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Economic evaluation and access strategy development for the 20-valent pneumococcal conjugate vaccine (PCV20) in Spanish adults

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ABSTRACT

Background: The Advisory Committee on Immunization recommends vaccination against pneumococcus in adult population in Spain. Immunization strategies include 13-valent pneumococcal conjugate vaccine (PCV13) and 23-valent pneumococcal polysaccharide vaccine (PPV23), but schedule recommendations may differ regionally depending on age and background risk. New PCV vaccines including additional serotypes (PCV15/PCV20) are becoming available soon. We assessed the economic implications of funding an expanded pneumococcal immunization program in Spain.

Methods: A microsimulation cost-effectiveness model depicting lifetime burden and costs of invasive pneumococcal disease (IPD) and all-cause non-bacteremic pneumonia (NBP) was developed. PPV23 effectiveness was based on published literature, and for PCV on CAPiTA trial. Model was populated with local data, including herd effects from the pediatric immunization program. Outcomes and costs were evaluated considering existing and fore coming vaccines, alone and sequential schedules, according to its availability, serotype hierarchy and national/regional recommendations. Base case compared PPV23 versus PCV20 in the entire adult population. Alternative strategies were also tested. Incremental cost-effectiveness ratios (ICERs) per quality adjusted life-year (QALY) gained were computed from the perspective of the National Healthcare System in year 2018.

Results: Over a lifetime horizon, PCV20 would prevent 64,624 inpatient NBP, 27,772 outpatient NBP and 7,794 IPD cases in comparison with PPV23, accounting for a total cost-saving of 139.9 million euros. Additionally, 14,150 related deaths would be averted. ICERs were cost-saving or cost-effective for PCV20 in the base case and in all other scenarios analyzed. Univariate and probabilistic sensitivity analyses confirmed model robustness.

Conclusions: At the commonly applicable willingness-to-pay thresholds for cost-effectiveness in Spain, PCV20 vaccination would be an efficient immunization program compared to PPV23 and alternatives strategies including sequential or other conjugate vaccines in Spain. Expanding current recommendation to replace existing pneumococcal vaccination schedules by PCV20 alone would be a cost-saving health policy in Spain regardless of age and background risk.

Key words: *pneumococcal infection, pneumococcal pneumonia, cost-effectiveness, PCV20, pneumococcal vaccines, 20-valent pneumococcal vaccine.*

1. INTRODUCTION

Streptococcus pneumoniae (pneumococcus) is an important cause of morbidity, mortality, and associated costs in the adult population. Invasive pneumococcal disease (IPD)—including bacteremia and meningitis—is most common in the very young, the elderly, and specific risk groups, such as immunocompetent persons with chronic diseases (at risk) and those with immunocompromising conditions[1,2]. Pneumococcal community-acquired pneumonia (CAP) can be both invasive and non-invasive; noninvasive/non-bacteremic pneumonia (NBP) is more common but is difficult to diagnose[3]. To reduce the burden of pneumococcal disease in Spain, the Spanish National Advisory Committee on Immunization recommends sequential use of 13-valent pneumococcal conjugate vaccine (PCV13) and the 23-valent pneumococcal polysaccharide vaccine (PPV23) among adults aged ≥ 18 years who are immunocompromised and PPV23 alone in adults aged ≥ 65 years and at risk[3]. Regional immunization programs generally follow national or international recommendations but require regional vaccine advisory committee recommendations to be funded and fully implemented at local level[4,5]. Most Spanish regions fund PPV23 for the prevention of pneumococcal disease in immunocompetent adults at risk aged ≥ 18 years, and sequential vaccination with PCV13+PPV23 for adults with immunocompromising medical conditions. Even, recently, a few regions recommend PCV13 in some circumstances only[4,5]. PPV23 is recommended for routine vaccination in adults ≥65 years of age in several countries and in Spain[4–6], but provides less protection than PCVs due to a lack of immunological memory[7]. Therefore, PCVs generally induce more robust immune responses that are associated with longer-term protection[8,9]. Introduction of PCV13 in the adult calendar of certain Spanish regions reduced up to 25% the IPD cases, showing a decrease of serotype 3 when PCV13 was used[10]. In this way, three years after the introduction of PCV13 in US, the incidence of IPD decreased by 12%-32% (depending of age) among adults[11]. Despite these reductions, vaccine coverage of non-PCV13 serotypes still constitutes a significant unmet need[12,13]. New conjugates vaccines against pneumococcus are under last phases of development, and will became available soon[14,15]. In addition to the new PCV15 that includes all components of PCV13 plus polysaccharide conjugates of 2 additional serotypes (11A, 22F)[14], PCV20 with all components of PCV15 plus polysaccharide conjugates of 5 additional serotypes (8, 10A, 12F, 15B, 33F) will be available to broaden pneumococcal disease coverage[14,15]. Although 6 out of 7 serotypes are also present in PPV23, PCV20 is expected to provide stronger protection than PPV23 for common serotypes between PCV20 and PPV23, thus further reducing the global pneumococcal disease burden[16].

Several evaluations indicate that adult use of PCV13 has a reasonable cost-effectiveness (CE) profile, these

studies were based on epidemiologic and economic inputs from other countries and Spain, thus may be reflective of the current experience[17–23].Therefore, in consideration of new efficacy data from CAPiTA, and current funding for PCV13 and PPV23, and fore coming new conjugate vaccines, an evaluation was undertaken to assess the clinical and economic consequences of expanding current pneumococcal vaccination recommendations among Spanish adult population aged ≥18 years compared to immunization based on PPV23 and other alternative vaccination strategies.

2. METHODS

2.1. Model description

The model utilizes a microsimulation framework and a Markov-type process to depict expected lifetime risks of clinical and economic outcomes (IPD, inpatient and outpatient all-cause NBP, and associated costs) in a Spanish population of adults aged 18 years and older (Figure 1). A similar model has previously been used by other investigators in pneumococcus vaccination[19,23]. Upon model entry, each person's age (in one-year increments), risk profile (low risk [immunocompetent without chronic comorbidities or comorbidities unrelated with PD], moderate risk [immunocompetent with ≥ 1 chronic comorbidity associated with PD], or immunocompromised or high risk), and history of vaccination with PCV13 are assigned. The model population is initially characterized based on age (18-49, 50-64, 65-74, 75-84 and ≥85 years) and mentioned risk profile (low, moderate, or high risk of PD). Persons may receive PPV23, PCV13, PCV15, PCV20, PCV13 → PPV23, PCV15 → PPV23, PCV20 → PPV23, or neither vaccine strategy at model entry; vaccine coverage may vary by age and risk profile. Expected outcomes are evaluated for each person in the model population on an annual basis, from model entry through the end of the modeling horizon, which may be varied from 1 year to a lifetime (82 years). Pneumococcal-related outcomes are projected for each person in the hypothetical population based on age, risk profile, vaccination status, vaccine type, and time since vaccination. IPD is stratified by condition (bacteremia and meningitis, Supplementary Table S1), and all-cause NBP is stratified by setting of care (inpatient and outpatient). The magnitude of vaccine-associated risk reduction may differ based on clinical presentation (IPD or all-cause NBP), as well as by vaccination strategy, time since vaccination, disease serotype distribution, history of prior receipt of PCV13, age, and risk profile. Risk of death from IPD and all-cause NBP, as well as from general causes, is assumed to depend upon age and risk profile.).

Expected costs of medical treatment for IPD and all-cause NBP are generated in relation to setting of care (inpatient vs. outpatient), age, and risk profile, based on estimated event risks and costs of different types

of care. The costs of vaccination, including vaccine cost and administration, are tallied at model entry and in year 2 for sequential regimens. Clinical outcomes and economic costs are projected over remaining years of life for each person in the model population for the vaccination strategies considered and include numbers of cases of IPD (bacteremia and meningitis) and all-cause NBP (inpatient and outpatient), deaths due to IPD and all-cause NBP, life-years (unadjusted and quality-adjusted-QALY-), costs of medical treatment for IPD and all-cause NBP, and costs of vaccination (including vaccine cost and administration).

2.2. *Population*

Values for the size of the Spain population aged 18 years and older were obtained from Spanish National Statistical Institute data for calendar year 2018[24]. Stratification was considered by the following age groups: 18-49, 50-64, 65-74, 75-84 and ≥85 years and by three different risk groups: low risk, moderate risk, and high risk. This segmentation was chosen to increase the accuracy of model calculations and were based in published literature and the Spanish National Advisory Committee[5,24] . The percentage of persons in each age group at low, moderate, and high risk was estimated based on analyses of data from a retrospective real-world all cause community acquired pneumonia cost-of-illness study conducted recently in Spain[26]. High-risk conditions included immunodeficiency patients of any kind, immunosuppressed by immunosuppressive therapy including systemic corticosteroids, HIV, solid and hematological cancer, chronic renal failure (states 4 or 5), Down syndrome, anatomical or functional asplenia, malnutrition, solid organ and progenitor transplantation, cirrhosis and/or a history of invasive pneumococcal disease. Patients were at moderate risk if they were immunocompetent and had at least two medical claims of the same condition with primary diagnoses for a particular chronic condition related with pneumococcal disease. Moderate risk condition include chronic respiratory system diseases (COPD; asthma, etc.), cardiovascular system (except high blood pressure), diabetes in treatment with insulin or oral antidiabetics, severe neurological and neuromuscular diseases, chronic liver disease (except cirrhosis), chronic renal failure (state <4), smoking and/or chronic alcoholism, cochlear implant, hemophilia and other chronic hemorrhagic disorders, morbid obesity, hemoglobinopathies, and chronic inflammatory diseases. Persons not classified as moderate or high risk were considered at low risk.

2.3. Vaccination strategy

The base-case scenario assessed the clinical and economic consequences of a single dose of PCV20 among Spanish adult population aged ≥18 years, irrespective of background risk for PD, compared to PPV23 alone. This is because this approach allows to meet the following criteria: first and latest expected available

pneumococcal vaccine for adult population, vaccines with highest number of serotypes included, all adult population regardless of age or risk group according with expected vaccination uptake. Nonetheless, and since adult national recommendations may be implemented at regional level with different criteria of vaccination with respect to age and type of vaccine, up to 19 alternative vaccination strategies were considered in this economic evaluation. Such additional alternatives included different age and risk group and different sequential immunization assuming that current regional recommendations are broad and evolving (Supplementary Table S2). This evolution considered chronology of vaccines availability and hierarchy of included serotypes. As future immunization uptake is unknown, vaccine coverage was estimated using as a proxy the history of pneumococcal vaccination (any time) according with age and risk group values observed in the above mentioned retrospective real world cost-of-illness study[26]. This study was chosen because collected recent data from seven regions of Spain and recorded values were aligned with that from Vila-Córcoles et al (2017) study collecting data in one region only[27].

2.4. Model parameters and assumptions

Most model parameters and assumptions are included in Table 1.

2.4.1. Vaccination History

The percentage of persons previously vaccinated with PCV13 in Spain by age and risk were based on Vila Corcoles et al. (2017) publication[27]. Due to the lack of stratification by the publication, it has been considered the same percentage for these two different age ranges: 18-64 and ≥65 years. The model requires this information to avoid double counting in outcomes avoided due to vaccines included in the model.

2.4.2. Vaccination Effectiveness

Vaccine effectiveness (VE) of PCV against IPD and NBP caused by serotypes included in PCV vaccine (VT-IPD and VT-NBP, respectively) for immunocompetent persons in year 1 were estimated based on data from the modified intention-to-treat (mITT) population in CAPiTA (Community-Acquired Pneumonia Immunization Trial in Adults) trial and the Dutch CE analysis publication by the CAPiTA investigators[8,17]. The vaccine effectiveness estimate PCV against VT-IPD and VT-NBP from the mITT population in CAPiTA (75.8% and 41.1%, respectively) was "anchored" to persons aged 73 years (mean age in the CAPiTA trial) and multiplied by the relative change in VE vs. VT-IPD by age (vs. 73 years) from Mangen (2015) to get VE by single year of age[13]. VE of PPV23 against VT-IPD were based on estimates for persons aged 65-74, 75-84, and 85-99 years from Djennad et al. (2019)[28] allocated by risk distribution in the United Kingdom. VE for persons

aged <65 years was estimated using a logarithmic curve fit to point estimates for VE for persons aged 65-74, 75-84, and 85-99 years[28–30]. VE of PPV23 against VT-NBP in year 1 of the modeling horizon was assumed to be 0% in the base case for all age/risk groups based on numerous sources and consistent with assumptions of previously published studies, including Spain[18–22,29]. VE-PCV against VT-IPD and VT-NBP was assumed to be the same irrespective of age and risk group, as follows: 5 years of stable durability (Bonten 2015)[8] followed waning effect during years 6-15, and no effectiveness was assumed from year 16 onwards (Mangen 2015)[17]. Waning of VE-PPV23 against VT-IPD was based on Djennad (2019)[28] (Supplementary Table S3 and Table S4).

2.4.3. Vaccine Serotype Coverage and Indirect Effects

The percentage of IPD and NBP due to vaccine serotypes for each vaccine analyzed and in year 1 of the modeling horizon were based on data from the 2018 European Centre for Disease Prevention and Control (ECDC) for Spain for IPD, and in the CAPA study for serotypes distribution in NBP in the same year[31,32]. In both cases were assumed to be the same percentage within these two different age ranges: 18-64 and ≥65 years, regardless of level of risk for pneumococcal disease (Table 1). To account for pediatric herd effects, the percentage reduction of IPD and NBP due to vaccine serotypes included in the model were entered by year of the modeling horizon (for up to 10 years). Serotype percentage reduction was calculated by a trend line of best fit analysis for both IPD and NBP feeding the analysis with serotypes distributions from years 2010 to 2018 as displayed in ECDC and CAPA study, respectively[31,32]. R^2 statistic was used to choose the best fitted equation (Supplementary Figure S1 and Table S5). Reduction in total disease (vaccine and non-vaccine serotypes) due to indirect effects during each year of the modeling horizon was not considered in the base case, as the model already account for reduction in cases caused by vaccines serotypes due to pediatric herd effects as mentioned above.

2.4.4. Clinical data

For incidence rates of IPD and all-cause NBP hospitalizations were based on age-specific data from the Spanish database which uses International Classification of Diseases 10 (ICD). The data base was RAE-CMBD, Registro de Actividad de Atención Especializada – Conjunto Mínimo Básico de Datos (Registry of Specialized Health Care – Minimum Basic Data Set)[33], from the Spanish Ministry of Health (Table 1). These data were apportioned between low, moderate, and high-risk groups using the distribution observed in the mentioned retrospective real world cost-of-illness study[26]. The ICD 10 codes to obtain IPD-bacteremia cases data from the Spanish database are included in Supplementary table S1. To avoid double counting for J13 code, which includes invasive and

non-invasive pneumococcal pneumonia, J13 cases were adjusted by the distribution of invasive and non-invasive pneumococcal pneumonia observed in CAPA trial[22]: thus, 16.6% of J13 cases were accounted as invasive pneumococcal pneumonia. Similarly, primary bacteremia due to pneumococcus was accounted by the combination of codes R78.81 plus B95.3. In the same way, all-cause NBP hospitalization incidence was estimated from the RAE-CMBD adjusted by the corresponding percentage of non-invasive all-cause hospitalized pneumonia observed in the CAPA study: 83.4%. Incidence rates of outpatient NBP were calculated from the Rivero et al. (2016)[34] publication which reflected age-incidence 18+ years of age between 2009 and 2013 and used the Spanish Computerized Database for Pharmacoepidemiological Studies in Primary Care (BIFAP). BIFAP healthcare database, hold by Ministry of Health, includes electronic medical records data from most regions in Spain. Distribution of outpatient NBP incidence by risk group was estimated by applying such distribution observed in the above mentioned retrospective real world cost-of-illness study[26]. The distribution of hospitalized/outpatient NBP in the BIFAP database was also confirmed using a prior similar publication using BIFAP database[35].

2.4.5. Utilities

Self-assessed health state (or utility) scores measure the individual's preferences for specific outcomes and were used to calculate QALY. Estimates for age and risk subgroup utilities in the general Spanish population were based on The Spanish National Health Survey (year 2012) where the quality-of-life questionnaire EQ-5D-5L was used (Table 1)[36]. Disutilities due to hospitalized disease (bacteremia, meningitis, and all-cause NBP) were based on the utility difference between patients with and without suspected pneumonia at one-year post-discharge (from pneumonia hospitalization)[17]. All disutilities were assumed to be the same irrespective of age and risk (Table 1).

2.4.6. Resource consumption and costs

Medical costs considered in this model were IPD (sum of bacteremia plus meningitis cost) and all-cause NBP (inpatient and outpatient) management costs (Table 1). To reflect the management costs for meningitis and bacteremia, the data were obtained from Spanish database RAE-CMBD which collected the cost of pneumococcal meningitis and bacteremia in the entire country[33]. Cost for all-cause NBP, by age and risk group, both hospitalized and outpatient care, were obtained from the retrospective real world cost-of-illness study[26]. Vaccines cost of PPV23 was set at €10.20 per dose, and for PCV13 was set at €42,69, which were obtained from the public tender agreement in 2018[37]. As the cost of PCV20 and PCV15 are unknown, the model

assumed to be the same as the cost of PCV13. Vaccine administration costs were €6 based on published study in Spain 2020[38]. All costs are presented in euros (€) adjusted to 2018 prices (€, 2018).

2.4.7. Time horizon, perspective, and discount rate.

Lifetime horizon (82 years maximum) was adopted for base case following all patients until death. The analysis considered the perspective of the National Healthcare System (NHS), thus direct healthcare costs and cost of vaccines and administration were included only. Additionally, an annual 3% discount rate was applied within the model for both health outcomes and costs, following the recommendations for health economic evaluation conducted in the Spanish setting[39]. Lifetime horizon was chosen to allow the model captures the entire vaccination effect in preventing pneumococcal disease.

2.4.8. *Mortality*

The age-specific general population mortality rates (Table 1) were allocated across risk groups based on corresponding population weights from the INE (2018)[24]. Subsequently, this mortality rates were adapted by age ranges and risk groups using relative risk (RR) of mortality which was assumed to be 1.5 for moderate risk (vs. low risk) and 2.0 for high risk (vs. low risk). 30-days IPD case-fatality rates (CFR) were calculated from the Spanish RAE-CMBD database which uses ICD-10 and adjusted by the distribution observed in the retrospective real-world study[26], due to the Spanish database allows obtaining the CFR by age range but not by risk group. CFR for patients with all-cause NBP requiring outpatient care and hospitalized all-cause NBP was based on data from the mentioned real-world study[26]. Long-term annual case fatality rates were not considered in the model since such data is unknown in the Spanish population.

2.4.9. Outcomes and analyses

Clinical outcomes and economic costs in the base-case scenario were projected over the lifetime for stratified population by age and risk group (n = 38.77M). Clinical outcomes included pneumococcal meningitis, other forms of invasive pneumococcal disease summarized as number of bacteremia cases, hospitalized NBP cases, outpatient NBP cases, deaths and life years gained both unadjusted and quality-of-life adjusted (QALY). For each of these populations, outcomes and costs were evaluated in the base case and in any of the alternative vaccination strategies. Clinical outcomes and economic costs were simulated a total of 1.000 times, and each simulation included a population of 38.77 million persons (an approximate minimum number of persons required to produce stable results for all model outcomes in each age and risk group in the base case). For each given vaccination strategy, population was adjusted according with the number of inhabitant in each age group

and the percentage distribution of population by risk of pneumococcal disease according with retrospective real world study[24,26]. The CE of more expected effective vaccine strategy is calculated in terms of the incremental cost per life-year gained and per QALY gained ratios (ICERs), dividing the difference in cost between the difference in effects (life-years or QALYs) of the new alternative, more effective, compared with existing strategy[39]. In the base case, the new alternative is PCV20 and the existing PPV23, both administered alone. Different alternative vaccination strategies were tested in this evaluation as mentioned before (Supplementary Table S2). Since there is no official CE threshold in Spain yet, interpretation of ICER was based in two CE thresholds: €21,000 per QALY gained as the one stated by the GENESIS initiative group (the most used in Spain) which represent the perspective of the Spanish Society of Hospital Pharmacy[40], and 1 time the growth domestic product per capita as per WHO guidelines which in year 2018 was €25,771[40,41].

2.4.10. Sensitivity analysis

Sensitivity analyses (deterministic and probabilistic) were performed to verify the robustness of the model's results. As mentioned previously, and to test the robustness of the immunization with PCV20 alone, 19 vaccination strategies different than base case were analyzed (Supplementary Table S2). Due to uncertainty surrounding effectiveness of PPV23 against NBP both hospitalized and outpatient, regardless of age and risk group, a scenario analysis adjudicating a 24.0% vaccine effectiveness against NBP for serotypes including in PPV23 vaccine in persons 18-64 years, and 33.5% above 65 years according to Lawrence et al (2020) and Suzuki et al publications were also carried out[43,44]. Univariate and probabilistic sensitivity analysis were conducted in the base case analysis and in all different immunization strategies as well.

One-way sensitivity analysis

One-way deterministic sensitivity analyses were undertaken to evaluate the potential impact of parameter value uncertainty on the base-case scenario and the other different immunization strategies. In the absence of information regarding the uncertainty of specific parameters, a broad range of ±25% in inputs were applied, to reflect the possible uncertainty of the parameter values. Up to 27 parameters were modified in this analysis included the percentage of the vaccinated population, herd effects, disease incidence rates, medical costs, vaccine price, utilities/disutilities, case-fatality rates and vaccine effectiveness.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was performed on the base-case scenario and on the different vaccination strategies by varying all the model inputs simultaneously and randomly within their probability distributions (n

= 1.000 replications). A Monte Carlo simulation was employed to account for uncertainty surrounding disease incidence rates and medical costs, vaccine price, utilities/disutilities, case-fatality rates, vaccine effectiveness and herd effects in estimation of clinical outcomes, economic costs, and incremental cost-effectiveness ratios. Triangular distributions were used for the disease incidence, vaccine effectiveness, vaccine price and mortality/case-fatality rates, log-normal for medical cost, and uniform for indirect effects and utility values.

3. RESULTS

3.1. Base case

The administration of PCV20 for Spanish population ≥18 years regardless of background risk, under base case assumptions that estimated 13.1% of adult population could be vaccinated (38.1% 65 years old and above), would account for higher health benefits than with PPV23. Overall, compared to PPV23 the inclusion of one dose of PCV20, would avoid 7,794 IPD cases (7,477 bacteremia and 317 meningitis), 64,624 inpatient all-cause NBP and 27,772 outpatient all-cause NBP cases for a lifetime horizon (Table 2). Additionally, 14,150 related deaths would be averted. Medical plus vaccination costs per person obtained in the model would imply €493 and €490 for PPV23 and PCV20, respectively, for the NHS in a lifetime period, which would account for a cost-saving in medical care of 305.2 million Euros in persons vaccinated with PCV20 versus PPV23, that completely would offset the extra cost of vaccination with conjugate vaccine of 165.3 million Euros: net saving of 139.9 million Euros in a lifetime horizon (Table 2). Total survival gains in terms of life years (LYG) and QALY gained would be slightly higher with PCV20 vaccination compared to PPV23 by mean increase in 0.0019 LYG and 0.0013 QALY per person, respectively. ICERs obtained for ≥18 years old groups showed PCV20 to be a cost-saving option vs PPV23 both per life-year (€-2,105) and per QALY (€-3,125) gained, respectively. Table 2 and 3 also shows results using alternatives vaccination strategies. PCV15 vaccination was a cost-effective strategy versus PPV23 but cost-saving in 44% of cases only, while PCV20 was cost-saving versus PCV15 in 100% of cases. Since some model variables were inferred, additional analyses were assessed to further investigate the relationship between parameters and CE results and to confirm the model robustness. Univariate sensitivity analysis showed PCV20 to be a robust cost-saving option in 27 parameters analyzed (Figure 2, Tornado graph). Probabilistic sensitivity analysis results are included in Figure 3 (CE plane and acceptability curve) and Table 3 revealed that PCV20 vaccination strategy was a cost-effective option on 100% (84% cost-savings) of 1,000 simulations performed. Also, PCV20 would still be cost-saving (55% of cases) or cost-effective (100%) of cases

versus PPV23 although the model would incorporate effectiveness for PPV23 against VT-NBP (Supplementary Table S6).

3.2 Immunization scenarios

Different scenarios were assessed to clarify the most appropriate immunization strategy between several scenarios for decision-making.

3.2.1 Immunocompromised (high risk) aged ≥ 18 years old

Current vaccination schedule in immunocompromised patients aged 18 years and above (56.7% vaccine uptake all ages and 61.0% in 65 years old and above) with PCV13+PPV23 was a vaccination strategy dominated by sequential immunization with PCV15+PPV23: cost-saving in 100% of cases (Table 3 and Table 4), while sequential immunization with PCV20+PPV23 was also cost-saving in 100% of cases when compared with PCV15+PPV23 (also dominant versus PCV13+PPV23 for extending dominance). Sequential PCV15+PPV23 accounted by 13.2 million Euros net saving compared with PCV13+PPV23, while PCV20+PPV23 showed incremental net saving of 77.3 million when compared with PCV15+PPV23 (Table 4). Probabilistic sensitivity analyses confirmed such results in this group of high-risk patients (Table 3). However, sequential immunization with either PCV20+PPV23 or PCV15+PPV23 both compared with PCV20 alone were not cost-effective or dominated strategies since would incur in an extra cost of 31.2 and 108.5 million Euros, respectively, with few additional health benefits in term of QALY gain, or cases of disease averted in the case of PCV20+PPV23 or substantial lower outcomes in case of PCV15+PPV23 (Table 3, Table 4 and Supplementary Table S7).

3.2.2 Immunocompetent at risk (moderate risk) aged ≥ 18 years old

Immunocompetent at risk ≥ 18 years old are currently recommended vaccination with PPV23 or sequential with PCV13+PPV23, depending on the region. PPV23 immunization in this group of patients (17.4% vaccine uptake all ages and 41.3% in 65 years old and above) was not cost-effective compared with no vaccination: incremental cost-effective ratio of €63,154 (95% confidence interval: 8,091-197,776)/QALY gained, with only 22%-26% of cases being cost-effective (Table 3 and Supplementary Table S8). PCV15 or sequential PCV15+PPV23 both were vaccination strategies cost-saving or cost-effective in 52% to 100% of cases compared with PPV23 alone or sequential PCV13+PPV23 (Table 3 and Table 5). However, PCV20 alone or sequential PCV20+PPV23 were dominant options (more cost-saving and higher QALY gain) versus both PCV15 alone or sequential PCV15+PPV23 in 100% of cases and also dominant compared with PPV23 or PCV13+PPV23 for extending

dominance (Table 3 and Table 5). While PCV15 showed incremental cost versus PPV23, PCV20 alone accounted for net economic benefit of 49.7 million Euros versus PCV15, and sequential PCV20+PPV23 accounted by 47.6 million Euros net saving compared with PCV15+PPV23 (Table 5). However, sequential immunization with PCV20+PPV23 compared with PCV20 alone was not cost-effective or a dominated schedule since would incur in an extra cost of 25.0 million Euros with few additional health benefits in term of QALY gain or cases of disease averted (Table 3 and Table 5). Sequential PCV20+PPV23 versus PCV15+PPV23 and PCV20 versus PPV23 would still be cost-saving (70% of cases) or cost-effective (100%) even in the case the model would adjudicate effectiveness for PPV23 against VT-NBP (Supplementary Table S6).

3.2.3 Population aged ≥ 65 years old

The results of cost-effectiveness analysis in persons 65 years old and above who vaccine uptake was collected in 38.0% of the population are shown in Table 3 and Table 6. PPV23 immunization in this group of patients was not cost-effective compared with no vaccination: incremental cost-effective ratio of €56,153 (95% confidence interval: 3,592-232,639)/QALY gained, with only 33%-37% of cases being cost-effective (Table 3 and Supplementary table S9). Compared with PPV23 or PCV13, PCV15 was cost-effective in 98%-100% of cases (cost-saving in 63% versus PPV23), while PCV20 was cost-saving compared with PCV15 in 100% of cases (and versus PCV13 and PPV23 for extending dominance, Table 3). PCV20 alone would account for a net saving of up to 99.7 million Euros (Table 6). In regions where this population is recommended to receive a sequential schedule with PCV13+PPV23, combination of PCV15+PPV23 would be a dominant strategy in 100% of cases compared with former vaccination, and also sequential PCV20+PPV23 would be cost-saving versus PCV15+PPV23 also in 100% of cases (Table 3 and Table 6), the last accounting for up to 96.2 million Euros in a lifetime horizon. As in previous vaccination risk groups, sequential PCV20+PPV23 vaccination was not cost-effective versus PCV20 alone in persons 65 years old and above (Table 3 and Table 6) and would be associated with an incremental cost of 48.4 million Euros with few additional health benefits: 46 deaths and 213 IPD cases averted with sequential schedule in a lifetime horizon for an unaffordable ICER of €486,581 (95% CI: 76,840-1,500,522)/QALY gained (Table 3). Including effectiveness for PPV23 against VT-NBP did not change main findings in this population group for PCV20 or sequential PCV20+PPV23 but was sensitive for PCV15 which would be reduced the % of cases being cost-effective versus PPV23 to 58%-63% (Supplementary Table S6).

4 DISCUSSION

Despite major reductions in global pneumococcal burden following PCV13 introduction, serotypes beyond those included in the vaccine continue to cause disease[45]. In Spain, following PCV13 introduction in 2010, during the 2009-2018 period, the decrease in IPD cases in adults due to PCV13 serotypes was 71% in 18–64 years and 53% in ≥65 years, although there are still many cases due to serotypes 3 and 19A. In the territories that vaccinate adults with PCV13, cases of IPD due to PCV13 serotypes were reduced by 35% during the period 2017-2018, while in the territories this reduction is 9%[10]. Conjugate vaccines such as PCV13 induce robust T-cell–dependent immune responses associated with immunological memory and thus have the potential to provide substantial and prolonged protection against pneumococcal disease[7–9]. Conversely, polysaccharide vaccines such as PPV23 induce T-cell–independent immune responses that are short-lived and deplete peripheral B cells, which may explain why subsequent ("booster") administration elicits an attenuated immune response[7,9,46]. Therefore, conjugate vaccines with more serotypes are preferable. PCV20 is the only conjugate vaccine under development with highest number of serotype close to PPV23. Thus, PCV20 may represent an important public health improvement in pneumococcal disease prevention by facilitating broader serotype coverage like PPV23 coupled with the advantages of a conjugate vaccine[14,15,46].

In this study, an evaluation was undertaken to assess the clinical and economic consequences of use of a single dose of PCV20 among Spanish adult population aged ≥18 years compared to immunization based on PPV23 or other alternative vaccination strategies according with Spanish national and regional recommendations for immunization against pneumococcus in the adult population. A strength of conducting this economic evaluation is that we included all existing and future vaccines against pneumococcus and all possible vaccination schedules recommended both at national and regional levels. To the best of our knowledge, we could not find an economic evaluation in the literature including next generation against pneumococcus conjugate vaccines and variety of vaccination strategies evaluated. Also, several adult groups of patients depending on age or background risk for pneumococcal disease were evaluated in this CE analysis. All scenarios in the model suggest that, from the Spanish NHS perspective, implementation of an expanded vaccination program with PCV20 in all adults aged ≥ 18 years, and in different age and risk subgroups, would reduce the number of cases of pneumococcal disease and pneumococcal-related deaths and would be a cost-effective strategy compared to current vaccination with PPV23 or other combination with existing or future pneumococcal vaccines. Such finding, from the NHS perspective, were not only assuming the common WTP threshold in Spain from around €21,000 per additional

QALY[40] which is consistent with that of the WHO[41], but also because PCV20 or sequential PCV20+PPV23 were both cost-saving vaccination strategies versus other possible combination including PCV13, PCV15 alone or sequentially with PPV23.

There should not surprise such results since PCV20 is a conjugate vaccine with the highest effectiveness against pneumococcal disease, covering a percentage of serotypes causing the disease near to PPV23, and, due that is unknown at present, the analysis used the same acquisition cost for all conjugate vaccines. On the opposite, what was an additional interesting observation in the economic analysis is that vaccination with PPV23 alone was not a cost-effective strategy in patients 18 years old or above at risk (moderate risk for pneumococcal disease) or in persons 65 years old and above. Also, we noticed that sequential vaccination with PCV20+PPV23 was not a cost-effective option when compared with PCV20 alone in any of the situations analyzed. This is because the additional protection given for the sequential strategy is poor in term of cases of disease or related deaths averted compared with PCV20 alone, while the incremental cost of administering two vaccines timely separated is high. The last could be a meaningful finding since it could simplify vaccination strategy against pneumococcus, guaranteeing effective vaccination of people at a lower cost while maintaining the highest level of protection. It should be pointed out that the model assumes all vaccinated subjects with a sequential scheme would receive both vaccines in a lasting period between 12 weeks and one year, which may be too optimistic under real world conditions of care in Spain[27].

In our analysis, we followed a sequential step by step analysis comparing the efficiency of existing or next vaccines according with its chronological past or future availability, hierarchy of serotypes included in the vaccines, subgroup of patients according to age and background risk and current national and regional recommendation in Spain, in order to provide health decision makers at Public Health Authorities with as much information as possible. Nonetheless, a limitation of this assessment is the uncertainty surrounding some of the parameter estimates. Available data on levels and duration of PPV23 effectiveness against IPD among immunocompetent persons, on an overall basis, as well as by age, risk, and time since receipt, are currently limited. In the absence of percentage of persons previously vaccinated with PCV13, we assumed similar percentage between 18-64 years and ≥ 65 years. Some parameters such as waning of the vaccine protection over the long-term and indirect effects are uncertain. However, a conservative estimate for indirect effects was employed for the base case scenario and sensitivity analyses for waning effect confirmed robustness of results. Furthermore, the present model did not include indirect costs that could be useful for a societal analysis.

However, the inclusion of indirect costs would lead to a lower ICER, as the working-age population (≥ 18 years) is expected to have less work loss due to pneumococcal pneumonia. For PPV23 effectiveness against all-cause NBP, we assumed the vaccine conferred no benefit, consistent with the findings of recent metaanalysis[30]. Nonetheless, a complementary analysis including effectiveness of PPV23 for VT-NBP raised by some authors was included in a sensitivity analysis[43,44]. Finally, the model could not incorporate long term consequences (one or more years) of pneumococcal disease such augmented mortality at one year or health consequences consuming resources and, therefore, costing to the NHS and the society.

5 CONCLUSION

All Spanish regions fund PPV23 for the prevention of pneumococcal disease in adults aged ≥ 18 years at risk and in all persons 65 years and above, and sequential with PCV13+PPV23 in immunocompromised subjects. However, based on reasonable assumptions regarding existing and future conjugate vaccines and PPV23 effectiveness as well as available epidemiologic and cost data, the use of one dose of PCV20 for patients aged ≥18 years at risk and with immunocompromising medical conditions, and in persons 65 years old and above, instead of immunization with PPV23 (or sequential with PCV13+PPV23), would lead to a decline in IPD, inpatient and outpatient NBP cases, and related deaths, while saving monetary resources to the NHS. The results of this research suggest that implementing a comprehensive immunization program with PCV20 alone for the prevention of pneumococcal disease among all Spanish adults aged ≥ 18 years (especially those who are immunocompromised or at risk) would be a highly cost-effective option compared to current vaccination schemes.

KEY POINTS

The administration of 20-valent conjugate pneumococcal vaccine in a ≥18 years population would account higher health benefits than current vaccination policy with polysaccharide vaccine.

Vaccination with 20-valent conjugate pneumococcal vaccine in patients aged ≥18-years was a cost-effective strategy in Spain.

COMPLIANCE WITH ETHICAL STANDARDS

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Conflicts of interest

The author has no conflicts of interest to declare.

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TABLES

Table 1. Model parameter estimates of population size, disease rates, case-fatality rates, serotype coverage and associated costs in year 2018.

Age (years) / Risk profile	18-49			50-64			65-74			75-84			85+			Sources
	Low	Moderate	High	Low	Moderate	High	Low	Moderate	High	Low	Moderate	High	Low	Moderate	High	
Population, n		19,768,452			9,836,898			4,623,808			3,014,619			1,526,603		INE
(%)	76.8	20.2	3.1	56.9	30.5	12.6	49.6	31.9	18.5	40.9	35.4	23.8	39.4	33.2	27.4	Rejas J et al. ECCMID 2021
Incidence (cases/100,000 inhabitants-year)																
IPD																CMBD, CAPA study & Rejas J et al. ECCMID 2021
Bacteremia	4.3	12.7	58.4	16.9	27.6	68.4	20.1	39.8	68.9	32.1	50.9	101.5	43.9	86.6	132.1	
Meningitis	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	
All-cause NBP																CMBD, CAPA study, BIFAP & Rejas J et al. ECCMID 2021
Hospitalized	41.5	122.5	563.9	165.1	269.8	667.6	392.1	776.0	1344.4	939.0	1488.7	2964.4	1857.6	3663.0	5587.2	
Outpatient care	197.3	260.2	271.3	266.2	323.0	337.9	427.7	492.4	531.0	647.1	700.2	803.3	1096.1	1203.2	1230.9	
30-days case fatality rate (per 100)[1]																
Bacteremia	2.65	6.82	14.82	2.04	7.01	29.74	3.10	8.51	31.82	7.63	17.98	31.89	24.70	28.52	37.38	CMBD
Meningitis	2.95	7.59	16.49	1.29	4.43	18.79	2.14	5.88	27.78	7.49	17.64	31.29	40.24	46.47	60.90	
Hospitalized NBP	0.06	1.80	2.60	0.46	2.30	7.40	1.60	4.40	20.80	4.5	10.60	18.80	22.60	26.10	34.20	Rejas J et al. ECCMID 2021
Vaccine serotype coverage (%)																
IPD																
PCV13	28.3	28.3	28.3	28.3	28.3	28.3	33.3	33.3	33.3	33.3	33.3	33.3	33.3	33.3	33.3	ECDC 2018
PCV15	35.3	35.3	35.3	35.3	35.3	35.3	37.3	37.3	37.3	37.3	37.3	37.3	37.3	37.3	37.3	
PCV20	66.6	66.6	66.6	66.6	66.6	66.6	62.0	62.0	62.0	62.0	62.0	62.0	62.0	62.0	62.0	
PPV23	72.3	72.3	72.3	72.3	72.3	72.3	67.9	67.9	67.9	67.9	67.9	67.9	67.9	67.9	67.9	
All-cause NBP																
PCV13	12.5	12.5	12.5	12.5	12.5	12.5	13.2	13.2	13.2	13.2	13.2	13.2	13.2	13.2	13.2	CAPA study
PCV15	13.2	13.2	13.2	13.2	13.2	13.2	15.3	15.3	15.3	15.3	15.3	15.3	15.3	15.3	15.3	
PCV20	27.7	27.7	27.7	27.7	27.7	27.7	21.3	21.3	21.3	21.3	21.3	21.3	21.3	21.3	21.3	
PPV23	29.7	29.7	29.7	29.7	29.7	29.7	23.2	23.2	23.2	23.2	23.2	23.2	23.2	23.2	23.2	
Health state utility for general population	0.9680	0.9280	0.8882	0.9279	0.8338	0.8091	0.9038	0.7876	0.7891	0.8264	0.6866	0.6853	0.6516	0.4868	0.4547	Spanish National Health Survey, 2012
Reduction in utility (IPD/hospitalized NBP)		0.0709			0.0709			0.0709			0.0709			0.0709		Mangen J et al. 2015

Reduction in utility (outpatient NBP)	0.0045			0.0045			0.0045			0.0045			0.0045			Mangen J et al. 2015
Vaccine uptake[2] (%)	0.4	0.9	37.8	1.3	15.0	59.1	6.6	31.1	48.3	35.6	46.1	66.9	69.5	60.7	77.0	Rejas J et al. ECCMID 2021
Cost per episode (€)																
IPD																
Bacteremia	8,578	8,578	8,578	8,701	8,701	8,701	8,284	8,284	8,284	7,204	7,204	7,204	6,399	6,399	6,399	CMBD
Meningitis	9,804	9,804	9,804	10,128	10,128	10,128	12,150	12,150	12,150	10,195	10,195	10,195	9,104	9,104	9,104	
All-cause NBP																
Hospitalized	3,266	3,844	3,703	3,411	3,695	4,180	3,366	4,396	4,389	3,822	4,633	4,598	3,568	4,024	4,313	Rejas J et al. ECCMID 2021
Outpatient care	396	451	627	420	533	686	474	639	700	525	654	787	556	597	697	

IPD: Invasive pneumococcal disease; NBP: Non-bacteremic pneumonia; PCV: Pneumococcal conjugate vaccine; PPV: Pneumococcal polysaccharide vaccine; INE: Instituto Nacional de Estadística (National Institute on Statistic), http://www.ine.es/ (Accessed: 4 August 2021); CMBD: Conjunto Mínimo Básico de Datos (Minimum basic data set), Ministry of Health https://pestadistico.inteligenciadegestion.mscbs.es/publicoSNS/N/rae-cmbd/cmbd-h (Accessed: 4 August 2021); CAPA study (Torres A et al. Clin Infect Dis. 2021.doi: 10.1093/cid/ciab307); BIFAP -Spanish Computerized Database for Pharmacoepidemiological Studies in Primary Care - database (Rivero-Calle I et al. *BMC Infect Dis* 2016; 16, 645. doi.org/10.1186/s12879-016-1974-4); ECDC. Surveillance Atlas of Infectious Diseases for Invasive Bacterial Diseases, Spain 2018 data, available at: https://atlas.ecdc.europa.eu/public/index.aspx (Accessed 5 August 2021).

[1]Excess mortality for outpatient NBP is assumed to be 0 (same than in the general population) in the model, [2] Model assumes that in sequential vaccination strategies, both vaccines uptake is at the same percentage.

Table 2. Cost-effectiveness results in the base case analysis.

Population ≥ 18 years at model entry (n= 38.77 million inhabitants, vaccine uptake: 13.1% all ages, 38.0% 65+ years old)	**PPV23**	**PCV20**	**Difference**
Outcomes (No. of cases)			
IPD	368,446	360,652	-7,794
Bacteremia	352,745	345,268	-7,477
Meningitis	15,701	15,384	-317
NBP			
Requiring inpatient care	8,044,299	7,979,675	-64,624
Requiring outpatient care	5,700,313	5,672,541	-27,772
No. of deaths	1,092,138	1,077,988	-14,150
Life-years (discounted)	742,491,547	742,569,088	77,541
Quality-adjusted life-years (discounted)	646,825,635	646,876,036	50,401
Total costs (€, in thousands)			
Medical care	19,048,937	18,743,781	-305,157
Vaccination	82,400	247,659	165,259
Medical + vaccination	19,131,338	18,991,440	-139,898
Incremental cost-effectiveness ratio (Healthcare system perspective, €)			
Incremental cost per life-year gained	-	-	-1,804
Incremental cost per quality-adjusted life-year gained	-	-	-2,766
	PPV23	**PCV15**	**Difference**
Outcomes (No. of cases)			
IPD	368,446	365,215	-3,225
Bacteremia	352,745	349,632	-3,106
Meningitis	15,701	15,583	-119
NBP			
Requiring inpatient care	8,044,299	8,010,485	-33,814
Requiring outpatient care	5,700,313	5,686,081	-14,232
No. of deaths	1,092,138	1,084,689	-7,449
Life-years (discounted)	742,491,547	742,530,318	38,770
Quality-adjusted life-years (discounted)	646,825,635	646,852,774	27,139
Total costs (€, in thousands)			
Medical care	19,048,937	18,894,885	-154,053
Vaccination	82,400	247,659	165,259
Medical + vaccination	19,131,338	19,142,544	11,206
Incremental cost-effectiveness ratio (Healthcare system perspective, €)			
Incremental cost per life-year gained	-	-	289

Incremental cost per quality-adjusted life-year gained	-	-	413

	PCV15	PCV20	Difference
Outcomes (No. of cases)			
IPD	365,215	360,652	-4,563
Bacteremia	349,632	345,268	-4,364
Meningitis	15,583	15,384	-199
NBP			
Requiring inpatient care	8,010,485	7,979,675	-30,810
Requiring outpatient care	5,686,081	5,672,541	-13,540
No. of deaths	1,084,689	1,077,988	-6,701
Life-years (discounted)	742,530,318	742,569,088	77,541
Quality-adjusted life-years (discounted)	646,852,774	646,876,036	50,401
Total costs (€, in thousands)			
Medical care	18,894,885	18,743,781	-151,104
Vaccination	247,659	247,659	0
Medical + vaccination	19,142,544	18,991,440	-151,104
Incremental cost-effectiveness ratio (Healthcare system perspective, €)			
Incremental cost per life-year gained	-	-	-1,949
Incremental cost per quality-adjusted life-year gained	-	-	-2,998

IPD: Invasive pneumococcal disease; NBP: Non-bacteremic pneumonia; PCV: Pneumococcal conjugate vaccine; PPV: Pneumococcal polysaccharide vaccine

Table 3. Probabilistic cost-effectiveness analysis of pneumococcal vaccination strategies with Pneumococcal Conjugate and Polysaccharide vaccines in development in Spanish adults.

Population	Vaccination strategy[1]	Cost-effectiveness analysis[2]			
		ICER[3] (95% probabilistic CI)	Likelihood of cost-saving (% of iterations)	Likelihood of cost-effective (% of iterations)	
				By GENESIS threshold (€21,000/QALY)	By WHO threshold (€25,770/QALY)
18+ years old	PCV15 vs PPV23	1,575 (-9,441; 18,493)	44%	98%	99%
	PCV20 vs PCV15	-8,619 (-25,660; -2,442)	100%	100%	100%
	PCV20 vs PPV23	-2,823 (-9,451; 3,404)	84%	100%	100%
18+ years old **immunocompromised** (high risk)	Sequential PCV15+PPV23 vs seq PCV13+PPV23	-6,478 (-23,096; -1,785)	100%	100%	100%
	Sequential PCV20+PPV23 vs seq PCV15+PPV23	-6,365 (-16,916; -1,947)	100%	100%	100%
	PCV20 alone vs seq PCV15+PPV23	-9,738 (-26,458; -2,439)	100%	100%	100%
	Sequential PCV20+PPV23 vs PCV20 alone	216,545 (39,335; 770,551)	0%	0%	0%
18+ years old **at risk** (moderate risk)	PPV23 vs No vaccination	63,154 (8,091; 197,776)	0%	22%	26%
	PCV15 vs PPV23	977 (-18,850; 36,123)	52%	96%	96%
	PCV20 vs PCV15	-13,827 (-38,743; -3,774)	100%	100%	100%
	Sequential PCV15+PPV23 vs seq PCV13+PPV23	-15,151 (-36,867; -4,117)	100%	100%	100%
	Sequential PCV20+PPV23 vs seq PCV15+PPV23	-14,679 (-36,418; -3,843)	100%	100%	100%
	Sequential PCV20+PPV23 vs PCV20 alone	498,698 (106,295; 1,420,061)	0%	0%	0%
65+ years old (all risk groups)	PPV23 vs No vaccination	56,153 (3,592; 232,639)	0%	33%	37%
	PCV15 vs PPV23	189 (-15,229; 18,202)	63%	98%	98%
	PCV15 vs PCV13	-9,020	100%	100%	100%

	(-27,406; -2,827)			
PCV20 vs PCV15	-10,353 (-28,903; -2,726)	100%	100%	100%
Sequential PCV15+PPV23 vs seq PCV13+PPV23	-11,229 (-31,122; -2,381)	100%	100%	100%
Sequential PCV20+PPV23 vs seq PCV15+PPV23	-10,720 (-35,654; -3,012)	100%	100%	100%
Sequential PCV20+PPV23 vs PCV20	486,581 (76,840; 1,500,522)	0%	0%	0%

PCV: Pneumococcal conjugate vaccine; PPV: Pneumococcal polysaccharide vaccine; CI: Confidence interval; seq: sequential
[1]Model horizon is lifetime (82 years) in all strategies; [2]Cost-effectiveness probabilistic analysis by Montecarlo simulation; [3]ICER: Incremental cost-effectiveness ratio in Euros/QALY gained.

Table 4. Cost-effectiveness results in immunocompromised (high risk) patients according with different vaccination schedules.

Immunocompromised ≥ 18 years at model entry (n= 3.83 million inhabitants, vaccine uptake: 56.7% all ages, 61.0% 65+ years old)	**PCV13+PPV23**	**PCV15+PPV23**	**Difference**
Outcomes (No. of cases)			
IPD	58,411	57,962	-449
Bacteremia	55,885	55,457	-428
Meningitis	2,526	2,505	-21
NBP			
Requiring inpatient care	1,260,991	1,258,531	-2,460
Requiring outpatient care	388,854	388,041	-813
No. of deaths	291,447	290,811	-636
Life-years (discounted)	47,492,568	47,496,782	4,214
Quality-adjusted life-years (discounted)	35,616,649	35,619,330	2,682
Total costs (€, in thousands)			
Medical care	4,133,784	4,120,636	-13,148
Vaccination	137,877	137,878	1
Medical + vaccination	4,271,661	4,258,514	-13,147
Incremental cost-effectiveness ratio (Healthcare system perspective, €)			
Incremental cost per life-year gained	-	-	-3,120
Incremental cost per quality-adjusted life-year gained	-	-	-4,902
	PCV15+PPV23	**PCV20+PPV23**	**Difference**
Outcomes (No. of cases)			
IPD	57,962	55,660	-2,302
Bacteremia	55,457	53,262	-2,195
Meningitis	2,505	2,398	-107
NBP			
Requiring inpatient care	1,258,531	1,243,155	-33,814
Requiring outpatient care	388,041	382,952	-14,232
No. of deaths	290,811	286,990	-7,449
Life-years (discounted)	47,496,782	47,521,299	24,517
Quality-adjusted life-years (discounted)	35,619,330	35,636,186	16,856
Total costs (€, in thousands)			
Medical care	4,120,636	4,043,293	-77,343
Vaccination	137,878	137,885	7
Medical + vaccination	4,258,514	4,181,178	-77,336
Incremental cost-effectiveness ratio (Healthcare system perspective, €)			
Incremental cost per life-year gained	-	-	-3,154
Incremental cost per quality-adjusted life-year gained	-	-	-4,588

	PCV20	PCV20+PPV23	Difference
Outcomes (No. of cases)			
IPD	55,777	55,660	-117
Bacteremia	53,374	53,262	-112
Meningitis	2,403	2,398	-5
NBP			
Requiring inpatient care	1,243,144	1,243,155	11
Requiring outpatient care	382,949	382,952	3
No. of deaths	287,023	286,990	-33
Life-years (discounted)	47,520,997	47,521,299	303
Quality-adjusted life-years (discounted)	35,635,975	35,636,186	217
Total costs (€, in thousands)			
Medical care	4,044,144	4,043,293	-851
Vaccination	105,834	137,885	32,051
Medical + vaccination	4,149,978	4,181,178	31,200
Incremental cost-effectiveness ratio (Healthcare system perspective, €)			
Incremental cost per life-year gained	-	-	102,964
Incremental cost per quality-adjusted life-year gained	-	-	143,539

IPD: Invasive pneumococcal disease; NBP: Non-bacteremic pneumonia; PCV: Pneumococcal conjugate vaccine; PPV: Pneumococcal polysaccharide vaccine.

Table 5. Cost-effectiveness results in at risk (moderate risk) patients according with different vaccination schedules.

Immunocompetent with moderate risk ≥ 18 years at model entry (n= 10.03 million inhabitants, vaccine uptake: 17.4% all ages, 41.3% 65+ years old)	**PPV23**	**PCV15**	**Difference**
Outcomes (No. of cases)			
IPD	110,383	109,376	-1,007
Bacteremia	105,531	104,558	-973
Meningitis	4,852	4,818	-34
NBP			
Requiring inpatient care	2,348,865	2,337,122	-11,744
Requiring outpatient care	1,343,728	1,338,341	-5,387
No. of deaths	314,902	312,813	-2,089
Life-years (discounted)	170,707,053	170,716,082	9,029
Quality-adjusted life-years (discounted)	136,671,383	136,676,399	5,016
Total costs (€, in thousands)			
Medical care	6,289,054	6,236,095	-52,959
Vaccination	28,274	84,980	56,706
Medical + vaccination	6,317,328	6,321,075	3,747
Incremental cost-effectiveness ratio (Healthcare system perspective, €)			
Incremental cost per life-year gained	-	-	415
Incremental cost per quality-adjusted life-year gained	-	-	747
	PCV15	**PCV20**	**Difference**
Outcomes (No. of cases)			
IPD	109,376	108,026	-1,350
Bacteremia	104,558	103,265	-1,293
Meningitis	4,818	4,761	-57
NBP			
Requiring inpatient care	2,337,122	2,326,757	-10,365
Requiring outpatient care	1,338,341	1,333,230	-5,111
No. of deaths	312,813	311,074	-1,739
Life-years (discounted)	170,716,082	170,723,105	7,023
Quality-adjusted life-years (discounted)	136,676,399	136,681,416	5,016
Total costs (€, in thousands)			
Medical care	6,236,095	6,186,406	-49,689
Vaccination	84,980	84,980	0
Medical + vaccination	6,321,075	6,271,387	-49,689
Incremental cost-effectiveness ratio (Healthcare system perspective, €)			
Incremental cost per life-year gained	-	-	-7,076
Incremental cost per quality-adjusted life-year gained	-	-	-9,906

	PCV13+PPV23	PCV15+PPV23	Difference
Outcomes (No. of cases)			
IPD	109,200	108,985	-215
Bacteremia	104,390	104,184	-206
Meningitis	4,810	4,801	-9
NBP			
Requiring inpatient care	2,338,795	2,337,132	-1,663
Requiring outpatient care	1,339,168	1,338,345	-823
No. of deaths	313,036	312,754	-282
Life-years (discounted)	170,715,078	170,716,082	1,004
Quality-adjusted life-years (discounted)	136,676,399	136,677,403	1,003
Total costs (€, in thousands)			
Medical care	6,241,286	6,233,247	-8,039
Vaccination	110,718	110,718	0
Medical + vaccination	6,352,005	6,343,966	-8,039
Incremental cost-effectiveness ratio (Healthcare system perspective, €)			
Incremental cost per life-year gained	-	-	-8,007
Incremental cost per quality-adjusted life-year gained	-	-	-8,013

	PCV15+PPV23	PCV20+PPV23	Difference
Outcomes (No. of cases)			
IPD	108,985	107,924	-1,061
Bacteremia	104,184	103,167	-1,017
Meningitis	4,801	4,757	-44
NBP			
Requiring inpatient care	2,337,132	2,326,760	-10,372
Requiring outpatient care	1,338,345	1,333,231	-5,114
No. of deaths	312,754	311,057	-1,696
Life-years (discounted)	170,716,082	170,724,108	8,026
Quality-adjusted life-years (discounted)	136,677,403	136,681,416	4,013
Total costs (€, in thousands)			
Medical care	6,233,247	6,185,682	-47,565
Vaccination	110,718	110,721	3
Medical + vaccination	6,343,966	6,296,403	-47,562
Incremental cost-effectiveness ratio (Healthcare system perspective, €)			
Incremental cost per life-year gained	-	-	-5,926
Incremental cost per quality-adjusted life-year gained	-	-	-11,852

	PCV20	PCV20+PPV23	Difference
Outcomes (No. of cases)			
IPD	108,026	107,924	-102
Bacteremia	103,265	103,167	-98
Meningitis	4,761	4,757	-4
NBP			
Requiring inpatient care	2,326,757	2,326,760	3
Requiring outpatient care	1,333,230	1,333,231	1
No. of deaths	311,074	311,057	-16
Life-years (discounted)	170,723,506	170,723,607	100
Quality-adjusted life-years (discounted)	136,681,752	136,681,817	65
Total costs (€, in thousands)			
Medical care	6,186,406	6,185,682	-724
Vaccination	84,980	110,721	25,741
Medical + vaccination	6,271,387	6,296,403	25,017
Incremental cost-effectiveness ratio (Healthcare system perspective, €)			
Incremental cost per life-year gained	-	-	249,364
Incremental cost per quality-adjusted life-year gained	-	-	383,637

IPD: Invasive pneumococcal disease; NBP: Non-bacteremic pneumonia; PCV: Pneumococcal conjugate vaccine; PPV: Pneumococcal polysaccharide vaccine

Table 6. Cost-effectiveness results in patient 65 years old and above according with different vaccination schedules.

All risk patient ≥ 65 years at model entry (n= 9.17 million inhabitants, vaccine uptake: 38.0%)	**PPV23**	**PCV15**	**Difference**
Outcomes (No. of cases)			
IPD	56,081	53,769	-2,312
Bacteremia	54,329	52,085	-2,244
Meningitis	1,752	1,684	-68
NBP			
Requiring inpatient care	1,676,343	1,648,374	-27,969
Requiring outpatient care	753,656	742,692	-10,965
No. of deaths	341,928	335,303	-6,624
Life-years (discounted)	81,223,612	81,251,565	27,953
Quality-adjusted life-years (discounted)	58,709,166	58,725,938	16,772
Total costs (€, in thousands)			
Medical care	6,086,026	5,961,769	-124,257
Vaccination	56,355	169,378	113,023
Medical + vaccination	6,142,381	6,131,147	-11,234
Incremental cost-effectiveness ratio (Healthcare system perspective, €)			
Incremental cost per life-year gained	-	-	-402
Incremental cost per quality-adjusted life-year gained	-	-	-670
	PCV15	**PCV20**	**Difference**
Outcomes (No. of cases)			
IPD	53,769	51,495	-2,274
Bacteremia	52,085	49,883	-2,202
Meningitis	1,684	1,612	-72
NBP			
Requiring inpatient care	1,648,374	1,626,463	-21,911
Requiring outpatient care	742,692	734,092	-8,600
No. of deaths	335,303	330,060	-5,243
Life-years (discounted)	81,251,565	81,273,653	22,088
Quality-adjusted life-years (discounted)	58,725,938	58,739,319	13,381
Total costs (€, in thousands)			
Medical care	5,961,769	5,862,059	-99,709
Vaccination	169,378	169,378	0
Medical + vaccination	6,131,147	6,073,782	-99,709
Incremental cost-effectiveness ratio (Healthcare system perspective, €)			
Incremental cost per life-year gained	-	-	-4,514
Incremental cost per quality-adjusted life-year gained	-	-	-7,452

	PCV13+PPV23	PCV15+PPV23	Difference
Outcomes (No. of cases)			
IPD	53,415	53,030	-385
Bacteremia	51,744	51,371	-373
Meningitis	1,671	1,659	-12
NBP			
Requiring inpatient care	1,652,014	1,648,406	-3,608
Requiring outpatient care	744,124	742,702	-1,422
No. of deaths	336,011	335,144	-867
Life-years (discounted)	81,248,633	81,252,390	3,758
Quality-adjusted life-years (discounted)	58,724,288	58,726,488	2,200
Total costs (€, in thousands)			
Medical care	5,973,560	5,956,905	-16,656
Vaccination	219,141	219,143	2
Medical + vaccination	6,192,702	6,176,048	-16,654
Incremental cost-effectiveness ratio (Healthcare system perspective, €)			
Incremental cost per life-year gained	-	-	-4,432
Incremental cost per quality-adjusted life-year gained	-	-	-7,571

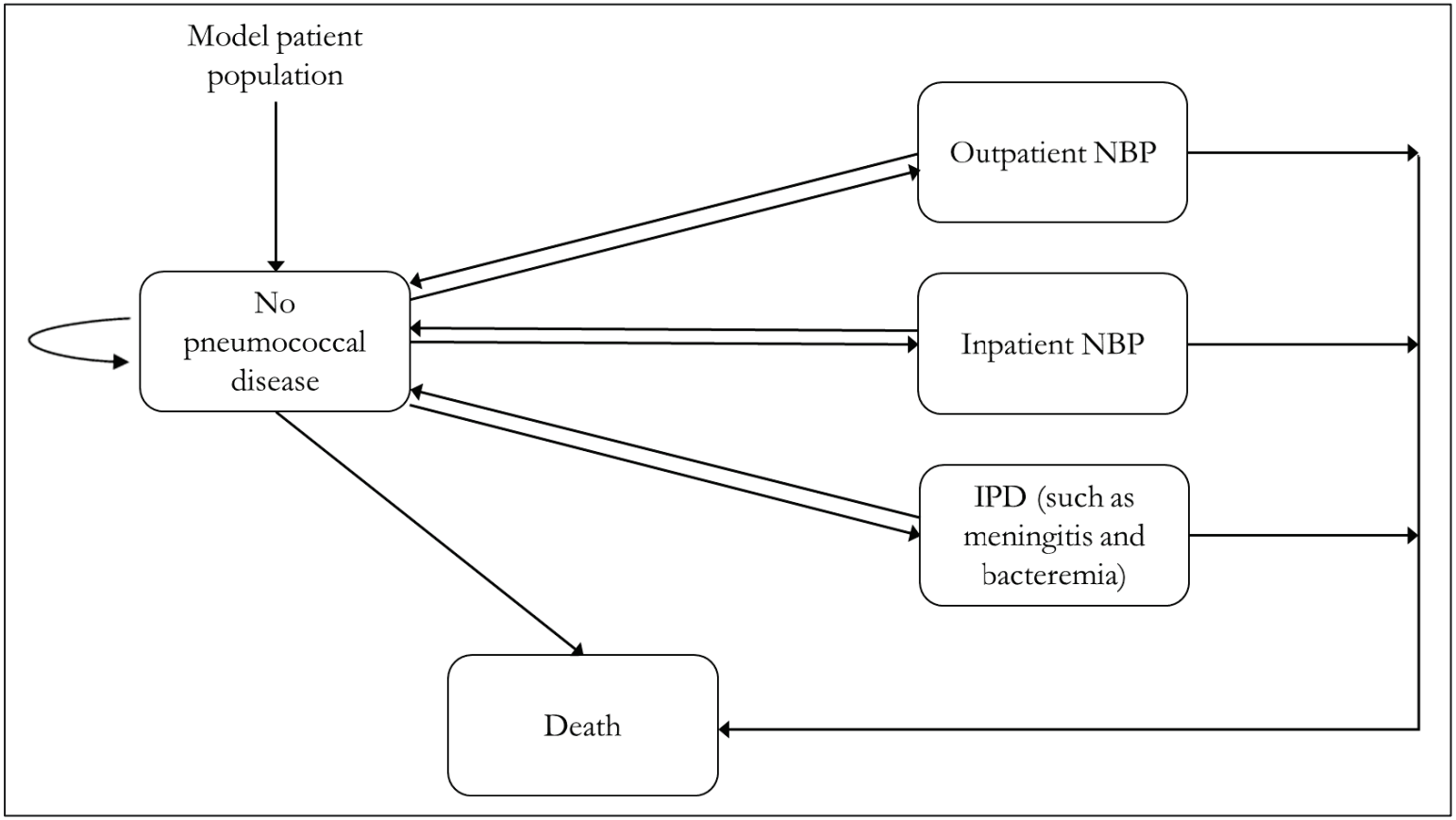
	PCV15+PPV23	PCV20+PPV23	Difference
Outcomes (No. of cases)			
IPD	53,030	51,282	-1,748
Bacteremia	51,371	49,677	-1,694
Meningitis	1,659	1,605	-54
NBP			
Requiring inpatient care	1,648,406	1,626,472	-21,934
Requiring outpatient care	742,702	734,095	-8,608
No. of deaths	335,144	330,014	-5,130
Life-years (discounted)	81,252,390	81,273,928	21,538
Quality-adjusted life-years (discounted)	58,726,488	58,739,502	13,014
Total costs (€, in thousands)			
Medical care	5,956,905	5,860,679	-96,226
Vaccination	219,143	219,153	10
Medical + vaccination	6,176,048	6,079,832	-96,216
Incremental cost-effectiveness ratio (Healthcare system perspective, €)			
Incremental cost per life-year gained	-	-	-4,467
Incremental cost per quality-adjusted life-year gained	-	-	-7,393

	PCV20	PCV20+PPV23	Difference
Outcomes (No. of cases)			
IPD	51,495	51,282	-213
Bacteremia	49,883	49,677	-206
Meningitis	1,612	1,605	-7
NBP			
Requiring inpatient care	1,626,463	1,626,472	9
Requiring outpatient care	734,092	734,095	3
No. of deaths	330,060	330,014	-46
Life-years (discounted)	81,273,653	81,273,928	275
Quality-adjusted life-years (discounted)	58,739,319	58,739,502	183
Total costs (€, in thousands)			
Medical care	5,862,059	5,860,679	-1,380
Vaccination	169,378	219,153	49,755
Medical + vaccination	6,073,782	6,079,832	48,394
Incremental cost-effectiveness ratio (Healthcare system perspective, €)			
Incremental cost per life-year gained	-	-	194,963
Incremental cost per quality-adjusted life-year gained	-	-	303,885

IPD: Invasive pneumococcal disease; NBP: Non-bacteremic pneumonia; PCV: Pneumococcal conjugate vaccine; PPV: Pneumococcal polysaccharide vaccine

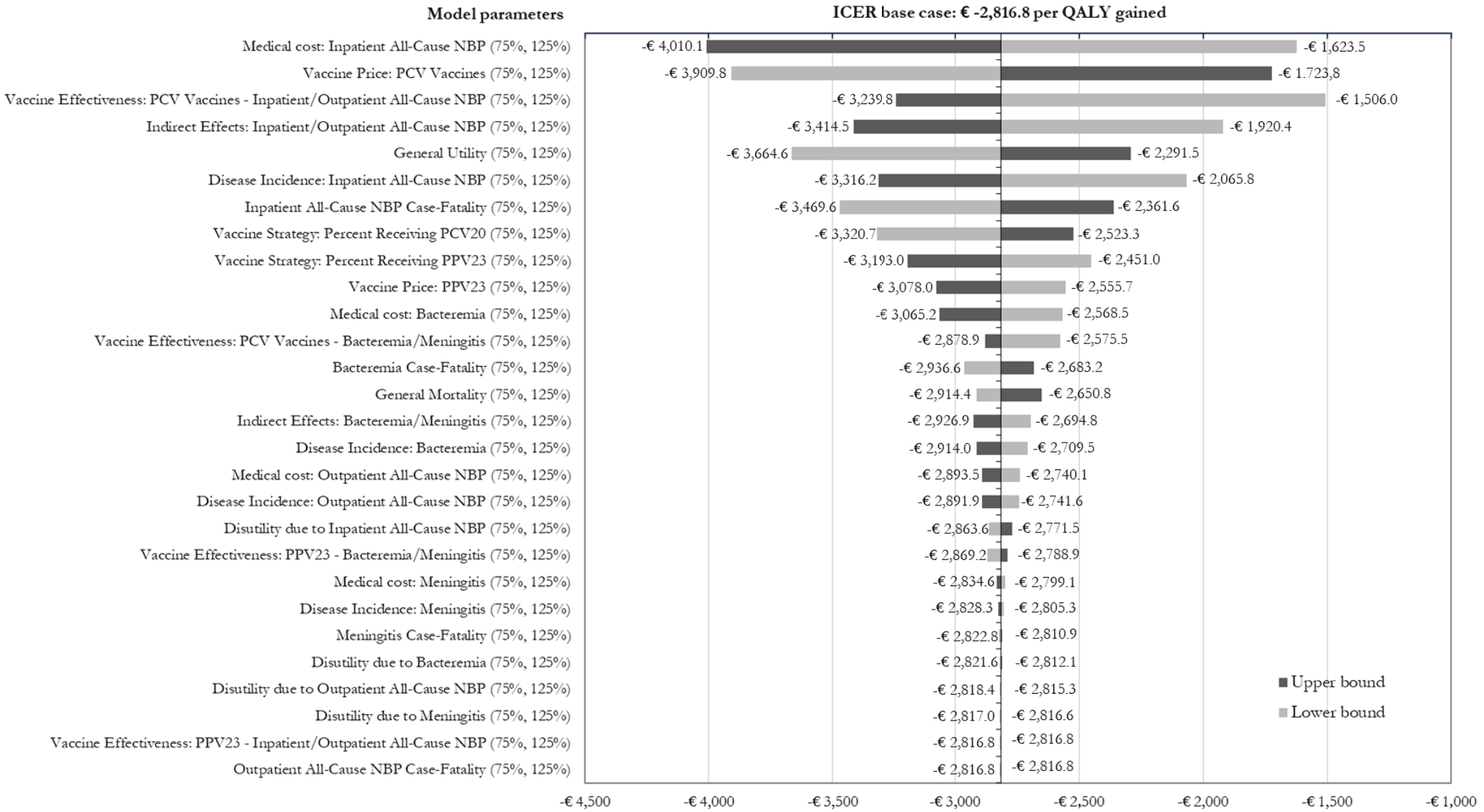
FIGURES

Figure 1. Model structure



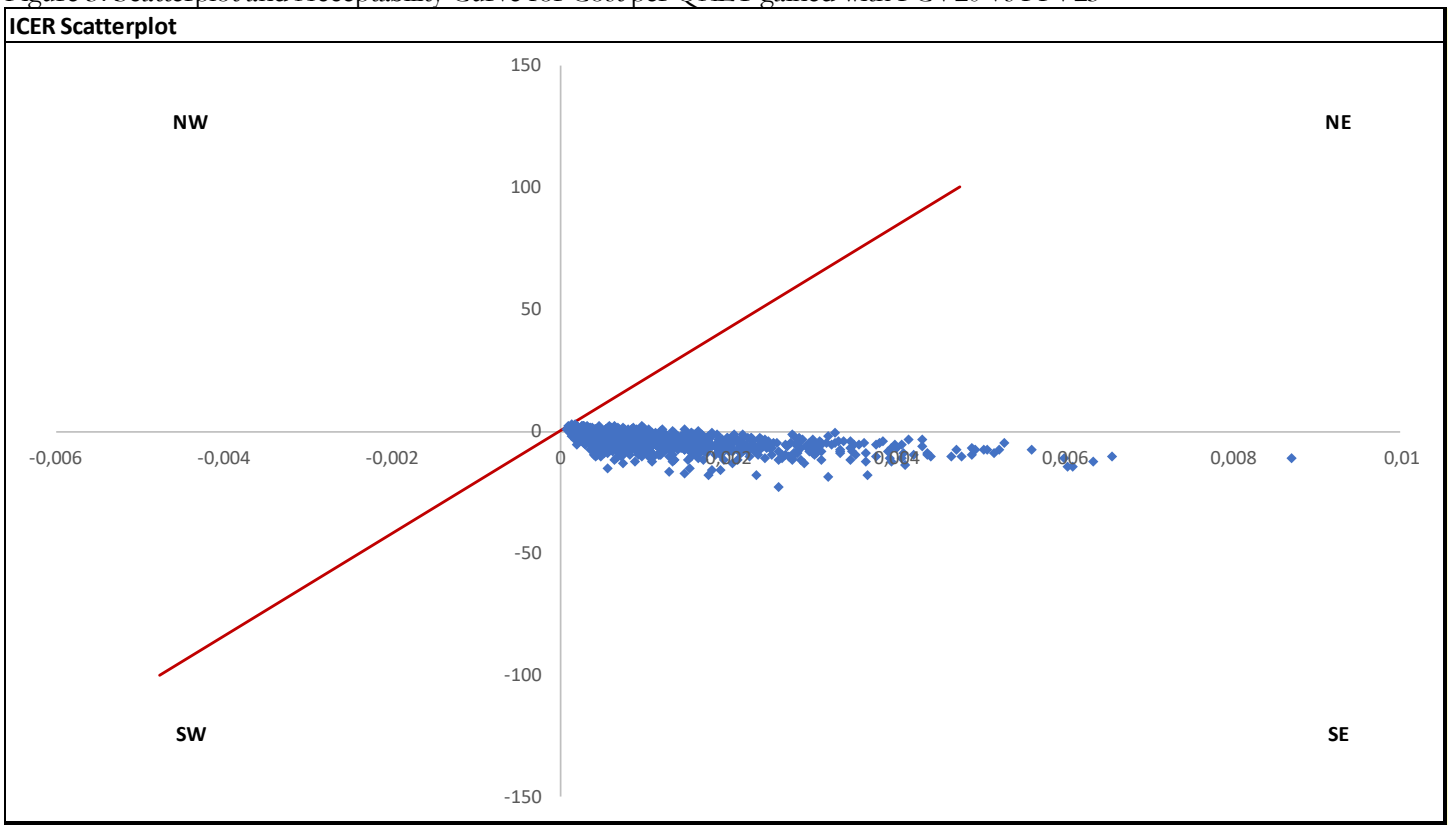
IPD: Invasive pneumococcal disease; NBP: Non-bacteremic pneumonia

Figure 2. Tornado Plot for One-Way Sensitivity Analysis for Cost per QALY gained with PCV20 vs PPV23



ICER: Incremental cost-effectiveness ratio in Euros/QALY gained; IPD: Invasive pneumococcal disease; NBP: Non-bacteremic pneumonia; PCV: Pneumococcal conjugate vaccine; PPV: Pneumococcal polysaccharide vaccine; QALY: Quality adjusted life years.

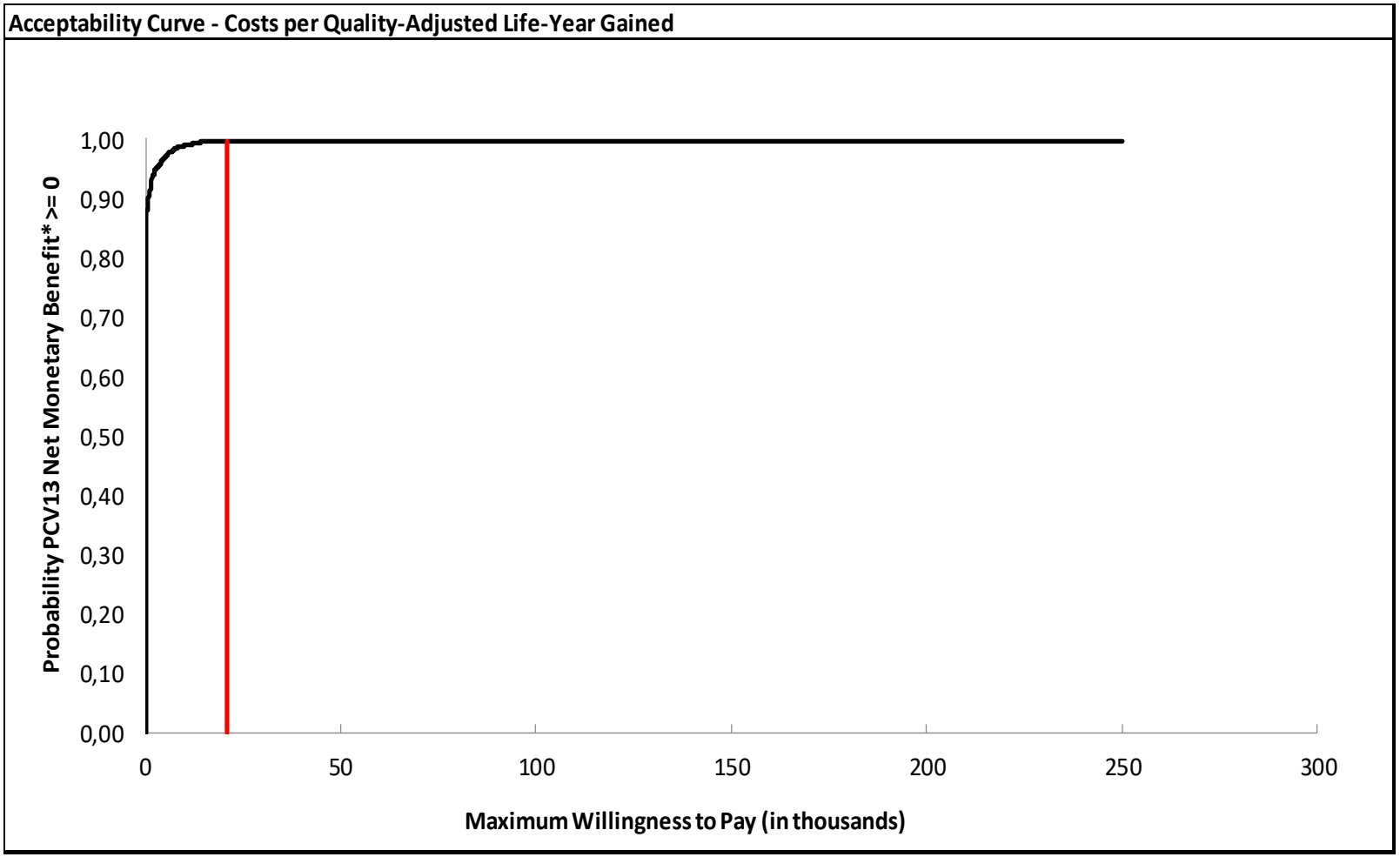
Figure 3. Scatterplot and Acceptability Curve for Cost per QALY gained with PCV20 vs PPV23



Differences = PCV20 - PPV23.

Quadrant*	Incremental Cost (IC)	Incremental Effectiveness (IE)	ICER	ICER vs WTP	Simulations	
					Number	Percent
SE	IC < 0	IE > 0	Dominant	---	867	87%
NE	IC > 0	IE > 0	ICER > 0	ICER < WTP	132	13%
SW	IC < 0	IE < 0	ICER > 0	ICER < WTP	0	0%
NE	IC > 0	IE > 0	ICER > 0	ICER > WTP	1	0%
SW	IC < 0	IE < 0	ICER > 0	ICER > WTP	0	0%
NW	IC > 0	IE < 0	Dominated	---	0	0%

ICER: Incremental cost-effectiveness ratio in Euros/QALY gained; PCV: Pneumococcal conjugate vaccine; PPV: Pneumococcal polysaccharide vaccine; WTP: Willingness to pay.
*Simulations in NE quadrant represent ICERs for PCV20 (vs PPV23); simulations in the SW quadrant represent ICERs for PPV23 (vs PCV20)



Red line represents the WTP threshold in Spain from around €21,000[40]

Supplementary Material

This appendix has been provided by the author to give additional information about their work.

Supplement to: Economic evaluation and access strategy development for the 20-valent pneumococcal conjugate vaccine (PCV20) in Spanish adults.

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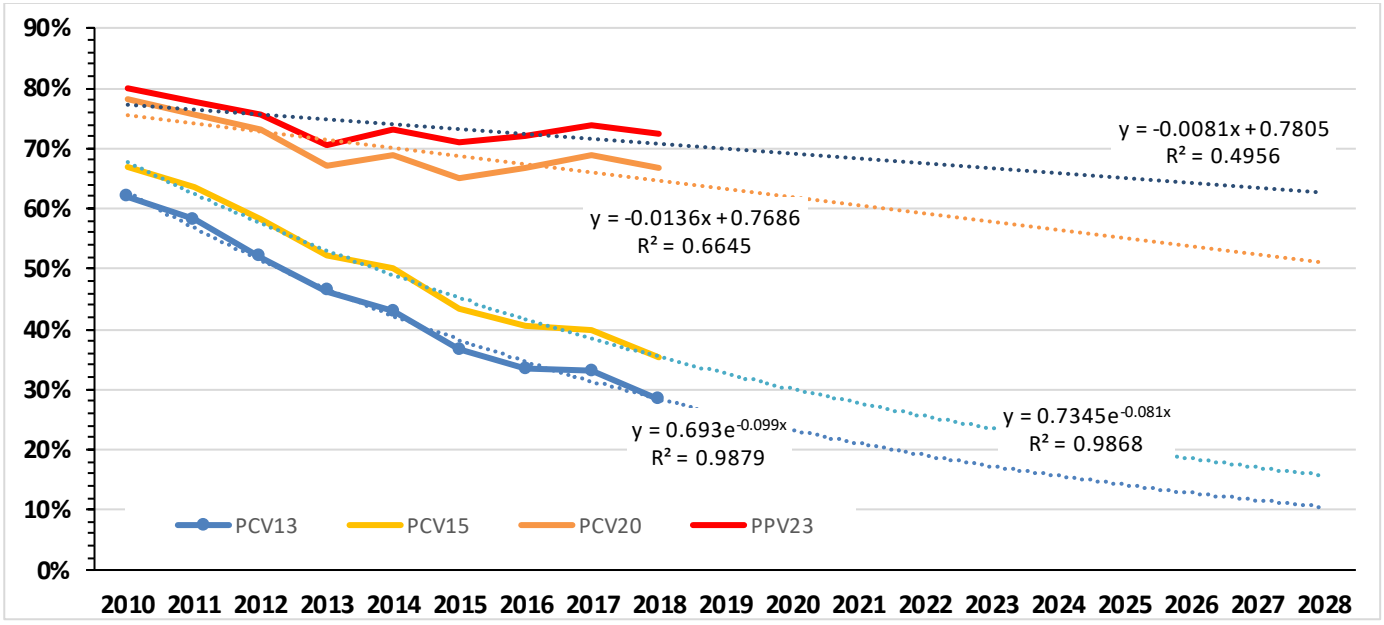
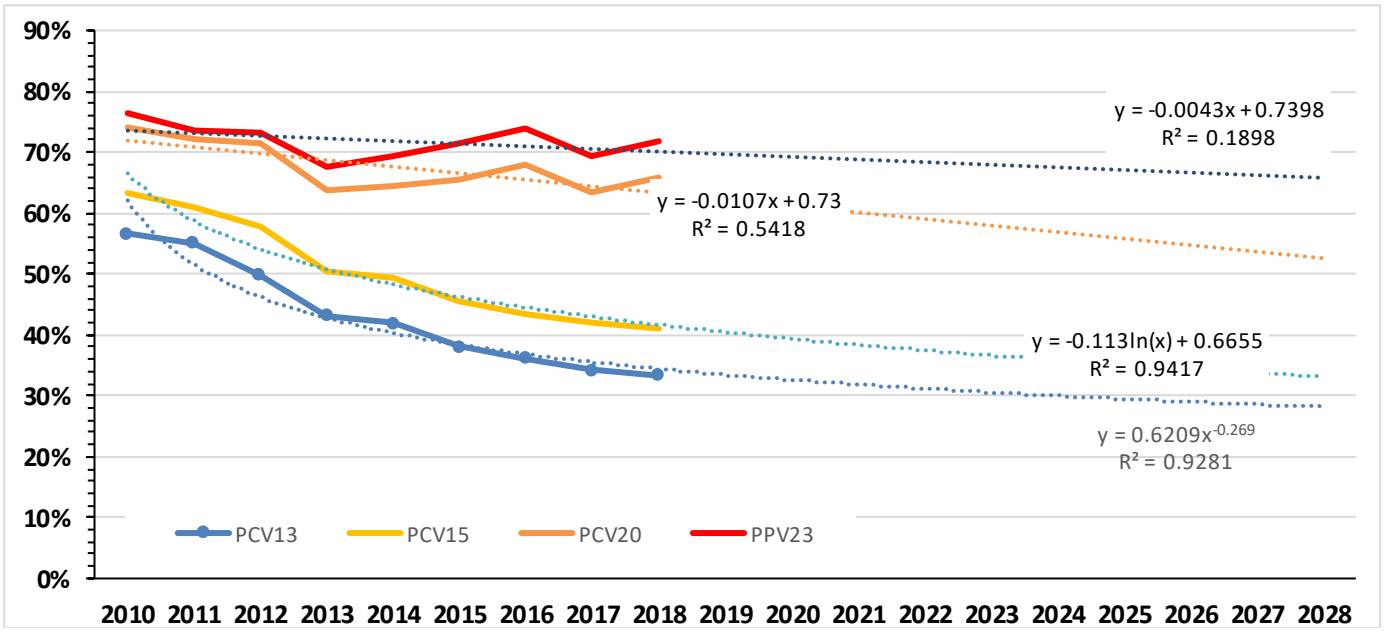
Figure S1. Vaccine serotype coverage and indirect effect for IPD, observed and projected by fitting the best line trend in persons 18-64 years old (graph A) and aged ≥ 65 years (graph B).

Graph A



Graph B



IPD: Invasive pneumococcal disease.

Table S1. International Classification of Diseases-10 codes included in IPD and all-cause NBP

		International Classification of Diseases-10 (ICD-10)			
		IPD		All-cause NBP	
ICD-10 codes	Disease	Bacteremia	Meningitis	Hospitalized	Outpatient care
R78.81	Bacteremia	X	-	-	-
B95. 3	Streptococcus pneumoniae as the cause of diseases classified elsewhere	X	-	-	-
K65	Peritonitis	X	-	-	-
A40.3	Sepsis due to Streptococcus pneumoniae	X	-	-	-
G00.1	Pneumococcal meningitis	-	X	-	-
M00.1-M00.19	Pneumococcal arthritis (mono or polyarthritis)	X			
J13	Pneumonia due to Streptococcus pneumoniae	X	-	X	X
J10.0	Influenza with pneumonia, seasonal influenza virus identified	-	-	X	X
J10.1	Influenza (broncho)pneumonia, seasonal influenza virus identified	-	-	X	X
J11	Influenza, virus not identified	-	-	X	X
J12	Viral pneumonia, not elsewhere classified	-	-	X	X
J14	Pneumonia due to Haemophiles influenzae	-	-	X	X
J15	Bacterial pneumonia, not elsewhere classified	-	-	X	X
J16	Pneumonia due to other infectious organisms, not elsewhere classified	-	-	X	X
J17	Pneumonia in diseases classified elsewhere	-	-	X	X
J18	Pneumonia, organism unspecified	-	-	X	X

IPD: Invasive pneumococcal disease; NBP: Non-bacteremic pneumonia.

Table S2. Vaccination strategies analyzed of funding an expanded adult pneumococcal immunization program in Spain.

Vaccination strategy[1]	Population
Base case: PCV20 vs PPV23	18+ years old in all risk groups
PCV15 vs PPV23	18+ years old in all risk groups
PCV20 vs PCV15	18+ years old in all risk groups
Sequential PCV15+PPV23 vs seq PCV13+PPV23	18+ years old immunocompromised (high risk)
Sequential PCV20+PPV23 vs seq PCV15+PPV23	18+ years old immunocompromised (high risk)
PCV20 alone vs seq PCV15+PPV23	18+ years old immunocompromised (high risk)
Sequential PCV20+PPV23 vs PCV20 alone	18+ years old immunocompromised (high risk)
PPV23 vs No vaccination	18+ years old at risk (moderate risk)
PCV15 vs PPV23	18+ years old at risk (moderate risk)
PCV20 vs PCV15	18+ years old at risk (moderate risk)
Sequential PCV15+PPV23 vs seq PCV13+PPV23	18+ years old at risk (moderate risk)
Sequential PCV20+PPV23 vs seq PCV15+PPV23	18+ years old at risk (moderate risk)
Sequential PCV20+PPV23 vs PCV20 alone	18+ years old at risk (moderate risk)
PPV23 vs No vaccination	65+ years old in all risk groups
PCV15 vs PPV23	65+ years old in all risk groups
PCV15 vs PCV13	65+ years old in all risk groups
PCV20 vs PCV15	65+ years old in all risk groups
Sequential PCV15+PPV23 vs seq PCV13+PPV23	65+ years old in all risk groups
Sequential PCV20+PPV23 vs seq PCV15+PPV23	65+ years old in all risk groups
Sequential PCV20+PPV23 vs PCV20	65+ years old in all risk groups

PPV: Pneumococcal polysaccharide vaccine; PCV: Pneumococcal conjugate vaccine.
[1]Model horizon is lifetime (82 years) in all strategies except when specified a different time horizon.

Table S3. Vaccine effectiveness against VT-IPD and after applying the waning effect by age and risk group.

Age (years) / Risk group	PCV, by No. Years Since Receipt of Vaccine					PPV23, by No. Years Since Receipt of Vaccine				
	Year 1	Year 5	Year 10	Year 15	Year 16+	Year 1	Year 5	Year 10	Year 15	Year 16+
18-49										
Low	82	82	63	37	0	59	45	0	0	0
Moderate	82	82	63	37	0	33	25	0	0	0
High	65	65	51	30	0	17	13	0	0	0
50-64										
Low	79	79	61	36	0	58	45	0	0	0
Moderate	79	79	61	36	0	32	25	0	0	0
High	63	63	49	29	0	17	13	0	0	0
65-74										
Low	75	75	58	34	0	56	43	0	0	0
Moderate	75	75	58	34	0	31	24	0	0	0
High	60	60	46	27	0	16	12	0	0	0
75-84										
Low	75	75	58	34	0	51	39	0	0	0
Moderate	75	75	58	34	0	28	22	0	0	0
High	60	60	46	27	0	15	11	0	0	0
85-99										
Low	75	75	58	34	0	38	29	0	0	0
Moderate	75	75	58	34	0	21	16	0	0	0
High	60	60	46	27	0	11	8	0	0	0

IPD: Invasive pneumococcal disease; PCV: Pneumococcal conjugate vaccine; PPV: Pneumococcal polysaccharide vaccine.

Table S4. Vaccine effectiveness against VT-NBP and after applying the waning effect by age and risk group.

Age (years) / Risk group	PCV, by No. Years Since Receipt of Vaccine					PPV23, by No. Years Since Receipt of Vaccine				
	Year 1	Year 5	Year 10	Year 15	Year 16+	Year 1	Year 5	Year 10	Year 15	Year 16+
18-49										
Low	56	56	43	25	0	0	0	0	0	0
Moderate	56	56	43	25	0	0	0	0	0	0
High	45	45	34	20	0	0	0	0	0	0
50-64										
Low	51	51	40	24	0	0	0	0	0	0
Moderate	51	51	40	24	0	0	0	0	0	0
High	41	41	32	19	0	0	0	0	0	0
65-74										
Low	45	45	35	21	0	0	0	0	0	0
Moderate	45	45	35	21	0	0	0	0	0	0
High	36	36	28	16	0	0	0	0	0	0
75-84										
Low	45	45	35	21	0	0	0	0	0	0
Moderate	45	45	35	21	0	0	0	0	0	0
High	36	36	28	16	0	0	0	0	0	0
85-99										
Low	45	45	35	21	0	0	0	0	0	0
Moderate	45	45	35	21	0	0	0	0	0	0
High	36	36	28	16	0	0	0	0	0	0

NBP: Non-bacteremic pneumonia; PCV: Pneumococcal conjugate vaccine; PPV: Pneumococcal polysaccharide vaccine.

Table S5. Vaccine serotype coverage and indirect effect for all cause Non Bacteremic Pneumonia (NBP), observed and projected by fitting the best line trend in persons 18-64 and aged ≥ 65 years.

Vaccine	PCV13	PCV15	PCV20	PPV23
Year of modelling	**18-64 years old**			
Year 1	12.0%	14.9%	28.1%	30.5%
Year 2	10.9%	13.8%	27.3%	29.7%
Year 3	9.8%	12.7%	27.0%	29.6%
Year 4	8.9%	11.7%	26.8%	29.4%
Year 5	8.1%	10.8%	26.7%	29.3%
Year 6	7.3%	10.0%	26.5%	29.2%
Year 7	6.6%	9.2%	26.3%	29.1%
Year 8	6.0%	8.5%	26.2%	29.0%
Year 9	5.4%	7.8%	26.1%	28.9%
Year 10	4.9%	7.2%	25.9%	28.8%
Year of modelling	**≥ 65 years old**			
Year 1	14.1%	15.7%	26.2%	28.7%
Year 2	13.7%	15.7%	26.2%	28.7%
Year 3	13.3%	15.6%	26.0%	28.6%
Year 4	13.0%	15.1%	25.9%	28.5%
Year 5	12.7%	14.7%	25.7%	28.4%
Year 6	12.4%	14.3%	25.6%	28.3%
Year 7	12.2%	13.9%	25.4%	28.2%
Year 8	11.9%	13.6%	25.3%	28.2%
Year 9	11.7%	13.3%	25.2%	28.1%
Year 10	11.5%	13.0%	25.1%	28.0%

IPD: Invasive pneumococcal disease; NBP: Non-bacteremic pneumonia; PCV: Pneumococcal conjugate vaccine; PPV: Pneumococcal polysaccharide vaccine.

Table S6. Sensitivity scenario analysis including PPV23 effectiveness against hospitalized and outpatient NBP in dominant strategies according with age and risk group vaccination recommendation.

Population	Vaccination strategy[1,2]	Cost-effectiveness analysis[3]			
		ICER[4] (95% probabilistic CI)	Likelihood of cost-saving (% of iterations)	Likelihood of cost-effective (% of iterations)	
				By GENESIS threshold (€21,000/QALY)	By WHO threshold (€25,770/QALY)
18+ years old	PCV20 vs PPV23	-1,010 (-9,152; 7,668)	55%	100%	100%
18+ years old **immunocompromised** (high risk)	PCV20 alone vs seq PCV15+PPV23	-10,372 (-26,532; -2,405)	100%	100%	100%
18+ years old **at risk** (moderate risk)	PCV20 vs PPV23	-121 (-10,554; 17,887)	70%	98%	98%
	Sequential PCV20+PPV23 vs seq PCV15+PPV23	-14,435 (-33,784; -4,463)	100%	100%	100%
65+ years old (all risk groups)	PCV15 vs PPV23	29,600 (2,634; 137,016)	0%	58%	63%
	PCV20 vs PPV23	289 (-10,152; 10,633)	60%	100%	100%
	Sequential PCV20+PPV23 vs seq PCV15+PPV23	-10,7759 (-24,603; -3,234)	100%	100%	100%

PPV: Pneumococcal polysaccharide vaccine; PCV: Pneumococcal conjugate vaccine; CI: Confidence interval; seq: sequential; NBP: Non bacteremic pneumonia.

[1]Model horizon is lifetime (82 years) in all strategies; [2]NBP effectiveness, both hospitalized and outpatient, for PPV23 in persons aged 18 years old and above was set at 24.0% first year of modelling with a 24% wanning effect during the first 5 years of modelling according to Lawrence H et al., PLoS Med 2020; 17(10): e1003326, and in persons aged 65 years old and above was set at 33.5% with the same wanning effect in the first 5 years of modelling according to Suzuki M. et al., Lancet Infect Dis 2017; 17: 313-21; [3]Cost-effectiveness probabilistic analysis by Montecarlo simulation; [4]ICER: Incremental cost-effectiveness ratio in Euros/QALY gained.

Table S7. Cost-effectiveness results in immunocompromised (high risk) patients PCV20 versus sequential vaccination with PCV15+PPV23.

Immunocompromised ≥ 18 years at model entry (n=3.83 million inhabitants, vaccine uptake: 56.7% all ages, 61.0% 65+ years old)	**PCV15+PPV23**	**PCV20**	**Difference**
Outcomes (No. of cases)			
IPD	57,962	55,777	-2,185
Bacteremia	55,457	53,374	-2,083
Meningitis	2,505	2,403	-102
NBP			
Requiring inpatient care	1,258,531	1,243,144	-15,387
Requiring outpatient care	388,041	382,949	-5,092
No. of deaths	290,811	287,023	-3,788
Life-years (discounted)	47,496,782	47,520,997	24,215
Quality-adjusted life-years (discounted)	35,619,330	35,635,975	16,645
Total costs (€, in thousands)			
Medical care	4,120,636	4,044,144	-76,492
Vaccination	137,878	105,834	-32,044
Medical + vaccination	4,258,514	4,149,978	-108,536
Incremental cost-effectiveness ratio (Healthcare system perspective, €)			
Incremental cost per life-year gained	-	-	-4,482
Incremental cost per quality-adjusted life-year gained	-	-	-6,521

IPD: Invasive pneumococcal disease; NBP: Non-bacteremic pneumonia; PCV: Pneumococcal conjugate vaccine; PPV: Pneumococcal polysaccharide vaccine.

Table S8. Cost-effectiveness results in immunocompetent at risk (moderate risk) patients PPV23 versus no vaccination.

Immunocompetent with moderate risk ≥ 18 years at model entry (n=10.03 million inhabitants, vaccine uptake: 17.4% all ages, 41.3% 65+ years old)	**No vaccination**	**PPV23**	**Difference**
Outcomes (No. of cases)			
IPD	111,182	110,383	-799
Bacteremia	106,297	105,531	-766
Meningitis	4,885	4,852	-33
NBP			
Requiring inpatient care	2,348,841	2,348,865	24
Requiring outpatient care	1,343,719	1,343,728	9
No. of deaths	315,027	314,902	-125
Life-years (discounted)	170,706,150	170,707,053	903
Quality-adjusted life-years (discounted)	136,670,882	136,671,383	501
Total costs (€, in thousands)			
Medical care	6,294,823	6,289,054	-5,769
Vaccination	0	28,274	28,274
Medical + vaccination	6,294,823	6,317,328	22,505
Incremental cost-effectiveness ratio (Healthcare system perspective, €)			
Incremental cost per life-year gained	-	-	24,930
Incremental cost per quality-adjusted life-year gained	-	-	44,888

IPD: Invasive pneumococcal disease; NBP: Non-bacteremic pneumonia; PPV: Pneumococcal polysaccharide vaccine.

Table S9. Cost-effectiveness results in immunocompetent persons 65 years old and above with PPV23 versus no vaccination.

Immunocompetent ≥ 65 years at model entry (n=9.17 million inhabitants, vaccine uptake: 38.0)	**No vaccination**	**PPV23**	**Difference**
Outcomes (No. of cases)			
IPD	57,704	56,081	-1,623
Bacteremia	55,897	54,329	-1,568
Meningitis	1,807	1,752	-55
NBP			
Requiring inpatient care	1,676,269	1,676,343	74
Requiring outpatient care	753,633	753,656	23
No. of deaths	342,277	341,928	-350
Life-years (discounted)	81,221,687	81,223,612	1,925
Quality-adjusted life-years (discounted)	58,707,883	58,709,166	1,283
Total costs (€, in thousands)			
Medical care	6,096,721	6,086,026	-10,695
Vaccination	0	56,355	56,355
Medical + vaccination	6,096,721	6,142,381	45,660
Incremental cost-effectiveness ratio (Healthcare system perspective, €)			
Incremental cost per life-year gained	-	-	23,724
Incremental cost per quality-adjusted life-year gained	-	-	35,586

IPD: Invasive pneumococcal disease; NBP: Non-bacteremic pneumonia; PPV: Pneumococcal polysaccharide vaccine.