HUMAN VACCINES & IMMUNOTHERAPEUTICS
2019, VOL. 15, NO. 4, 850–858
https://doi.org/10.1080/21645515.2018.1560769

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RESEARCH PAPER

Cost-effectiveness of the 13-valent pneumococcal conjugate vaccine in adults in Portugal *versus* "no vaccination" and *versus* vaccination with the 23-valent pneumococcal polysaccharide vaccine

Miguel Gouveia[a], Gonçalo Jesus[b], Mónica Inês[c], João Costa[b,d,e], and Margarida Borges[b,d,f]

[a]Católica Lisbon School of Business and Economics, Universidade Católica Portuguesa, Lisboa, Portugal; [b]Centro de Estudos de Medicina Baseada na Evidência, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal; [c]Health Economics and Outcomes Research, Pfizer Portugal, Porto Salvo, Portugal; [d]Laboratório de Farmacologia Clínica e Terapêutica, Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal; [e]Unidade de Farmacologia Clínica, Instituto de Medicina Molecular, Lisboa, Portugal; [f]Unidade de Farmacologia Clínica, Centro Hospitalar Lisboa Central EPE, Lisbon, Portugal

ABSTRACT

The burden of pneumococcal disease in adults is substantial from a social and economic point of view. This study assessed the cost-effectiveness of the 13-valent pneumococcal conjugate vaccine (PCV13) for the prevention of invasive pneumococcal disease and pneumococcal pneumonia in adults *versus* "no vaccination" and *versus* vaccination with the 23-valent pneumococcal polysaccharide vaccine (PPSV23). A Markov model was used to simulate three strategies: no vaccination, complete vaccination with PPSV23 and complete vaccination with PCV13. The comparison between strategies allowed the estimation of clinical and economic outcomes including incremental cost-effectiveness ratios (ICER) and incremental cost-utility ratios (ICUR). The model took into account the distributions of age, risk profile, vaccination status, type of immunization and time since vaccination in the population. A societal perspective was adopted and a lifetime horizon was considered. Different sources of data and assumptions were used to calibrate PPSV23 and PCV13 effectiveness. Inpatient costs were based on the 2013 diagnosis-related group (DRG) database for National Health Service (NHS) hospitals and expert opinion; NHS official tariffs were the main source for unitary costs. PCV13 shows ICURs of €17,746/QALY and €13,146/QALY *versus* "no vaccination" and vaccination with PPSV23, respectively. Results proved to be robust in univariate sensitivity analyses, where all ratios were below a €20,000 threshold, with the exception of the scenario with PCV13 effectiveness halved. In a probabilistic sensitivity analysis, 94% of simulations showed cost-effectiveness ratios lower than €20,000/QALY, in both strategies. It was found that PCV13 is a cost-effective strategy to prevent pneumococcal disease in adults in Portugal.

ARTICLE HISTORY
Received 31 July 2018
Revised 27 November 2018
Accepted 8 December 2018

KEYWORDS
Pneumococcal disease; PCV13; invasive pneumococcal disease; community-acquired pneumonia; cost-effectiveness

Introduction

Pneumococcal disease (PD) is caused by *Streptococcus pneumoniae* (*S. pneumoniae* or SP), a bacterium responsible for a large spectrum of infections that can be classified as invasive (e.g., septicemia and meningitis) or non-invasive (e.g., pneumonia without bacteremia or pleural effusion).[1] The burden of PD in adults is substantial, both from a societal and an economic point of view,[2] since PD is responsible for about 1.6 million annual deaths worldwide.[3]

According to the Portuguese National Statistics Institute (PNSI), no major variation in the pneumonia mortality rate has been documented in recent years. Pneumonia was responsible for almost 6,000 deaths in 2013 in Portugal.[4] The pneumonia-related standardized mortality rate in Portugal is 25.1 deaths per 100,000 inhabitants, according to the last available report from the Directorate-General of Health.[5] Community-acquired pneumonia (CAP) is associated with significant health care resource consumption both in outpatient and especially in hospital settings.[6–8] In Portugal, 93% of CAP-related hospitalizations occur in adults.[9] In addition to an increased risk of morbidity and mortality, pneumonia significantly decreases health-related quality of life. After a pneumonia episode, resuming daily activities and fully recovering global function may take four weeks or more.[10–12]

Despite the use of antibiotics, PD remains an important disease with a significant impact on adult morbidity and mortality, suggesting that vaccination is likely to be the only intervention with a significant impact on the incidence of pneumococcal pneumonia and invasive pneumococcal disease (IPD), as highlighted by the World Health Organization (WHO).[13] The 13-valent pneumococcal conjugate vaccine (PCV13) is indicated for the prevention of invasive disease, pneumonia and acute otitis media caused by *S. pneumoniae*. Except for otitis, the approved population includes all age groups.[14] In July 2015, PCV13 was included in the Portuguese National Immunization Program for infants born after January 1, 2015.[15] Two 2015 guidelines from the national Directorate-General of Health further define the risk groups for IPD in individuals under 18 years old[16] and over 18 years old[17] for which PCV13 is recommended (either with co-payment or free of charge). In immunocompetent adults, PCV13 vaccination is

CONTACT Miguel Gouveia margarida.borges@medicina.ulisboa.pt Faculdade de Medicina da Universidade de Lisboa, Av. Prof. Egas Moniz, Lisboa, 1649-023, Portugal

recommended for individuals with cerebrospinal fluid fistulas or cochlear implants, patients with some chronic diseases (e.g., diabetes, heart, respiratory, liver and renal diseases), pre-transplantation patients, and bone marrow donors.[17] In immunocompromised adults, PCV13 is recommended for individuals with asplenia or splenic dysfunction, active neoplastic disease, transplant recipients, primary immunodeficiency, human immunodeficiency virus (HIV) infection, nephrotic syndrome, iatrogenic immunosuppression, or Down syndrome.[17]

In this context, it is relevant to estimate the cost-effectiveness of PCV13 for the prevention of IPD and pneumonia in adults, compared to "no vaccination" and to the other available vaccine (23-valent pneumococcal polysaccharide vaccine: PPSV23), in the Portuguese setting.

Results

In the base-case scenario considering the overall Portuguese adult population (18 years and older) over a lifetime horizon, PCV13 averted 5,712 and 5,597 deaths for PD when compared to "no vaccination" and PPSV23, respectively. The PCV13-attributable reduction of in-hospital PD episodes was 25,104 and 4,813 *versus* "no vaccination" and PPSV23, respectively.

PCV13 was associated with an increase in quality-adjusted life-years (QALYs) and life-years (LY) at an expense of higher costs *versus* "no vaccination" and PPSV23. Overall, the lifetime per-patient additional costs of the PCV13 vaccination strategy were €47 and €33 *versus* "no vaccination" and PPSV23, respectively. Cost-effectiveness ratios were higher *versus* "no vaccination" than *versus* PPSV23, both considering LY gained (LYG) (incremental cost-effectiveness ratio [ICER]: €11,082/LYG *versus* €8,151/LYG) and QALYs (incremental cost-utility ratio [ICUR]: €17,746/QALY *versus* €13,146/QALY) (Table 1).

Results for univariate sensitivity analyses showed some variation of cost-effectiveness ratios around the base-case results, although all ratios were below the €20,000 threshold with the exception of the scenario where PCV13 effectiveness was reduced by 50% (ICER €23,570/LYG and €18,650/LYG; ICUR: €37,515/QALY and €30,096/QALY; both *versus* "no vaccination" and PPSV23, respectively) (Table 2).

Probabilistic sensitivity analysis (PSA) results were consistent with the deterministic results for the base-case scenario, since 94% of the simulations showed cost-effectiveness ratios lower than €20,000/QALY, in both comparisons.

PCV13 vaccination strategy outperforms "no vaccination" with at least a 50% probability if willingness-to pay (WTP) for an incremental QALY is above €15,000/QALY, with a 75% probability if WTP is above €17,000/QALY and in all simulations if the WTP is above €25,900/QALY. The PCV13 vaccination strategy outperforms the PPSV23 vaccination strategy with at least a 50% probability if the WTP is above €10,900/QALY, with a 75% probability if the WTP is above €12,600/QALY and in all simulations if the WTP is above €24,100/QALY.

Table 1. Results of base-case scenario.

	PCV13	No vaccine	PPSV23
Overall number of PD episodes over the lifetime horizon in the population			
Bacteremia or sepsis infections	29,728	32,200	30,389
Meningitis infections	6,471	7,131	6,642
Inpatient pneumonia	2,372,771	2,396,994	2,397,043
Outpatient pneumonia	3,203,157	3,252,062	3,252,130
Deaths for PD	641,565	647,277	647,162
Outcomes and costs *per capita*			
LY	15.206	15.202	15.202
QALY	12.048	12.045	12.045
Costs (€)	407.03	360.38	373.92
Cost-effectiveness and costs-utility ratios			
ICER			
PCV13 vs. no vaccine		11,082 €/LYG	
PCV13 vs. PPSV23		8,151 €/LYG	
ICUR			
PCV13 vs. no vaccine		17,746 €/QALY	
PCV13 vs. PPSV23		13,146 €/QALY	

LY = Life-years; LYG = Life-year gained; QALY = Quality-adjusted life-years; ICER = Incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio.

Table 2. Results of univariate sensitivity analyses.

		PCV13 *vs.* PPSV23		PCV13 vs. no vaccination	
Scenario		ICER (€/LYG)	ICUR (€/QALY)	ICER (€/LYG)	ICUR (€/QALY)
Base-case		8,151	13,146	11,082	17,746
No indirect costs		8,420	13,580	11,380	18,224
Inclusion of travel costs[a]	50% incurs in travel costs	8,151	13,146	11,570	18,526
Discount rate	0%	4,214	6,803	5,764	9,234
	3%	6,429	10,374	8,766	14,041
Herd effect	No herd effect	8,045	12,974	10,802	17,270
	+50%	8,204	13,233	11,226	17,991
Immunization rate[b]	50.1% (≥65 years) 5.0% (<65 years)	2,590	4,408	3,931	6,675
Inpatient CAP incidence	−20%	10,476	16,904	13,937	22,292
	+20%	6,591	10,620	9,142	14,641
Outpatient CAP incidence	−20%	8,409	13,648	11,331	18,254
	+20%	8,086	13,022	11,020	17,620
Effectiveness of PCV13	−50%	18,650	30,096	23,570	37,515
	+50%	2,825	4,556	4,416	7,095

CAP = Community-acquired pneumonia; LYG = Life-Year-Gained; QALY = Quality-adjusted life years; ICER = Incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio. [a]Unit cost for non-urgent transportation to Primary Care was recently estimated for Portugal at 4.10€ (two ways).[18] We assumed 50% of users have a contact with the system only because of vaccination. [b]Uptake rates of vaccination similar to the immunization rate reported in Portugal in 2015–2016 for Influenza vaccination.[19]

Discussion

The results of this cost-effectiveness study comparing the PCV13 vaccination strategy *versus* "no vaccination" and PPSV23 show that PCV13 is a cost-effective option for the overall Portuguese adult population, with ICERs of €17,746/QALY and €13,146/QALY, respectively. These results proved robust to a variety of changes in the model parameters and assumptions. In almost all univariate analyses, the ICER was below €20,000/QALY. The robustness of these results is reinforced by PSA in which 94% of the simulations showed cost-effectiveness ratios lower than €20,000/QALY both in comparison to "no vaccination" and to vaccination with PPSV23.

This study has several limitations. First, the PCV13 effectiveness source used in the analysis (Community-Acquired Pneumonia Immunization Trial in Adults [CAPiTA])[20] included

only immunocompetent adults aged 65 years or older. In our study, the analysis considered the overall adult population (aged 18 years and older) for which PCV13 is reimbursed in Portugal. Therefore, adjusted PCV13 effectiveness was estimated for other age groups considering the rate of change of PPSV23 effectiveness with age (see Supplementary Material, Table S2 for further detail). Although this assumption introduces uncertainty, it seems reasonable because PCV13 vaccination has proven to be effective in both children[21-24] and the elderly, both in clinical trial [20] and real world settings.[25] PCV13 is likely to have similar efficacy in younger adults as immune responses in this population are comparable or better than in older adults.[26] In fact, in the case of PPSV23, effectiveness was also documented for the younger adult population for IPD[27] being even higher in this population (18 to 55 years). Furthermore, our results proved quite robust when PCV13 effectiveness was hypothetically halved in a univariate sensitivity analysis (Table 2).

Second, to the best of our knowledge, no head-to-head trial exists comparing PCV13 and PPSV23 efficacy in adult populations. Therefore, different sources and assumptions were used to calibrate PCV13 and PPSV23 effectiveness.

Third, the epidemiological calibration of the model was based on the diagnosis-related group (DRG) administrative database. It has been reported that the ICD coding scheme in DRGs may be inaccurate in the classification of patients with IPD.[28] Furthermore, ICD-9 codes have been associated with low to modest sensitivity for detecting CAP in hospital administrative databases. In particular, at least one quarter of pneumonia cases are undetected. Therefore, the true incidence of inpatient CAP has probably been underestimated in our study, although the incidence rates of hospitalised CAP reported in this study are similar to other European estimations from studies conducted in Denmark, Finland, France, Hungary, Poland and Norway.[29] Our results also proved robust when the incidence rate of inpatient pneumonia varied by ± 20% (Table 2).

Fourth, the analysis assumed an immunization rate of 100% among adults. Although this rate of immunization is impossible to achieve, this assumption has been used in previous studies[28,30,31] and probably represents a conservative approach. The model only took into consideration the herd effects from the paediatric vaccination program and not the potential small benefits associated with herd protection externalities generated by adults' vaccination,[32] although the pneumococcal carriage rate in adults is very low (<5% in CAPiTA study).[20] In this study, the inclusion of herd effect generated by children's vaccination leads to a reduction in the incidence of IPD among the adult population, therefore reducing the maximum public health potential benefits of vaccinating adults. In fact, the cost-effectiveness ratio (Table 2) is lower when herd effects from childhood vaccination are excluded from the analysis. The model assumes a linear link between impact and costs of the vaccination program. Therefore, providing that immunization rate is similar across all age groups, coverage does not affect the cost-effectiveness results. In a sensitivity analysis, we explored the effect of different uptake rates of vaccination among adults age groups by considering the immunization rate reported in Portugal in 2015–2016 for Influenza vaccination (50.1% in subjects ≥65 years and 5.0% in younger adults).[19] In comparison to the base-case scenario, the PCV13 ICER in this sensitivity analysis is lower *versus* both PPSV23 and no vaccination, due to the higher uptake rate among people which benefit the most from vaccination.

Most previously published adult PCV13 cost-effectiveness studies assumed that the effectiveness of adult vaccination is similar to the paediatric effectiveness.[8,30,34–37] The current study employs effectiveness estimates specific to the adult population, based on the published CAPiTA study,[20] which may increase the accuracy of the results hereby presented. Recent European cost-effectiveness studies of PCV13 vaccination in the adult population that used effectiveness data from the CAPiTA study present considerable variability in results.[39–47] The heterogeneity of the results in published literature might be explained by differences in the comparators (PPSV23 or no vaccination), target age for vaccination, assumptions regarding resource use and costs, approaches followed to include the indirect effect of childhood vaccination in the models, dynamics of vaccination serotype coverage over time, calibration of the PPSV23 effectiveness and the incidence rate of IPD in adult population, in particular of hospitalized pneumonia.

The impact that some parametric options (calibration and modelling) have on the cost-effectiveness results of PCV13 in particular, and of immunization programs in general, highlights the need to be cautious in interpreting and extrapolating results of one particular study for other settings.

Materials and methods

Model structure

A cohort model with a Markov-type process (cycle length of one year) was used to estimate the clinical and economic outcomes of PCV13 vaccination, which include incremental cost-effectiveness and cost-utility ratios. The model starts from the overall Portuguese population aged 18 years or older and follows this cohort throughout the modelling horizon under three different strategies: no immunization, 100% immunization with PPSV23 and 100% immunization with PCV13 ("intervention strategy"). Results compare the intervention strategy with the other two alternative strategies. A lifetime modelling horizon was considered in base-case analyses for all cohorts. Benefits and costs were discounted at 5% as recommended by the National Authority of Medicines and Health Products (INFARMED) guidelines.[48] The model estimates the disease risk (incidence and fatality) based on population characteristics (distribution per age and risk profile). This model has been previously validated for other countries and used as a basis for publications by other authors.[42,45] The economic model structure is presented in Figure 1.

Expected outcomes were evaluated for each person in the model population on an annual basis, taking into consideration age, risk profile, vaccination status, type of immunization (PCV13 or PPSV23) and time since vaccination. Clinical results include the estimation in each scenario of IPD incidence (inpatient), number of hospitalizations and outpatient visits associated with pneumonia, mortality due to CAP or IPD, life-

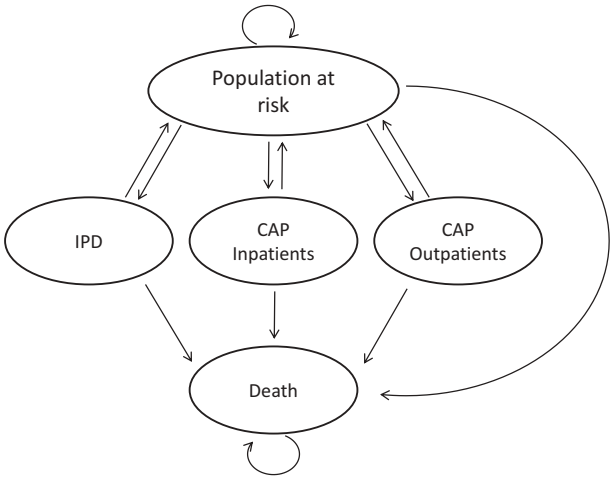

Figure 1. Economic model.

IPD: invasive pneumococcal disease. CAP: Community Acquired PneumoniaAll transition probabilities vary with age, risk profile (low, moderate or high) and time since vaccination.

years and quality-adjusted life-years. Economic results presented include direct medical and indirect costs due to loss of productivity, and incremental cost-effectiveness and cost-utility ratios.

Demographic and epidemiological parameters

Estimates of the overall continental Portuguese population aged 18 years and older were obtained from National Statistics Office (INE) for 2013.[49] Population was grouped according to the level of risk for PD and/or related complications: 1) low-risk individuals are immunocompetent without any chronic medical conditions; 2) moderate-risk includes immunocompetent individuals with one or more chronic medical conditions, such as cardiovascular, liver, or pulmonary disease, or diabetes; 3) high-risk includes immunocompromised individuals as a result of splenic dysfunction, neoplasms (including Hodgkin's disease, lymphoma), HIV, organ transplant, or chronic renal failure.[50]

The proportion of individuals in each age group with low, moderate, or high risk was estimated using National Health Survey 2005/2006 microdata.[51] These were the most recent available data at the time of the analysis. The high-risk group prevalence was adjusted in order to include HIV prevalence estimates since these were not available in the National Health Survey. Retrieving data from official annual reports,[52,53] HIV prevalence by sex and age was estimated considering year of diagnosis, mortality by year of diagnosis and patient age.

The incidence of IPD was estimated in two steps. First, the incidence of pneumococcal bacteremia, sepsis and meningitis were taken into account. Second, the serotype coverage of PCV13 and PPSV23 were factored in. In the case of pneumonia, the model was calibrated with the incidence for both inpatient and outpatient all-cause nonbacteremic pneumonia. This calibration is due to the fact that the model considers vaccine effectiveness rates against all-cause nonbacteremic pneumonia.

Pneumococcal bacteremia incidence was estimated from unpublished data. Since 1999, the Portuguese Group for the Study of Streptococcal Infections has monitored pneumococci causing invasive infections in Portugal. This is a laboratory-based surveillance system, in which 30 microbiology laboratories throughout Portugal are asked to identify all isolates responsible for IPD and to send them to a central laboratory for characterization.[54] For the purpose of our study, we had access to detailed data from 1,265 isolates responsible for adult IPD between 2009 and 2011, which allowed us to estimate Pneumococcal bacteremia incidence rates by age-group in 2011.

Pneumococcal meningitis, pneumococcal sepsis and overall inpatient pneumonia incidence rates were estimated using 2013 microdata from the DRG database that includes the discharges from Portuguese public hospitals.[55] Since a significant number of meningitis and sepsis episodes had no pathogen identified, the proportion of pneumococcal disease in the group of invasive infections with an unidentified pathogen was assumed to be the same as in episodes with an identified pathogen. Supplementary Table S1 presents the ICD-9 codes used to select the relevant episodes. The percentage of bacteremia and meningitis cases due to SP serotypes covered by the vaccine was estimated from Horácio *et al.* (2013)[56] for all IPD. It was assumed that the serotypes responsible for the meningitis and bacteremia were the same as the serotypes responsible for all IPD.

Due to lack of data, we assumed that outpatient pneumonia incidence rates for Portugal were proportional to inpatient rates multiplied by the ratio between the outpatient and inpatient pneumonia incidence rates found in the US population.[56]

Portuguese general population mortality rates for all causes were calibrated using published mortality tables for 2011/2013[57] and adjusted for mortality due to meningitis, bacteremia and pneumonia, in order to avoid double counting. Pneumonia-specific mortality rates for 2013 were published by INE.[58] PD mortality rates were estimated from the 2013 DRG database[55] considering the episodes with a primary diagnosis of pneumococcal meningitis (ICD-9-CM 320.1), pneumococcal septicemia (ICD-9-CM 038.2), bacteremia[1] (ICD-9-CM 790.7) or pneumococcal pneumonia (ICD-9-CM 481).

Utility values by age group and sex were taken from Sisk *et al.* (2003)[59] and disutilities associated with each disease were the same as in Melegaro and Edmunds (2004).[60]

Table 3 describes the main demographic and epidemiological parameters used in the base-case scenario, as well as health-state utilities and yearly disutilities.

Effectiveness of PCV13 and PPSV23

Different sources of data and assumptions were used to calibrate effectiveness results for PPSV23 and PCV13. For both, effectiveness data were estimated according to age group, risk group and time since vaccination for each outcome (IPD and pneumonia).

For PPSV23, the model included data reported by Smith *et al.* (2008),[33] which estimated the cost-effectiveness of PPSV23 versus "no vaccination" among adults aged 50 years and over. In the Smith *et al.* study,[33] effectiveness of PPSV23 in preventing IPD was based on a Delphi panel of experts. The panel primarily relied on the results from Shapiro *et al.* (1991),[27] a large hospital-

Table 3. Demographic and epidemiological parameters.

Portugal population, by age and risk group[a]				
Age group	Population	Low risk	Moderate risk	High risk
18–49	4,080,167	88.9%	8.6%	2.4%
50–64	1,987,704	72.4%	21.6%	6.0%
65–74	1,017,870	62.1%	30.6%	7.3%
75–84	734,643	57.3%	33.2%	9.5%
> 84	246,150	62.2%	28.3%	9.5%
Total	8,066,534	63.6%	14.2%	3.5%

Annual incidence of invasive pneumococcal diseases and all-cause pneumonia per 100,000 persons assuming no vaccination[b]				
Age group	Bacteremia and sepsis	Meningitis	Pneumonia inpatient	Pneumonia outpatient
18–49	3.49	1.02	53.87	315.76
50–64	8.51	2.92	199.68	754.21
65–74	11.07	3.47	548.20	1,325.38
75–84	21.32	5.04	1,780.73	2,449.95
> 84	54.47	5.28	5,243.96	3,349.64
Total	8.86	2.29	467.84	838.16

Mortality rates for the general population and fatality rates of IPD and pneumonia[c]				
Age group	General population adjusted mortality	Bacteremia and sepsis	Meninigits	Pneumonia (inpatient)
18–49	0.08%	4.26%	6.0%	5.37%
50–64	0.37%	3.80%	6.0%	11.04%
65–74	1.12%	2.79%	6.0%	16.81%
75–84	3.48%	7.65%	6.0%	22.44%
> 84	15.19%	7.40%	6.0%	30.82%
Total	1.05%	4.37%	6.0%	10.54%

Health-state utility and yearly disutilities[d]					
Age group	General population	Bacteriemia and sepsis	Meningitis	Pneumonia inpatient	Pneumonia outpatient
18–49	0.90	0.0079	0.0232	0.0060	0.0040
50–64	0.80	0.0079	0.0232	0.0060	0.0040
65–74	0.74	0.0079	0.0232	0.0060	0.0040
75–84	0.66	0.0079	0.0232	0.0060	0.0040
>84	0.53	0.0079	0.0232	0.0060	0.0040

[a]INE 2014,[50] NHS 2005/2006[51] and INSA 2013[52], INSA 2014[53] and authors' estimations. [b]DRG 2013[55] and Prof. Dr. Melo Cristino, 2013. [c]INE 2013,[57] INE 2014,[58] DRG 2013[55] and authors' estimations. [d]Sisk *et al.* 2003,[59] and Melegaro and Edmunds 2004.[60]

based case-control study evaluating PPSV23 effectiveness (Supplementary Material, Table S2).

Effectiveness of PPSV23 against all-cause nonbacteremic pneumonia was considered to be null, as assumed in other studies.[31,33,61–67] The rate of decline in PPSV23 effectiveness against vaccine-type IPD over time was based on Smith *et al.* (2008),[33] and was applied beginning one year following vaccination.

For PCV13, effectiveness was based on the results of the per-protocol population of the CAPiTA study[20] (Supplementary Material, Table S2). CAPiTA[20] was a randomized, double-blind, placebo-controlled trial involving 84,496 adults aged 65 years or older, evaluating the efficacy of PCV13 in preventing first episodes of vaccine-type strains of pneumococcal CAP, nonbacteremic and non-invasive pneumococcal CAP, and IPD. Per-protocol population included all participants who met the criteria for the modified intention-to-treat population (episode of CAP or IPD with the onset of symptoms at least 14 days after vaccination), were eligible for the study (absence of immuno-compromising conditions), received a vaccination and had no other major protocol violations.

Effectiveness of PCV13 against all-cause nonbacteremic pneumonia was estimated as the product of PCV13 efficacy in preventing vaccine-type nonbacteremic and non-invasive CAP[20] and the proportion of all-cause nonbacteremic pneumonia due to PCV13 serotypes (19.4%), as reported for the Spanish population[67] (Supplementary Material, S3). It was assumed that PCV13 effectiveness in preventing IPD and pneumonia did not wane over the initial 5 years of the modelling horizon, based on the observation that PCV13 effectiveness appeared to be stable during the CAPiTA follow-up period (mean, 3.97 years).[20] Afterwards, it was assumed that the rate of PCV13 effectiveness decline was 50% of the PPSV23 effectiveness decline (Supplementary Material, Table S2 and Table S3).

Effectiveness of both vaccines was assumed to be the same irrespective of previous vaccination experience and no revaccination was assumed. Effectiveness of each vaccine (i.e., PPSV23 and PCV13) across vaccine-specific serotypes was assumed to be the same.

The model includes the herd effect due to widespread use in of PCV13 in young children. The herd effect on IPD is based on estimates by Miller *et al.* (2013) for England and Wales.[68] The elasticity of adult IPD incidence reduction took into account the difference in vaccine coverage between Portugal (61%)[69] and England/Wales (96%).[70] The indirect effect of PCV13 on all-cause nonbacteremic pneumonia is less well studied. In line with other authors,[71] it was assumed that for Portugal this effect would be proportional to the IPD herd effect, representing on average a 1% reduction in pneumonia incidence.

Resource use and costs

Inpatient costs by age group were estimated using 2013 DRG microdata.[55] Inpatient episode costs were the sum of hospitalization and follow-up costs occurring after hospital discharge.

Portuguese NHS tariffs, in particular Order no. 20/2014, were used as the source of unitary costs. Due to the small number of meningitis episodes registered in the database, an average cost was used for all age groups.

Follow-up costs after hospitalization were estimated according to the opinion of a nationally representative panel of experts and by applying Order no. 20/2014 tariffs for unitary costs. Meningitis, bacteremia and sepsis follow-up consumption included two physician visits and two sets of blood tests,[2] resulting in a cost estimate of €90.54 per episode. For pneumonia, experts considered that follow-up included one set of blood tests, with 20% of the patients having two physician visits, 30% of the patients measuring oximetry and all receiving a chest X-ray. Pneumonia follow-up costs were estimated at €98.2 per episode.

Pneumonia costs per outpatient episode were estimated at €137, including two physician visits and chest X-rays for all patients, emergency department admission for 70% of the patients and a set of blood tests for 10% of the patients. Prescription drugs were also included in the cost estimates.

Vaccine acquisition costs were taken from INFOMED (INFARMED drug database).[72] Value-added tax was excluded and an administration cost of €3.70 was considered.[3] The overall cost per vaccine administration resulted in €15.59 and €59.46 for PPSV23 and PCV13, respectively. In the base-case scenario, vaccination was assumed to occur in the context of regular contacts with the health system that would have occurred anyway. Therefore, additional travel costs were not included in the base-case scenario.

The study adopted a societal perspective as recommended by INFARMED guidelines for economic evaluation.[48] The cost related to employees' lost productivity was the only indirect cost included. The work cost per day was computed using the average wage in official labor market statistics[73] and adjusted for the employment rate as reported in the employment survey of the 4th quarter of 2014.[74] Disease-attributable work-loss days were approximated as two times the average length of stay observed in the DRG database for inpatient episodes. For outpatient pneumonia episodes, 7 work-loss days were assumed. The overall direct and indirect costs per episode are presented by age and PD group (Table 4).

Sensitivity analysis

In order to assess the robustness of these results in relation to the assumptions made in the base-case scenario, both univariate analyses and PSAs were performed. In univariate analyses, the parameters more uncertain were varied, in particular, the herd effect size resulting from childhood vaccination, the incidence rate of pneumonia in inpatient and outpatient care, the effectiveness values of PCV13, the rate of adults' immunization, and alternative discount rates. We further included a scenario where travel costs were considered for 50% of the vaccinated population (Table 2).

In the PSA, 5,000 simulations were run simultaneously varying several model parameters. Beta distributions were assumed for incidence rates, effectiveness rates and case-fatality rates. Lognormal distributions were used for costs, while utilities were considered uniformly distributed.

Table 4. Direct and indirect costs per episode by age and disease (including inpatient and outpatient costs of inpatient follow-up).

Age group	Bacteremia and sepsis	Meningitis	Pneumonia inpatient	Pneumonia outpatient
Direct medical costs				
18–49	11,268.24 €	7,880.74 €	4,053.24€	136.92 €
50–64	5,532.87 €	7,880.74 €	3,959.52€	136.92 €
65–74	6,669.53 €	7,880.74 €	2,991.39€	136.92 €
75–84	5,221.06 €	7,880.74 €	2,882.72 €	136.92 €
> 84	4,808.52 €	7,880.74 €	2,515.02 €	136.92 €
Indirect costs				
18–49	1,288.78 €	795.64 €	674.96 €	244.55 €
50–64	1,260.45 €	938.72 €	731.96 €	239.47 €
65–74	138.62 €	163.87 €	137.24 €	41.80 €
75–84	0.00 €	0.00 €	0.00 €	0.00 €
> 84	0.00 €	0.00 €	0.00 €	0.00 €

Source: Experts' opinion, DRG 2013[55] and order no. 20/2014.

Conclusions

This study shows that adult vaccination (aged 18 years and older) in Portugal with PCV13 is cost-effective, producing health gains at costs below the usual acceptable willingness to pay threshold. The results are robust in all sensitivity analyses, with the exception of the scenario where effectiveness of PCV13 is very low. The PCV13 vaccination strategy is associated with a reduction of the pneumococcal disease burden, avoiding up to 5,712 deaths (compared with no vaccination) over the modelling horizon. These results strongly suggest that PCV13 should be added to the national therapeutic arsenal for preventing pneumococcal disease in adults.

Notes

1. When estimating mortality rates, all bacteremia cases were considered due to the limited number of observations identified as pneumococcal bacteremia.
2. Complete blood count, blood glucose test, urea, creatinine, ionogram, serum AST and PCR.
3. Unit cost based on Order no. 20/2014.

Acknowledgments

The authors express their gratitude to Professor Dr. Melo Cristino (Director of the Department of Clinical Pathology at Centro Hospitalar Lisboa Norte, EPE) for having provided access to further anonymous and detailed data regarding the results published by Horácio *et al.* (2013), which allowed us to estimate the incidence of pneumococcal bacteremia by age group.

Disclosure of potential conflicts of interest

The study was sponsored by Pfizer Portugal. Sponsoring was independent of the study outcome.

Mónica Inês holds Pfizer stock and/or stock options.

Funding

This work was supported by the Pfizer Biofarmacêutica, Sociedade Unipessoal Lda. ;

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