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Cost-effectiveness of introducing infant vaccination against pneumococcal disease in Poland – comparison of non-typeable Haemophilus influenzae protein D (PHiD-CV) and 13-valent (PCV-13) pneumococcal conjugate vaccines

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Abstract

Background: Streptococcus pneumoniae can cause invasive pneumococcal diseases (IPD), pneumonia and acute otitis media (AOM), a common childhood infection that may require antibiotics. There were 3,236 IPD cases detected in Poland between 2006-2016, with incidence peaks among infants and the elderly. The case-fatality rate in 2016 was 6.7% among infants and 49.3% among the elderly. Since 2009, two infant pneumococcal conjugate vaccines are available in Poland (the pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine [PHiD-CV], and the 13-valent pneumococcal conjugate vaccine [PCV-13]). The objective of this study was to assess the cost-effectiveness of routine PHiD-CV versus no vaccination and versus PCV-13.

Methods: A previously published Markov cohort model was adapted for Poland to compare PHiD-CV to no vaccination and PCV-13 from the public payer perspective, regarding lifetime direct costs and quality-adjusted life years (QALYs) associated with morbidity and mortality due to IPD, pneumonia and AOM. PHiD-CV and PCV-13 were assumed to have the same efficacy for their ten common vaccine serotypes, and PHiD-CV was assumed to have conservative cross-protection effectiveness against serotypes 6A and 19A, and to be more protective against AOM due to its effectiveness against non-typeable Haemophilus influenzae. Scenario analyses assessed outcomes when vaccine price parity was assumed, when the effectiveness of PHiD-CV against serotype 19A IPD was omitted or increased, and, when the effectiveness of PCV-13 against serotype 3 IPD was varied.

Results: PHiD-CV was a cost-effective option versus no vaccination, with a cost per QALY gained of Polish złoty (PLN) 94,933 (below the threshold for cost-effectiveness of PLN 134,514). Both vaccines had comparable health outcomes regarding IPD and pneumonia, while PHiD-CV achieved better health outcomes against AOM. PHiD-CV was the dominant strategy for Poland versus PCV-13 (resulting in a gain of 170 QALYs at a direct cost-saving of PLN 61.1 million). In scenario and sensitivity analyses, PHiD-CV remained the dominant strategy versus PCV-13.

Conclusions: The introduction of PHiD-CV in the Polish national immunization programme is likely to reduce the disease burden due to IPD, pneumonia and AOM. It is a cost-effective strategy (versus no vaccination) and a cost-saving strategy (versus PCV-13) for the healthcare payer.

Introduction

Pneumococcal disease is an infection caused by the Streptococcus pneumoniae (S. pneumoniae) bacterium. There are currently over 90 serotypes (STs) recognized worldwide, 15 of which cause the majority of disease.[1] The burden of disease is important, as infection is a leading cause of life-threatening invasive pneumococcal disease (IPD) which mainly includes meningitis and bacteraemia, as well as non-invasive illness such as pneumonia and acute otitis media (AOM).[2] In Poland, between 2010 and 2016, the National Reference Center for Diagnosis of Central Nervous System Infections (KOROUN) detected 3,447 IPD cases. There were significant differences between provinces and between the analyzed periods in the same provinces. Data reported suggested underreporting and the differences among provinces most likely reflect inconsistence medical practices i.e., low number of blood cultures and serotyping test performed. In 2016, the highest incidence rates of 4.76 and 5.43 per 100,000 people in Poland were observed in those aged over 65 years and under two years, respectively. The IPD case fatality rate was 49.3% (over 65-year-olds), 38.4% (45-64-year-olds), 33.3% (25-44 and 5-9-year-olds), and 6.7% in children under two years.[3] AOM is a very common childhood disease typically treated with antibiotics, with 60-70% of clinical cases caused by bacteria.[4] A meta-analysis reports that on average 35.9% of AOM episodes are caused by S. pneumoniae and 32.3% by non-typeable Haemophilus influenzae (NTHi).[5]

Vaccination in infants is an effective means of preventing diseases, not only in vaccinated but even in unvaccinated infants and in older age groups due to herd immunity.[6-10] Moreover, it plays an important role given increased antimicrobial resistance among some pneumococci.[11-13] A recent Polish study found antibiotic resistance in children with AOM was an important cause of treatment failure.[14] Pneumococcal conjugate vaccines are recommended by the World Health Organization (WHO)[15] for routine immunisation of infants and in many countries introduced in their National Immunization Programme

(NIP). There are two licensed conjugate vaccines available in Poland: the pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV; Synflorix, GSK), and the 13-valent pneumococcal conjugate vaccine (PCV-13; Prevenar13, Pfizer). Since 2017, PHiD-CV is administered as part of the NIP for all healthy infants, in a 2+1 schedule given at two, four and 13 months of age. The vaccine is intended to protect against all spectrum of pneumococcal disease i.e., IPD, pneumonia and AOM. Both vaccines can be used for risk groups in a 3+1 schedule.[16] While the vaccine STs contained in the two vaccines differ to some extent i.e., number of STs, carrier protein, there is evidence of protection exerted from PHiD-CV against cross-related STs. Recently, WHO's global systematic review[10,17] on the impact of PHiD-CV and PCV-13, and 2 other industry-independent studies, concluded that at this stage, there is no evidence of difference on the net impact on pneumococcal diseases despite the difference of composition between the two vaccines.[18,19] Regardless of the vaccine used and of local epidemiology, countries which have implemented a childhood pneumococcal immunization program with a high coverage, observed a significant reduction in the burden of IPD in children.[20]

The objective of this study was to assess the cost-effectiveness of introducing a routine infant vaccination programme against pneumococcal disease in Poland. Two analyses were performed: comparing PHiD-CV to no vaccination, and, comparing PHiD-CV to PCV-13.

Materials and Methods

2.1. Model and population

A previously published Markov cohort model[21] was adapted for Poland to assess the cost-effectiveness of introducing routine infant vaccination against pneumococcal disease, from the public payer perspective. Vaccination with PHiD-CV was compared to no vaccination and to vaccination with PCV-13.

The model is an age-compartmental, deterministic, static cohort model that assesses the health and economic impact of IPD caused by S. pneumoniae (i.e., meningitis and bacteraemia), all-cause pneumonia, and AOM caused by S. pneumoniae and NTHi, in a birth cohort over lifetime, using monthly cycles. Fig. 1 shows the flow diagram of the model.[22]

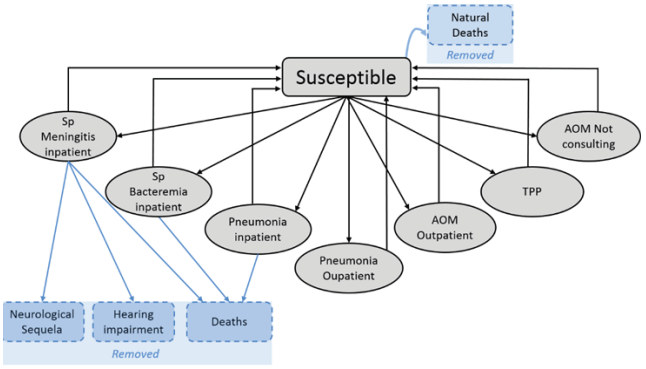

Figure 1. Model flow diagram

Circle boxes represent mutually-exclusive health states. Dashed rectangles (sequelae and deaths) and natural deaths in susceptible individuals show the populations removed from the model. Age-specific incidence was applied monthly to the susceptible population. Costs and benefits were calculated monthly and aggregated over the cohort's lifetime. Non-consulting AOM were included in the quality of life impact calculation. Redrawn from Delgleize et al.[22] AOM: acute otitis media; Sp: Streptococcus pneumoniae; TPP: tympanostomy tube placement.

A Polish birth cohort of 373,527 babies[23] was modelled; during each model cycle, the probability of an individual entering a specific health state was governed by age-specific incidence rates and applicable vaccine efficacy (VE) levels. Infants received, in the vaccine arms, two primary doses of one of the vaccines, at two and four months old, with a booster dose at 13 months old.[4,24] Age-specific overall monthly mortality rates for the general population were obtained from Polish life expectancy tables.[25] Age-specific disease incidence and disease progression were represented by health states (i.e., disease with or without general practitioner (GP) visits, hospitalisation, complications, long-term sequelae or death), linked to resource utilisation (e.g., hospitalisation, GP visits, and specific interventions such as myringotomies for AOM), resulting in direct costs and quality-adjusted life years (QALYs) over lifetime.

In the model, lifetime direct costs and QALYs associated with morbidity and mortality due to IPD, pneumonia and AOM were compared for PHiD-CV versus no vaccination and PHiD-CV versus PCV-13. The incremental cost per QALY gained or incremental cost-effectiveness ratio (ICER), expressed as Polish złoty (PLN)/QALY, was calculated for both comparisons.

2.2. Comparators and vaccine effectiveness assumptions

The model compared vaccination with PHiD-CV versus no vaccination and versus vaccination with PCV-13. A 2+1 regimen as previously described was used for both vaccines.

The vaccines have never been compared directly in trials. As they contain different STs, vaccine effectiveness against IPD, pneumonia and AOM were based on ST-specific efficacy from clinical trials (Table 1). Both vaccines directly protect against disease caused by 10 common STs 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. In addition, PCV-13 directly protects against STs 6A, 19A and 3,[4,24] while PHiD-CV, which includes STs 6B and 19F, has shown evidence of cross-protection against 19A[8] and a decrease of 6A in real-world evaluations after its introduction.[26] Cross-protection occurs when a vaccine demonstrates effectiveness against STs not included in the vaccine. and 19A.[8] Cross-protection occurs when a vaccine demonstrates effectiveness against STs not included in the vaccine.

Eight of ten STs of PHiD-CV are conjugated to a protein D from NTHi, eliciting robust immune responses.[27] Higher serum antibody levels to protein D have been

Table 1. Vaccine effectiveness: model inputs and assumptions

	VE % (95%CI)		Source
	PHiD-CV	PCV-13	
IPD			
Ten common STs for PHiD-CV and PCV-13a	94.7 (87.0; 99.9)	94.7 (87.0; 99.9)	[30]
ST 3	0.0	26.0 (-69.0; 68.0)b	[32,34]
ST 6A	76.0 (39.0; 90.0)	94.7 (87.0; 99.9)	[30,36]
ST 19A	62.0 (20.0; 85.0)c	94.7 (87.0; 99.9)	[30,39]
Pneumonia			
% reduction in hospitalisations	21.8 (7.7; 33.7)	21.8 (7.7; 33.7)	[43]
% reduction in GP visits	8.7 (3.8; 13.4)	8.7 (3.8; 13.4)	[43]
Outpatient AOM			
Ten common STs for PHiD-CV and PCV-13a	69.9 (29.8; 87.1)	69.9 (29.8; 87.1)	[43]
NVTs	-33.0 (-80.0; 1.0)	-33.0 (-80.0; 1.0)	[44]
ST 6A	63.7 (-13.9; 88.4)	69.9 (29.8; 87.1)	[43,45]
ST 6C	0.0	63.7 (-13.9; 88.4)	PCV-13 same as 6A for PHiD-CV[49]
ST 19A	45.8d (model calculation)	69.9 (29.8; 87.1)	[43]
NTHi	21.5 (-43.4; 57.0)	-11.0 (-34.0; 8.0)	[43,44]
Inpatient AOM			
% reduction in TTP (AOM hospitalisation) e	21.2 (model calculation)	12.7 (model calculation)	[48,50]

AOM: Acute otitis media; GP: General Practitioner; IPD: Invasive pneumococcal disease; NVTs: non-vaccine serotypes; PCV-7: 7-valent pneumococcal conjugate vaccine; PCV-13: 13-valent pneumococcal conjugate vaccine; PHiD-CV: Pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine; NTHi: Non-typeable Haemophilus influenzae; ST: Serotype; TTP: Tympanostomy tube placement; VE: Vaccine effectiveness.

a PHiD-CV and PCV-13 assumed to have the same ST efficacy for the ten common STs as the average VE of PCV-7 vaccine STs (94.7% for IPD and 69.9% for AOM).

b For ST 3, 26% VE was used for PCV-13 in the base case based on Andrews et al. (26%, 95% CI: -69; 68, not significant)[32] and 0%[34] and 79.5%[35] in scenario analyses.

c For ST 19A, 62% VE was used for PHiD-CV [39] in the base case and 0% (assume no protection)[37] and 82.2% (95%CI: 10.7; 96.4)[38] in scenario analyses

d PHiD-CV efficacy was estimated by taking the ratio of the vaccines' efficacy against IPD ST 19A;

e Extrapolated VE estimates were well in agreement with findings of the FinIP study[29]

found to be associated with reduced risk of future AOM.[28] Efficacy against NTHi caused IPD was omitted in this analysis for both vaccines. Vaccine efficacy was assumed to increase with the number of doses (i.e., 50% efficacy with dose one, 90% with dose two and 100% with dose three),[29,30] and to wane exponentially from three until ten years of age.

The model assumed 97% coverage for both vaccines, as they will be co-administered with other vaccines in the NIP that have reported coverage no less than 97% (data from 2012-2013).[31]

2.3. Effectiveness against IPD

PHiD-CV and PCV-13 were assumed to have the same VE (94.7%, [95% confidence interval (CI): 87.0; 99.9]) for the ten common STs, calculated as the average efficacy of STs contained in the predecessor of PCV-13, i.e. the 7- valent pneumococcal conjugate vaccine (PCV-7).[30] PHiD-CV was assumed to have no efficacy against ST3, while PCV-13 was assumed to have 26% VE (95%CI: -69; 68).[32] Even not being significant, this assumption was made as this value was previously used in health technology assessment and tender discussions with the government. Many post-marketing surveillance studies[32-34] have shown no consistent impact of PCV-13 on ST 3 IPD, with most studies showing no impact or lack of effectiveness against ST 3 IPD.[8] As diverse vaccine effectiveness can be found in literature, the impact of 0% and 79.5% (95%CI: 30.3; 94.8) VE against ST 3 IPD (i.e., the highest published[35]) was tested in scenario analyses.

Since PHiD-CV was shown to elicit a similar antibody response to PCV-7 against ST 6A, a cross-protection effectiveness of 76% (95%CI: 39.0; 90.0) was assumed in the model.[36] PHiD-CV was shown to elicit a stronger response against ST 19A than PCV-7.[36-39] Recent large effectiveness studies observed a clear cross-protective effect against ST 19A ranging from 62% (95%CI: 20; 85) to 82% (95%CI: 10.7; 96.4).[37-39] This prompted many countries to update the Summary of Product Characteristics (SmPC) to include protection against 19A.[37-40]Therefore, the base case analysis assumed a conservative cross-protection effectiveness against ST 19A (62%)[39] which was left out (0%) and increased to 82% in the scenario analyses.[38]

VE against STs 6A and 19A IPD was assumed to equal the other STs in PCV-13 (94.7%, 95%CI: 87.0; 99.9).

Indirect or herd protection resulting from continual vaccination of sequential birth cohorts was taken into account for IPD only (we conservatively assumed no herd protection for pneumonia and AOM). Serotype replacement offsets the incremental effect of indirect protection resulting in a net indirect effect. In the model, indirect protection adjusted for the opposing impact of serotype replacement was applied as a fixed effect to the residual disease incidence. This net indirect effect was estimated at 30%, removing the necessity to account separately for the effect of serotype replacement.[41,42] All efficacy estimates and the net indirect effect applied in the model are in line with Tregnaghi et al.[43] and were validated by a panel of experts (GSK PHiD-CV Health Economics Advisory Board. Leuven, Belgium, September, 2013).[22]

2.4. Effectiveness against pneumonia

Both vaccines were assumed to have the same effectiveness in reducing GP visits (by 8.7%) and hospitalisation (by 21.8%) due to S. pneumoniae.[43]

2.5. Effectiveness against AOM

Efficacy against AOM was modelled against S. pneumoniae vaccine STs (VT) and against non-vaccine STs (NVTs), as efficacy data by ST or by dose were not available. Vaccine effectiveness against the ten common pneumococcal vaccine STs was assumed to be the same for both vaccines, based on the COMPAS study for PHiD-CV; i.e., 69.9% (95%CI: 29.8; 87.1).[43] As STs 6A and 19A are included in PCV-13, VE of PCV-13 against STs 6A and 19A AOM were also assumed to be 69.9%, based on the COMPAS study findings for vaccine types included in PHiD-CV. Effectiveness against NVTs was also assumed to be the same for both vaccines, based on PCV-7 data (FinOM study); i.e., -33% (95%CI: -80.0; 1.0).[44] Negative numbers indicate ST or pathogen replacement, despite no replacement being observed for PHiD-CV in the COMPAS study.[43 Effectiveness of PHiD-CV was 63.7% (95%CI: -13.9; 88.4)[45] against ST 6A, 0% against ST 6C, and, 45.8% against ST 19A (estimated by taking the ratio of the vaccines' efficacy against ST 19A IPD). Effectiveness of PCV-13 against ST 6C was assumed to be 63.7% (based on same effectiveness used for PHiD-CV against ST 6A).

Efficacy was also modelled against NTHi. Conservatively, PHiD-CV was assumed to have an efficacy against NTHi caused AOM of 21.5% (95%CI: -43.5; 57.0)[43,46] versus -11.0% (95%CI: -34.0; 8.0) for PCV-13, based on FinOM study for PCV-7.[43,44] NTHi efficacy was included in the overall reduction of AOM-related GP visits and myringotomy procedures. The latest was used as proxy for inpatient AOM estimated to be 21.2% with PHiD-CV and 12.7% with PCV-13. With PCV-7, Black and colleagues (2000)[47] observed a reduction in ventilatory tube placement (tympanostomy tube placement, TTP) of 20.1% (95%CI: 1.5; 35.2%) and a reduction in AOM episodes of 7.0% (95%CI: 4.1; 9.7%). The VE of PCV-7 against TTP was found, based on the FinOM[44] and Kaiser Permanente[48] studies, to depend on the incidence of TTP, assuming an inverted exponential relationship. According to the Polish incidence of TTP, VE for PCV-7 was estimated using this exponential relationship, and extrapolated to PHiD-CV a ratio of the modelled overall VE against

Table 2. Resource use, costs and utilities: inputs and assumptions			
	Value		Source and assumptions
Pneumococcal meningitis			
Annual hospitalisation rate	100%		Assumption
Pneumococcal bacteraemia			
Annual hospitalisation rate	100%		Assumption
Annual GP visit rate	0%		Assumption
All-cause pneumonia			
Annual hospitalisation rate per 100,000			
0-4y	1,364.2		Based on [53,56]
5-74y	81.5		
75-90+y	846.4		
Annual GP visit rate per 100,000			
<1y	675.7		[53], expert opinion
1-4y	4,092.5		
5-74y	244.6		
75+y	2,539.3		
AOM			
Annual GP visit rate per 100,000			
<1y	16,701.6		[54], expert opinion
1-4y	25,789.4		
5-9y	10,509.0		
10-14y	5,610.5		
15-19y	1,686.5		
20+y	1,090.1		
TTP procedures per 100,000			
<1y	8,748.4		[54], expert opinion
1-4y	4,640.6		
5-9y	1,891.0		
10-14y	1,009.6		
15-19y	303.5		
20+y	196.1		
Costs (PLN, 2016)			
Vaccine cost per dose	100 (PHiD-CV) 150 (PCV-13)		Public vaccine prices[49,58]
Cost per acute episode	<16y	>=16y	
Meningitis - first year	4,841.12	5,402.66	National health fund[57], expert opinion
Bacteraemia - hospitalised	5,961.41	3,669.14	
Pneumonia - hospitalised	3,244.65	3,244.65	
Pneumonia - outpatient	82.59	82.59	
AOM hospitalised myringotomy	1,242.33	1,242.33	
AOM GP consultations	51.96	51.96	
Annual cost long-term sequelae			
Meningitisa	690.69		National health fund[57], expert opinion
Bacteraemia	690.69		
Utilities – normative population values			
<24y	0.941		[61]
25-34y	0.939		
35-44y	0.929		
45-54y	0.900		
55-64y	0.894		
≥65y	0.798		
Disutilities (95%CI)			
Short-term disutilities per episode			
Inpatient meningitis	0,0232 (0,0099; 0,0419)		[62]
Inpatient/outpatient bacteraemia	0,0079 (0,0030; 0,0150)		[62]
Inpatient pneumonia	0,0080 (0,0031; 0,0151)		Assumed same as inpatient bacteraemia
Outpatient pneumonia	0,0060 (0,0015; 0,0134)		[62]
Outpatient AOM	0.005 (0.004;0.006)		[63]
Inpatient TTP/myringotomy	0.005 (0.004;0.006)		Assumed same as AOM
Long term disutilities per year			
Neurologic sequelae (meningitis)	0,4000 (0,3200; 0,4800)		[64]
Hearing loss (meningitis)	0,2000 (0,1800; 0,2200)		[64,65] assumes cochlear implant
Hearing loss (AOM)	0,0900 (0,0720; 0,1080)		[66] assumes no cochlear implant

AOM: Acute otitis media; CI: confidence interval; GP: general practitioner; PLN: Polish złoty; TTP: Tympanostomy tube placement; y: year
a Estimate cost as weighted average from hearing loss (690.69 PLN) and neurological sequelae (690.69 PLN) according prevalence of both sequelae due to Sp. Meningitis.

AOM of PHiD-CV (23.8%) over PCV-13 (14.3%), i.e 1.7. The FinIP[29] and POET[45] study estimates are in line with this extrapolation.

2.6. Health outcomes, resources, costs and utilities

Health and economic benefits that could be achieved through vaccination with either PHiD-CV or PCV-13 were a reduction in cases, sequelae, resource use, healthcare costs, and, a gain in QALYs.

The age-specific population data, incidence and deaths related to IPD, pneumonia and AOM, as well as disease management (e.g. rates of GP visits and hospitalisations) were specific to Poland from available evidence and expert opinion (Table 2).[3,51-56] (See Online Resource 1 for epidemiology inputs). The ST distribution in IPD in Poland from 2006 to 2016 was estimated from recent national laboratory surveillance reports.[3,51,52,55] (See Online Resource 2).

Data from the National Health Fund[57] and expert opinion were used to estimate the average cost of an acute episode of meningitis, bacteraemia, pneumonia and AOM, and annual costs for the management of sequelae (e.g., hearing loss or neurological) for the reference year 2016. The base case analyses used the published vaccine prices[49,58] of PHiD-CV (PLN 100) and PCV-13 (PLN 150), while in a scenario analysis, price parity between the vaccines was assumed (i.e., PLN 125: average of PHiD-CV and PCV-13 published prices). The cost-effectiveness threshold of PLN 134,514/QALY was defined as 3x Gross Domestic Product (GDP)/capita according to the Polish Agency for Health Technology Assessment and Tariff System[59] (based on PLN 44,838 per capita for 2013–2015). [60]

Normative population utilities by age group were based on data from Poland.[61] Disease specific disutility data from Poland were not available. Therefore, values from the United Kingdom (UK) were used and applied for an inpatient or outpatient episode of meningitis, bacteraemia, pneumonia or AOM, and, for their long-term sequelae assumed to persist over the individual's remaining lifetime.

2.7. Currency, price date, and discounting

All costs are in PLN and were updated to 2016 values. Costs and QALYs were discounted at 5.0% and 3.5% per annum, respectively, as per Polish health technology assessment (HTA) guidelines.[67]

2.8. Sensitivity and scenario analyses

2.8.1. One-way sensitivity analyses

The impact of any important model input on the outcome was evaluated in a one-way sensitivity analysis, whereby key model inputs (e.g., epidemiology, resource use, costs and disutility inputs) were varied one by one, using the lower and upper limits of their 95% confidence interval or in some cases, a range based on plus or minus 20%. A tornado diagram presents the most important impacts on the ICER.

2.8.2. Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to assess the robustness of the ICER when uncertainty in key model inputs was considered simultaneously. In each PSA simulation, the model randomly draws from a probability distribution describing each parameter, thus varying each input simultaneously with every PSA run. The result from 2,000 simulations is presented in a cost-effectiveness plane and cost-effectiveness acceptability curve.

2.8.3. Scenario analyses

Several scenario analyses were also conducted. The first scenario analysis compared PHiD-CV to PCV-13, assuming price parity; with both vaccines costing PLN 125, the average of their published prices. The next scenario analysis (of PHiD-CV versus PCV-13) assessed the impact of parametrising vaccine effectiveness of PHiD-CV against ST19A IPD from the conservative base case value of 62% to a no protection (0%) or to a more optimistic 82.2%, based on recent studies.[38] A final scenario analysis assessed the impact of changing vaccine effectiveness of PCV-13 against ST3 IPD from the base case value of 26% to both 0% and 79.5%, based on post-marketing studies .[32-35]

Results

3.1. Base case results for PHiD-CV versus no vaccination

Based on the model, the introduction of PHiD-CV vaccination versus no vaccination reduced the number of undiscounted IPD cases from 269 to 164 (by 39.2%), pneumonia cases from 261,609 to 252,468 (by 3.5%) and AOM cases from 1,213,534 to 1,113,705 (by 8.2%). This resulted in an increase of 978 QALYs (undiscounted) and a decrease in healthcare costs of PLN 39.6 million(M) (undiscounted), with vaccination costs of PLN 108.5M (undiscounted). The overall incremental cost of the vaccination programme was PLN 71.4M (5% discounted) with 752 QALYs gained (3.5% discounted), resulting in a cost per QALY gained of PLN 94,933 for PHiD-CV versus no vaccination. Therefore, under these assumptions, PHiD-CV was a cost-effective option versus no vaccination, with the cost per QALY gained well below the threshold for cost-effectiveness of PLN 134,514 (Tables 3&4).

3.2. Base case results for PHiD-CV versus PCV-13

When comparing the two vaccines, PHiD-CV had comparable outcomes to PCV-13 regarding IPD and pneumonia health outcomes. PHiD-CV, however, achieved better health outcomes against AOM with fewer inpatient and

Table 3. Undiscounted health and costs outcomes (PLN) (per birth cohort)			
Undiscounted outcomes and costs	No vaccination	PHiD-CV	PCV-13
Meningitis			
Cases	102	59	58
Long-term sequelae	3	2	2
Deaths	20	13	13
QALYs lost	78	34	33
Direct costs (meningitis) (PLN)	532,374	312,245	307,874
Direct costs (meningitis sequelae) (PLN)	183,220	79,820	76,185
Bacteraemia			
Cases	167	105	104
Long-term sequelae	3	2	1
Deaths	77	53	53
QALYs lost	69	29	27
Direct costs (bacteraemia) (PLN)	686,381	407,303	402,014
Direct costs (bacteraemia sequelae) (PLN)	163,230	67,315	63,802
Pneumonia (in/outpatient)			
Cases	261,609	252,468	252,468
Deaths	6,240	6,233	6,233
QALYs lost	1,707	1,643	1,643
Direct costs (PLN)	238,477,576	223,503,460	223,503,508
AOM (in/outpatient)			
Cases	1,213,534	1,113,705	1,152,167
QALYs lost	6,068	5,569	5,761
Direct costs (PLN)	304,939,441	280,985,886	290,490,383
Total QALYs	26,065,183	26,066,806	26,066,623
Vaccine costs (PLN)	0	108,463,366	162,695,052
Total direct costs* (PLN)	544,982,222	613,819,394	677,538,819

AOM: Acute otitis media; PLN: Polish złoty; QALY: quality-adjusted life-years
* Inclusive vaccine and vaccination costs

Table 4. Base case incremental health and cost outcomes and cost-effectiveness (5% discount on costs and 3.5% discount on effects)			
PHiD-CV versus no vaccination	PHiD-CV	No vaccination	Difference
QALYs gained	9,235,407	9,234,655	752
Direct costs* (PLN)	366,302,875	294,936,703	71,366,172
ICER (cost per QALY gained)	94,933 (below cost-effectiveness threshold**)		
PHiD-CV versus PCV-13	PHiD-CV	PCV-13	Difference
QALYs gained	9,235,407	9,235,237	170
Direct costs* (PLN)	366,302,875	427,411,268	-61,108,392
ICER (cost per QALY gained)	PHiD-CV dominant over PCV-13		

PLN: Polish złoty; QALY: quality-adjusted life-years.
* Inclusive vaccine and vaccination costs
**Cost-effectiveness threshold of PLN 134,514 (=3x GDP)

outpatient cases (38,462), and lower discounted direct costs (PLN 8.3M). Overall, PHiD-CV was associated with a gain in 170 QALYs (discounted at 3.5%) and a reduction in direct disease management costs (- PLN 61.1M, discounted at 5%) compared with PCV-13. Thus, PHiD-CV was the dominant strategy for Poland (Tables 3&4).

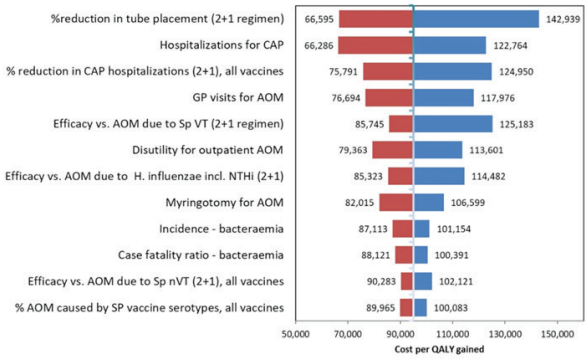

Figure 2. One-way sensitivity analysis results (PHiD-CV versus no vaccination)

The 12 model inputs that had the biggest impact on the ICER (comparing PHiD-CV to no vaccination) when varied in the one-way sensitivity analysis. The central line indicates the base case cost per QALY. Blue: using a lower input, Red: using a higher input for the variable at the left side. AOM: acute otitis media; CAP: community acquired pneumonia; H. influenza: Haemophilus influenzae; NTHi: non-typeable H. influenza; nVT: non-vaccine type; QALY: quality-adjusted life-years; Sp: Streptococcus pneumoniae; VT: vaccine type.

3.3. One-way sensitivity analyses

Using the one-way sensitivity analysis, the tornado diagrams in Fig. 2 and Fig. 3 show the 12 most impactful model inputs on the ICER when comparing PHiD-CV to no vaccination (Fig. 2) and to PCV-13 (Fig. 3).

When comparing PHiD-CV to no vaccination, the most influential factors were variations in the percent reduction in tube placement, hospitalisations for community-acquired pneumonia (CAP) and percent reduction in CAP hospitalisation. Only a very unrealistic 10% increase in tube placement after vaccination would result in an ICER above the threshold (i.e., PLN 142,939). In all analyses, PHiD-CV resulted in a gain in QALYs versus no vaccination and remains below the threshold of PLN 134,514. Therefore PHiD-CV remained cost-effective (Fig. 2).

When comparing PHiD-CV to PCV-13, assumptions around AOM were the most influential factors, as present in 10 of the top 12 variables. Variations in the value for 'GP visits for AOM' had the largest impact on the ICER; with the cost per QALY ranging from -PLN 512,565 to -PLN267,675 per QALY gained. In all analyses, PHiD-CV resulted in a gain in QALYs versus PCV-13 and was cost-saving. Therefore, despite variations in the ICER, PHiD-CV remained the dominant choice over PCV-13 in all cases (Fig. 3).

3.4. Probabilistic sensitivity analysis

The PSA results showed that the model outcomes are robust to simultaneous probabilistic variation of key model inputs. When comparing PHiD-CV to no vaccination, PHiD-CV was cost-effective in 79.6% of simulations (Fig. 4). When comparing PHiD-CV to PCV-13, PHiD-CV was the dominant strategy in 94.1% of the simulations (Fig. 5).

3.5. Results of scenario analyses

Results of all scenarios are summarised in Table 5.

3.5.1. Scenario analysis: PHiD-CV versus PCV-13, assuming vaccine price parity (PLN 125)

As in the base case, PHiD-CV resulted in more QALYs gained versus PCV-13, and when assuming price parity between the vaccines, PHiD-CV costs remained lower (by PLN 8.2M) than in the PCV-13 arm, making PHiD-CV the dominant strategy over PCV-13.

3.5.2. Scenario analysis: PHiD-CV versus PCV-13, assuming 0% and 82.2% VE for PHiD-CV against ST 19A IPD

Omitting any cross protection from PHiD-CV against 19A reduced the incremental QALYs gained from 170 to 147, and the total cost saving from PLN 61.1M to 60.0M, however PHiD-CV will still be dominant in this scenario.

Increasing the VE of PHiD-CV against ST 19A IPD from the base case value of 62% to 82.2% resulted in a further gain of QALYs versus PCV-13 (from 170 to 178 QALYs) as well as an extra cost savings of PLN 310,000 versus base case, due to better health outcomes achieved. As a result, PHiD-CV remained the dominant strategy versus PCV-13 in both scenarios.

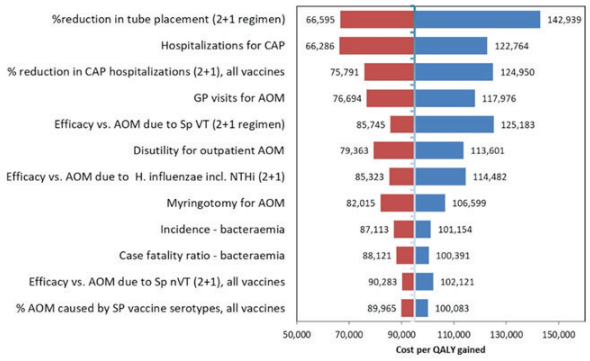

Figure 3. One-way sensitivity analysis results (PHiD-CV versus PCV-13) *The 12 model inputs that had the biggest impact on the ICER (comparing PHiD-CV to PCV-13) when varied in the one-way sensitivity analysis. The central line indicates the base case cost per QALY. Blue: using a lower input, Red: using a higher input for the variable at the left side. AOM: Acute otitis media; IPD: Invasive pneumococcal disease; GP: General Practitioner; H. influenza: Haemophilus influenzae; PCV-13: 13-valent pneumococcal conjugate vaccine; PHiD-CV: Pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine; NTHi: Non-typeable Haemophilus influenzae; Sp VT: Streptococcus pneumoniae vaccine type.*

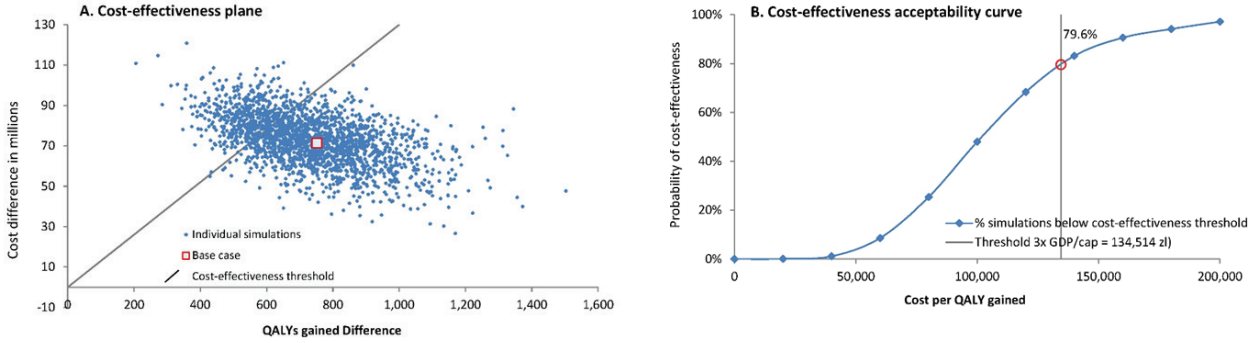

Figure 4. Cost-effectiveness plane (A) and acceptability curve (B) for PHiD-CV vs no vaccination. *Panel A: Cost-effectiveness plane. Each PSA run is represented by a dot in terms of difference in direct costs against difference in QALYs gained for PHiD-CV compared to no vaccination. Results below the cost-effectiveness threshold (3xGDP/capita = PLN 134,514/QALY) are considered cost-effective. The red box represents the base case result. Panel B: The cost-effectiveness acceptability curve shows the probability (i.e., proportion of PSA runs) that PHiD-CV is cost-effective compared to no vaccination for increasing cost-effectiveness threshold values. The red circle highlights the proportion of PSA runs when the cost per QALY gained remains below the threshold value (3xGDP/capita = PLN 134,514/QALY). GDP: Gross Domestic Product; cap: capita; QALY: quality-adjusted life-year.*

Table 5. Incremental health and cost outcomes as well as cost-effectiveness (5% discount on costs and 3.5% discount on effects) for different scenarios

Scenario1: vaccine price parity (PLN 125)	PHiD-CV	PCV-13	Difference
QALYs gained	9,235,407	9,235,237	170
Direct costs* (PLN)	392,735,159	400,978,983	-8,243,824
ICER (cost per QALY gained)	PHiD-CV was dominant over PCV-13		
Scenario: PHiD-CV effectiveness against ST 19A IPD: 0%	PHiD-CV	PCV-13	Difference
QALYs gained	9,235,384	9,235,237	147
Direct costs* (PLN)	367,254,011	427,411,268	-60,157,257
ICER (cost per QALY gained)	PHiD-CV was dominant over PCV-13		
Scenario: PHiD-CV effectiveness against ST 19A IPD: 82.2%	PHiD-CV	PCV-13	Difference
QALYs gained	9,235,414	9,235,237	178
Direct costs* (PLN)	365,992,989	427,411,268	-61,418,279
ICER (cost per QALY gained)	PHiD-CV was dominant over PCV-13		
Scenario: PCV-13 effectiveness against ST 3 IPD: 0%	PHiD-CV	PCV-13	Difference
QALYs gained	9,235,407	9,235,236	171
Direct costs* (PLN)	366,302,875	427,414,558	-61,111,683
ICER (cost per QALY gained)	PHiD-CV was dominant over PCV-13		
Scenario: PCV-13 effectiveness against ST 3 IPD: 79.5%	PHiD-CV	PCV-13	Difference
QALYs gained	9,235,407	9,235,238	169
Direct costs* (PLN)	366,302,875	427,406,662	-61,103,787
ICER (cost per QALY gained)	PHiD-CV was dominant over PCV-13		

ICER: incremental cost-effectiveness ratio; PLN: Polish złoty; PCV-13: 13-valent pneumococcal conjugate vaccine; PHiD-CV: Pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine; QALY: quality-adjusted life-years.
* Inclusive vaccine and vaccination costs

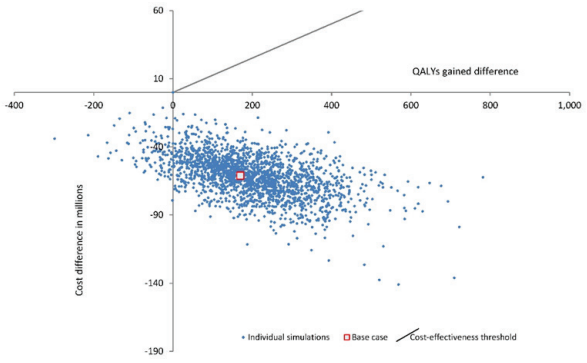

Figure 5. Cost-effectiveness plane (PCV-13 vs PHiD-CV). *Each PSA run is represented by a dot in terms of difference in direct cost against difference in QALYs gained for PHiD-CV compared to PCV-13. Results in the South-East quadrant represent dominance of PHiD-CV over PCV-13 (i.e. PHiD-CV provides more QALY gain at a lower cost than PCV-13). The red box represents the base case result.GDP: Gross Domestic Product; PCV-13: 13-valent pneumococcal conjugate vaccine; PHiD-CV: Pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine; QALY: quality-adjusted life-year.*

3.5.3. Scenario analysis: PHiD-CV versus PCV-13, assuming 0% and 79.5% VE for PCV-13 against ST 3 IPD

Changing the VE of PCV-13 against ST 3 from the base case value of 26% to 0% or to 79.5% had a limited impact on the overall health and economic outcomes for PCV-13 versus PHiD-CV; i.e., loss or gain of 1 QALY respectively versus PHiD-CV, and, increasing the cost difference by PLN 3,000 or decreasing the cost difference by PLN 5,000, respectively. PHiD-CV remained dominant versus PCV-13 in both scenarios.

Discussion

Based on a previously published Markov model,[21] this analysis estimated that adding PHiD-CV to the NIP in Poland will improve health outcomes in the population by reducing cases, and associated long-term sequelae and deaths, of IPD, pneumonia and AOM. Despite the additional cost of vaccination, routine infant vaccination is a cost-effective strategy for healthcare payers (ICER of PLN 94,933 per QALY gained) versus no vaccination.

When comparing the two pneumococcal conjugate vaccines, PHiD-CV and PCV-13, despite some differences between them (e.g., potentially higher effectiveness of PCV-13 against STs 6A and 19A), the overall effectiveness of PHiD-CV was significantly higher. The model predicted very similar health outcomes with both vaccines for IPD and pneumonia which is in line with industry-independent systematic reviews, showing no significant differences in the two vaccines impact on IPD and pneumonia.[17-19] However, the model projected a stronger reduction in AOM with PHiD-CV versus PCV-13, and the direct costs associated with PCV-13 were much higher than with PHiD-CV.

The impact of PCV programs on the incidence of overall IPD and the distribution of VTs and NVTs in children <5 years was analysed from post-marketing studies and from high-quality surveillance data (available for at least two years before and three years after implementation of programmes with PHiD-CV or PCV-13. The study shows that there was a substantial reduction in the burden of overall IPD following introduction of either vaccines in countries with high coverage, regardless of the PCV used and of differences in pneumococcal epidemiology. IPD was mainly due to VTs before PCV introduction, whereas NVTs are the major contributor today in children and adults.[20] As AOM is less severe in nature than IPD, it might not be the primary focus of vaccination programs. However, it is a frequent cause of physician visits and it leads to a significant use of antibiotic use, both of which can result in a high impact on the public health budget. The prevention of a large number of AOM cases through vaccination may be an important contributor to minimising the growing problem of antibiotic resistance,[9] as well as reducing indirect costs due to parent absenteeism from work. Based on the clinical FinIP trial setting, a recent study showed that vaccinating 5 infants with PHiD-CV prevented one antimicrobial purchase for uncomplicated AOM during 24 months after administration of the first dose in 2+1 and 3+1 vaccination schedules combined.[68]

Overall, PHiD-CV was the dominant strategy compared with PCV-13, providing more health gains (+170 QALYs) at a cost-saving (-PLN 61.1M). PHiD-CV has a lower public price than PCV-13 in Poland, however, the scenario analysis comparing the two vaccines at the same price also found PHiD-CV to be the dominant strategy. Similarly, in scenario analyses assuming lower vaccine effectiveness for PHiD-CV against ST19A IPD or higher effectiveness for PCV-13 against ST3, PHiD-CV remained the dominant option. This can, on one hand, be argued with observations of recent systematic reviews confirming no consistent impact of PCV-13 on ST3 diseases, with most studies showing no impact or a lack of VE for PCV-13 against ST3 IPD.[8,18] On the other hand, considering the relatively low proportion of 19A caused illnesses, the favoring differences for PCV13 over PHiD-CV to protect against 19A diseases[8] can be out-weighted by the benefit of PHiD-CV to prevent other PCV related diseases, such as AOM preventable diseases[68] and/or potentially to reduce the replacement by PCV-13 non-vaccine type IPD.[18,69,70] Moreover, varying the vaccine effectiveness against ST3 and ST19A of both vaccines according published 95% confidence limits was found to have

almost no effect on health and economic outcomes regarding IPD and pneumonia for the UK and Canada.[68] Finally, these findings were supported by a recent health economic evaluation from an industry-independent organisation in Quebec (INSPQ, Canada), estimating that for most of the realistic increases of 19A over time when using PHiD-CV, the cost-effectiveness ratio will remain in favour of PHiD-CV (at least 39 and 94 more cases of 19A-IPD per year must be averted in children under 5 years of age by PCV-13 compared to PHiD-CV in order to outweigh the extra cost difference per dose (25$) and to become cost-effective against PHiD-CV at 1x and 3x GDP/capita - for a birth-cohort of about 83,000 newborns).[71,72] Therefore, from a public health perspective, it is more important to consider the overall impact, i.e. the overall effectiveness, of both vaccines rather than to link protection with the number or ST coverage of each vaccine.

In one-way sensitivity analyses versus no vaccination, PHiD-CV remained cost-effective in all analyses except when assuming a lower percent reduction in tube placement. However, the estimated assumption used for the lower reduction is lower than 0, reflecting an increase in TTP when children are vaccinated, which is very unlikely based on results of clinical trials, even for both vaccines.[29,50] One-way sensitivity analyses versus PCV-13 found that AOM inputs and assumptions had the greatest influence on outcomes, however PHiD-CV remained dominant in all analyses. Uncertainty in model inputs was tested in probabilistic sensitivity analyses, and the outcomes for PHiD-CV were found to be robust, with PHiD-CV remaining cost-effective versus no vaccination in 79.6% of simulations and remaining dominant versus PCV-13 in 94.1% of simulations.

The findings of this study in Poland are comparable to other cost-effectiveness studies comparing PHiD-CV to PCV-13, where the comparable benefits of both vaccines in preventing IPD and pneumonia were complemented by the larger benefits of PHiD-CV regarding AOM prevention. For example, for studies in Sweden[73], Norway[74], and the UK[22], the outcome was a gain in QALYs with PHiD-CV at a cost-saving. A recent systematic review of 46 pneumococcal vaccine studies concluded that PCV-13 and PHiD-CV are relatively comparable, with PHiD-CV tending to be more cost-effective due to its additional effect on prevention of AOM, which although less severe than IPD, is more prevalent.[75] A study in Germany, by contrast, found PCV-13 to be more cost-effective than PHiD-CV, if the assumptions made around additional indirect effects with PCV-13 were significant.[76] Finally, a recent comparison of the two vaccines' effectiveness in reducing the incidence of IPD in Sweden, where PCV-13 is used in some counties and PHiD-CV in the others, found no significant differences between the vaccines' overall effect on IPD, despite serotype differences.[18]

This analysis had some limitations, principally due to the use of a static model to evaluate the impact of herd effect or serotype replacement. Serotype replacement was represented in the model by reducing VE, and herd effect was included as a fixed effect at equilibrium. A dynamic model would be better able to model indirect effects such as serotype replacement and herd effect. Moreover, some inputs were from other countries when Polish data were lacking (e.g., disutility data). A conservative approach was taken when assumptions were made.

The analysis also did not consider the burden or costs due to adverse events from vaccine administration in either vaccination arm. However, based on clinical trial and post-marketing safety data, this is likely to be marginal. Indirect costs due to work absenteeism of patients or parents of patients were out of scope for this study as well as health benefits and cost savings of reducing antibiotic resistance. The latest is hard to be estimated due to lack of data, however this is likely to make both vaccines somewhat more cost-effective that what has been estimated here.

Conclusion

Introducing mass vaccination of infants in Poland with PHiD-CV is likely to reduce the disease burden due to IPD, pneumonia and AOM, while being a cost-effective strategy (versus no vaccination) and a cost-saving strategy (versus PCV-13) for the healthcare payer.

End 2016 the Ministry of Health selected PHiD-CV for their NIP.[77,78]

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7. Compliance with Ethical Standards

GlaxoSmithKline Biologicals SA funded this analysis and was involved in all stages of research conduct, including analysis of the data. GlaxoSmithKline Biologicals SA also took in charge all costs associated with the development and publication of this manuscript.

JO, AK and RR are employees of the GSK group of com-

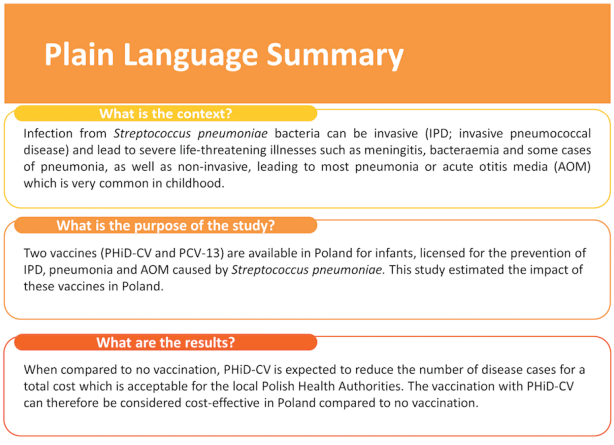
panies. BS, KW and IK were employed by GSK at the time of the study. MMG is a partner of Pracownia HTA Company which received remuneration from the GSK group of companies for the development of a HTA report on Synflorix (analysis disclosed in the present manuscript) and other vaccines. AR discloses no conflict of interest.

8. Trademark

Synflorix is a trademark of the GSK group of companies. Prevenar13 is a trademark owned or licensed by Wyeth LLC.

Supplementary Materials

Sup. 1. Plain Language Summary



References

1. Government of Canada. Invasive pneumococcal disease. https://www.canada.ca/en/public-health/services/immunization/vaccine-preventable-diseases/invasive-pneumococcal-disease/health-professionals.html. Accessed 11-04-2018.
2. Centers for Disease Control and Prevention. Global Pneumococcal Disease and Vaccine. 2017. https://www.cdc.gov/pneumococcal/global.html. Accessed 11-04-2018 2017.
3. National Reference Center for Diagnosis of Central Nervous System Infections - KOROUN. Invasive pneumococcal disease in Poland in 2016. 2016. http://www.koroun.edu.pl/pdf/ICHP2016.pdf. Accessed 11-04-2018 2017.
4. European Medicines Agency. Summary of Product Characteristics - Synflorix. 2017. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000973/WC500054346.pdf. Accessed 11-04-2018.
5. Leibovitz E, Jacobs MR, Dagan R. Haemophilus influenzae: a significant pathogen in acute otitis media. Pediatr Infect Dis J. 2004;23(12):1142-52.
6. Ladhani SN, Collins S, Djennad A, Sheppard CL, Borrow R, Fry NK et al. Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000-17: a prospective national observational cohort study. The Lancet Infectious diseases. 2018;18(4):441-51. doi:10.1016/S1473-3099(18)30052-5.
7. Vissers M, Wijmenga-Monsuur AJ, Knol MJ, Badoux P, van Houten MA, van der Ende A et al. Increased carriage of non-vaccine serotypes with low invasive disease potential four years after switching to the 10-valent pneumococcal conjugate vaccine in The Netherlands. PloS one. 2018;13(3):e0194823. doi:10.1371/journal.pone.0194823.
8. Cohen O, Knoll MJ, O'Brien K, Ramakrishnan M, Constenla D, Privor-Dumm L et al. Pneumococcal Conjugate Vaccine (PCV) Product Assessment. International Vaccine Access Center (IVAC); 2017.
9. Palmu AA, Rinta-Kokko H, Nohynek H, Nuorti JP, Jokinen J. Impact of National Ten-Valent Pneumococcal Conjugate Vaccine Program on Reducing Antimicrobial Use and Tympanostomy Tube Placements in Finland. The Pediatric Infectious Disease Journal. 2018;37(1):97-102. doi:10.1097/inf.0000000000001810.
10. World Health Organization (WHO). Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper - February 2019. Weekly epidemiological record 2019.
11. Kyaw MH, Lynfield R, Schaffner W, Craig AS, Hadler J, Reingold A et al. Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant Streptococcus pneumoniae. N Engl J Med. 2006;354(14):1455-63. doi:10.1056/NEJMoa051642.
12. Ladhani SN, Slack MP, Andrews NJ, Waight PA, Borrow R, Miller E. Invasive pneumococcal disease after routine pneumococcal conjugate vaccination in children, England and Wales. Emerg Infect Dis. 2013;19(1):61-8. doi:10.3201/eid1901.120741.
13. Lipsitch M, Siber GR. How Can Vaccines Contribute to Solving the Antimicrobial Resistance Problem? MBio. 2016;7(3). doi:10.1128/mBio.00428-16.
14. Zielnik-Jurkiewicz B, Bielicka A. Antibiotic resistance of Streptococcus pneumoniae in children with acute otitis media treatment failure. International journal of pediatric otorhinolaryngology. 2015;79(12):2129-33. doi:10.1016/j.ijporl.2015.09.030.
15. World Health Organization (WHO). WHO recommendations for routine immunization - summary tables. WHO, Geneva, Switzerland. 2009. https://www.

who.int/immunization/policy/immunization_tables/en/. Accessed 24-07-2019.

16. Dziennik Urzedowy Ministra Zdrowia. Komunikat Głównego Inspektora Sanitarnego - w sprawie Programu Szczepien Ochronnych na rok 2017 2017. https://gis.gov.pl/images/ep/so/pso_2017_-_nowelizacja.pdf. Accessed 10-04-2018.
17. Cohen O, Knoll M, O'Brien K, Ramakrishnan M, Farrar J, Pilishvili T et al. Pneumococcal Conjugate Vaccine (PCV) Review of Impact Evidence (PRIME). Summary of Findings from Systematic Review. Geneva, Switzerland: World Health Organization (WHO); 2017.
18. Naucler P, Galanis I, Morfeldt E, Darenberg J, Ortqvist A, Henriques-Normark B. Comparison of the impact of PCV10 or PCV13 on invasive pneumococcal disease in equivalent populations. Clin Infect Dis. 2017;65(11):1780-9. doi:4061316 [pii];10.1093/cid/cix685 [doi].
19. de Oliveira LH, Camacho LA, Coutinho ES, Martinez-Silveira MS, Carvalho AF, Ruiz-Matus C et al. Impact and Effectiveness of 10 and 13-Valent Pneumococcal Conjugate Vaccines on Hospitalization and Mortality in Children Aged Less than 5 Years in Latin American Countries: A Systematic Review. PloS one. 2016;11(12):e0166736. doi:10.1371/journal.pone.0166736.
20. Izurieta P, Bahety P, Adegbola R, Clarke C, Hoet B. Public health impact of pneumococcal conjugate vaccine infant immunization programs: assessment of invasive pneumococcal disease burden and serotype distribution. Expert review of vaccines. 2017. doi:10.1080/14760584.2018.1413354.
21. Knerer G, Ismaila A, Pearce D. Health and economic impact of PHiD-CV in Canada and the UK: a Markov modelling exercise. J Med Econ. 2012;15(1):61-76. doi:10.3111/13696998.2011.622323 [doi].
22. Delgleize E, Leeuwenkamp O, Theodorou E, Van d, V. Cost-effectiveness analysis of routine pneumococcal vaccination in the UK: a comparison of the PHiD-CV vaccine and the PCV-13 vaccine using a Markov model. BMJ Open. 2016;6(11):e010776. doi:bmjopen-2015-010776 [pii];10.1136/bmjopen-2015-010776 [doi].
23. Główny Urząd Statystyczny. Prognoza ludnosci na lata 2014-2050. 2014. http://demografia.stat.gov.pl/bazademografia/Prognoza.aspx. Accessed 11-04-2018.
24. European Medicines Agency. Summary of Product Characteristics - Prevenar 13. 2017. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001104/WC500057247.pdf. Accessed 11-04-2018 2017.
25. System Wspomagania Analiz i Decyzji (SWAiD). Life expectancy tables for Poland. 2016. http://swaid.stat.gov.pl/Demografia_dashboards/Raporty_predefiniowane/RAP_DBD_DEM_15.aspx. Accessed 11-04-2018.
26. Rinta-Kokko H, Palmu AA, Auranen K, Nuorti JP, Toropainen M, Siira L et al. Long-term impact of 10-valent pneumococcal conjugate vaccination on invasive pneumococcal disease among children in Finland. Vaccine. 2018;36(15):1934-40. doi:https://doi.org/10.1016/j.vaccine.2018.03.001.
27. Clarke C, Bakaletz LO, Ruiz-Guinazu J, Borys D, Mrkvan T. Impact of protein D-containing pneumococcal conjugate vaccines on non-typeable Haemophilus influenzae acute otitis media and carriage. Expert review of vaccines. 2017;16(7):1-14. doi:10.1080/14760584.2017.1333905.
28. Almudevar A, Pichichero ME. Haemophilus influenzae-protein D specific antibody correlate with protection against acute otitis media in young children. Vaccine. 2018;36(9):1133-5. doi:10.1016/j.vaccine.2018.01.021.
29. Palmu AA, Jokinen J, Borys D, Nieminen H, Ruokokoski E, Siira L et al. Effectiveness of the ten-valent pneumococcal Haemophilus influenzae protein D conjugate vaccine (PHiD-CV10) against invasive pneumococcal disease: a cluster randomised trial. Lancet. 2013;381(9862):214-22. doi:S0140-6736(12)61854-6 [pii];10.1016/S0140-6736(12)61854-6 [doi].
30. Whitney CG, Pilishvili T, Farley MM, Schaffner W, Craig AS, Lynfield R et al. Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease: a matched case-control study. Lancet. 2006;368(9546):1495-502. doi:S0140-6736(06)69637-2 [pii];10.1016/S0140-6736(06)69637-2 [doi].
31. Department of Epidemiology and Surveillance of Infectious Diseases - Laboratory of Monitoring and Epidemiological Analysis. Vaccinations in Poland (annual report). National Institute of Public Health. 2017. http://wwwold.pzh.gov.pl/oldpage/epimeld/index_a.html#05. Accessed 11/04/2018.
32. Andrews NJ, Waight PA, Burbidge P, Pearce E, Roalfe L, Zancolli M et al. Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: a postlicensure indirect cohort study. The Lancet Infectious diseases. 2014;14(9):839-46. doi:10.1016/s1473-3099(14)70822-9.
33. Miller E, Andrews NJ, Waight PA, Slack MP, George

RC. Effectiveness of the new serotypes in the 13-valent pneumococcal conjugate vaccine. Vaccine. 2011;29(49):9127-31. doi:S0264-410X(11)01554-4 [pii];10.1016/j.vaccine.2011.09.112 [doi].

34. Weinberger R, van der Linden M, Imohl M, von KR. Vaccine effectiveness of PCV13 in a 3+1 vaccination schedule. Vaccine. 2016;34(18):2062-5. doi:S0264-410X(16)00214-0 [pii];10.1016/j.vaccine.2016.02.043 [doi].

35. Moore MR, Link-Gelles R, Schaffner W, Lynfield R, Holtzman C, Harrison LH et al. Effectiveness of 13-valent pneumococcal conjugate vaccine for prevention of invasive pneumococcal disease in children in the USA: a matched case-control study. Lancet Respir Med. 2016;4(5):399-406. doi:S2213-2600(16)00052-7 [pii];10.1016/S2213-2600(16)00052-7 [doi].

36. Vesikari T, Wysocki J, Chevallier B, Karvonen A, Czajka H, Arsene JP et al. Immunogenicity of the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) compared to the licensed 7vCRM vaccine. Pediatr Infect Dis J. 2009;28(4 Suppl):S66-S76. doi:10.1097/INF.0b013e318199f8ef [doi];00006454-200904001-00002 [pii].

37. Deceuninck G, De SG, Boulianne N, Lefebvre B, De WP. Effectiveness of three pneumococcal conjugate vaccines to prevent invasive pneumococcal disease in Quebec, Canada. Vaccine. 2015;33(23):2684-9. doi:S0264-410X(15)00458-2 [pii];10.1016/j.vaccine.2015.04.005 [doi].

38. Domingues CM, Verani JR, Montenegro Renoiner EI, de Cunto Brandileone MC, Flannery B, de Oliveira LH et al. Effectiveness of ten-valent pneumococcal conjugate vaccine against invasive pneumococcal disease in Brazil: a matched case-control study. Lancet Respir Med. 2014;2(6):464-71. doi:S2213-2600(14)70060-8 [pii];10.1016/S2213-2600(14)70060-8 [doi].

39. Jokinen J, Rinta-Kokko H, Siira L, Palmu AA, Virtanen MJ, Nohynek H et al. Impact of ten-valent pneumococcal conjugate vaccination on invasive pneumococcal disease in Finnish children--a population-based study. PLoS One. 2015;10(3):e0120290. doi:10.1371/journal.pone.0120290 [doi];PONE-D-14-41389 [pii].

40. Verani JR, Domingues CM, de Moraes JC. Indirect cohort analysis of 10-valent pneumococcal conjugate vaccine effectiveness against vaccine-type and vaccine-related invasive pneumococcal disease. Vaccine. 2015;33(46):6145-8. doi:S0264-410X(15)01418-8 [pii];10.1016/j.vaccine.2015.10.007 [doi].

41. Pilishvili T, Lexau C, Farley MM, Hadler J, Harrison LH, Bennett NM et al. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. J Infect Dis. 2010;201(1):32-41. doi:10.1086/648593.

42. Whitney CG, Farley MM, Hadler J, Harrison LH, Bennett NM, Lynfield R et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. N Engl J Med. 2003;348(18):1737-46. doi:10.1056/NEJMoa022823.

43. Tregnaghi MW, Saez-Llorens X, Lopez P, Abate H, Smith E, Posleman A et al. Efficacy of pneumococcal nontypable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) in young Latin American children: A double-blind randomized controlled trial. PLoS Med. 2014;11(6):e1001657. doi:10.1371/journal.pmed.1001657 [doi];PMEDICINE-D-13-02837 [pii].

44. Eskola J, Kilpi T, Palmu A, Jokinen J, Haapakoski J, Herva E et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. N Engl J Med. 2001;344(6):403-9. doi:10.1056/NEJM200102083440602 [doi].

45. Prymula R, Peeters P, Chrobok V, Kriz P, Novakova E, Kaliskova E et al. Pneumococcal capsular polysaccharides conjugated to protein D for prevention of acute otitis media caused by both Streptococcus pneumoniae and non-typable Haemophilus influenzae: a randomised double-blind efficacy study. Lancet. 2006;367(9512):740-8. doi:S0140-6736(06)68304-9 [pii];10.1016/S0140-6736(06)68304-9 [doi].

46. Saez-Llorens X CM, Rowley S, Wong D, Calvo A, Rodriguez M, Lommel P, Hausdorff W,, editor. Efficacy of 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) against acute otitis media in children in Panama. ISAAR; 2013.

47. Black S, Shinefield H, Fireman B, Lewis E, Ray P, Hansen JR et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Northern California Kaiser Permanente Vaccine Study Center Group. Pediatr Infect Dis J. 2000;19(3):187-95.

48. Fireman B, Black SB, Shinefield HR, Lee J, Lewis E, Ray P. Impact of the pneumococcal conjugate vaccine on otitis media. Pediatr Infect Dis J. 2003;22(1):10-6. doi:10.1097/01.inf.0000045221.96634.7c [doi].

49. Zaklad Zamówien Publicznych przy Ministrze Zdrowia. Szczepionka Skoniugowana Przeciwko Pneumokokom Dla Dzieci. 2017. http://www.zzp-przymz.pl/archiwum/wyniki-zakonczonych-postepowan.php?filtr=a&id=1212. Accessed 11-04-2018 2017.

50. Palmu AA, Verho J, Jokinen J, Karma P, Kilpi TM. The seven-valent pneumococcal conjugate vaccine reduces tympanostomy tube placement in children. Pediatr Infect Dis J. 2004;23(8):732-8. doi:00006454-200408000-00007 [pii].

51. Skoczynska A, Sadowy E, Bojarska K, Strzelecki J, Kuch A, Golebiewska A et al. The current status of invasive pneumococcal disease in Poland. Vaccine. 2011;29(11):2199-205. doi:S0264-410X(10)01442-8 [pii];10.1016/j.vaccine.2010.09.100 [doi].

52. Skoczynska A, Kuch A, Sadowy E, Wasko I, Markowska M, Ronkiewicz P et al. Recent trends in epidemiology of invasive pneumococcal disease in Poland. Eur J Clin Microbiol Infect Dis. 2015;34(4):779-87. doi:10.1007/s10096-014-2283-8 [doi].

53. Harat R, Gorny G, Jorgensen L, Pluta J, Gray S, Dartois N et al. A retrospective study of hospitalized pneumonia in two Polish counties (2006-2008). Pneumonol Alergol Pol. 2013;81(5):429-38. doi:VM/OJS/J/35518 [pii].

54. Monasta L, Ronfani L, Marchetti F, Montico M, Vecchi BL, Bavcar A et al. Burden of disease caused by otitis media: systematic review and global estimates. PLoS One. 2012;7(4):e36226. doi:10.1371/journal.pone.0036226 [doi];PONE-D-12-03723 [pii].

55. Skoczyńska A, Kuch A, Golełębiewska A, Wasśko I, Ronkiewicz P, Markowska M et al. Inwazyjna choroba pneumokokowa w Polsce w roku 2010. . Pol Merk Lek 2011;XXXI(182):80-5. 2017.

56. Wysocki J, Sluzewski W, Gutterman EM, Jouve S, Moscariello M, Balter I. Active hospital-based surveillance of invasive pneumococcal disease and clinical pneumonia in infants and young children in two Polish counties. Arch Med Sci. 2016;12(3):629-38. doi:10.5114/aoms.2016.59936.

57. Narodowy Fundusz Zdrowia. Narodowy Fundusz Zdrowia Database. 2017. http://www.nfz.gov.pl/. Accessed 11-04-2018 2017.

58. Zaklad Zamowien Publicznych przy Ministrze Zdrowia. Szczepionka skoniugowana przeciwko pneumokokom dla dzieci kompatybilna ze szczepionka PCV13 - do kontynuacji szczepien. 2017. http://www.zzp-przymz.pl/archiwum/wyniki-zakonczonych-postepowan.php?filtr=a&id=1112. Accessed 11-04-2018 2017.

59. Agency for Health Technology Assessment and Tariff System (AOTMiT). Wysokosc progu kosztu uzyskania dodatkowego roku zycia. 2015. http://wwwold.aotm.gov.pl/index.php?id=1064. Accessed 11-04-2018.

60. Central Statistical Office. Per capita GDP estimates for 2013-2015. 2017. http://stat.gov.pl/sygnalne/komunikaty-i-obwieszczenia/lista-komunikatow-i-obwieszczen/obwieszczenie-w-sprawie-szacunkow-wartosci-produktu-krajowego-brutto-na-jednego-mieszkanca-w-latach-2013-2015-na-poziomie-wojewodztw-nts2-i-podregionow-nts3,281,4.html. Accessed 11-04-2018 2017.

61. Golicki D, Niewada M, Jakubczyk M, Wrona W, Hermanowski T. Self-assessed health status in Poland: EQ-5D findings from the Polish valuation study. Pol Arch Med Wewn. 2010;120(7-8):276-81.

62. Bennett JE SW, Downs SM, Jaffe DM, . Parents' utilities for outcomes of occult bacteremia. Arch Pediatr Adolesc Med. 2000;154(1):43-8.

63. Oh PI, Maerov P, Pritchard D, Knowles SR, Einarson TR, Shear NH. A cost-utility analysis of second-line antibiotics in the treatment of acute otitis media in children. Clin Ther. 1996;18(1):160-82. doi:S0149-2918(96)80188-3 [pii].

64. Morrow A, De Wals P, Petit G, Guay M, Erickson LJ. The burden of pneumococcal disease in the Canadian population before routine use of the seven-valent pneumococcal conjugate vaccine. Can J Infect Dis Med Microbiol. 2007;18(2):121-7.

65. Cheng AK, Niparko JK. Cost-utility of the cochlear implant in adults: a meta-analysis. Arch Otolaryngol Head Neck Surg. 1999;125(11):1214-8.

66. Oostenbrink R, Oostenbrink JB, Moons KG, Derksen-Lubsen G, Essink-Bot ML, Grobbee DE et al. Cost-utility analysis of patient care in children with meningeal signs. Int J Technol Assess Health Care. 2002;18(3):485-96.

67. The Agency for Health Technology Assessment and Tariff System. Health Technology Assessment Guidelines v3.0. 2017. http://www.aotm.gov.pl/www/wp-content/uploads/wytyczne_hta/2016/20161104_HTA_Guidelines_AOTMiT.pdf. Accessed 11-04-2018 2017.

68. Palmu AA, Jokinen J, Nieminen H, Rinta-Kokko H, Ruokokoski E, Puumalainen T et al. Vaccine-preventable disease incidence of pneumococcal conjugate vaccine in the Finnish invasive pneumococcal disease vaccine trial. Vaccine. 2018;36(14):1816-22. doi:10.1016/j.vaccine.2018.02.088.

69. Mungall B, Owen C, Lourdes-Bibera G, Nieto Guevara J. Comparable reductions in overall IPD with both pneumococcal conjugate vaccines in children and older adults [Abstract]. XVIII Congreso Latinoamericano de Infectologia Pediatrica SLIPE 2019; Cartagena, Colombia2019.

70. Savulescu C, Krizova P, Valentiner-Branth P, Ladhani SN, Nuorti P, Danis K et al., editors. Impact of 10 and 13-valent pneumococcal conjugate vaccines

on invasive pneumococcal disease in children under five years of age: results of a european multicentre study. European Society for Paediatric Infectious Diseases (ESPID); 2019; Ljubljana, Slovenia.

71. De Wals P, Brousseau N, Deceuninck G, Zhou Z, Gilca R. Évaluation de la pertinence d'utiliser le vaccin pneumococcique conjugué 13-valent plutôt que 10-valent dans une perspective économique au Québec. Gouvernement du Québec; 2019.

72. Olbrecht J, Simone B, Izurieta P. A uniform probabilistic approach to manage uncertainties regarding vaccine effectiveness against serotype 3, 19A, NTHI and herd effect in the base case of a cost-effectiveness analysis comparing non-typeable haemophilus influenzae protein D (PHiD-CV) with 13-valent pneumococcal conjugate vaccines (PCV13) in infants. Value in Health. 2017;20(9):A737-A8. doi:10.1016/j.jval.2017.08.2028.

73. By A, Sobocki P, Forsgren A, Silfverdal SA. Comparing health outcomes and costs of general vaccination with pneumococcal conjugate vaccines in Sweden: a Markov model. Clin Ther. 2012;34(1):177-89. doi:S0149-2918(11)00842-3 [pii];10.1016/j.clinthera.2011.12.007 [doi].

74. Robberstad B, Frostad CR, Akselsen PE, Kvaerner KJ, Berstad AK. Economic evaluation of second generation pneumococcal conjugate vaccines in Norway. Vaccine. 2011;29(47):8564-74. doi:S0264-410X(11)01431-9 [pii];10.1016/j.vaccine.2011.09.025 [doi].

75. Ciapponi A, Lee A, Bardach A, Glujovsky D, Rey-Ares L, Luisa CM et al. Interchangeability between Pneumococcal Conjugate Vaccines: A Systematic Review and Meta-Analysis. Value Health Reg Issues. 2016;11:24-34. doi:S2212-1099(16)00002-9 [pii];10.1016/j.vhri.2015.12.001 [doi].

76. Kuhlmann A, von der Schulenburg JG. Modeling the cost-effectiveness of infant vaccination with pneumococcal conjugate vaccines in Germany. Eur J Health Econ. 2017;18(3):273-92. doi:10.1007/s10198-016-0770-9 [doi];10.1007/s10198-016-0770-9 [pii].

77. Szczepienia -Medycyna Praktyczna dla lekarzy. Przetarg na szczepionkę przeciwko pneumokokom rozstrzygnięty. https://www.mp.pl/szczepienia/aktualnosci/153571,przetarg-na-szczepionke-przeciwko-pneumokokom-rozstrzygniety. Accessed 09-08-2018.

78. Szczepienia -Medycyna Praktyczna dla lekarzy. Medycyna Praktyczna dla lekarzy. Rozstrzygnięto przetarg na szczepionkę przeciwko pneumokokom. https://www.mp.pl/szczepienia/aktualnosci/176895,rozstrzygnieto-przetarg-na-szczepionke-przeciwko-pneumokokom. Accessed 09-08-2018.