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ORIGINAL PAPER

Modeling the cost-effectiveness of infant vaccination with pneumococcal conjugate vaccines in Germany

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Abstract
Background In 2009, the European Medicines Agency granted approval for two higher-valent pneumococcal conjugate vaccines. This study aims to evaluate the cost-effectiveness of universal infant (<2 years old) vaccination with a 13-valent pneumococcal conjugate vaccine (PCV13) in comparison with a 10-valent pneumococcal conjugate vaccine (PCV10) for the prevention of pneumococcal disease in Germany.
Methods A population-based Markov model was developed to estimate the impact of PCV13 and PCV10 on invasive pneumococcal disease (IPD), non-invasive pneumonia (PNE), and acute otitis media (AOM) over a time horizon of 50 years. The model included the effects of the historical vaccination scheme in infants as well as indirect herd effects and replacement disease. We used German epidemiological data to calculate episodes of IPD, PNE, and AOM, as well as direct and indirect effects of the vaccination. Parameter uncertainty was tested in univariate and probabilistic sensitivity analyses.
Results In the base-case analysis, the ICER of PCV13 versus PCV10 infant vaccination was EUR 9826 per quality-adjusted life-year (QALY) gained or EUR 5490 per life-year (LY) gained from the societal perspective and EUR 3368 per QALY gained or EUR 1882 per LY gained from the perspective of the German statutory health insurance. The results were particularly sensitive to the magnitude of indirect effects of both vaccines.
Conclusions Universal infant vaccination with PCV13 is likely to be a cost-effective intervention compared with PCV10 within the German health care system, if additional net indirect effects of PCV13 vaccination are significant.

Keywords Pneumococcal conjugate vaccine · Cost-effectiveness · Herd protection · Vaccination · Economic evaluation · Costs

JEL Classification I19

Background

Streptococcus pneumonia is a major cause of morbidity and mortality worldwide. Pneumococcal infections are the leading cause of death in children aged <5 years. Meningitis, bacteremia, and pneumonia with bacteremia and/or empyema are invasive diseases caused by pneumococci. Risk factors for invasive pneumococcal disease (IPD) include age, ethnicity, geographic location, concomitant chronic illnesses, and attendance in day care centers [1]. O'Brien et al. [2] estimated that about 14.5 million episodes of serious pneumococcal disease occurred in 2000 worldwide, resulting in about 826,000 deaths in children aged 1–59 months.

In 2001, a 7-valent pneumococcal vaccine (PCV7) was approved in Europe. It provides protection against seven of the 94 (to date) discovered serotypes. After the Standing Vaccination Committee (STIKO) at the German Robert Koch Institute had recommended PCV7 vaccination for children who were particularly vulnerable to pneumococcal

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disease [3], it expanded its recommendation to all children <2 years of age in mid-2006 [4]. As a result of the universal infant vaccination in Germany, the incidence of IPD decreased in children <16 years of age [5, 6]. In addition, indirect herd effects were observed in vaccine-type (VT) IPD [7, 8]. Replacement disease caused by non-vaccine serotypes had not been reported until mid-2008 [5], but during the following 2 years, the incidence of non-VT IPD had increased significantly in children <16 years old [6].

In 2009, the European Medicines Agency approved two other vaccines for the vaccination of infants against pneumococcal disease: a 10-valent conjugate vaccine (PCV10) and a 13-valent conjugate vaccine (PCV13). PCV10 includes the serotypes of PCV7 as well as three additional serotypes, whereas PCV13 covers the serotypes of PCV10 and three additional serotypes. While PCV7 and PCV13 are conjugated to a nontoxic diphtheria CRM197 carrier protein, PCV10 uses non-typeable *Haemophilus influenzae* protein D as its carrier.

In August of 2009, PCV10 was introduced to the German market. In the beginning of 2010, PCV7 was withdrawn from the market and completely replaced by PCV13. At the time of the launch of PCV10 and PCV13, about 54 % of IPD in children <16 years old and 36 % of IPD in people 16+ years old were caused by PCV10-serotypes, while 76 and 62 %, respectively, were caused by PCV13 serotypes [9].

After the introduction of the higher-valent conjugate vaccines in Germany, the number of reported PCV7-serotype IPD episodes has continued to decline in children <16 years of age. In addition, the additional six serotypes included in PCV13 have also started to decrease, while an ongoing increase in the number of IPD episodes caused by non-PCV13 serotypes has been observed [10].

Several studies [11–30] examined the cost-effectiveness of PCV13 in comparison with PCV10. The results of the analyses differed substantially due to varying assumptions on input parameters. Therefore, the objectives of this study were to evaluate the cost-effectiveness of universal infant vaccination using PCV13 only or PCV10 only in Germany, and to estimate the impact of higher-valent conjugate vaccines on the burden of pneumococcal disease compared with a reference scenario in which children <2 years old were still vaccinated with PCV7.

Methods

We developed a population-based Markov model in Microsoft EXCEL 2010 to estimate the effects of childhood vaccination (<2 years) over a time horizon of 50 years (2013–2062). The model took into account the historical vaccination scheme pre 2013 (burn-in see Fig. 1) to calculate the serotype-specific incidence of invasive pneumococcal disease at the start of the evaluation phase. The cycle length of the model was 1 year.

The model consists of three arms:

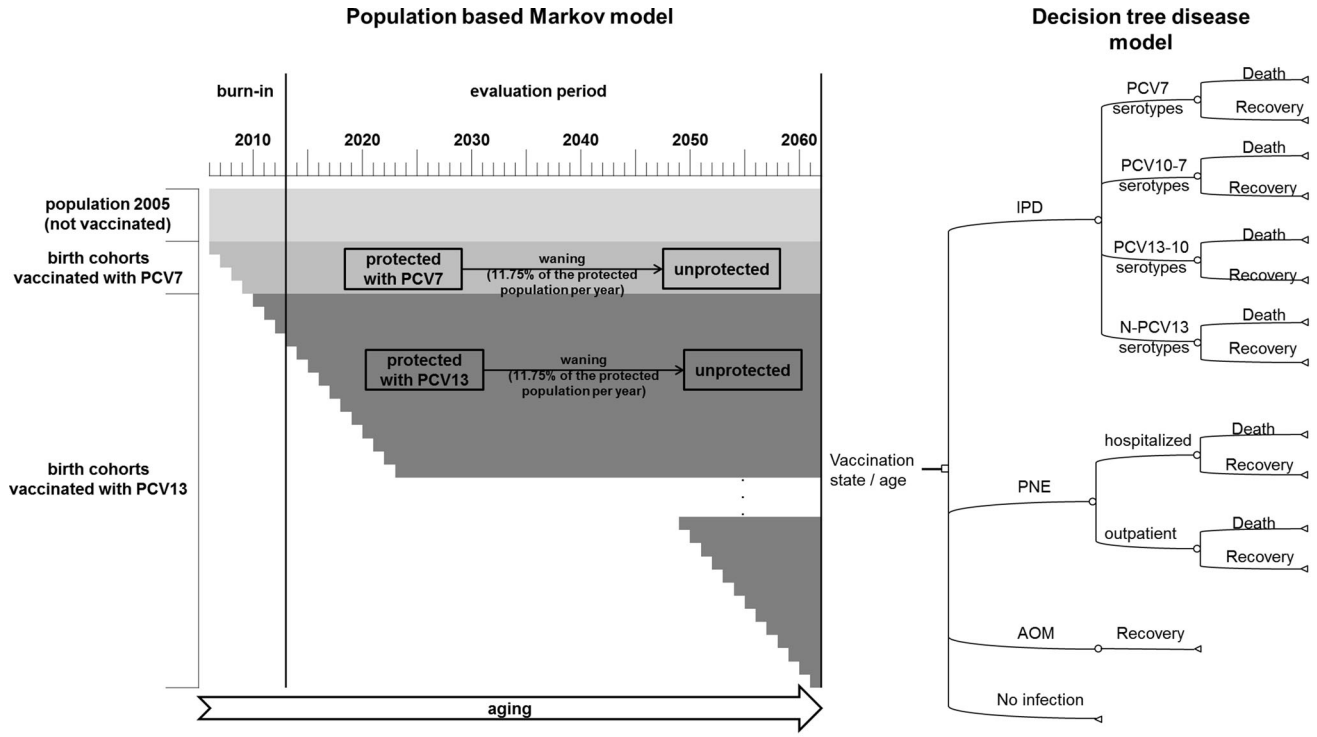
1. Vaccination of infants with PCV7 from 2006 to 2009; vaccination of infants with PCV13 from 2010 to 2062
2. Vaccination of infants with PCV7 from 2006 to 2009; vaccination of infants with PCV10 from 2010 to 2062
3. Vaccination of infants with PCV7 from 2006 to 2062. This arm served as a reference scenario to estimate the effect of the higher-valent vaccines on the burden of pneumococcal diseases.

On average, transitions between states occur in the middle of each cycle [31]. Therefore, to compensate for the timing of transition, we performed half cycle corrections by averaging the outcomes of two cycles ($\text{outcome}_{half-cycle_t} = \frac{\text{outcome}_{\text{cycle}_t} + \text{outcome}_{\text{cycle}_{t+1}}}{2}$) [32].

The evaluation was conducted from the perspective of the statutory health insurance (SHI) and the societal perspective. Quality-adjusted life-years (QALY) and life-years (LY) gained served as primary outcomes. Both costs and outcomes were discounted by 3 % following the recommendations of the Institute for Quality and Efficiency in Health Care (IQWiG) [33]. The price year was 2013.

Model structure

The population was divided into 101 age groups (0–100 years). The simulation started with the German population structure of 2005. Each cycle, the population aged 1 year and a new cohort of newborns was added. The entire population (including the new birth cohorts) was followed up until the end of the evaluation period (2062). Infants received vaccination during the first year of life. Over the course of time, immunized individuals might lose vaccine protection against pneumococcal disease (waning). The population-based Markov model was used to track vaccination states and simulate the aging process. We coupled the model with a decision tree to calculate the annual episodes of pneumococcal diseases and mortality for each age/vaccination state. Afterwards, the annual all cause death rates were corrected by the number of deaths related to pneumococcal disease. In case of IPD, the simulation distinguished between four groups of serotypes: serotypes included in PCV7 (PCV7), serotypes included in PCV10 but not in PCV7 (PCV10-7), serotypes included in PCV13 but not in PCV10 (PCV13-10) and serotypes not covered by PCV13 (N-PCV13). The model structure of the PCV13 arm is illustrated in Fig. 1.



IPD: invasive pneumococcal disease; PNE: non-invasive pneumonia; AOM: acute otitis media; 7: PCV7; 13: PCV13, U: unvaccinated/waned immunity, PCV7 serotypes : serotypes covered by PCV7, PCV10-PCV7 serotypes : serotypes covered by PCV10 but not by PCV7, PCV13-PCV10 serotypes : serotypes covered by PCV13 but not by PCV10, N-PCV13 serotypes: serotypes not covered by PCV13

Fig. 1 Model structure (PCV13 arm)

Demography

To project the German population, we used a recently developed demographic model [34] that generated the all-cause death rates, number of newborns and life expectancy for each age group per calendar year. Results of the model were in line with projections of the German Federal Statistical Office [34]. Figure 2 shows the results of the projection for 2010, 2040, and 2060.

Epidemiology of pneumococcal disease in Germany

In Germany, two independent reporting systems perform nationwide surveillance of IPD for children <16 years old [6]. The German pediatric surveillance unit (ESPED) collects IPD data from all children's hospitals and all pediatric wards in general hospitals [35]. The second system is a laboratory-based passive (web-based) sentinel surveillance operated by the Robert Koch Institute [6, 8]. IPD incidences are estimated by capture recapture calculations [5, 6, 36]. Due to stable IPD numbers, the hospital surveillance was stopped in 2003 and was resumed in January 2007 after the recommendation for universal infant PCV7 vaccination [5]. Therefore, pre-vaccination pneumococcal meningitis and non-meningitis IPD incidences from 1997 to 2003 served as model inputs.

In the absence of nationwide notification requirements for IPD cases and an active hospital-based surveillance, there is a lack of national data on IPD incidence in adults. The only German source that reported incidences in the population >15 years of age, was a laboratory-based surveillance study conducted in the state North-Rhine Westphalia between 2001 and 2003 [37]. Due to poor blood culturing practices in Germany, we adjusted non-meningitis IPD incidence rates for under-ascertainment [37, 38]. The pre-vaccination serotype distribution for the period from 2005 to 2006 was obtained from the National Reference Center for Streptococci (NRZ) [9].

A detailed microbiological diagnosis is usually not performed in non-invasive pneumonia (PNE) and acute otitis media (AOM). Therefore, we used data of all-cause PNE and AOM. Age-specific incidences of hospitalized PNE were estimated based on German pre-vaccination hospital admission data [39]. Due to significant annual fluctuations in the reported cases, we took the average incidence rates of the period 2003–2005. Outpatient PNE data were derived from a representative pharmaceutical prescription panel [40]. Schnoor et al. estimated an incidence of PNE ranging from 370 to 1230 cases per

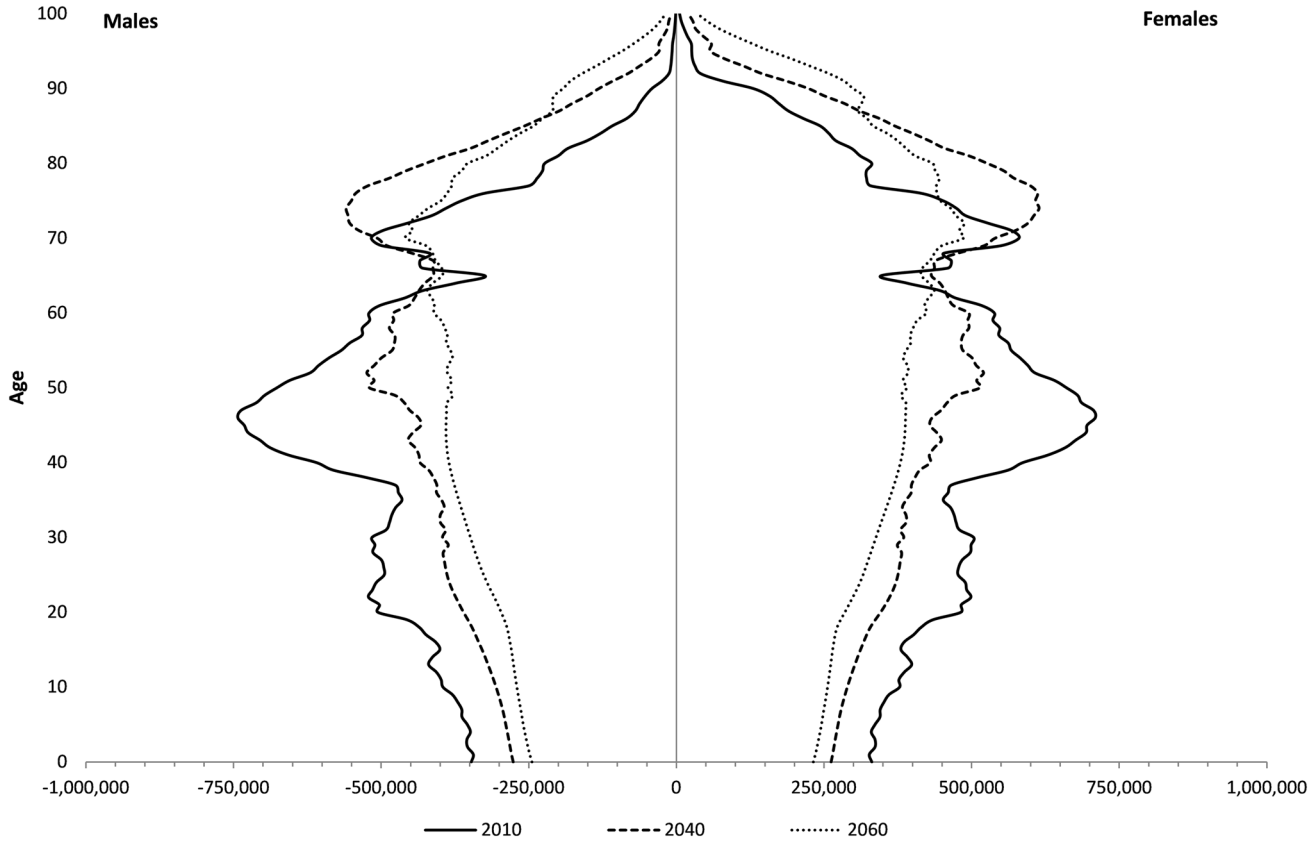


Fig. 2 Results of the population projection

100,000 adults [41], which was in line with the hospital admission data (approximately 1,200 cases per 100,000 adults).

The majority of AOM episodes occur in childhood with a peak in children <5 years old. Schnabel et al. [42] observed 3097 German children born between November 1997 and January 1999. Of these, 18.7, 30.0, and 21.2 % suffered from AOM in their first, second until fifth, and sixth year of life, respectively. Grueber et al. [43] prospectively observed 1314 children born in 1990 in the MAS-90 study. For children from 7 to <12 years old, the annual risk of developing an AOM episode was 8 %. Finally, incidence of AOM in adolescents (12–13 years of age: 4.3 %, and 14–17 years of age: 3.5 %) was taken from the KiGGS-Study [44]. In 15 per 100,000 hospitalized children <2 years old, and 5 per 100,000 hospitalized children >2 years old surgical treatment was needed (e.g., tympanostomy tube placement) [45, 46] (Tables 1, 2).

A significant proportion of survivors of pneumococcal meningitis and non-meningitis IPD suffer from serious sequelae, such as neurological disorders or hearing loss. According to ESPED, sequelae were present in 20.6 % of children with pneumococcal meningitis and in 3.8 % with non-meningitis IPD. Hearing loss occurred in 9.1 % of meningitis survivors [36]. As the ESPED data comprised only acute incidents with the observation ending at hospital discharge, late sequelae were not documented.

In Germany, the pediatric case fatality ratios (CFR) of pneumococcal meningitis and non-meningitis IPD were 7.5 and 2.0 % [36], respectively. IPD-specific CFRs for adults were taken from an analysis of 22,000 IPD patients in England (March 2002–March 2009) [47]. Age-specific CFRs for hospitalized PNE were estimated based on national hospital statistics [39]. For outpatient PNE, we assumed CFRs of 0 % for patients <60 years old and 0.5 % for patients ≥60 years old (Table 3).

Vaccine uptake

Recent analyses hinted high acceptance of the primary immunization in Germany. However, deficits existed in the application of the booster dose in the second year of life [48]. Surveillance of vaccination coverage based on data from 17 regional associations of SHI physicians suggested that the current uptake for the first three doses was about 90 % [49] and for the fourth dose about 75 % [50]. In the model, we applied an uptake of 90 % for all four doses.

Table 1 Incidence (per 100,000 individuals) of pneumococcal diseases in Germany

Parameter	Age group	Base-case value	Distribution	Distribution parameter	References
Meningitis	<2	7.70	Beta	$\alpha = 120$, $\beta = 1{,}562{,}217$	[6, 36]
	2 to <5	1.70		$\alpha = 39$, $\beta = 2{,}317{,}608$	
	5 to <15	0.40		$\alpha = 42$, $\beta = 10{,}374{,}959$	
Non-meningitis invasive pneumococcal disease	0 to <2	34.29*	Beta	$\alpha = 535$, $\beta = 1{,}561{,}802$	[6, 36]
	2 to <5	9.45*		$\alpha = 225$, $\beta = 2{,}317{,}442$	
	5 to <15	2.16*		$\alpha = 218$, $\beta = 10{,}374{,}783$	
Invasive pneumococcal disease	15 to <45	6.75*	Beta	$\alpha = 487$, $\beta = 7208$	[37]
	45 to <65	22.95*		$\alpha = 1059$, $\beta = 4{,}613{,}929$	
	65 to <75	65.07*		$\alpha = 711$, $\beta = 1{,}091{,}750$	
	75 to <85	27.81*		$\alpha = 525$, $\beta = 1{,}886{,}563$	
	85+	67.77*		$\alpha = 200$, $\beta = 295{,}473$	
Community-acquired pneumonia hospitalized	<1	1493	Beta	$\alpha = 1050$, $\beta = 69{,}278$	[39]
	1 to <5	814		$\alpha = 2424$, $\beta = 295{,}328$	
	5 to <15	136		$\alpha = 1133$, $\beta = 831{,}882$	
	15 to <45	59		$\alpha = 1992$, $\beta = 3{,}373{,}602$	
	45 to <65	165		$\alpha = 3529$, $\beta = 2{,}134{,}956$	
	65 to <75	518		$\alpha = 4478$, $\beta = 860{,}059$	
	75 to <85	1294		$\alpha = 6531$, $\beta = 498{,}153$	
	85+	2894		$\alpha = 4120$, $\beta = 138{,}230$	
Community-acquired pneumonia outpatient	<1	2447	Beta	$\alpha = 172$, $\beta = 6861$	[40]
	2 to <5	8492		$\alpha = 2529$, $\beta = 27{,}247$	
	5 to <15	2793		$\alpha = 2326$, $\beta = 80{,}975$	
	15 to <45	622		$\alpha = 2099$, $\beta = 335{,}461$	
	45 to <65	1009		$\alpha = 2158$, $\beta = 211{,}691$	
	65 to <75	1417		$\alpha = 1225$, $\beta = 85{,}229$	
	75 to <85	1532		$\alpha = 773$, $\beta = 49{,}695$	
	85+	1967		$\alpha = 280$, $\beta = 13{,}955$	
Acute otitis media	<2	18,700		$\alpha = 2607$, $\beta = 11{,}333$	[42]
	2	31,600		$\alpha = 2245$, $\beta = 4860$	
	3	31,700		$\alpha = 2297$, $\beta = 4948$	
	4	29,700		$\alpha = 2203$, $\beta = 5215$	
	5	31,300		$\alpha = 2427$, $\beta = 5326$	
	6	21,200		$\alpha = 1648$, $\beta = 6126$	
	7 to <12	8000		$\alpha = 3187$, $\beta = 36{,}656$	[43]
	12 to <14	4300		$\alpha = 716$, $\beta = 15{,}935$	[44]
	14 to <18	3500		$\alpha = 1325$, $\beta = 36{,}519$	
Sequelae after non-meningitis IPD	0 to <16	3.77 %		$\alpha = 13$, $\beta = 587$	[36]
Sequelae after meningitis	0 to <16	20.60 %		$\alpha = 96$, $\beta = 628$	
Hearing loss after meningitis	0 to <16	9.12 %		$\alpha = 66$, $\beta = 658$	

IPD invasive pneumococcal disease

* Including a factor of 2.7 for underreporting according to Rueggeberg et al. [38]

Direct effects of vaccination

IPD efficacy data (Table 4) were derived from the trial of the Northern California Kaiser Permanente (NCKP) Health Maintenance Organization [51] and the FinIP trial [52]. In the intention to treat analysis of the NCKP trial, the effectiveness of PCV7 against vaccine serotypes was 93.9 %. We assumed that the efficacy of PCV13 was equal to PCV7 for all vaccine serotypes. In the FinIP trial, PCV10 showed an effectiveness of 100 % against VT IPD in children receiving a 3 + 1 schedule and 92 % in children receiving a 2 + 1 schedule.

Table 2 Serotype distribution of invasive pneumococcal diseases

Parameter	Age group	Group of serotypes	Base-case value (%)	Distribution	Distribution parameter	References
Meningitis	<2	PCV7	67.25	Dirichlet (based on gamma distributions)	$\alpha = 269, \beta = 1$	[9]
		PCV10-PCV7	11.75		$\alpha = 47, \beta = 1$	
		PCV13-PCV10	7.25		$\alpha = 29, \beta = 1$	
		N-PCV13	13.75		$\alpha = 55, \beta = 1$	
	2 to <5	PCV7	68.67	Dirichlet (based on gamma distributions)	$\alpha = 103, \beta = 1$	
		PCV10-PCV7	8.00		$\alpha = 12, \beta = 1$	
		PCV13-PCV10	6.00		$\alpha = 9, \beta = 1$	
		N-PCV13	17.33		$\alpha = 26, \beta = 1$	
	5 to <15	PCV7	39.20	Dirichlet (based on gamma distributions)	$\alpha = 49, \beta = 1$	
		PCV10-PCV7	4.80		$\alpha = 6, \beta = 1$	
		PCV13-PCV10	16.80		$\alpha = 21, \beta = 1$	
		N-PCV13	39.20		$\alpha = 49, \beta = 1$	
Non-meningitis IPD	<2	PCV7	64.55	Dirichlet (based on gamma distributions)	$\alpha = 497, \beta = 1$	[9]
		PCV10-PCV7	8.83		$\alpha = 68, \beta = 1$	
		PCV13-PCV10	12.21		$\alpha = 94, \beta = 1$	
		N-PCV13	14.41		$\alpha = 111, \beta = 1$	
	2 to <5	PCV7	74.18	Dirichlet (based on gamma distributions)	$\alpha = 250, \beta = 1$	
		PCV10-PCV7	11.57		$\alpha = 39, \beta = 1$	
		PCV13-PCV10	4.75		$\alpha = 16, \beta = 1$	
		other	9.50		$\alpha = 32, \beta = 1$	
	5 to <15	PCV7	30.26	Dirichlet (based on gamma distributions)	$\alpha = 69, \beta = 1$	
		PCV10-PCV7	43.42		$\alpha = 99, \beta = 1$	
		PCV13-PCV10	8.77		$\alpha = 20, \beta = 1$	
		N-PCV13	17.55		$\alpha = 40, \beta = 1$	
IPD	16 to <50	PCV7	38.24	Dirichlet (based on gamma distributions)	$\alpha = 39, \beta = 1$	[9]
		PCV10-PCV7	27.45		$\alpha = 28, \beta = 1$	
		PCV13-PCV10	7.84		$\alpha = 8, \beta = 1$	
		N-PCV13	26.47		$\alpha = 27, \beta = 1$	
	50 to <60	PCV7	47.62	Dirichlet (based on gamma distributions)	$\alpha = 40, \beta = 1$	
		PCV10-PCV7	15.48		$\alpha = 13, \beta = 1$	
		PCV13-PCV10	16.67		$\alpha = 14, \beta = 1$	
		N-PCV13	20.23		$\alpha = 17, \beta = 1$	
	60 to <75	PCV7	47.98	Dirichlet (based on gamma distributions)	$\alpha = 95, \beta = 1$	
		PCV10-PCV7	14.14		$\alpha = 28, \beta = 1$	
		PCV13-PCV10	18.18		$\alpha = 36, \beta = 1$	
		N-PCV13	19.70		$\alpha = 39, \beta = 1$	
	75+	PCV7	49.11	Dirichlet (based on gamma distributions)	$\alpha = 83, \beta = 1$	
		PCV10-PCV7	11.24		$\alpha = 19, \beta = 1$	
		PCV13-PCV10	18.93		$\alpha = 32, \beta = 1$	
		N-PCV13	20.72		$\alpha = 35, \beta = 1$	

IPD invasive pneumococcal disease, *PCV7* serotypes covered by PCV7, *PCV10-PCV7* serotypes covered by PCV10 but not by PCV7, *PCV13-PCV10* serotypes covered by PCV13 but not by PCV10, *N-PCV13* serotypes not covered by PCV13

In the absence of pathogen-specific data, we used estimates of the effectiveness against all causes of non-invasive pneumonia. PCV7 and PCV10 showed comparable effects against pneumonia [53, 54], while clinical data on the impact of PCV13 on non-invasive pneumococcal pneumonia in children does not exist to date. Due to a lack of clinical evidence, we assumed that the effectiveness of the higher-valent vaccine increased proportionally to the serotype coverage in IPD [17]. PCV7 effectiveness data from the NCKP trial [55] (11.1 % against hospitalized PNE

Table 3 Case fatality ratio (CFR) of pneumococcal-related diseases

Parameter	Age group	Group of serotypes	Base-case value (%)	Distribution	Distribution parameter	References
Meningitis	<2	PCV7	67.25	Dirichlet (based on gamma distributions)	$\alpha = 269, \beta = 1$	[9]
		PCV10-PCV7	11.75		$\alpha = 47, \beta = 1$	
		PCV13-PCV10	7.25		$\alpha = 29, \beta = 1$	
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	2 to <5	PCV7	68.67	Dirichlet (based on gamma distributions)	$\alpha = 103, \beta = 1$	
		PCV10-PCV7	8.00		$\alpha = 12, \beta = 1$	
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		N-PCV13	17.33		$\alpha = 26, \beta = 1$	
	5 to <15	PCV7	39.20	Dirichlet (based on gamma distributions)	$\alpha = 49, \beta = 1$	
		PCV10-PCV7	4.80		$\alpha = 6, \beta = 1$	
		PCV13-PCV10	16.80		$\alpha = 21, \beta = 1$	
		N-PCV13	39.20		$\alpha = 49, \beta = 1$	
Non-meningitis IPD	<2	PCV7	64.55	Dirichlet (based on gamma distributions)	$\alpha = 497, \beta = 1$	[9]
		PCV10-PCV7	8.83		$\alpha = 68, \beta = 1$	
		PCV13-PCV10	12.21		$\alpha = 94, \beta = 1$	
		N-PCV13	14.41		$\alpha = 111, \beta = 1$	
	2 to <5	PCV7	74.18	Dirichlet (based on gamma distributions)	$\alpha = 250, \beta = 1$	
		PCV10-PCV7	11.57		$\alpha = 39, \beta = 1$	
		PCV13-PCV10	4.75		$\alpha = 16, \beta = 1$	
		other	9.50		$\alpha = 32, \beta = 1$	
	5 to <15	PCV7	30.26	Dirichlet (based on gamma distributions)	$\alpha = 69, \beta = 1$	
		PCV10-PCV7	43.42		$\alpha = 99, \beta = 1$	
		PCV13-PCV10	8.77		$\alpha = 20, \beta = 1$	
		N-PCV13	17.55		$\alpha = 40, \beta = 1$	
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		PCV13-PCV10	7.84		$\alpha = 8, \beta = 1$	
		N-PCV13	26.47		$\alpha = 27, \beta = 1$	
	50 to <60	PCV7	47.62	Dirichlet (based on gamma distributions)	$\alpha = 40, \beta = 1$	
		PCV10-PCV7	15.48		$\alpha = 13, \beta = 1$	
		PCV13-PCV10	16.67		$\alpha = 14, \beta = 1$	
		N-PCV13	20.23		$\alpha = 17, \beta = 1$	
	60 to <75	PCV7	47.98	Dirichlet (based on gamma distributions)	$\alpha = 95, \beta = 1$	
		PCV10-PCV7	14.14		$\alpha = 28, \beta = 1$	
		PCV13-PCV10	18.18		$\alpha = 36, \beta = 1$	
		N-PCV13	19.70		$\alpha = 39, \beta = 1$	
	75+	PCV7	49.11	Dirichlet (based on gamma distributions)	$\alpha = 83, \beta = 1$	
		PCV10-PCV7	11.24		$\alpha = 19, \beta = 1$	
		PCV13-PCV10	18.93		$\alpha = 32, \beta = 1$	
		N-PCV13	20.72		$\alpha = 35, \beta = 1$	

IPD invasive pneumococcal disease, *PCV7* serotypes covered by PCV7, *PCV10-PCV7* serotypes covered by PCV10 but not by PCV7, *PCV13-PCV10* serotypes covered by PCV13 but not by PCV10, *N-PCV13* serotypes not covered by PCV13

and 6.0 % against outpatient PNE) provided the basis for the calculations.

In a systematic literature review of the impact of pneumococcal conjugate vaccine on AOM, Taylor et al. [56] identified three randomized controlled trials (RCT) for PCV7. While two trials [51, 57–59] reported comparable effects of 5.8–8.9 %, one study [60] in high-risk American natives failed to demonstrate effectiveness of PCV7 against AOM. However, the failure to detect a statistically significant impact might be due to a lack of statistical power [56,

60]. Again, we took data from the NCKP trial [58] and increased the effectiveness of PCV13 proportionally to the serotype coverage in IPD. Two studies [61, 62] suggested an additional benefit of PCV10 in preventing AOM due to its effectiveness against *Haemophilus influenza* AOM. Therefore, we applied an effectiveness of 19 % against all cause AOM [62], instead of extrapolating the PCV7-effectiveness.

For children >5 years old, we adjusted the effectiveness of each vaccine against non-invasive pneumococcal disease according to its serotype coverage for IPD.

Melegaro et al. [63] calculated an average duration of vaccine protection of 8 years. In the absence of empirical data on the effects of waning immunity for pneumococcal conjugated vaccines, we applied the estimate of Melegaro in our model. We assumed a constant waning rate. Hence, every year 11.75 % ($1 - \exp[-1/8]$) of the immunized people lost their protection completely.

Indirect effects

The introduction of PCV7 vaccination in infants had led to indirect herd effects and had changed the epidemiology of pneumococcal disease [64–70]. In Germany, indirect herd effects after the implementation of universal childhood vaccination with PCV7 were also detected [7, 8]. The emergence of replacement disease was not observed after 2 years of universal pneumococcal conjugate infant vaccination [5]. However, after 4 years a significant increase in the incidence of IPD caused by non-vaccine serotypes was reported [6].

Jiang et al. [71] used cumulative gamma distributions fitted to United States (US) data to calculate indirect herd effects and serotype replacement as a function of the cumulative vaccination coverage in children. We modeled indirect effects as a function of the cumulative vaccine coverage adjusted for waning (CVCW). The CVCW at time t was an outcome of the Markov model.

$$\begin{aligned}\text{CVCW}_t = {} & \text{cumulative vaccination coverage}_t \\ & - \text{cumulative proportion of vaccinated infants} \\ & \text{who lost vaccine protection}_t\end{aligned}$$

We used two parametric sigmoid functions of the form $\frac{\alpha}{1+\beta\cdot(\text{CVCW}_t)^{-\gamma}}$ to calculate indirect effects. The decline of VT IPD incidence and replacement disease in unvaccinated persons and vaccinated individuals who lost protection against *S. pneumonia* at time t ($t = 0$: start of the vaccination program) was modeled as follows:

Indirect herd effects

$$\text{VT IPD incidence}_t = \text{VT IPD incidence}_0 \cdot \left(1 - \frac{\alpha_{\text{HE}}}{1 + \beta_{\text{HE}} \cdot \text{CVCW}_t^{-\gamma_{\text{HE}}}}\right)$$

Replacement disease

$$\text{non VT IPD incidence}_t = \text{non VT IPD incidence}_0 \cdot \left(1 + \frac{\text{VT IPD incidence}_0}{\text{non VT IPD incidence}_0} \cdot \frac{\alpha_{\text{HE}} \cdot \alpha_{\text{RD}}}{1 + \beta_{\text{RD}} \cdot \text{CVCW}_t^{-\gamma_{\text{RD}}}}\right)$$

The sum of both functions gave the net indirect effects at time t:

$$\text{Net indirect effects}_t = \text{VT IPD incidence}_0 \cdot \left(\frac{\alpha_{\text{HE}} \cdot \alpha_{\text{RD}}}{1 + \beta_{\text{RD}} \cdot \text{CVCW}_t^{-\gamma_{\text{RD}}}} - \frac{\alpha_{\text{HE}}}{1 + \beta_{\text{HE}} \cdot \text{CVCW}_t^{-\gamma_{\text{HE}}}}\right)$$

Replacement disease also occurred in vaccinated infants with direct protection against VT IPD and reduced the overall effectiveness of the vaccine.

$$\text{Net effects}_t = \text{VT IPD incidence}_0 \cdot \left(\frac{\alpha_{\text{HE}} \cdot \alpha_{\text{RD}}}{1 + \beta_{\text{RD}} \cdot \text{CVCW}_t^{-\gamma_{\text{RD}}}} - \text{efficacy against VT IPD}\right)$$

Figure 3 illustrates the indirect effects in a simple scenario without vaccine replacement (from PCV7 to higher-valent PCVs) for the fitted parameters α_{HE}, β_{HE}, γ_{HE}, α_{RD}, β_{RD} and γ_{RD} (Table 7), the vaccination coverage shown in Fig. 4 and a waning rate of 11.75 % per year. The effects are presented relative to the VT IPD incidence in 2005 and can easily be calculated relative to the IPD incidence by multiplying with the proportion of VT IPD in 2005 (Table 2).

Diel et al. analyzed retrospective data from the German IMS-Health-VIP® and found indirect herd effects in PNE [72] and AOM [73] of the infant vaccination with PCVs. We modeled the impact of indirect effects on non-invasive pneumococcal disease incidences as follows:

- The direct vaccine effect was reduced proportionally with the decrease in direct effects against IPD due to replacement disease.
- Net indirect effects in unprotected individuals were calculated by multiplying the net indirect effects on IPD in unvaccinated individuals by the quotient of vaccine effectiveness against non-invasive pneumococcal disease and vaccine effectiveness against invasive pneumococcal disease (Table 7).

The most recent German IPD data in adults [74] showed that the number of serotype 3 cases remained stable after the introduction of the universal infant vaccination with PCV13, while the number of all other PCV13-serotype IPD decreased. Therefore, we reduced the indirect effects in PCV13-PCV10 serotypes by the proportion of serotype 3 in 2009 (the year

Table 4 Direct effects of vaccination

Parameter	Vaccine	Serotypes	Age group	Base-case value	Distribution	Distribution parameter	References
IPD	PCV7	Vaccine	<5	0.939	1-Lognormal	Mean −2.796 SE 0.666	[51]
			5+				Assumption
	PCV10	Vaccine	<5	1	–	–	[52]
			5+				Assumption
	PCV13	Vaccine	<5	0.939	1-Lognormal	Mean −2.796 SE 0.666	Assumption
			5+				Assumption
PNE hospitalized	PCV7	–	<5	0.111	1-Lognormal	Mean −0.118 SE 0.126	[55]
			5+	Adjusted according to IPD serotype distribution	–	–	Assumption
	PCV10	–	<5	0.127			Assumption
			5+	Adjusted according to IPD serotype distribution			Assumption
	PCV13	–	<5	0.146			Assumption
			5+	Adjusted according to IPD serotype distribution			Assumption
PNE outpatient	PCV7	–	<5	0.060	1-Lognormal	Mean −0.062 SE 0.034	[55]
			5+	Adjusted according to IPD serotype distribution	–	–	Assumption
	PCV10	–	<5	0.069			Assumption
			5+	Adjusted according to IPD serotype distribution			Assumption
	PCV13	–	<5	0.079			Assumption
			5+	Adjusted according to IPD serotype distribution			Assumption
AOM	PCV7	–	<5	0.064	1-Lognormal	Mean −0.066 SE 0.013	[51]
			5+	Adjusted according to IPD serotype distribution	–	–	Assumption
	PCV10	–	<5	0.19	1-Lognormal	Mean −0.211 SE 0.085	[62]
			5+	Adjusted according to IPD serotype distribution			Assumption
	PCV13	–	<5	0.084			Assumption
			5+	Adjusted according to IPD serotype distribution			Assumption

IPD inpatient pneumococcal disease, *PNE* non-invasive pneumonia, *AOM* acute otitis media

before the introduction of universal infant vaccination with PCV13). This meant that PCV13 still had an indirect effect on serotype 3, since, in contrast to non-vaccine serotypes, serotype 3 was stopped from spreading further.

Health economic parameters

To evaluate costs from the perspective of the SHI (Table 5), we applied the current German recommendations [75] for the valuation of resource usage. It was assumed that all IPD cases were treated in hospitals. Hospitalization costs were derived from official German Diagnosis Related Groups codes (G-DRGs) [76]. For each disease, the weighted average of different DRGs was calculated according to Cleas et al. [77]. We applied the official German Uniform Evaluation Scheme (EBM) [78] to calculate outpatient physician costs. In 2013, a physicians received a flat payment of EUR 37.60, EUR

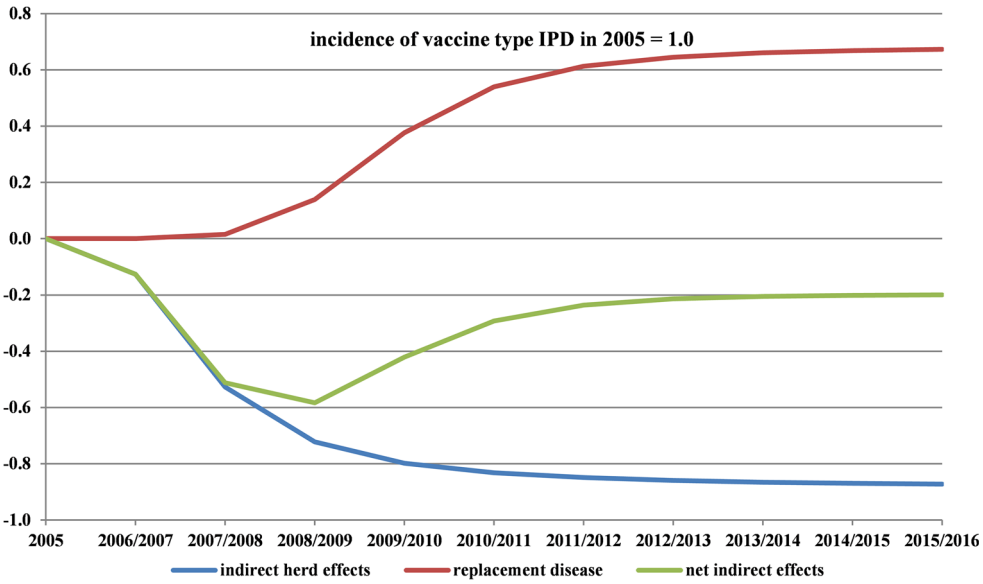

Fig. 3 Net indirect effects in a simple scenario without vaccine replacement

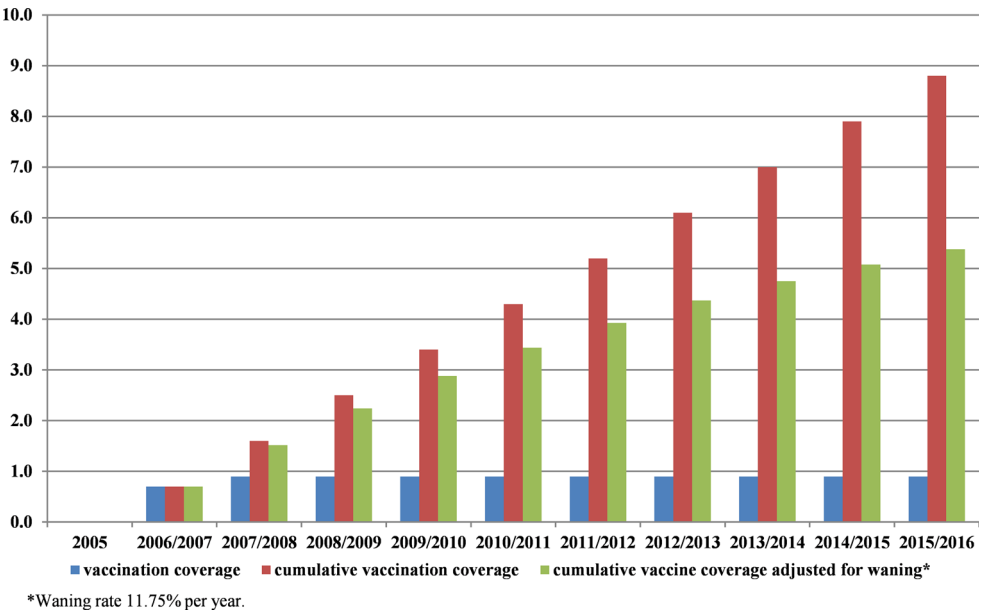

Fig. 4 Vaccination coverage, cumulative vaccination coverage and cumulative vaccination coverage adjusted for waning in a simple scenario without vaccine replacement

29.00, EUR 26.20, EUR 29.70 and EUR 35.00 for standard health care services in outpatient care for children <4 years old, 5- to 18-year-old, 19- to 54-year-old, 55- to 75-year-old and elderly ≥76 years old, respectively [78].

Systemic antibiotics made up for the main part of the prescriptions in AOM, which on average cost EUR 8.09 per episode [40]. According to expert opinions (a Delphi panel survey of German pediatricians experienced as clinical investigators) about 22 % of the AOM patients needed an operation in the ambulatory setting (e.g., tympanostomy tube placement) which cost EUR 385. Costs of outpatient PNE treatment included the capitation fee and average compensation for prescriptions of EUR 23.91 per episode [40]. Costs of long-term health services for children with sequelae were derived from a German cost-benefit analysis of pediatric cochlear implantation [79] and a German cost-effectiveness analysis of PCV7 [77].

Indirect costs of productivity loss were calculated according to the friction cost approach (FCA). Thus, costs of long-term production loss were limited to a friction period that was assumed to be 77 days [80]. Data from the German Federal Health monitoring [81] were used to calculate days off work in patients with IPD and PNE. Age-specific work loss ranged between 7.4 and 18.7 days. Employment rates were derived from the Federal Statistical Office of Germany [82]. We assumed that hospitalized

Table 5 Costs and resource use

Parameter	Perspective	Age group	Unit	Base-case value	Distribution	Distribution parameter	Reference and notes
PCV10 vaccine	SHI, societal	–	Dose	EUR 52.57	–	–	[84]
PCV13 vaccine	SHI, societal	–	Dose	EUR 55.82			
Vaccine administration	SHI, societal	–	Dose	EUR 6.95	–	–	German vaccination agreements of SHIs
Meningitis	SHI, societal	0–15	Case	EUR 6628	Gamma*	$\alpha = 96, \beta = 69$	[76]
Non-meningitis IPD	SHI, societal	0–15	Case	EUR 6383	Gamma*	$\alpha = 96, \beta = 66$	[76]
IPD	SHI, societal	16+	Case	EUR 9006	Gamma*	$\alpha = 96, \beta = 94$	[76]
Co-payments	Societal	18+		EUR 145		$\alpha = 96, \beta = 1.5$	[76, 87]
Hearing loss	SHI, societal	0–15	Case	EUR 90,000	Gamma*	$\alpha = 96, \beta = 937$	[79]
Multiple sequelae	SHI, societal	0–15	Case	EUR 50,000	Gamma*	$\alpha = 96, \beta = 521$	Assumption
PNE hospitalized moderate	SHI, societal	0–17	Case	EUR 2552	Gamma*	$\alpha = 96, \beta = 27$	[76], 80 % of hospitalized cases
		18+		EUR 5119		$\alpha = 96, \beta = 53$	
Co-payments	Societal	18+		EUR 67		$\alpha = 96, \beta = 0.7$	[76, 87], 20 % of hospitalized cases
PNE hospitalized severe	SHI, societal	0–17	Case	EUR 8372	Gamma*	$\alpha = 96, \beta = 87$	[76], 20 % of hospitalized cases
		18+		EUR 8254		$\alpha = 96, \beta = 86$	
Co-payments	Societal	18+		EUR 118		$\alpha = 96, \beta = 1.3$	[39, 76, 87], 20 % of hospitalized cases
PNE outpatient	SHI, societal	0–4	Case	EUR 62	Gamma*	$\alpha = 96, \beta = 0.6$	[40, 78]
		5–18		EUR 53		$\alpha = 96, \beta = 0.6$	
		19–54		EUR 50		$\alpha = 96, \beta = 0.5$	
		55–75		EUR 54		$\alpha = 96, \beta = 0.6$	
		76+		EUR 59		$\alpha = 96, \beta = 0.6$	
AOM hospitalized	SHI, societal	0–10	Case	EUR 1392	Gamma*	$\alpha = 96, \beta = 15$	[76], 0.5 % of AOM cases
AOM outpatient	SHI, societal	0–4	Case	EUR 50	Gamma*	$\alpha = 96, \beta = 0.5$	[40, 78]
		5–17		EUR 39		$\alpha = 96, \beta = 0.4$	
		0–17		EUR 385		$\alpha = 96, \beta = 4$	(Surgical procedures), 22 % of AOM cases
Production loss	Societal	15–74	Day	EUR 85	Gamma*	$\alpha = 96, \beta = 0.9$	[82]

IPD inpatient pneumococcal disease, *PNE* non-invasive pneumonia, *AOM* acute otitis media, *SHI* statutory health insurance

* 95 % CI assumed to be ±20 % of the mean

children <12 years of age caused seven days of parental work absence and children in need of outpatient treatment 3 days [77]. Daily cost of work disability was calculated from the average compensation of employees in 2013 [83].

Prices of PCV10 and PCV13 were EUR 52.57 and EUR 55.82 per dose (pack of 10 price excluding discounts to the SHI), respectively [84]. The average physician fee was EUR 6.95 based on a sample of German vaccination agreements between the Association of SHI Physicians and the SHI. Costs of adverse reactions were not included in the model due to the low incidence of the vaccine side effects [57].

The baseline QALY weights were obtained from studies of the EuroQol Group [85]. Utility losses related to pneumococcal disease were derived from Melegaro et al. [86] and Rozenbaum et al. [17] (Table 6).

Sensitivity analysis

Univariate and a probabilistic sensitivity analyses (PSA) were performed to explore parameter uncertainty and to ensure stability of the results. Parameters used in the

Table 6 Health-related quality of life

Parameter	Age group	Unit	Base-case value	Distribution	Distribution parameter	Reference and notes
General population (no pneumococcal disease)	<18	Year	0.884	Beta	$\alpha = 1{,}1151$, $\beta = 151$	Assumption
	18 to <30		0.884		$\alpha = 1151$, $\beta = 151$	[85]
	30 to <40		0.870		$\alpha = 651$, $\beta = 97$	
	40 to <50		0.833		$\alpha = 546$, $\beta = 110$	
	50 to <60		0.794		$\alpha = 646$, $\beta = 167$	
	60 to <70		0.742		$\alpha = 722$, $\beta = 251$	
	70 to <80		0.755		$\alpha = 302$, $\beta = 98$	
	80+		0.589		$\alpha = 71$, $\beta = 50$	
Meningitis	All	Case	0.0232	Beta*	$\alpha = 94$, $\beta = 3949$	[86]
Non-meningitis IPD	All	Case	0.0079	Beta*	$\alpha = 95$, $\beta = 11{,}965$	[86]
IPD	All	Case	0.0079	Beta*	$\alpha = 95$, $\beta = 11{,}965$	Assumption
PNE hospitalized	All	Case	0.0060	Beta*	$\alpha = 95$, $\beta = 15{,}814$	[86]
PNE outpatient	All	Case	0.0040	Beta*	$\alpha = 96$, $\beta = 23{,}817$	[86]
AOM	All	Case	0.0050	Beta*	$\alpha = 96$, $\beta = 19{,}015$	[86]
Multiple sequelae	All	Year	0.5300	Beta*	$\alpha = 45$, $\beta = 40$	[17]
Hearing loss	All	Year	0.0900	Beta*	$\alpha = 95$, $\beta = 10{,}479$	[86]

IPD inpatient pneumococcal disease, *PNE* non-invasive pneumonia, *AOM* acute otitis media

* 95 % CI assumed to be ±20 % of the mean

sensitivity analyses were estimated from the referenced literature or assumed. The PSA was run for 10,000 iterations.

Calibration of indirect effects parameters

Calibration (nonlinear optimization) of the parameters α_{HE}, β_{HE}, γ_{HE}, α_{RD}, β_{RD} and γ_{RD} (Table 7) was performed with the Excel Solver tool by minimizing the squared differences between modeled and observed pneumococcal meningitis episodes in children <16 years of age. The Excel Solver routine iteratively solved the whole model (Markov model, decision tree disease model, demographic model) and changed the parameters of the functions systematically using gradient methods until the residual sum of squares reached a minimum.

It is likely that ascertainment bias due to a change in blood culturing practices has significantly impacted the reported incidence rates of non-meningitis IPD [6]. Hence, we only used pneumococcal meningitis data for fitting purposes. The fit between model outcomes and observed pneumococcal meningitis incidences are shown in Figure S1 of the supplementary material.

Results

Base-case analysis of PCV13 and PCV10 versus the PCV7 reference scenario

In the period from 2013 to 2062, 44,161 IPD episodes, 556,497 PNE episodes (including 149,700 hospitalized cases), and 5,019,108 AOM episodes could be prevented in Germany, if infants were vaccinated with PCV10 instead of vaccination with PCV7. Vaccinating children <2 years of age with PCV13 could further reduce the burden of pneumococcal disease by 21,057 IPD episodes, 188,138 PNE episodes (including 81,390 hospitalized cases), but AOM episodes would increase by 3,990,948 episodes. Figure S3 in the supplementary material shows the development of IPD episodes in the period from 2013 to 2062 for each vaccination strategy in comparison with the reference scenario (maintenance of PCV7). The prevented cases of pneumococcal disease corresponded to a total (discounted) gain of 134,372 life-years or 111,565 QALYs for PCV10, and 209,291 life-years or 153,423 QALYs for PCV13 (Table 8).

Incremental analysis of PCV13 versus PCV10

Compared with PCV10, the universal infant vaccination with PCV13 would result in a gain of 74,919 life-years or 41,859 QALYs in the base-case analysis. In addition, EUR 43.36 million of direct disease costs could be saved from the perspective of the SHI. From the societal perspective, the disease costs would increase by EUR 270.35 million due to the indirect costs of AOM episodes. Additional costs of vaccination would sum up to EUR 184.3 million. From the societal perspective, the ICER of PCV13 versus PCV10 was EUR 9826 per QALY gained or EUR 5490 per LY gained. Excluding co-payments and indirect disease costs (SHI perspective), ICERs decreased to EUR 3368 per QALY gained or EUR 1882 per LY gained (Table 9).

Table 7 Calibrated indirect effects of PCV infant vaccination in Germany

Disease	Effect	Serotypes	Formula	Distribution	Distribution parameter	Reference
IPD	Indirect herd effects	Vaccine	$\frac{0.89^{***}}{1+2.23^{***}\cdot\left(\mathrm{CVCW}_t^{*}\right)^{-2.8^{***}}}$	Uniform	Min = 0.84, Max = 0.94	Assumption
	Replacement disease	Non-vaccine	$\frac{0.77^{***}\cdot\mathrm{IRVS}^{**}}{1+610^{***}\cdot\left(\mathrm{CVCW}_t^{*}\right)^{-6.3^{***}}}$	Uniform	Min = 0.69, Max = 0.85	Assumption
Non-IPD	Net indirect effects	–	Direct effect $\cdot \frac{\text{indirect effect onIPD}}{\text{direct effect on IPD}}$	–	–	Assumption

IPD inpatient pneumococcal disease

* CVCW: cumulative vaccine coverage adjusted for waning

** IRVS: max. incidence reduction in vaccine serotypes through indirect effects

*** Fitted

Table 8 Results of the base-case analysis

	IPD	hPNE	oPNE	AOM	Total
Episodes (undiscounted)					
PCV7	768,768	17,469,169	53,674,449	72,205,312	–
PCV10	724,606	17,309,610	53,277,511	67,186,204	–
PCV13	703,550	17,228,220	53,170,764	71,177,152	–
Avoidable episodes compared with PCV7 (undiscounted)					
PCV10	44,161	159,559	396,938	5,019,108	–
PCV13	65,218	240,949	503,686	1,028,160	–
Life-years gained compared with PCV7					
PCV10	60,360	72,092	1919	0	134,371
PCV13	89,576	116,559	3156	0	209,291
QALYs gained compared with PCV7					
PCV10	47,639	48,047	2170	13,708	111,565
PCV13	70,496	76,760	3227	2940	153,423
Cost savings within the SHI compared with PCV7, excluding vaccination costs (EUR 1000s)					
PCV10	222,571	449,035	12,172	380,164	1,063,942
PCV13	325,378	686,256	15,483	80,182	1,107,298
Cost savings related to productivity loss and co-payments compared with PCV7 (EUR 1000s)					
PCV10	58,002	31,247	76,365	398,098	563,709
PCV13	74,364	41,750	95,864	81,379	293,357
Vaccination costs (EUR 1000s)					
PCV10	–	–		–	3,375,752
PCV13	–	–		–	3,560,080

IPD inpatient pneumococcal disease, *hPNE* hospitalized non-invasive pneumonia, *oPNE* non-invasive pneumonia treated in outpatient care, *AOM* acute otitis media, *QALY* quality-adjusted life-years

Sensitivity analyses

The results were robust to variations of most model input parameters (Table S1 of the supplementary material). Indirect vaccine effects had a major impact on the cost-effectiveness of the vaccines. Without indirect effects, PCV10 vaccination of infants would dominate the PCV13 strategy or would be highly cost-effective. Substantial additional net-indirect effects of PCV13 resulted in the vaccine being cost-effective or dominant. PCV10 would also be cost-effective, if its effectiveness against AOM was 33.6 % and PCV13 did not provide additional benefits in the prevention of PNE at the same time.

The probability that PCV13 was cost-effective at a willingness-to-pay threshold of EUR 20,000 per QALY gained was 79 % from the SHI perspective and 64 % from the societal perspective. At a threshold of EUR 30,000 the probability would increase to 85 and 74 %, respectively. At ICER thresholds above EUR 100,000, there was still a small probability that PCV13 was not cost-effective (Fig. 5) due to

Table 9 Cost-effectiveness of PCV13 versus PCV10

	SHI perspective	Societal perspective
Additional vaccination cost (EUR)	184,327,876	184,327,876
Cost savings due to disease prevention (EUR)	43,355,918	−270,352,102
Life-years gained	74,919	74,919
QALYs gained	41,859	41,859
ICER (additional costs per life-year gained; EUR)	1882	5490
ICER (additional costs per QALY gained; EUR)	3368	9826

SHI statutory health insurance, *QALY* quality-adjusted life-years

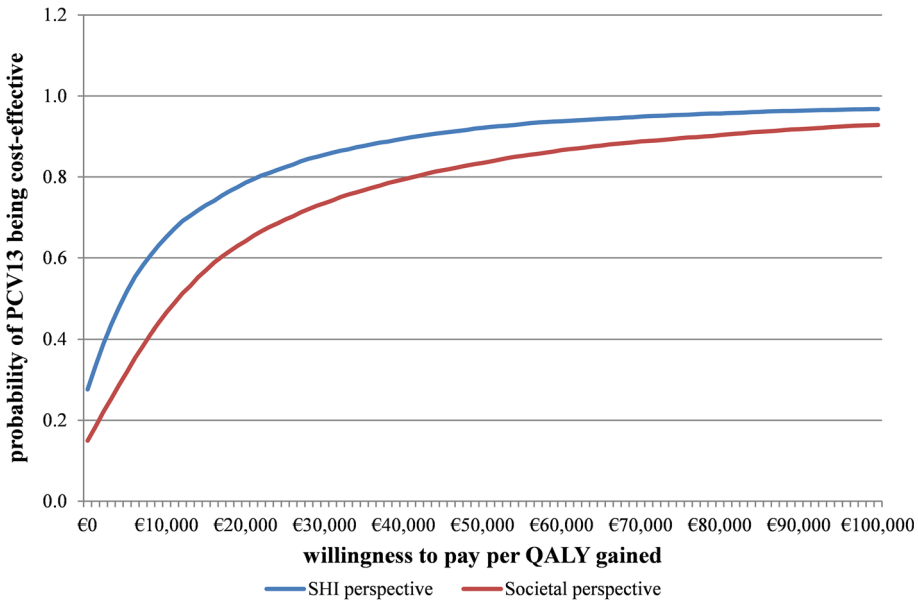

Fig. 5 Cost-effectiveness acceptability of PCV13 versus PCV10

QALY: quality-adjusted life year, SHI: statutory health insurance

the combined uncertainty of indirect effects, the effectiveness of PCVs against all cause PNE and the magnitude of additional benefits of PCV10 in preventing all case AOM.

Discussion

This study is the first German economic evaluation of universal infant pneumococcal vaccination programs that included time-dependent indirect herd effects and replacement disease for the entire German population. Base-case results of our analysis indicated that PCV13 was cost-effective compared with PCV10 from the perspective of the SHI and the societal perspective.

Impact of pneumococcal conjugate vaccination of infants on pneumococcal disease in Germany

Our model predicted a rapid decline of pneumococcal diseases covered by PCVs (Figure S1–S3 of the supplementary material) and an increase of non-VT disease in all age groups. Indirect herd effects and replacement disease have been reported in several studies for PCV7 [6, 88–92] and PCV13 [93–97] infant vaccination programs. German incidence data of invasive pneumococcal disease in adults does only exist for the pre-PCV period. Therefore, we simulated the impact of PCV7 infant vaccination on all age groups based on pneumococcal meningitis data in <16 years old and extrapolated the effects for the higher-valent vaccines. Comparing the modeled serotype distribution in IPD in adults with the observed distribution (Figure S2 of the supplementary material) reveals that the model gave good prediction for the age group 16–59 years old but underestimated either indirect herd effects or replacement disease in the age group 60+ years old.

Table S2 of the supplementary material compares the predicted short-term impact of PCV infant vaccination predicted by our model with reported IPD incidences from other Western European countries. The results of our model were in the range of the observed data, which varied

considerably between countries. The exception were vaccination programs with PCV10 which did not have an impact on the IPD incidence in adults in Finland but reduced the total number of IPD cases substantially in our model, if we assumed indirect effects of PCV10.

The long-term effects of PCV infant vaccination estimated by our model are shown in Table S3 of the supplementary material. Depending on the administered PCV vaccine, infant vaccination programs could prevent about 1649–2953 IPD episodes, 7397–12,216 hospitalized PNE episodes, 8963–19,036 PNE episodes treated in outpatient care and 13,759-114,141 AOM episodes on average per year compared with the number of pneumococcal disease cases (adjusted for demographic trends) in the pre-PCV period.

Pneumococcal disease data in Germany

This study is limited by a lack of German epidemiologic data. In Germany, nationwide notification requirements for pneumococcal disease do not exist to date. One passive surveillance unit [8] collects IPD cases in adults, but only a fraction of German laboratories send samples to the system and the number of participating laboratories changes every year [8]. The only study which reports IPD incidences in adults is a laboratory-based surveillance study conducted in the state North-Rhine Westphalia between 2001 and 2003 [37]. However, several correction factors (for laboratories not participating, hospitals not sending samples to laboratories and a lack of blood culturing in pneumonia cases) were applied to generate reasonable incidence estimates [37].

Furthermore, it is very likely that an ascertainment bias due to a change in blood culturing practices has a substantial impact on the reported incidence rates of non-meningitis IPD in <16 years old [6]. For instance, the estimated incidence in 2–15 years old increased by a factor of two after the introduction of universal infant vaccination with PCV7 [6]. Therefore, we adjusted the non-meningitis IPD incidence using an underreporting factor of 2.7 derived from the study in North-Rhine Westphalia [37] and only included pneumococcal meningitis cases in the calibration process of indirect herd effect parameters.

The burden of non-invasive pneumococcal disease is unknown in Germany. The CAPNETZ study [98] estimates that around 30 % of all pneumonia cases are caused by *S. pneumonia* but data on the serotype distribution do not currently exist.

Direct effects of higher-valent PCVs

PCV10 efficacy against VT-IPD was derived from the FinIP trial [52]. For PCV13, we assumed an efficacy of 93.9 % against all VT-IPD. This figure is based on efficacy estimates for PCV7 in the NCKP trial [51]. Andrews et al. [99] calculate a lower effectiveness of PCV13 against serotype 3 but the CAPITA study does not provide any evidence for a lower effectiveness against serotype 3 in comparison with other vaccine serotypes [100]. In addition, adjusting for the impact of age at vaccination in the CAPITA data, van Werkhoven et al. [101] estimate an effectiveness of PCV13 against VT bacteremic pneumococcal pneumonia of >90 % in 50 years old which corresponds with the efficacy applied in our model.

In the absence of pathogen-specific epidemiologic data in Germany, we used effectiveness estimates against all causes of non-invasive pneumonia and AOM. We assumed that the effectiveness of the higher-valent vaccine increased proportionally to the serotype coverage in IPD [17]. Since the CAPITA study does not provide evidence for a reduced effectiveness of PCV13 against non-PCV7 serotypes in preventing non-invasive pneumonia [100], this assumption seems to be justified if the serotype distribution in non-invasive pneumococcal disease is comparable to the distribution in IPD. The letter may not be the case, hence, we tested different scenarios in the sensitivity analyses. If both higher-valent PCVs do not provide additional benefits in preventing non-invasive pneumonia, the cost-effectiveness of PCV13 will be questionable.

Indirect effects of higher-valent PCVs

The evolution of pneumococcal serotypes in Western Europe showed a decrease of the total IPD incidence in all age groups due to the implementation of childhood vaccination programs with pneumococcal conjugate vaccines [97]. While positive net indirect effects have been well documented for PCV7 [6, 88–92] and PCV13 in the prevention of IPD [93–97] and pneumococcal pneumonia [95], this has not been the case for PCV10. The introduction of infant vaccination programs with PCV10 has not reduced the overall incidence of IPD in non-vaccinated age groups in Finland [97]. In the Netherlands, a reduction of PCV10-PCV7 serotypes has been observed in unvaccinated persons in the third year after the implementation of PCV10 vaccination [102], but the effects on the overall IPD incidence are unclear [103]. Hence, by assuming positive net indirect effects for PCV10, we may have overestimated its effects on the entire population substantially.

In contrast to previous German analyses [18, 71, 104], we estimated indirect effects based on German instead of US data which led to more conservative estimates. A dynamic transmission model of universal infant vaccination with PCV7 fitted to UK data [105] calculated a 9 % reduction of IPD cases in the long term, which is in line

with the results of our model. However, a similar model calibrated to US data calculated a 34 % decline of IPD cases [63].

Model type

Dynamic transmission models are the preferred method to evaluate vaccination programs that induce indirect effects. Markov cohort models are not able to simulate transmission dynamics of infectious disease and, therefore, do not endogenously capture indirect effects of vaccination. However, the lack of data on pneumococcal carriage and disease incidences in Germany, as well as poor knowledge of the mechanism of serotype competition, cause substantial additional uncertainty in dynamic models that may counter its advantages.

We included additional parameters to model protection against pneumococcal disease in unvaccinated individuals. Herd effects and replacement disease were estimated using German pneumococcal meningitis data of children <16 years old and applying the results to other age groups. This approach is problematic since it neglects social contact patterns and other factors that may affect the transmission process. However, epidemiologic outcomes of our model are comparable to a dynamic model that evaluated PCV7 vaccination of infants in the UK [105]. Another UK-model [106], which included PCV13, predicted the elimination of PCV13-serotype IPD around 8 years after the implementation of a vaccination program with the higher-valent PCV. In our model, infant vaccination with PCV13 did not result in a complete elimination of VT pneumococcal diseases in the long term. A small fraction of PCV10 serotypes would persist and PCV13 serotypes not covered by PCV10 would still cause a substantial number of pneumococcal diseases due to the adjustment of indirect effects for serotype 3.

Comparison with previously published studies comparing the cost-effectiveness of PCV10 and PCV13

Several recently published economic evaluations of universal pneumococcal infant vaccination (direct or indirect) compared PCV13 with PCV10 [11–23]. While the majority of studies [11, 12, 16–18, 21, 23, 25, 27] found PCV13 cost saving or at least cost-effective compared with PCV10, some analyses reported the exact opposite [15, 19, 20, 22, 30]. The contradictory results can be explained through different assumptions on the vaccine effects, which varied significantly among the different studies [107]. We did not incorporate cross protection in our model but included positive net indirect effects of PCV10 vaccination, additional benefits of PCV10 in the prevention of all cause AOM and reduced indirect herd effects of PCV13 against PCV13-PCV10 serotypes. Thus, our model may underestimate the value of infant vaccination programs with PCV13 compared with PCV10 in Germany.

Conclusions

In comparison with PCV10, universal infant vaccination with PCV13 is likely to be a cost-effective intervention within the German healthcare system, if additional net indirect effects of vaccination with the higher-valent vaccine are significant.

Authors' contributions AK constructed and implemented the model in Excel, performed the analysis of the results and drafted the manuscript. JMGvdS reviewed the manuscript and revised it critically for important intellectual content.

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