Cost–effectiveness of vaccinating adults with the 23-valent pneumococcal polysaccharide vaccine (PPV23) in Germany

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EXPERT REVIEWS

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The introduction of routine infant vaccination against pneumococcal disease has resulted in a decreased overall invasive pneumococcal disease incidence in adults but also a change in invasive pneumococcal disease serotypes. This study aimed to assess the cost–effectiveness of 23-valent pneumococcal polysaccharide vaccine (PPV23) in Germany in this context. A population-based Markov model was developed. A cohort of adults currently eligible for vaccination was followed until death. Adult vaccination with PPV23 was associated with an incremental cost–effectiveness ratio of €17,065/quality-adjusted life years gained from the third-party payer's perspective. Univariate sensitivity analyses showed that the incremental cost–effectiveness ratio was below €50,000/quality-adjusted life years gained in most test scenarios. The model suggests that adult PPV23 vaccination is cost effective in Germany, due to its broad serotype coverage. This is despite epidemiological changes in *Streptococcus pneumoniae* serotypes caused by wider use of pneumococcal conjugate vaccines during childhood.

Pneumococcal diseases

Streptococcus pneumoniae bacteria are lancet-shaped, Gram-positive, facultative anaerobic organisms. They typically present in pairs (diplococci) but may also occur singularly or in short chains. Some pneumococci are encapsulated, their surfaces composed of complex polysaccharides and it is these organisms that are pathogenic for humans, whereas organisms without capsular polysaccharides are nonpathogenic. Indeed, the polysaccharide capsule acts as a virulence factor for the bacterium and it is antigenic, forming the basis for classifying pneumococci by serotypes. More than 90 different serotypes have been identified and these differ by virulence, prevalence and extent of drug resistance [101]. *S. pneumoniae* can lead to noninvasive pneumonia (i.e., nonbacteremic pneumonia, which accounts for approximately 80% of all pneumococcal pneumonia) as well as invasive pneumonia (i.e., bacteremic pneumonia, which accounts for 80–90% of all invasive disease) and other invasive diseases (such as meningitis and bacteremia [1–3]), and it is estimated to cause 1.6 million deaths annually worldwide [4]. Children, the elderly and people with predisposing factors, including immunodeficiency and chronic diseases (cardiovascular, pulmonary, renal and hepatic) are particularly vulnerable to invasive pneumococcal disease (IPD) [1–5]. It has been reported that in Germany alone, IPD accounts for approximately 1200 deaths each year [6,102].

Vaccination

Vaccination remains the only public health strategy that can reduce the burden of IPD [2]. Two types of vaccines are currently available in Germany.

Pneumococcal conjugate vaccines

A seven-valent pneumococcal conjugate vaccine (PCV7) obtained European market authorization

for use in children aged between 2 months and 5 years in 2001. This was later replaced by a 13-valent vaccine (PCV13) in 2009. The latter was indicated for children aged between 6 weeks and 5 years [103,104]. A ten-valent vaccine (PCV10) was licensed for children aged between 6 weeks and 2 years in 2009 and it was extended up to 5 years in 2011 [105]. The efficacy and safety of PCV7 have been demonstrated in clinical trials in the pediatric population [7,8] and evidence also supports the immunogenicity and tolerability of PCV10 and PCV13 in children [9,106]. The efficacy of PCV vaccines has not yet been demonstrated in adults. In Germany, PCV vaccination in children under the age of 24 months has been recommended since 2006 [10]. Before the introduction of the vaccines, serotypes associated with PCV7 accounted for 57.7% of cases of IPD in children (2001/2002), whereas the additional six serotypes included in PCV13 covered a further 24.9% of IPD cases [11]. After the introduction of PCV vaccines (2009/2010), the serotypes included in PCV7 covered only 16.5% of all IPD cases in children and the six additional serotypes in PCV13 covered a further 54.7% cases [11]. In Germany, the indication of PCV13 has recently been extended to include adults aged 50 years and older to prevent IPD [107].

At the present time, comparisons between PCV vaccines and pneumococcal polysaccharide vaccines (PPVs) are limited to immunogenicity studies [12–21] and no link between immune response and clinical effectiveness has been established [22].

Pneumococcal polysaccharide vaccine

A 23-valent vaccine (PPV23) is indicated for children in at-risk populations from the age of 2 years. It covers 80–90% of serotypes of IPD in Europe [23–25]. Recent German data (2009/2010) from the National Reference Center for Streptococci show that it covers 82.3% of serotypes causing IPD [11] and 86.5% of serotypes causing bacteremic pneumonia in adults [26]. The vaccine was introduced in 1982 in Germany. In the same year, it was recommended for use in at-risk adults [27], and the recommendation to vaccinate older people, aged 60 years or more, was issued in 1998 [28]. Efficacy and effectiveness of PPV23 have been demonstrated against IPD in immunocompetent adults, as well as in the immunosuppressed population (e.g., in patients infected with HIV [4,29,30]). Primary vaccination and revaccination after 5 years with PPV23 is generally well tolerated [4,22,31,32] and provides a sustainable immune response [33]. Over the past 10 years, many studies have shown that PPV23 vaccination of at-risk adults and the elderly is a cost-effective strategy in Germany, as well as in other European and American countries [22,34–42].

The impact of vaccinating children

The introduction of universal PCV7 vaccination in children in industrialized countries has dramatically changed the epidemiology of IPD. Reduction in the incidence of IPD associated with PCV7 serotypes in vaccinated children was observed in Europe and the USA [43,108]. As a result, the heaviest burden of IPD is now borne by the elderly and at-risk adults in these countries [43,108].

Following routine childhood vaccination, the reduction of IPD incidence and its effects on herd protection, has been witnessed
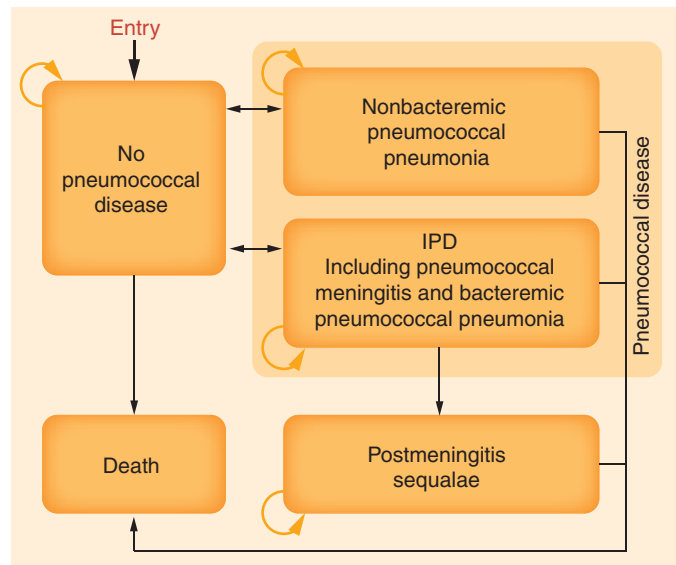

Figure 1. Model structure.
IPD: Invasive pneumococcal disease.

not only in unvaccinated children but also in unvaccinated adults (e.g., in the USA, the UK and Spain [44–46]). This has been explained as a consequence of decreased nasopharyngeal carriage of PCV7 serotypes [22]. However, concerns have been raised with regard to the increased incidence of IPD associated with non-PCV serotypes, known as a serotype replacement effect, which has been reported in several countries [46–49]. Such changes could offset some of the benefits of vaccination as a result of reduction in herd protection [50].

The recent switch from PCV7 to PCV13 in children is expected to accentuate the changes in the epidemiology of pneumococcal diseases in both children and adults, as the incidence of IPD associated with the additional six serotypes in PCV13 is expected to decrease in both children and adults while the incidence associated with serotypes not covered by the additional six serotypes is expected to increase. The increase in the incidence of IPD associated with non-PCV13 serotypes may be less than that associated with non-PCV7 serotypes observed following the introduction of PCV7 in children, since the additional six serotypes covered by PCV13 accounted for less than half of IPD cases caused by PCV7 serotypes in the period before the introduction of PCV vaccination [11]. Nevertheless, the cost–effectiveness profile of PPV23 vaccination in adults against the pneumococcal diseases may be impacted.

Objectives

This study aimed to assess the cost–effectiveness of PPV23 in the elderly and at-risk adults in Germany, and it takes into account the decreased incidence of IPD induced by universal vaccination of children with PCV7/13.

Modeling approach
Target population & model structure

A population-based Markov model was developed to analyze the cost–effectiveness of PPV23 vaccination compared with

Table 1. Clinical parameters.

Parameter	Base-case value (range used in univariate sensitivity analyses)	PSA assumptions	Ref. and notes
Split by risk group (%)	AR i.c.: 12.82 (12.81–12.82) AR i.s.: 0.25 (0.2–0.3; as a proportion of the size of nonelderly adult population		[55]
Incidence of IPD in 2005 (per 100,000 person-years) by age back in years (%)	16–44: 2.5 (2.0–3.0) 45–64: 8.5 (6.8–10.2) 65–74: 24.1 (19.3–28.9) 75+: 10.3 (8.2–12.4)	Beta distribution (α/β) 16–44: 180.2/7,209,180 45–64: 392.3/4,614,596 65–74: 263.3/1,092,197 75+: 194.4/1,886,893	[51]
Risk of developing IPD	AR i.c.: 5.494 AR i.s.: 35.833 (compared with the nonelderly adult population)	Log-normal distribution (implied mean/implied SE[†]) AR i.c.: 1.660/0.295 AR i.s.: 3.506/0.382	[54,55]
IPD incidence by serotype in 2005 (%)	PCV7: 45.7 PCV13: 76.3 6A: 3.1 PPV23: 89.4 Others: 7.7		[25]
Herd protection effect: decrease in incidence of IPD associated with PCV serotypes[‡]	Cumulative gamma distribution α: 0.5061 β: 3.0406 No herd protection; no decrease in PCV13 not PCV7	Uniform distribution With changes: 50% Without changes: 50%	[9,44,110]
Serotype replacement effect: increase in incidence of IPD associated with non-PCV serotypes[‡]	Cumulative gamma distribution α: 1.4086 β: 7.6955 No serotype replacement	The same as above	[9,44,110]
Incidence of nonbacteremic pneumonia (per 100,000 person-years) by age back in years (%)	18–19: 33.0 20–29: 44.0 30–39: 63.0 40–49: 77.0 50–59: 134.0 60–69: 298.0 70–79: 739.0 80–89: 1762.0 90+: 3581.0 (All age groups: 370; 600; 870; 1010)	Beta distribution (α/β) 18–19: 650/1,969,047 20–29: 4325/9,825,220 30–39: 7181/11,390,439 40–49: 10,463/13,577,200 50–59: 14,271/10,635,729 60–69: 29,475/9,861,297 70–79: 51,201/6,877,216 80–79: 55,612/3,100,546 90+: 21,003/565,509	[58]
Proportion of nonbacteremic pneumonia having pneumococcal origin (%)	40 (30–50)		[59]
Proportion of meningitis in IPD (%)	8.2		[11]

[†]Mean and standard error of implied normal distribution.
[‡]As a function of cumulative pneumococcal conjugate vaccine coverage in children.
AR: At-risk adults; i.c.: Immunocompetent; IPD: Invasive pneumococcal disease; i.s.: Immunosuppressed; NBPP: Nonbacteremic pneumococcal pneumonia; PCV: Pneumococcal conjugate vaccine; PMS: Postmeningitis sequelae; PPV: Pneumococcal polysaccharide vaccine; PSA: Probabilistic sensitivity analysis; SE: Standard error.

Table 1. Clinical parameters (cont.).

Parameter	Base-case value (range used in univariate sensitivity analyses)	PSA assumptions	Ref. and notes
Proportion of meningitis patients with PMS (%)	52 (22% with hearing loss and 30% with other neurological sequelae)		[62]
Case–fatality rate by age band in years: meningitis (%)	5–49: 21 (17–25)	Beta distribution (α/β)	[56]
		5–49: 5.7/21.6	
	50–64: 21 (17–25)	50–64: 9.1/34.2	
	65+: 39 (31–47)	65+: 19.2/30.0	
Case–fatality rate by age band in years: invasive pneumonia (%)	5–49: 1 (0.8–1.2)	Beta distribution (α/β)	[56]
		5–49: 0.6/59.3	
	50–64: 9 (7–11)	50–64: 13.9/140.5	
	65+: 20 (16–24)	65+: 136.4/545.6	
Relative risk of dying from IPD by serotype (%)	PCV13: 95.3 (91.8–98.4)	Lognormal distribution (implied mean/implied SE[†])	[57]
		PCV13: -4.9%/1.8%	
	PPV23 not PCV13/6A: 113.2 (105.4–122.0)	PPV23 not PCV13/6A (compared with PCV13): 17.1%/5.5%	
	Not PPV23/6A: 112.7 (102.7–124.0)	Not PPV23/6A (compared with PPV23 not PCV13/6A): -0.5%/1.1%	
Case–fatality rate: NBPP (%)	8.6 (6.9–10.3)	Beta distribution (α/β) 87.7/932.0	[59]; 95% CI assumed to be ± 20% of the mean

[†]Mean and standard error of implied normal distribution.
[‡]As a function of cumulative pneumococcal conjugate vaccine coverage in children.
AR: At-risk adults; i.c.: Immunocompetent; IPD: Invasive pneumococcal disease; NBPP: Nonbacteremic pneumococcal pneumonia; PCV: Pneumococcal conjugate vaccine; i.s.: Immunosuppressed; SE: Standard error; PMS: Postmeningitis sequelae; PPV: Pneumococcal polysaccharide vaccine; PSA: Probabilistic sensitivity analysis.

no vaccination as no alternative to PPV23 existed with clinical effectiveness data at the time of this study. The model accounted for future changes in the epidemiology of IPD in adults induced by the universal PCV vaccination of children. The corresponding approach is detailed in the following section. The model tracked a cohort of adults (aged 18 years and older) until death or 100 years of age.

The target population consisted of German adults eligible for PPV23 vaccination and who would receive the vaccination in 2011. It consisted of individuals younger than 60 years of age who were at higher risk of developing IPD diseases ('at-risk adults') and individuals aged 60 years or older ('the elderly'). A further distinction was made in the at-risk population such that the population was split between immunocompetent: those with chronic respiratory, cardiovascular conditions and/or diabetes; and immunosuppressed: those who were infected with HIV, had received immunosuppressant therapies (e.g., chemotherapy or high-dose corticosteroids) or had received a transplantation.

Five health states were considered in the Markov structure: no pneumococcal disease, nonbacteremic pneumococcal pneumonia (NBPP), IPD (including pneumococcal meningitis and bacteremic pneumococcal pneumonia), postmeningitis sequelae (PMS) and death (Figure 1). Individuals entered the model in the no pneumococcal disease state, and they risked developing IPD or NBPP. Patients with IPD or NBPP faced a higher risk of death than individuals without pneumococcal disease. Following IPD and/or NBPP, patients could recover and return to the no pneumococcal disease health state, and a proportion of patients with pneumococcal meningitis could develop PMS. It was assumed that following PMS, patients do not develop another episode of IPD or NBPP, a situation estimated as rare (less than one in a million [51]).

The cycle length of the model was 1 year so that the seasonality of pneumococcal diseases did not have to be reflected in the model [52]. The model was developed in compliance with guidelines published by the German health technology assessment body Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [109] and the principles of good practice for modeling by the International Society for Pharmacoeconomics and Outcomes Research [53].

Given the lack of evidence of indirect protection against pneumococcal diseases obtained through the vaccination of adults with PPV23, such an effect was not included in the model. This approach was conservative as it underestimates the effect of the vaccine (by ignoring the potential herd protection from vaccinating adults).

Table 2. Vaccine effectiveness.			
Parameter	Base-case value (range used in univariate sensitivity analyses)	PSA assumptions	Ref.
Vaccine effectiveness against IPD (%)	E and AR i.c.: 74 (50–80)	Log-normal distribution (implied mean/implied SE[†]) E and AR i.c.: -0.320/0.195	[29,30]
	E and AR i.s.: 35 (24–38)	E and AR i.s.: -1.132/0.405	
Vaccine effectiveness against NBPP (%)	E and AR i.c.: 39 (0–64)	Log-normal distribution (implied mean/implied SE[†]) E and AR i.c.: -1.025/0.408	[63]
	E and AR i.s.: 0	E and AR i.s.: 0%	
Waning function of vaccine effectiveness (proportion of remaining vaccine effectiveness; %)	Year 1: 82 (56–93) Year 2: 78 (41–91) Year 3: 72 (26–89) Year 4: 64 (17–87) Year 5: 54 (10–85) Year 6: 43 (3–83) Year 7: 30 (0–79) Year 8: 15 (0–30) Year 9: 0 (0–20) Year 10: 0 (0–10)	Triangular distribution with the mode being the mean value (minimum/maximum) Year 1: 56/93 Year 2: 41/91 Year 3: 26/89 Year 4: 17/87 Year 5: 10/85 Year 6: 3/83 Year 7: 0/79 Year 8: 0/30 Year 9: 0/20 Year 10: 0/10	[64,65]
Time to receive revaccination	5 years		[66]
Proportion of the vaccinated receiving revaccination	3%, only for those who received the initial vaccination below 60 years of age		[11]

[†]Mean and standard error of implied normal distribution.
AR: At-risk adults; E: The elderly; i.c.: Immunocompetent; i.s.: Immunosuppressed; IPD: Invasive pneumococcal disease; NBPP: Nonbacteremic pneumococcal pneumonia; PSA: Probabilistic sensitivity analysis; SE: Standard error.

Natural history of IPD & future epidemiology

The change in the incidence of IPD in adults induced by the vaccination of children (decreased incidence of vaccine serotypes and serotype replacement) was modeled through time-dependent probabilities of developing IPD. Due to a lack of data, a stable incidence of IPD was assumed between 2003 and 2005. This was based on findings from a prospective laboratory-based surveillance study conducted in the largest federal state, North-Rhine Westphalia, in Germany between 2001 and 2003 [51].

The recommendation of PCV7 in Germany since 2006 led to a change in the epidemiology of disease [11,25]. As the German data were not sufficient to simulate epidemiological trends, the changes were estimated based on US data. In the USA, it has been observed that increased PCV7 vaccine uptake in children is associated with a decreased incidence of IPD in adults caused by PCV7 serotypes [9] while the incidence of IPD associated with other serotypes has increased [44,110].

Based on US data observed during the 7 years following introduction of the PCV7 vaccine in children, the change in the incidence of IPD associated with PCV7 in adults was found to be related to cumulative vaccine uptake in children [11]. A parametric function estimating the change in IPD incidence as a function of cumulative vaccine coverage rate in children was

therefore estimated using the US data. A cumulative gamma distribution was selected for its goodness of fit. The cumulative coverage rates observed in German children were then used in order to estimate the change in IPD incidence from 2005. A stable incidence was assumed beyond 2012 (7 years after introduction of the vaccine in children) due to a lack of longer term data. A similar approach, based on the same US data, was selected to predict the expected increase in the incidence of IPD cases not associated with serotypes included in the vaccine used in children.

The model considered the effect of introducing universal PCV13 vaccination in children, which protects against six additional serotypes than PCV7. Due to a lack of data, it was assumed that the association between the corresponding incidence of IPD in adults and cumulative coverage of the additional six serotypes in children followed the same pattern as the PCV7 serotypes.

In at-risk adults, the incidence of IPD was adjusted for risk group using the following sources. The relative risks of developing IPD by risk group were based on data observed in the USA [54], and the proportion of patients in each risk group was derived from German sources [55]. The incidence of IPD by serotypes for this period was estimated according to the nationwide surveillance

Table 3. Costs and resource use.

Parameter	Base-case value (range used in univariate sensitivity analyses)	PSA assumptions	Ref. and notes
PPV23 vaccine (1-pack price)	TPP: €30.25		[113]
	Societal: €38.45		
Administration of PPV23 vaccine	TPP: €6.95 (€5.56–8.34)	Gamma distribution (α/β) TPP: 96.0/0.1	[11]; 95% CI assumed to be ± 20% of the mean
	Societal: €13.95 (€11.16–16.74)	Societal: TPP plus €10	
Meningitis	TPP: €11,664 (€9331–13,997)	Gamma distribution (α/β) TPP: 96.0/121.4	[69,114]; 95% CI assumed to be ± 20% of the mean
	Societal: €11,671 (€9337–14,005)	Societal: TPP plus €10	
Invasive pneumonia	TPP: €8075 (€6460–9690)	Gamma distribution (α/β) TPP: 96.0/84.1	[69,114]; 95% CI assumed to be ± 20% of the mean
	Societal: €8082 (€6466–9696)	Societal: TPP plus €10	
NBPP: inpatient	TPP: €5762 (€4610–6914)	Gamma distribution (α/β) TPP: 96.0/96.0	[69,114]; 95% CI assumed to be ± 20% of the mean
	Societal: €5769 (€4615–6923)	Societal: TPP plus €10	
NBPP: outpatient	TPP: €78 (€63–94)	Gamma distribution (α/β) TPP: 96.0/0.8	[69,114]; 95% CI assumed to be ± 20% of the mean
	Societal: €85 (€68–102)	Societal: TPP plus €10	
Proportion of NBPP patients hospitalized by age band in years (%)	5–55: 7.8		[69]; 95% CI assumed to be ± 20% of the mean
	56–64: 16.6		
	65+: 34.5		
PMS: hearing loss (per year)	TPP: €1552 (€1242–1863)	Gamma distribution (α/β) TPP: 96.0/16.2	[70,112]; 95% CI assumed to be ± 20% of the mean
	Societal: €1559 (€1247–1871)	Societal: TPP plus €10	
PMS: other neurological sequelae (per year)	TPP: €862 (€690–1035)	Gamma distribution (α/β) TPP: 96.0/9.0	[69,70,112]; 95% CI assumed to be ± 20% of the mean
	Societal: €869 (€695–1043)	Societal: TPP plus €10	
Cost per day off (societal)	€96† (€77–115)	Gamma distribution (α/β) 96.0/1.0	[118,119]; 95% CI assumed to be ± 20% of the mean
Productivity loss (societal)	IPD: 16.8 days		[62,117]
	NBPP: 16.8 days		
	PMS: 365.25 days		
Discount rate (%)	3 (0–5)		[109]

†Applied until 65 years old.
IPD: Invasive pneumococcal disease; NBPP: Nonbacteremic pneumococcal pneumonia; PMS: Postmeningitis sequelae; PPV: Pneumococcal polysaccharide vaccine; PSA: Probabilistic sensitivity analysis; TPP: Third-party payer.

from Germany [25]. The proportion of IPD cases by serotype was compared with German data reported by the National Reference Center for Streptococci between 2004 and 2009 as part of the model validation [11,25]. Due to a lack of German data, the IPD case–fatality rate was estimated from a retrospective surveillance study covering approximately 25% of the Dutch population, which was conducted between 2004 and 2006 [56]. As the case–fatality rate varies across serotypes, mortality by serotype was

estimated based on a Danish nationwide population-based study, which followed 18,858 IPD patients between 1977 and 2007 [57].

Natural history of IPD complications & other pneumococcal diseases

Few studies reporting the incidence of NBPP in Germany were identified. Ewig *et al.* reported the incidence of community-acquired pneumonia requiring hospitalization by age group based

Table 4. Health-related quality of life.

Parameter	Base-case utility, QALYs (range used in univariate sensitivity analyses)	PSA assumptions	Ref.
No pneumococcal diseases (low-risk; by age band in years)	18–54: 0.83	Triangular distribution with the mode being the mean value (minimum/maximum)	[41]
	55–59: 0.81		
	60–64: 0.77	18–54: 0.78/0.88	
	65–69: 0.76	55–59: 0.76/0.86	
	70–74: 0.74	60–64: 0.72/0.82	
	75–79: 0.70	65–69: 0.71/0.81	
	80–84: 0.63	70–74: 0.69/0.79	
	85–89: 0.51	75–79: 0.65/0.75	
	90–94: 0.51	80–84: 0.58/0.68	
	95–100: 0.51	85–89: 0.46/0.56	
No pneumococcal diseases (high-risk; by age band in years)	18–54: 0.72	Triangular distribution with the mode being the mean value (minimum/maximum)	[41]
	55–59: 0.69		
	60–64: 0.63	18–54: 0.67/0.77	
	65–69: 0.57	55–59: 0.64/0.74	
	70–74: 0.54	60–64: 0.58/0.68	
	75–79: 0.52	65–69: 0.52/0.62	
	80–84: 0.51	70–74: 0.49/0.59	
	85–89: 0.51	75–79: 0.47/0.57	
	90–94: 0.51	80–84: 0.46/0.56	
	95–100: 0.51	85–89: 0.46/0.56	
IPD	0.20 (0.16–0.24) for 34 days	Triangular distribution with the mode being the mean value (minimum/maximum)	[41]
	As health-state utility value	0.14/0.25	
NBPP	0 (0–0.01)	Triangular distribution with the mode being the mean value (minimum/maximum)	
		0/0.01	
PMS	Hearing loss: 0.8	Triangular distribution with the mode being the mean value (minimum/maximum)	[72]
	Other neurological sequelae: 0.6	Hearing loss: 0.6/1.0	
	As utility multiplier	Other neurological sequelae: 0.45/0.75	
Discount rate (%)	3 (0–5)		[109]

IPD: Invasive pneumococcal disease; NBPP: Nonbacteremic pneumococcal pneumonia; PMS: Postmeningitis sequelae; PSA: Probabilistic sensitivity analysis; QALY: Quality-adjusted life-year.

on the German program for quality in healthcare in 2005–2006 [58]. It was estimated that approximately 40% of community-acquired pneumonia cases were attributable to pneumococcal infection, based on the German Competence Network for Community-Acquired Pneumonia study [59]. Case–fatality rates also came from the Competence Network for Community-Acquired Pneumonia study [59]. Due to a lack of data, a similar incidence of NBPP was assumed across risk groups.

Following an episode of pneumococcal meningitis, patients may develop PMS, consisting of hearing loss and other neurological sequelae [60,61]. As noted in a review by des Portes (2009 [62]), 30%

of hospitalized adult patients develop moderate to severe neurological sequelae, which lead to an inability to work. Furthermore, 22% of surviving adult patients experience hearing loss. The prevalence rates were applied in the model to estimate the number of patients with PMS. No excess mortality was assumed for the PMS health state, due to a lack of data.

Demography

The size of the German population by age in 2011 was obtained from the 12th Coordinated Population Projection for Germany (12. Bevölkerungsvorausberechnungfür Deutschland) from

DESTATIS (Statistisches Bundesamt Deutschland) [111]. Linear interpolation between the two available data points were used where needed [EMMERLING D, PERS. COMM.]. The split by risk for the influenza vaccination in the German population aged between 5 and 49 years was applied to all age groups in the model due to the lack of data in the population aged 50 years and above (at-risk immunocompetent [with chronic cardiovascular or respiratory disease or diabetes] was 12.8%; and at-risk immunosuppressed [with HIV/AIDS or transplantations] was 0.2% (TABLE 1) [55]).

It was estimated that 3% of the eligible German population would receive PPV23 vaccination in 2011, leading to a target population size of 833,890 individuals. This was based on sales data for PPV23 [11], due to a lack of publicly available information on the vaccination coverage rate in Germany.

Vaccine effectiveness & revaccination

Vaccine effectiveness differs between the three risk groups (TABLE 2). In immunocompetent individuals, vaccine effectiveness against IPD was obtained from a recent Cochrane systematic literature review and meta-analysis of ten prospective clinical trials [29], whereas for at-risk immunosuppressed individuals, vaccine effectiveness against IPD was retrieved from a prospective trial conducted on HIV-infected patients in the USA [30].

Vaccine effectiveness against NBPP was taken from a prospective cohort study conducted between 2002 and 2005 in Spain of 11,241 individuals aged 65 years and older [63]. It was assumed that the vaccine did not protect the immunosuppressed patients against NBPP.

In the model, the same vaccine effectiveness was applied to all age groups due to the lack of data. It was assumed that vaccinated individuals were protected from the time of vaccination and were no longer protected after 8 years from the initial vaccination [64,65]. As per German recommendations, the model assumed that only people younger than 60 years at initial vaccination would receive a second dose of PPV23 after 5 years of the initial vaccination [66]. Based on the results from several observational studies, revaccination was assumed to provide the same vaccine effectiveness as the initial vaccination [31,67,68]. A total of 3% of vaccinated people were expected to receive revaccination, according to PPV23 sales data [11].

Resource utilization & costs

The resource utilization and cost analysis took the perspective of the German third-party payer (TPP, i.e., sickness funds), as well as a societal perspective in order to account for the inability
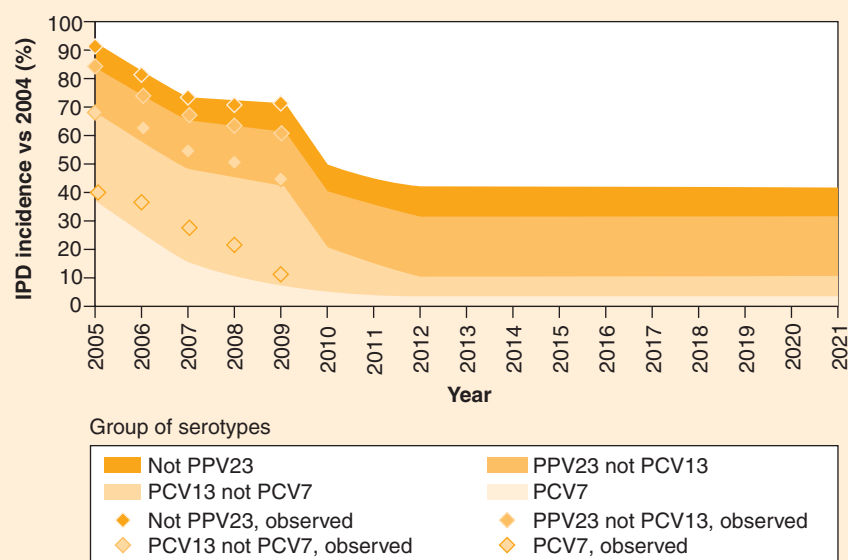
Figure 2. Observed and modeled seroepidemiological changes in the incidence of pneumococcal serotypes causing invasive pneumococcal disease over time from 2005 to 2021 in Germany.
IPD: Invasive pneumococcal disease; PCV: Pneumococcal conjugate vaccine; PPV: Pneumococcal polysaccharide vaccine.
Data taken from [11,25].

of patients with PMS to work (TABLE 3). All costs were estimated in 2010 Euros and the Harmonized Indices of Consumer Prices inflator for healthcare services was used when necessary [112]. Costs were discounted at 3%, following German guidelines on economic evaluations [109].

The vaccine's unit price (Pneumovax® 23, single dose pack; Sanofi Pasteur MSD) was taken from the LAUER-Taxe (as of 1 January 2011 [113]). The treatment of pneumococcal diseases and vaccine administration costs were obtained from German sources [11,114] and a German cost–effectiveness analysis conducted by Claes et al. [69]. For the treatment of hearing loss due to pneumococcal meningitis, the annual costs were estimated from a German cost–effectiveness analysis of cochlear implants in children [70]. The treatment costs of other neurological sequelae were estimated based on the ratio between the costs of treating hearing loss and other neurological sequelae in the study by Claes et al. [69]. A copayment of €7 was applied to treatment and vaccine

Table 5. Results: number of disease cases.

Parameter	PPV23	No vaccination
Size of the target population	833,890	
IPD cases	1261	1463
Change (%)	-13.9	
NBPP cases	63,236	67,781
Change (%)	-6.7	

IPD: Invasive pneumococcal disease; NBPP: Nonbacteremic pneumococcal pneumonia; PPV23: 23-valent pneumococcal polysaccharide vaccine.

Table 6. Results: costs from third-party payer perspective (in €1000).

Parameter	PPV23, undisc.	PPV23, disc.	No vaccination, undisc.	No vaccination, disc.	Incremental, undisc.	Incremental, disc.
Vaccine	24,662	24,640	0	0	24,662	24,640
Vaccine administration	5667	5661	0	0	5667	5661
IPD	10,551	6744	12,248	8308	-1697	-1565
NBPP	125,821	76,011	134,712	84,185	-8891	-8174
PMS	1198	526	1405	653	-206	-126
Total	167,899	113,582	148,364	93,145	19,534	20,436

disc.: Discounted; IPD: Invasive pneumococcal disease; NBPP: Nonbacteremic pneumococcal pneumonia; PMS: Postmeningitis sequelae; PPV: Pneumococcal polysaccharide vaccine; TPP: Third-party payer; undisc.: Undiscounted.

administration costs based on the assumption that 30% of the patients were fully exempted from a copayment of €10 [115,116].

The numbers of days off work in patients with IPD and NBPP were taken from the German Federal Health Monitoring (Gesundheitsberichterstattung des Bundes [117]). In 2009, the average length of stay was 13.5 days in patients with pneumonia due to *S. pneumoniae* (ICD10: J13) aged 15 years old and above and the figure was applied to both IPD and NBPP cases. Patients with postmeningitis sequelae were assumed to cease employment completely [62]. The cost of a day off was calculated from the average compensation of employees (Arbeitnehmerentgelt) in Germany [118]. It was assumed that the productivity loss applied until the legal retirement age of 65 years, as the higher retirement age (67 years) is only expected to be fully implemented within two decades [119].

Effectiveness

Effectiveness was measured in quality-adjusted life years (QALYs) in the model (**Table 4**). QALYs were discounted at 3% [109]. The baseline QALY weights were obtained from a US cost–effectiveness study which reported utility values by risk group based on data from the 1990 National Health Interview Survey [41]. The utility associated with the IPD health state was from the same study, which has been used in several other cost–effectiveness analyses [34,71]. Due to the scarcity of data on utility in patients with NBPP, a conservative approach was used and no utility decrement was

assumed for NBPP. For PMS, the utility multipliers used were from a Canadian cost–effectiveness study [72].

Economic analyses

The economic analyses compared PPV23 vaccination with no vaccination. The German health technology assessment authorities do not set a fixed threshold of incremental cost–effectiveness ratio (ICER) below which a health technology is considered as 'good value for money' [109]. In this study, an arbitrary threshold of €50,000 per QALY gained was considered as the primary threshold of cost–effectiveness, as it was commonly used in the German context [73–75]. A secondary threshold of €30,000 per QALY was also considered in the analysis.

Univariate sensitivity analyses were performed to examine the impact of individual parameters on the ICER. Selected parameters in the sensitivity analyses and corresponding variability were estimated from the sources or assumed, as reported in **Table 1**.

A probabilistic sensitivity analysis (PSA) was also conducted to quantify the uncertainty in the ICER as a result of the uncertainty in the different model parameters. The distribution associated with each model parameter was selected based on the German guidelines on economics evaluations [76] and the published literature (**Table 1**). To account for uncertainty around the epidemiological changes in IPD incidence as a result of vaccinating children, the presence of epidemiological change was also drawn randomly

Table 7. Results: cost from societal perspective (in €1000).

Parameter	PPV23, undisc.	PPV23, disc.	No vaccination, undisc.	No vaccination, disc.	Incremental, undisc.	Incremental, disc.
Vaccine	31,350	31,321	0	0	31,350	31,321
Vaccine administration	11,374	11,364	0	0	11,374	11,364
IPD	11,500	7356	13,345	9056	-1844	-1701
NBPP	130,998	79,415	140,535	88,195	-9537	-8779
Postmeningitis	12,369	6267	14,538	7710	-2168	-1443
Total	197,591	135,722	168,417	104,961	29,174	30,761

disc.: Discounted; IPD: Invasive pneumococcal disease; NBPP: Nonbacteremic pneumococcal pneumonia; PPV: Pneumococcal polysaccharide vaccine; undisc.: Undiscounted.

Table 8. Results: quality-adjusted life years (in 1000).

Parameter	PPV23, undisc.	PPV23, disc.	No vaccination, undisc.	No vaccination, disc.	Incremental, undisc.	Incremental, disc.
Vaccine	10,997	7503	10,993	7499	5	4
Vaccine administration	1	1	1	1	0	0
IPD	37	23	40	26	-3	-3
NBPP	0	0	1	0	0	0
PMS	10,997	7503	10,993	7499	5	4
Total	11,036	7527	11,034	7525	2	1

disc.: Discounted; PMS: Postmeningitis sequelae; PPV: Pneumococcal polysaccharide vaccine; QALY: Quality-adjusted life year; undisc.: Undiscounted.

when running the PSA, with a chance of 50%. The PSA was run for 1000 iterations and the cost–effectiveness acceptability curve was plotted.

Results

Model validation

The modeled epidemiological changes were compared with data observed in Germany [11,25]. As can be seen in FIGURE 2, overall, the model predictions matched the observed incidence data. However, the model underestimated the contribution of PCV13 serotypes on the incidence of IPD and overestimated the contribution of non-PCV13 serotypes. The modeled trend appears to better fit the observed data in more recent years, which correspond to the study period for the cost–effectiveness analysis. The significantly decreased incidence predicted by the model between 2009 and 2010 is explained by the switch from PCV7 to PCV13 in children when the coverage rate was already high, and the corresponding assumptions of the effect of PCV13 on the epidemiology of disease led to a switch from an increase to a decrease in IPD associated with non-PCV13 serotypes.

Base-case analysis

A cohort of 833,890 German individuals eligible to receive PPV23 vaccination was followed by the model until death or the age of 100 years. A total of 22% of them (182,358) were at-risk adults aged below 60 years at the time of initial vaccination. The detailed results are reported in TABLES 5–9. When compared with no vaccination, the ICER of PPV23 vaccination was estimated at €17,065 per QALY gained from the TPP's perspective, and at €25,687 from the societal perspective.

Sensitivity analyses

FIGURE 3 shows the variation of the ICER according to each parameter (univariate sensitivity analysis). The ICER was sensitive to the vaccine effectiveness against NBPP, waning function and incidence of NBPP. Except when assuming no vaccine effectiveness against NBPP, the ICER fell below the predefined 'good value for money' threshold of €50,000 per QALY gained. A threshold analysis found that a minimum of vaccine effectiveness of 11.6% against NBPP, which is much lower than the assumption in the base-case analysis (39.0%), would be

sufficient to achieve cost–effectiveness at a threshold of €50,000 per QALY gained.

When assuming no change in the age-specific incidence of IPD, the ICER was estimated to be 33.9% lower than in the base-case (€11,282 per QALY gained). As no change in epidemiology would correspond to a higher incidence rate in the unvaccinated population, more IPD cases could be prevented. When assuming no change in the number of IPD cases associated with PCV13 not PCV7 serotypes, the ICER decreased to €14,621 per QALY gained (85.7% of the base-case ICER).

FIGURES 4 & 5 report the results of the PSA. Each data point represents the incremental costs and effects obtained from each model simulation following the draw of model parameters from a predefined distribution reflecting the associated uncertainty. The variation of cost–effectiveness of PPV23 was limited. When compared with no vaccination, PPV23 was cost effective in 86.7% of the cases when the willing-to-pay was set at €30,000 per QALY gained, while the rate increased to 98.1% when the willing-to-pay was at €50,000 per QALY gained, both from a TPP perspective.

Discussion

Following a hypothetical cohort of adults eligible for pneumococcal vaccination, PPV23 was estimated to reduce the incidence of IPD by 13.9% and the incidence of NBPP by 6.7% under a lifetime horizon (TABLE 5). These relatively low changes may be explained by two main factors: low annual vaccination coverage rates and assumptions about the mean duration of protection conferred by the vaccine combined with a very low revaccination rate.

From the TPP perspective, it was estimated that 32.6% of the cost of vaccination including administration would be offset.

Table 9. Results: incremental cost–effectiveness ratio.

ICER	Costs per QALY gained
TPP perspective	€17,065
Societal perspective	€25,687

ICER: Incremental cost–effectiveness ratio; QALY: Quality-adjusted life year; TPP: Third-party payer.

From a societal perspective, cost offsets were relatively smaller (27.9%), as a result of a higher copayment on the vaccine (€8.2; as incremental costs) than for managing pneumococcal diseases (€7 per disease episode; as cost offset associated with reduced number of pneumococcal disease cases due to vaccination).

Despite epidemiological changes, PPV23 vaccination was still found to be cost-effective with an ICER well below €50,000 per QALY gained. Sensitivity analyses showed that the results were robust to the different model parameters. The ICER exceeded €50,000 only when the vaccine effectiveness against NBPP was assumed to be lower than 11.6%, which is much lower than the effectiveness reported in observational studies (39.0–63.0% [63,77,78]) and assumed in the base-case analysis (39.0%). This is due to the fact that although IPD is much more severe than NBPP, the absolute number of cases of noninvasive diseases, including NBPP, is much higher.

Strengths of the study

There are several strengths of the model. First, the model takes into account the changing epidemiology of IPD associated with the introduction of routine PCV vaccination of children. This approach better reflects the future environment in which the health technology will be used and assessed. A range of sensitivity analyses also allowed a better understanding of the impact of uncertainty around these assumptions.

Second, the model is based on local burden of disease and epidemiological data. The vaccine uptake of PCV7/13 in children and PPV23 was based on published sales data observed in Germany [11]. Furthermore, the results were compared with the real epidemiology of IPD reported by the German National Centre for Streptococci [11,25].

Limitations

This study has several limitations. Although the study used the German incidence and serotype coverage of IPD for the period before universal PCV vaccination in children, the epidemiological trend was based on data from the USA, another industrialized country. The overall validity of the approach has been assessed
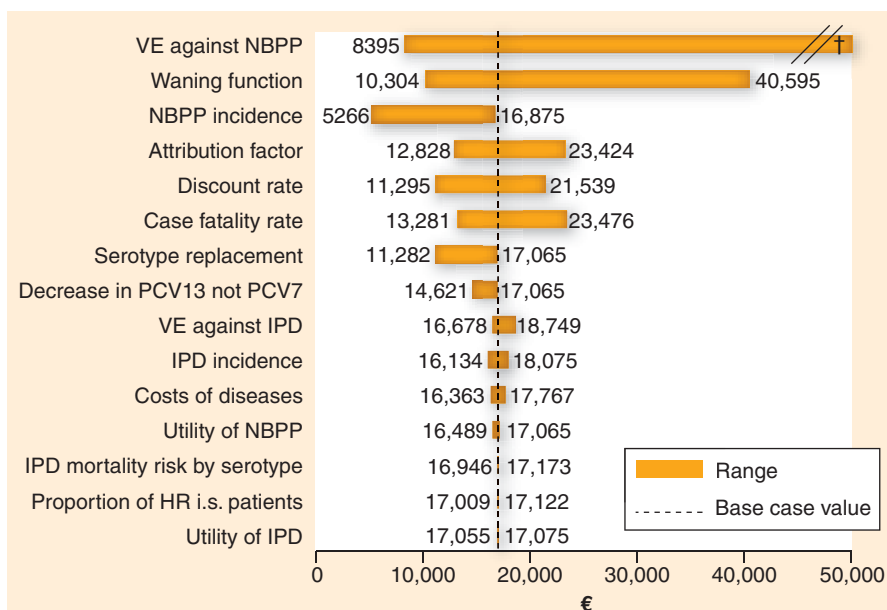

Figure 3. Univariate sensitivity analyses. Attribution factor refers to the proportion of nonbacteremic pneumonia having pneumococcal origin.
†The maximum value obtained in the sensitivity analysis was €118,382 per quality-adjusted life-year gained, when vaccine effectiveness of 23-valent pneumococcal polysaccharide vaccine against NBPP was assumed to be 0%. The incremental cost–effectiveness ratio was €75,664, €41,789 and €22,848 per quality-adjusted life-year gained, when vaccine effectiveness of 23-valent pneumococcal polysaccharide vaccine against NBPP was assumed to be 5, 15 and 30% in the elderly and at-risk immunocompetent adults, respectively.
HR: Hazard ratio; IPD: Invasive pneumococcal disease; i.s.: Immunosuppressed; NBPP: Nonbacteremic pneumococcal pneumonia; PCV: Pneumococcal conjugate vaccine; VE: Vaccine effectiveness.

by comparing model predictions to observed data, but exact trends differ (Figure 2). Sensitivity analyses were conducted to assess the impact of assumptions about epidemiological trends on the ICER.
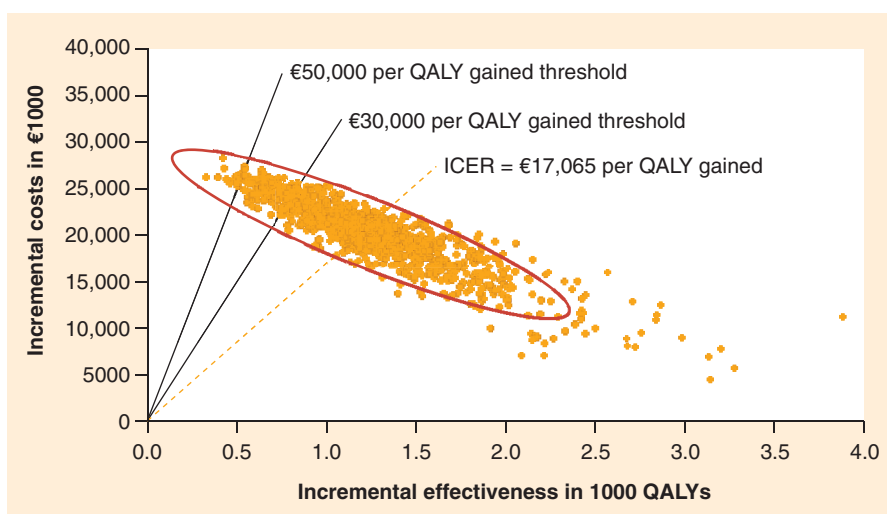

Figure 4. Probabilistic sensitivity analysis: cost–effectiveness plane.
ICER: Incremental cost–effectiveness ratio; QALY: Quality-adjusted life year.

The model was not designed to capture the herd protection induced by PPV23 vaccination (i.e., indirect protection of unvaccinated individuals), which consists of future reduction of pneumococcal diseases in both the vaccinated and unvaccinated. The reason for doing so was to avoid incorporating more uncertainty stemming from assumptions on the transmission of the disease, which are not well established.

Third, the effectiveness of PPV23 in the analysis was based on a meta-analysis of clinical trials in all individuals [29]. Some evidence suggests that the effectiveness might be lower in the elderly or immunocompetent people [4]. Therefore, the analysis might have biased down the ICER of PPV23 when compared with no vaccination.

Finally, it has been identified that NBPP is an important driver of cost–effectiveness and additional data are required to obtain a more reliable estimate of the incidence of NBPP.

Figure 5. Probabilistic sensitivity analysis: cost–effectiveness acceptability curve.
PPV23: 23-valent pneumococcal polysaccharide vaccine; QALY; Quality-adjusted life-year.

Comparison with previously published cost–effectiveness analyses

In 2009, Ogilvie et al. conducted a systematic literature review to document the cost–effectiveness analysis of PPV23 vaccination [39]. Five studies [34–36,41,79] were identified reporting costs per QALY gained when comparing PPV23 vaccination with no vaccination in elderly adults (50 or 65 above). In total, 18 of the 19 collected ICERs were below the threshold of US$50,000 per QALY gained (ICERs were expressed in 2007 USD) and the median ICER was about US$25,000 per QALY gained. The only study that included an analysis in the German context [35] reported an ICER of approximately US$26,000. This study focused on individuals aged 65 years old or older and only IPD was accounted for.

When converted to US dollars, the base-case ICER in the authors' study ranges from approximately US$15,000 to US$20,000 depending on the perspective and the scenario, which is in line with the literature. Further comparison is not possible because of different model structures and parameters.

Expert commentary & five-year view

The current study confirms the cost–effectiveness of PPV23 vaccination in an environment where the epidemiology of pneumococcal disease is changing. However, our estimate relies on trends observed in the USA and the applicability of these data to the German settings will need to be confirmed. This would require surveillance studies to explore the impact of universal PCV vaccination in children on adults.

Furthermore, with the recent extension of indication of PCV13 to adults aged 50 years and older to prevent IPD in Europe [107], the comparative cost–effectiveness between PPV23 and PCV13 should be assessed using a similar approach. It is crucial to
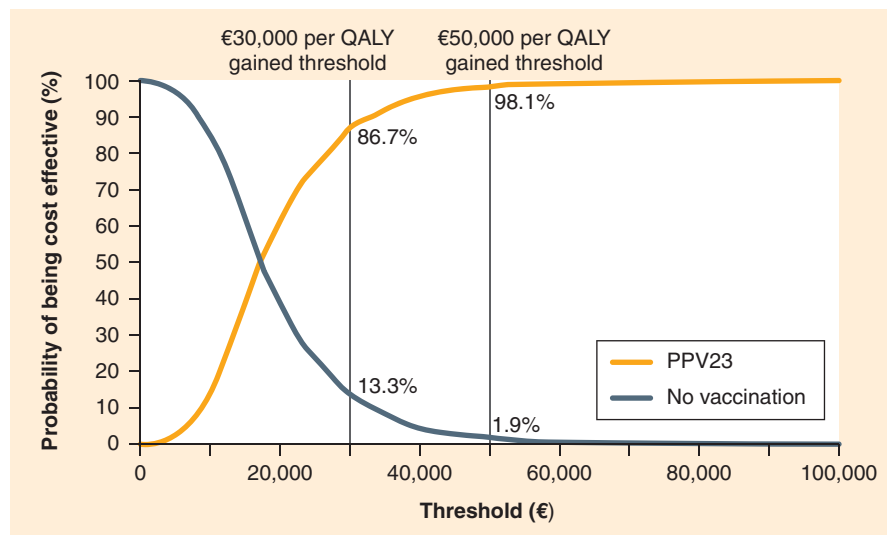
understand the extrinsic value of both vaccines given the changing epidemiology, before an informed decision can be made.

More broadly speaking, the epidemiological changes of IPD are not directly associated with the studied health technology, but arose as externalities (i.e., benefits to unvaccinated adults) of an earlier public health decision (i.e., universal vaccination of children). Future cost–effectiveness analyses should incorporate externalities whenever they are identifiable, together with associated uncertainties, to better reflect the expected benefit of a health technology in any given changing environment.

Conclusion

The recent introduction of universal PCV vaccination in children has led to a change in the epidemiology of IPD in adults. The incidence of IPD associated with PCV serotypes is expected to decrease and that associated with other serotypes is expected to increase in adults. Despite a reduction in the incidence of IPD, vaccinating the elderly and at-risk adults with PPV23 in Germany against IPD and NBPP remains a cost-effective strategy because of its broad serotype coverage.

Financial & competing interests disclosure

Key issues

- Infection with *Streptococcus pneumoniae* may lead to invasive pneumococcal disease (IPD) or noninvasive forms of pneumococcal diseases. In Germany, IPD alone accounts for approximately 1200 deaths each year.
- The introduction of universal pneumococcal conjugate vaccine (PCV) vaccination in children has led to a change in the epidemiology of IPD in vaccinated children, as well as in unvaccinated adults. It has been observed that in the USA, the incidence of IPD associated with PCV serotypes decreased and the incidence of IPD not associated with PCV serotypes increased in adults, with increasing cumulative PCV coverage in children.
- Even with the epidemiological changes, vaccinating the elderly and at-risk adults with 23-valent pneumococcal polysaccharide vaccine (PPV23) was still found to be cost effective in Germany, when compared with no vaccination, because of its broad serotype coverage.
- When assessing the cost–effectiveness of PPV23, it is crucial to take into account the changing epidemiology so that its extrinsic value can be estimated with greater accuracy. With the extension of the 13-valent PCV indication against IPD to elderly adults in Europe, its cost–effectiveness against PPV23 should be examined in a similar approach that captures the epidemiological change before an informed decision can be made.

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