed as per national and regional guidelines recommendations. PCV20 remained dominant in all of them, showing higher clinical benefits and higher total cost savings (Table 7).

3.3. Sensitivity analysis

Increasing or decreasing the model main parameters by 25% did not substantially affect the outcomes and PCV20 remained dominant to PCV15 + PPSV23 (Table 8). The same happened when varying the discount rate on both effects and costs to 0% and 5% (Table 8). The PSA further confirmed the robustness of the results, with all 1000 iterations favouring PCV20 in terms of clinical and economic benefits (dominant) for the base case analysis and the majority of cases in the alternative scenarios (Fig. 2, Table 7).

4. Discussion

All scenarios analysed in our model suggest that from the Spanish NHS perspective, a routine pneumococcal adult vaccination scheme with a single dose of PCV20 is likely to be the most efficient among the currently available vaccination strategies for adults. The savings generated by the additional avoided events (€64.6 M) led to a total of €85.7 M savings over 10 years. Most of the savings accrue from prevention of NBP due to its significantly higher incidence when compared to IPD.

Since their approval, several studies [41–46] have been published reporting the clinical and economic benefits of PCV vaccines in comparison with PPSV23 vaccination, in both children and adults and support their cost-effectiveness [41–43]. Although Spain is one of the most advanced countries in childhood immunisation, with coverage rates

Table 5
Base case analysis results.

AGE GROUP		60–64			65–74			75–84			85–99			TOTAL		
Vaccination strategy		PCV20	PCV15 + PPSV23	Δ	PCV20	PCV15 + PPSV23	Δ	PCV20	PCV15 + PPSV23	Δ	PCV20	PCV15 + PPSV23	Δ	PCV20	PCV15 + PPSV23	Δ
Clinical outcomes (events)																
	Meningitis	395	409	−14	786	837	−50	315	356	−41	58	70	−12	1,554	1,671	−117
	Bacteremia	3,145	3,257	−111	8,283	8,803	−520	6,644	7,487	−843	2,832	3,402	−570	20,905	22,948	−2,044
	NBP (inpatient)	93,685	94,313	−628	224,964	226,479	−1,515	170,754	172,870	−2,117	75,128	76,569	−1,441	564,530	570,231	−5,700
	NBP (outpatient)	98,979	99,922	−943	398,771	401,934	−3,163	423,180	428,747	−5,567	217,401	221,498	−4,097	1,138,331	1,152,101	−13,770
	Deaths	4,498	4,599	−102	40,004	40,492	−487	82,524	83,837	−1,313	70,893	72,387	−1,494	197,919	201,315	−3,396
Economic outcomes (€M)																
	Cost of vaccination	15.0	16.5	−1.5	56.1	61.9	−5.8	77.1	85.0	−7.9	57.3	63.2	−5.9	205.4	226.6	−21.2
	Cost of events	389.1	393.5	−4.4	1,625.1	1,641.0	−15.9	1,711.9	1,738.2	−26.3	843.3	861.3	−18.0	4,569.5	4,634.0	−64.6
	Cost of vaccination + cost of events	404.1	410.0	−5.9	1,681.2	1,702.9	−21.7	1,789.0	1,823.2	−34.3	900.6	924.4	−23.9	4,774.9	4,860.6	−85.7
Effectiveness																
Cohort (11,785,770 pts, in thousands)																
	LYs	23,290.8	23,291.2	0.4	35,466.8	35,468.5	1.7	17,863.9	17,867.6	3.7	5,409.6	5,412.8	3.2	82,040.1	82,031.1	8.9
	QALYs	20,387.3	20,3877	0.4	28,498.9	28,500.3	1.4	12,237.6	12,240.1	2.5	2,821.8	2,823.5	1.6	63,951.6	63,945.7	5.9
Per patient																
	LYs	8.4426	8.4428	0.0001	7.7782	7.7786	0.0004	6.0134	6.0147	0.0012	3.6145	3.6167	0.0021	6.9609	6.9602	0.0008
	QALYs	7.3902	7.3903	0.0001	6.2501	6.2504	0.0003	4.1195	4.1203	0.0008	1.8855	1.8865	0.0011	5.4262	5.4257	0.0005

LY: life years; QALY: quality adjusted life years; NBP: non-bacteremic pneumococcal pneumonia; PCV15: pneumococcal conjugate vaccine 15-valent; PCV20: pneumococcal conjugate vaccine 20-valent; PPSV23: pneumococcal polysaccharide vaccine 23-valent.

Table 6
Base case analysis results (Cohort).

Strategy	Cost(€M)	QALYs (in thousands)	Δcost(€M)	ΔQALYs (in thousands)	ICER (€)
PCV20	4,775	63,951.6	−85.7	+5.9	Dominant (-14,605)
PCV15 + PPSV23	4,861	63,945.7	–	–	–

ICER: incremental cost-effectiveness ratio; LY: life years; QALY: quality-adjusted life years; PCV15: Pneumococcal conjugate vaccine 15-valent; PCV20: pneumococcal conjugate vaccine 20-valent; PPSV23: Pneumococcal polysaccharide vaccine 23-valent.

Table 7
Scenario analysis.

Population	Comparator	Scenario	ICER (€, PSA Average)	% Dominant PSA
60+	PCV15 + PPSV23	Base case inputs	Dominant (−15,562)	100%
		Societal perspective	Dominant (−16,163)	100%
		Horizon 5 years	Dominant (−31,124)	100%
65+	PCV15 + PPSV23	Base case inputs	Dominant (−15,974)	100%
	PCV13 + PPSV23	Base case inputs	Dominant (−20,230)	100%
	PCV13	Base case inputs	Dominant (−8,869)	100%
	PPSV23	Base case inputs	Dominant (−2,681)	77%
18+	PCV15 + PPSV23	Risk profile: MR + HR	Dominant (−16,461)	100%
		Risk profile: HR	Dominant (−17,698)	100%
	PCV13 + PPSV23	Risk profile: HR	Dominant (−22,820)	100%
	PCV13	Risk profile: MR + HR	Dominant (−10,241)	100%
	PPSV23	Risk profile: MR + HR	Dominant (−2,575)	73%

ICER: incremental cost-effectiveness ratio; LY: life years; QALY: quality-adjusted life years; NBP: non-bacteremic pneumococcal pneumonia; PCV13:pneumococcal conjugate vaccine 13-valent; PCV15: pneumococcal conjugate vaccine 15-valent; PCV20: pneumococcal conjugate vaccine 20-valent; PPSV23: pneumococcal polysaccharide vaccine 23-valent.

above 97%, rates in adults remain low and, in some cases, decrease over time [44]. This study is the first economic evaluation of a national adult pneumococcal IP with PCV20 in Spain and is a potential evidence-based tool to support national vaccine decision makers when building the national immunization program and policy, in the context of an aging population with one of the highest life expectancies in the European Union (EU) [44].

Results are aligned with two recently published economic analyses performed in UK and Denmark which concluded that PCV20 is a cost-saving vaccination strategy compared to PPSV23 for different age and risk populations [20,21]. Economic evaluations in US and Japan also highlighted the clinical and economic benefits of the additional serotypes included in PCV20 [20,47] and confirmed the robustness of our conclusions.

The present study has some limitations and assumptions to be considered when interpreting the results. A literature review was performed to obtain the model inputs and when not available, assumptions or data adjustments had to be made. Extensive one-way and PSA mitigated the uncertainty around the magnitude of the model key parameters and expert opinion confirmed the totality of the assumptions.

It is noteworthy that PCV15 paediatric indication was recently approved by EMA and that PCV20 is also undergoing clinical development for paediatric vaccination, implying that in the next years, paediatric vaccination with high-valent conjugate vaccines may generate a herd effect over the older adult population that was not considered in this analysis.

To address the fact that there are no official definitions to describe specific risk groups for pneumococcal recommendations, we decided to use the epidemiological study with the definition of risk closest to the one used in the Spanish Ministry of Health (MoH) recommendations [48]. Compared to the Ochoa-Gondar *et al.* [25] study, the MoH high-risk definition includes Down syndrome, cirrhosis, and previous IPD, and the moderate-risk definition includes celiac disease and institutionalized patients. Ochoa-Gondar *et al.* consider alcoholism a moderate risk, while the MoH considers it a high risk [25]. Overall, Ochoa-Gondar *et al.* definitions are more restrictive, making the analysis more conservative [25].

While our analysis showed significant reduction of disease events and cost, one can argue that PCV20 showed a limited gain in QALYs. This is partly due to a series of conservative assumptions that were made to account for the absence of data. Several studies point out significant sequelae (particularly in meningitis), loss of quality of life and costs, following an acute event of PD [48–50]. However, there was scarce published data that could be used in the model.

In terms of economic parameters and assumptions, it is to be noted that this analysis was performed using the publicly reimbursed ex-factory prices of vaccines. To account for possible pricing variations around tender negotiations, a sensitivity analysis was performed, varying PCV15 and PCV20 prices separately with +/- 25%. Results showed that PCV20 remained dominant in all cases. Although in the analysis an administration cost is considered, costs may be underestimated since the model is not taking into account structural costs related to procurement (such as storage, stock administration, etc) due to a lack of data. This underestimation of real costs may also apply to indirect costs and to the healthcare costs regarding long-term sequelae due to the lack of published data.

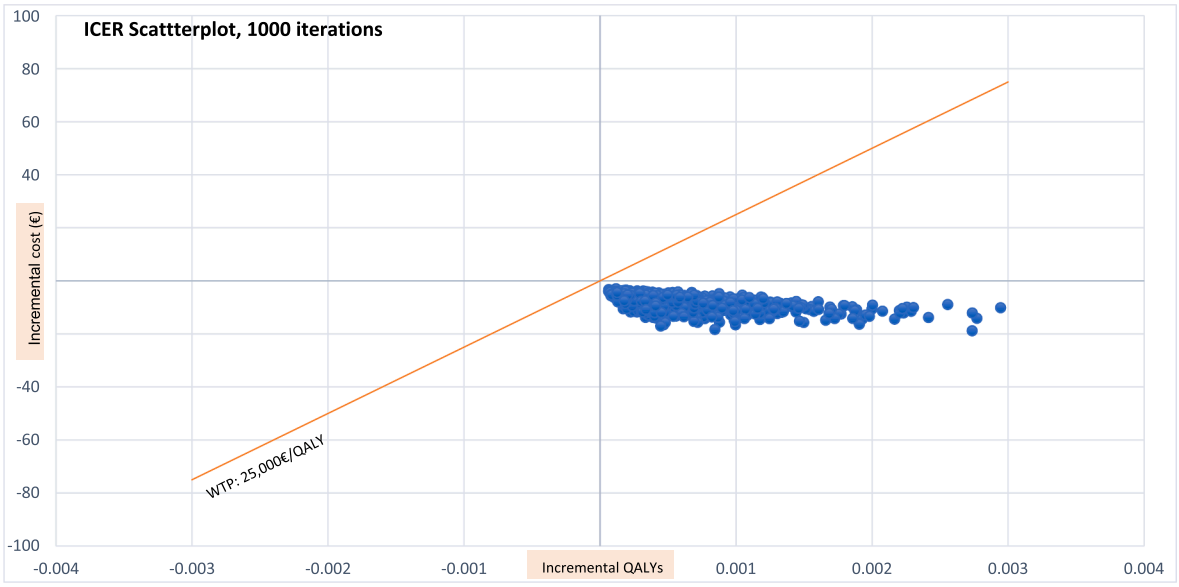
Table 8
Base case analysis results (sensitivity analysis).

Parameters	% Over base case	ICER
Discount	0%/5%	Dominant
Incidence (events)	+/-25%	Dominant
Utility values (general population)	+/-25%	Dominant
Disutility values (events)	+/-25%	Dominant
Mortality (general population)	+/-25%	Dominant
Mortality (events)	+/-25%	Dominant
Effectiveness vaccines	+/-25%	Dominant
Vaccine coverage	+/-25%	Dominant
Costs (events)	+/-25%	Dominant
Costs (productivity)	+/-25%	Dominant
Cost PCV20	+/-25%	Dominant
Cost PCV15	+/-25%	Dominant

ICER: incremental cost-effectiveness ratio; PCV15: pneumococcal conjugate vaccine 15-valent; PCV20: pneumococcal conjugate vaccine 20-valent.

5. Conclusion

In conclusion, our analysis suggests that, in Spain, a vaccination programme for the 60 years and older population based on a single dose



ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life years.; WTP: willingness-to-pay

Fig. 2. Probabilistic sensitivity analysis (per patient) ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life years.; WTP: willingness-to-pay.

of PCV20 could avoid a high number of cases of pneumococcal disease over 10 years while generating considerable savings for the NHS, thus being a more efficient strategy (dominant) when compared to a vaccination program based on the sequential vaccination with PCV15 and PPSV23. This vaccination strategy was further tested under several comparisons to reflect the current diverse Spanish regional context, showing consistent results throughout all comparisons.

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CRediT authorship contribution statement

David Cantarero: Writing – review & editing. **Daniel Ocaña:** Writing – review & editing. **María Ángeles Onieva-García:** Writing – review & editing. **Juan Rodríguez-García:** Writing – review & editing. **Paulina Gálvez:** Conceptualization, Writing – review & editing. **Cristina Méndez:** Conceptualization, Writing – review & editing. **Carlos Crespo:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Alejandra López-Ibáñez de Aldecoa:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Carlos Crespo reports financial support and article publishing charges were provided by Pfizer SLU. Carlos Crespo reports a relationship with Sanofi that includes: consulting or advisory. Carlos Crespo reports a relationship with GSK that includes: consulting or advisory. Carlos Crespo reports a relationship with AstraZeneca Pharmaceuticals LP that includes: consulting or advisory. Carlos Crespo reports a relationship with Boehringer Ingelheim Pharmaceuticals Inc that includes: consulting or advisory. Carlos Crespo reports a relationship with Angellini that includes: consulting or advisory. Carlos Crespo reports a relationship with Novartis Pharmaceuticals Corporation that includes: consulting or advisory. Carlos Crespo reports a relationship with Noucor that includes: consulting or advisory. Carlos Crespo works for Axentiva Solutions S.L. a consultancy firm working for several pharmaceutical companies. Cristina Mendez reports financial support was provided by Pfizer SLU. Cristina Mendez reports a relationship with Pfizer SLU that includes: employment and equity or stocks. Paulina Galvez Pineda reports financial support was provided by Pfizer SLU. Paulina Galvez Pineda reports a relationship with Pfizer SLU that includes: employment and equity or stocks. Alejandra Lopez Ibanez de Aldecoa reports financial support was provided by Pfizer SLU. Alejandra Lopez-Ibanez de Aldecoa reports a relationship with Pfizer SLU that includes: employment and equity or stocks. Daniel Ocana reports financial support was provided by Pfizer SLU. Daniel Ocana reports a relationship with Pfizer SLU that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Juan Rodriguez Garcia reports financial support was provided by Pfizer SLU. Juan Rodriguez Garcia reports a relationship with Pfizer SLU that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Juan Rodriguez Garcia reports a relationship with Pfizer SLU that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Juan Rodriguez Garcia reports a relationship with GSK that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Juan Rodriguez Garcia reports a relationship with Sanofi that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Maria Angeles Onieva Garcia reports financial support was provided by Pfizer SLU. Maria Angeles Onieva Garcia reports a relationship with Pfizer SLU that includes: consulting or advisory. David Cantarero reports financial support was provided by Pfizer SLU. David Cantarero reports a relationship with Pfizer SLU that includes: consulting or advisory.

Data availability

Data will be made available on request.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2023.07.016.

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