ORIGINAL RESEARCH

Cost-Effectiveness Evaluation of the 10-Valent Pneumococcal Non-typeable *Haemophilus influenzae* Protein D Conjugate Vaccine and 13-Valent Pneumococcal Vaccine in Japanese Children

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ABSTRACT

Introduction: Diseases caused by *Streptococcus pneumoniae* represent a major public health problem. The purpose of this study was to compare, in the Japanese context, the projected health benefits, costs and cost-effectiveness of the latest generation of pneumococcal conjugate vaccines which may provide important insight into the potential public health impact of interventions in the context of local disease-specific epidemiology.

Methods: A Markov model was used to compare two vaccination strategies which involve routine infant immunization with either the 13-valent pneumococcal conjugate vaccine (PCV-13; *Prevenar 13*™, Pfizer, Pearl River, NY, USA) or the 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV; *Synflorix*™, GlaxoSmithKline Biologicals SA, Rixensart, Belgium) over a time horizon of 5 years from the healthcare provider and societal perspectives. Estimates for key model parameters were obtained from locally

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available databases and published literature. Incremental benefits in terms of costs and quality-adjusted life-year and cost-effectiveness were assessed.

Results: A 3 + 1 vaccination schedule for infants with PHiD-CV is expected to have a similar impact on invasive pneumococcal disease and pneumonia and a larger impact on acute otitis media-related outcomes compared with PCV-13. Assuming price parity for these vaccines, the model projected that vaccination with PHiD-CV would result in cost savings of 1.9 and 3.9 billion Japanese yen from the provider and societal perspectives, respectively. This was largely due to a reduction in highly prevalent acute otitis media. Vaccination with PHiD-CV was expected to generate a gain of 433 quality-adjusted life-years compared to PCV-13 translating into dominance over PCV-13. Sensitivity analyses showed robustness of model outcome to changes in key model parameters and substantiated that the model outcome was consistently driven by the incremental benefit of PHiD-CV in averting acute otitis media.

Conclusion: In comparison to PCV-13, vaccination with PHiD-CV is projected to be cost saving for Japan from both the healthcare provider and societal perspectives.

Keywords: Acute otitis media; Cost-effectiveness; Invasive pneumococcal disease; Japan; NT*Hi*; PCV-13; PHiD-CV; Pneumonia; Serotype

INTRODUCTION

Worldwide, pneumococcal disease is associated with significant clinical and economic burden on healthcare systems and the society. *Streptococcus pneumoniae* (*Sp*) is responsible for both invasive and non-invasive respiratory infections causing diseases such as bacteremia, meningitis, pneumonia and acute otitis media (AOM) [1]. Vaccination with pneumococcal conjugate vaccines (PCVs) remains the cornerstone in preventing pneumococcal disease. Over the last decade, pneumococcal vaccines have been widely implemented in childhood universal mass immunization programs worldwide [1–7].

In Japan, the 7-valent PCV (PCV-7, *Prevnar/Prevenar*™, Pfizer, Pearl River, NY, USA) was officially recommended for use in children aged <5 years in 2010. PCV-7 was incorporated into the routine national vaccination schedule for children in April 2013 and eventually replaced by the 13-valent PCV (PCV-13, *Prevenar 13*™, Pfizer, Pearl River, NY, USA) on November 1, 2013. Local surveillance studies have shown a marked decrease in the prevalence of invasive pneumococcal infections in children aged <5 years {2011–2013 versus 2008–2010 as reflected by a 51% reduction with an associated incidence rate ratio (IRR) of 0.49 [95% confidence interval (CI) 0.37–0.63, $p < 0.0001$] [7]. In another study, it was reported that the incidence of meningitis and bacteremia attributable to vaccine serotypes substantially dropped from 73.3 to 14.7% in the period 2010–2013} [8]. Ihara et al. [9] estimated that incidence rates per 100,000 in children aged <5 years during 2012 (versus 2008–2010) for meningitis and bacteremia changed from 2.8 to 0.8 (IRR 0.27; $p < 0.0001$) and 22.2 to 10.6 (IRR 0.48; $p < 0.0001$), respectively. Due to these dramatic declines in disease burden due to PCV-7 types, non-PCV-7 serotype strains now constitute a predominant cause of residual pneumococcal disease burden in Japanese children [7–9]. A review of epidemiology of pediatric infections in Japan from 1990 onward shows that in addition to

pneumococci, another respiratory pathogen, non-typeable *Haemophilus influenzae* (NT*Hi*), causes significant morbidity in pediatric AOM, and, to a lesser extent, plays a role in lower respiratory diseases such as pneumonia [10, 11]. NT*Hi* has been also reported as an infrequent cause of invasive disease [12].

Bacterial infections often lead to high rates of prescription and antibiotic use [1, 13]. This is specifically the case with highly prevalent AOM which is recognized as a leading indication for the prescription of antibiotics to infants [13]. In Japan, resistance to commonly used antibiotics such as penicillins, macrolides and cephalosporins is increasingly observed for both *Sp* serotypes and NT*Hi*, thereby rendering treatment of such infections difficult [8, 12, 14, 15]. In the global context including Japan [8, 16], prevention of pneumococcal disease by vaccination could play a significant role in controlling the evolution of resistance which is essential from a health policy point of view.

Both PCV-13 and the 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV, *Synflorix*^TM, GlaxoSmithKline Biologicals SA, Rixensart, Belgium) have a broader serotype coverage than PCV-7. PHiD-CV covers three additional *Sp* serotypes (I, 5 and 7F) compared with PCV-7. This vaccine was designed to target *Sp* and potentially NT*Hi* infections due to the use of NT*Hi*-derived protein D as a carrier protein for the majority of its conjugates [17, 18]. Compared to PHiD-CV, PCV-13 contains three additional *Sp* serotypes (3, 6A and 19A), but clinical evidence shows that PHiD-CV offers protection for the cross-reactive *Sp* serotypes 6A [17, 19] and 19A [19–21]. To date, there is no conclusive evidence that PCV-13 prevents invasive pneumococcal disease (IPD), AOM or pneumonia due to serotype 3 [22, 23].

The choice of PCV for national immunization programs is usually determined by a combination of multiple factors which often include, but may not be limited to, pathogen epidemiology prevalent in the target group locally, vaccine formulation, vaccine supply and cost-effectiveness considerations. It is, therefore, important to assess the potential benefits that the new generation vaccines, PCV-13 or PHiD-CV, may offer in epidemiological and economic terms to ensure efficient allocation of healthcare resources based on evidence-driven trade-offs of competing healthcare options. The performed cost-effectiveness evaluation presented in this paper aims to estimate and compare the potential impact of two childhood universal immunization strategies: routine vaccination of infants with PHiD-CV and PCV-13, the latter of which is currently recommended for routine immunization of infants in Japan.

MATERIALS AND METHODS

Model Overview

A previously published Markov model [24, 25] was used to simulate the impact of pneumococcal vaccination on the incidence of *Sp* IPD, pneumonia and AOM, as well as NT*Hi*-AOM within a Japanese birth cohort ($n = 1,042,000$ new-born) in terms of resource use, cost implications and quality-adjusted life-year (QALY) losses. Cost-effectiveness was evaluated adopting the healthcare provider and societal perspectives. The model was used to compare $3 + 1$ regimens of PHiD-CV and PCV-13 with vaccine doses administered at 2, 3, 4 and 13 months of life.

The basic model construct is visualized in Fig. 1. Individuals were followed in the age-
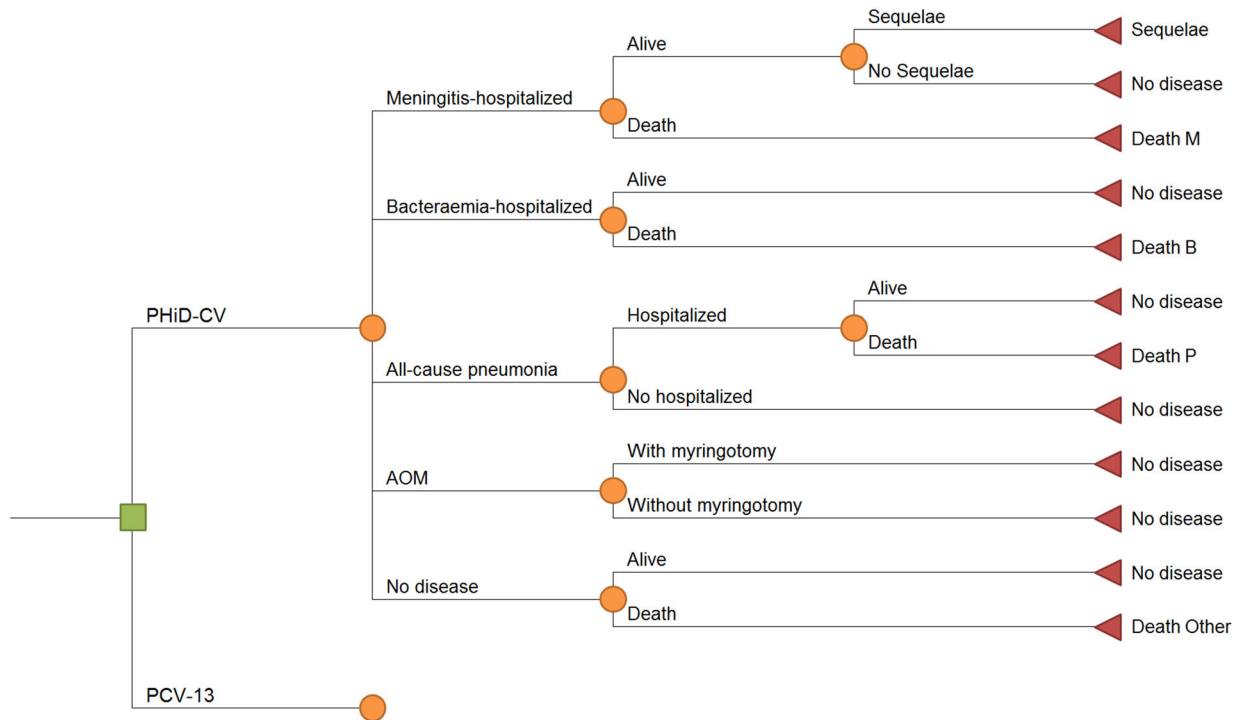
Fig. 1 Model structure. *AOM* acute otitis media, *B* bacteraemia, *M* meningitis, *PCV-13* 13-valent pneumococcal conjugate vaccine, *PHiD-CV* 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine, *P* pneumonia

stratified model over a time horizon of 5 years with a cycle length of 1 month. During each monthly cycle, the probability of an individual entering a specific health state is governed by age-specific *Sp* and NT*Hi*-AOM incidence rates and applicable vaccine efficacy (VE) levels. These transition probabilities determine hospitalization rates and frequency of medical visits in conjunction with the respective diseases considered in the model. To the respective disease conditions, unit costs and disease-specific disutilities were further added. In each cycle of the model, cost consequences and QALYs were estimated so that costs and QALY losses accumulated until the 5 year time horizon and converted into a corresponding incremental cost-effectiveness ratio (ICER) expressed in terms of costs per QALY gained.

Demographics and Epidemiological Data

Annual number of births and age-specific mortality rates were obtained from the "Estimation of population" (2013) [26] and the "Abridged life tables" (2012) [27], respectively, available in the Official Statistics of Japan (e-Stat) database. Epidemiological data used in the model are provided in Table 1. Age-specific incidence rates for IPD, hospitalized all-cause pneumonia and AOM were taken from locally available databases and published literature [9, 12, 14, 28]. The incidence rate for non-hospitalized all-cause pneumonia was derived by subtracting the number of pneumonia-related hospital admissions from the total number of pneumonia cases as provided by the "Patient survey" [29]. The frequency of meningitis sequelae was estimated from

Table 1 Model input for base case analysis: epidemiological data

Age-group	0 year	1 year	2 years	3 years	4 years	Reference/assumption
Pneumococcal hospitalized meningitis						
Incidence per 100,000	2.1	1.3	0.3	0.3	0.1	Ihara *et al.* [9]
CFR	2.1%					Kamiya *et al.* [28]
Sequelae	Neurological: 15.6%					Iwata *et al.* [30]
	Hearing impairment: 3.2%					Kamiya *et al.* [28]
Pneumococcal hospitalized bacteremia						
Incidence per 100,000	9.1	29.2	8.2	3.8	2.7	Ihara *et al.* [9]
CFR	0.4%					Kamiya *et al.* [28]
All-cause hospitalized pneumonia						
Incidence per 100,000	1748.3					Tanaka *et al.* [14]
CFR	0.091%					Vital statistics (2012) [54]
All-cause non-hospitalized pneumonia						
Incidence per 100,000	8450.1					Tanaka *et al.* [14] Patient survey (2012)[29]
AOM						
Incidence per 100,000	22,000	54,000	34,000	21,000	14,000	Otsuka *et al.* [12]
Myringotomy/TTP frequency	6.6%					**Table 2**
Serotype distribution for IPDs						
10 common serotypes for PHiD-CV and PCV-13	30.3%					Ihara *et al.* [9]
Serotype 3	2.2%					
Serotype 6A	2.2%					
Serotype 19A	24.7%					
Others	40.4%					
Pathogen and serotype distribution for AOM						
Sp	31.8%	10 common serotypes for PHiD-CV and PCV-13			38.0%	Otsuka *et al.* [12]
		Serotype 3			9.1%	
		Serotype 6A			8.3%	
		Serotype 19A			7.4%	
		Others			37.2%	
NT*Hi*	29.4%					

AOM acute otitis media, *CFR* case–fatality ratio, *IPD* invasive pneumococcal disease, *NTHi* non-typeable *Haemophilus influenzae*, *Sp Streptococcus pneumoniae*, *TTP* tympanostomy tube placement

Kamiya et al. [28] and Iwata et al. [30]. The frequency of myringotomy/tympanostomy tube placement (TTP) procedures was obtained from a retrospective survey (Table 1; for additional details on the retrospective survey see Appendix 1, Table 6).

Serotype distributions for IPD and AOM were obtained from published reports addressing the point in time when PCV-13 was introduced in Japan [9, 12]. The proportion of AOM cases due to *Sp* or NT*Hi* was estimated by calculating the ratio of confirmed number of *Sp* or NT*Hi*-related

cases and the total number of pathogen-confirmed cases (Table 1).

Direct Economic Burden, Resource Use and Quality of Life

Retrospective database analyses were performed involving two commercially available Japanese claims databases. The EBM provider developed by Medical Data Vision Co., Ltd (MDV-EBM provider) and Japan Medical Data Centre Claims Database (JMDC-CDB) were used to

Table 2 Model input for base case analysis: cost data

	No. of acute episodes	Average treatment cost per acute episode [JPY]
Average cost per acute episode		
Meningitis (hospitalized)	57	767,447
Bacteremia (hospitalized)	137	340,905
All-cause pneumonia (hospitalized)	440	286,209
All-cause pneumonia (outpatient)	759	16,998
AOM with myringotomy	193	45,853
AOM without myringotomy	2,742	18,185
Average annual costs for long-term sequelae [JPY]		
Neurological sequelae		452,260
Hearing loss		79,311

Work loss for parents	No. of admission days	No. of visits	Average time lost from work (days)[a]
Meningitis—acute episode	13.8	1.5	14.6
Bacteremia (hospitalized)	7.2	1.4	7.9
All-cause pneumonia (hospitalized)	6.1	1.9	7.1
All-cause pneumonia (outpatient)	NA	1.9	1.0
AOM with myringotomy/TTP	0.0	9.5	4.8
AOM without myringotomy	0.0	4.3	2.2

AOM acute otitis media, *JPY* Japanese yen, *TTP* tympanostomy tube placement, *NA* not applicable

[a] Estimated by adding up the number of hospital admission days and the number of outpatient visits (1 visit = 0.5 day lost)

gather information on resource use and costs for IPD, pneumonia and AOM, respectively. MDV-EBM provider is a hospital-based database which covers approximately five million patients and contains medical account data (inpatient and outpatient) with detailed inpatient information of patients of all ages. JMDC-CDB is a health insurance claims database which covers approximately 1% of Japanese population aged <75 years and contains data on inpatient, outpatient and pharmacy expenditure for employees and their family members in contracted health insurance societies. The database analyses provided estimates for the averages of the treatment cost per acute episode for each disease, the

number of admission days and the number of outpatient visits. The average treatment cost per acute episode was calculated based on the medical fee point for each procedure and National Health Insurance drug prices at the time of the medical treatment (Appendix 1, Table 7).

Indirect costs (2013) were evaluated as lost wages for parents providing care. The productivity loss per acute disease episode was equivalent to the number of work days lost estimated by adding up the number of hospital admission days and outpatient visits for the child (1 visit = 0.5 day lost). Daily wages were estimated on the basis of average annual salary of individuals aged 18–49 years [3,330,415.73

Japanese yen (JPY)] obtained from the "Basic survey of wage structure" (2013) [31] and "Survey of Labour force" [32]. Time lost from work for parents of sick children for each of the disease outcomes is provided in Table 2.

Two types of utility values were used in the model. Normative utility values were assumed to be at the maximum due to the short time horizon considered in the analysis. Disutility values for the disease conditions were obtained from sources provided in Table 3.

Vaccine Efficacy, Coverage and Costs

The time course of protection conferred by vaccination was modeled in children of ages of 2 months until 5 years, with a ramp-up phase coinciding with the course of vaccine dosing from the age of 2 months until 13 months and a full efficacy phase from the age of 13 months up until 5 years. In the ramp-up phase the level of protection established with the sequential doses was assumed to be 50, 90, 90 and 100% following the first three vaccine doses and booster vaccination, respectively. VE estimates used in this analysis were obtained from published clinical trials and post-marketing studies and validated by a panel of experts (Table 4).

The impact of vaccination on IPD disease burden was calculated by applying serotype-specific VE to the respective *Sp* serotypes causing disease in the target group for vaccination. Serotype-specific VE data were extrapolated from available efficacy and effectiveness PCV trials. It is assumed that PHiD-CV and PCV-13 have the same efficacy for the ten common serotypes equal to the average VE of the PCV-7 serotypes, as reported by Whitney et al. [19]. Although serotypes 6A and 19A are not contained in the PHiD-CV vaccine, these serotypes belong functionally to

the same serogroups as serotypes 6B and 19F, respectively, which are covered by the PHiD-CV vaccine. Protection conferred by PHiD-CV against cross-reactive serotypes 6A not contained in PHiD-CV was set at 76% in the light of similar antibody responses elicited by PCV-7 and PHiD-CV [19]. For serotype 19A, VE was set at 82.2% as observed for PHiD-CV in a case–control study [19, 20]. To date, there is no conclusive evidence that PCV-13 prevents serotype 3 disease [33] and, therefore, VE was assumed to be 0.0% in the base case analysis.

The model uses VE against World Health Organization (WHO)-defined X-ray-confirmed community-acquired pneumonia (CAP) (WHO-CAP) as a surrogate measure of efficacy against hospitalization for pneumonia. VE of PCVs, including PHiD-CV against WHO-CAP and suspected CAP, has been assessed in several large-scale, randomized, controlled efficacy trials, conducted in different settings [18, 34–37]. In these trials, WHO-CAP and clinically suspected CAP constituted the efficacy end points. VE in terms of reduction in hospitalization and outpatient consultation was in the ranges of 20–35% and 6–7%, respectively, based on defined end points not discriminating between causative pathogens [18, 34–37]. In the absence of PCV-13 estimates, and taking into account that available pneumonia efficacy data cannot easily predict the impact of a PCV on pneumonia by relying on the number of serotypes or support the notion that increasing numbers of serotypes beyond PCV-7 will result in a detectable increase in protection against pneumonia [38], the Clinical Otitis Media & Pneumonia Study (COMPAS, ClinicalTrials.gov Identifier: NCT00466947) efficacy estimates against WHO-CAP (23.4%) and suspected CAP (7.3%) for PHiD-CV were applied to PCV-13 as well [18].

Table 3 Model input for base case analysis: disutilities

Disease condition	Disutility value	Reference/assumption
Disutility per episode (short-term)		
Meningitis (hospitalized)	0.023	Bennett et al. [55]
Bacteremia (hospitalized)	0.008	
Pneumonia (hospitalized)	0.008	Assumed to be the same as for hospitalized bacteremia
Pneumonia (outpatient)	0.006	Bennett et al. [55]
AOM without myringotomy	0.005	Oh et al. [56]
AOM with myringotomy/TTP procedures	0.005	Assumed to be the same as for AOM without myringotomy
Disutility per year (long term)		
Neurological sequelae from meningitis	0.400	Morrow et al. [57]
Hearing loss from meningitis	0.200	Morrow et al. [57], Cheng et al. [58]

AOM acute otitis media, *TTP* tympanostomy tube placement

VE against AOM without myringotomy/TTP procedures was ascertained based on *Sp* and NT*Hi* prevalence. VE against *Sp* vaccine serotypes was assumed to be 69.9% for PHiD-CV [18]. Similar to VE estimation for IPD, partial protection efficacy levels of 63.7% against 6A [17] and 60.7% against serotype 19A were assumed for PHiD-CV. In the base case analysis, the same VE was assumed for the PHiD-CV serotypes in PCV-13 for which AOM-related efficacy estimates were not available. The same assumption was also used for the additional PCV-13 serotypes except for serotype 3 (Table 4). VE against serotype 3 was assumed to be 0.0% for both vaccines, as PHiD-CV does not include serotype 3 and PCV-13 effectiveness against serotype 3 is not confirmed. Although PCV-7 VE against *Sp* non-vaccine types and NT*Hi* has been reported as −33% and −11%, respectively (FIN-OM study [39], ClinicalTrials.gov Identifier: NCT00378417), we made conservative assumptions of 0.0%. VE against *Sp* non-

vaccine type AOM was assumed to be 0.0% for both vaccines (based on COMPAS for PHiD-CV [18]). VE against NT*Hi*-AOM was assumed to be 21.5% and 0.0% for PHiD-CV and PCV-13, respectively [17, 18, 39]. Reduction in myringotomy/TTP was estimated on the basis of PCV-7 efficacy obtained from a Kaiser Permanente study [40] and the FinOM study [41]. These reports indicate low VE against TTP at high incidences of TTP. This relationship was modeled by extrapolating PCV-13 and PHiD-CV VE from that of PCV-7. Extrapolated VE estimates were well in agreement with the findings of the FinIP study [42]. The likely higher efficacy of PHiD-CV compared to PCV-13 for AOM is reflected in the estimates of VE against myringotomy/TTP (Table 4).

For simplicity, vaccination coverage was assumed as 100% in the base case. Price parity of 7,776 JPY was assumed for both PHiD-CV and PCV-13. The administration cost per vaccine dose was assumed to be 4,212 JPY [43].

Table 4 Model input for base case analysis: vaccine efficacy

	VE% (95% CI)		Reference/assumption
	PHiD-CV	PCV-13	
IPD			
10 common serotypes for PHiD-CV and PCV-13	94.7% (87–100)	94.7% (87–100)	Whitney et al. [19]
Serotype 3	0.0% (0–0)	0.0% (0–89)	Expert opinion
			Moore et al. [33]
Serotype 6A	76.0% (39–90)	94.7% (87–100)	Whitney et al. [19]
Serotype 19A	82.2% (11–96)	94.7% (87–100)	Domingues et al. [20]
			Whitney et al. [19]
Pneumonia			
Hospitalization	23.4% (9–36)	23.4% (9–36)	Tregnaghi et al. [18]
Non-hospitalization	7.3% (2–12)	7.3% (2–12)	Tregnaghi et al. [18]
AOM without myringotomy			
10 common serotypes for PHiD-CV and PCV-13	69.9% (30–87)	69.9% (30–87)	Tregnaghi et al. [18]
Serotype 3	0.0% (0–0)	0.0% (0–0)	Expert opinion
Serotype 6A	63.7% (−14–88)	69.9% (30–87)	Prymula et al. [17]
			Tregnaghi et al. [18]
Serotype 19A	60.7% (8–71)	69.9% (30–87)	Expert opinion
			Tregnaghi et al. [18]
Others	0.0% (−33–15)	0.0% (−33–1)	Tregnaghi et al. [18]
			Prymula et al. [17]
			Eskola et al. [39]
			Expert opinion
NT*Hi*	21.5% (0–35)	0.0% (−11–8)	Tregnaghi et al. [18]
			Prymula et al. [17]
			Eskola et al. [39]
			Expert opinion
AOM with myringotomy/TTP			
Myringotomy/TTP	40.4% (−9–75)	27.0% (−14–50)	Fireman et al. [40]
			Palmu et al. [41]

The 95% CI values were used as the boundary in the sensitivity analyses

AOM acute otitis media, *PCV-13* 13-valent pneumococcal conjugate vaccine, *PHiD-CV* 10-valent pneumococcal NT*Hi* protein D conjugate vaccine, *TTP* tympanostomy tube placement

Analyses

Under base case assumptions, numbers of deaths and cases of IPD, all-cause pneumonia (hospitalized and non-hospitalized), and AOM (with and without myringotomy/TTP procedures) were estimated for both vaccines. The direct costs, including vaccination and treatment, and the indirect costs for each disease outcome were estimated. All costs are reported in JPY. The effects between the two vaccination strategies are reported as QALYs and life-years (LYs) gained, which are related to the defined health outcome that was determined. The ICER was estimated. A 3.0% discount rate was used for both cost and outcomes to allow a proper assessment of the benefit from the start of vaccination.

In addition to the base case analysis, several scenarios were modeled based on local interest wherein hypothetical considerations and different combinations of parameters were used to populate the model to examine their potential impact on cost and effect outcomes (Appendix 1). To account for uncertainty in the key model assumptions, two types of sensitivity analyses were performed. A one-way sensitivity analysis was done in which model parameters such as VE, disease epidemiology and management were varied within a pre-specified range of ±20% if 95% CI was unavailable. A probabilistic sensitivity analysis (PSA) was performed by sampling simultaneously, from probability distributions linked to VE (log-normal distribution), disease incidence (beta distribution), disutility values (beta distribution) and costs (triangular distribution). An ICER below 5,000,000 (5 million) JPY per QALY gained was considered cost-effective for Japan [44]. All the analyses were done using Microsoft Excel™ 2007/2010 (Microsoft Corporation, Washington, USA).

Trademark Disclosure

Synflorix is a trademark of the GSK group of companies, *Prevnar/Prevenar* is a trademark of Wyeth/Pfizer and *Prevnar 13* is a trademark of Pfizer.

Compliance with Ethics Guidelines

This article does not contain any new studies with human or animal subjects performed by any of the authors. Where applicable, data were obtained from previously conducted studies.

RESULTS

Base Case: Impact of Vaccination on Disease Burden and Cost-Effectiveness

In a birth cohort of 1,042,000 newborn in Japan (2013), model projections indicate that PCV-13 and PHiD-CV were expected to provide equivalent impact in the prevention of deaths caused by IPD and all-cause pneumonia. While the estimated impact of PHiD-CV and PCV-13 were broadly similar for pneumococcal meningitis and bacteremia, and all-cause pneumonia, the model showed that PHiD-CV was expected to prevent a significantly larger number of AOM cases (92,467 AOM episodes) compared to PCV-13 (Table 5).

By assuming price parity for both PHiD-CV and PCV-13, a vaccination program with PCV-13 is shown to generate marginal cost savings for both meningitis and bacteremia; while PHiD-CV vaccination was expected to save an additional 1.9 billion JPY and 2.0 billion JPY in direct costs and indirect costs (undiscounted), respectively. The aggregate cost savings of 1.9 (direct costs, discounted) and 3.9 billion JPY (direct and indirect costs, discounted) with PHiD-CV were due to a reduction in AOM-

Table 5 Model outcomes for base case analysis

	PHiD-CV	PCV-13	Difference (PHiD-CV-PCV-13)
Disease-related outcomes			
Deaths due to IPDs, all-cause pneumonia and AOM	66	66	0
Cases of pneumococcal meningitis	24	23	1
Cases of pneumococcal bacteremia	286	268	18
Cases of all-cause pneumonia	479,841	479,841	0
Cases of AOM	1,228,971	1,321,438	−92,467
Cases of meningitis sequelae	4	4	0
Economic outcomes [JPY]			
Direct costs (undiscounted)			
Vaccination	49,916,940,488	49,916,940,845	−357
Pneumococcal meningitis	18,258,447	17,305,345	953,102
Meningitis sequelae	7,341,933	6,988,325	353,608
Pneumococcal bacteremia	97,762,048	91,511,944	6,250,104
All-cause pneumonia	27,229,316,268	27,229,317,920	−1,652
AOM	24,033,839,820	26,066,680,756	−2,032,840,936
Indirect costs			
Wages lost (acute episode)	34,436,663,525	36,591,103,326	−2,154,439,801
Cost-effectiveness outcomes (undiscounted)			
Total direct costs (JPY)	101,303,459,004	103,328,745,135	−2,025,286,132
Total direct and indirect costs (JPY)	135,740,122,528	139,919,848,461	−4,179,725,932
Total LYs gained	5,197,521	5,197,522	0
Total QALYs gained	5,188,347	5,187,885	462
ICER (healthcare provider perspective)	–	–	Dominant[a]
ICER (societal perspective)	–	–	Dominant[a]
Cost-effectiveness outcomes (discounted)			
Total direct costs (JPY)	97,339,123,665	99,237,387,104	−1,898,263,439
Total direct and indirect costs (JPY)	129,652,473,264	133,570,122,617	−3,917,649,353
Total LYs gained	4,837,775	4,837,775	0
Total QALYs gained	4,829,175	4,828,742	433
ICER (healthcare provider perspective)	–	–	Dominant[a]
ICER (societal perspective)	–	–	Dominant[a]

AOM acute otitis media, *JPY* Japanese yen, *ICER* incremental cost-effectiveness ratio, *IPD* invasive pneumococcal disease, *LY* life-year, *PCV-13* 13-valent pneumococcal conjugate vaccine, *PHiD-CV* 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine, *QALY* quality-adjusted life-years

[a] PHiD-CV is dominant because it exhibits both lower costs and higher number of QALYs (effectiveness) compared to PCV-13

related cases and myringotomy/TTP procedures resulting in a QALY gain of 433 (462 undiscounted) compared to PCV-13. Cost consequences and QALYs gain translated into ICERs of −4.4 million JPY and −9.1 million JPY per QALY gained for the provider and societal perspectives, thereby showing dominance of PHiD-CV over PCV-13 in the base case analysis (Table 5).

Scenario and Sensitivity Analysis

For most of the modeled scenarios, PHiD-CV vaccination, in comparison to PCV-13, is
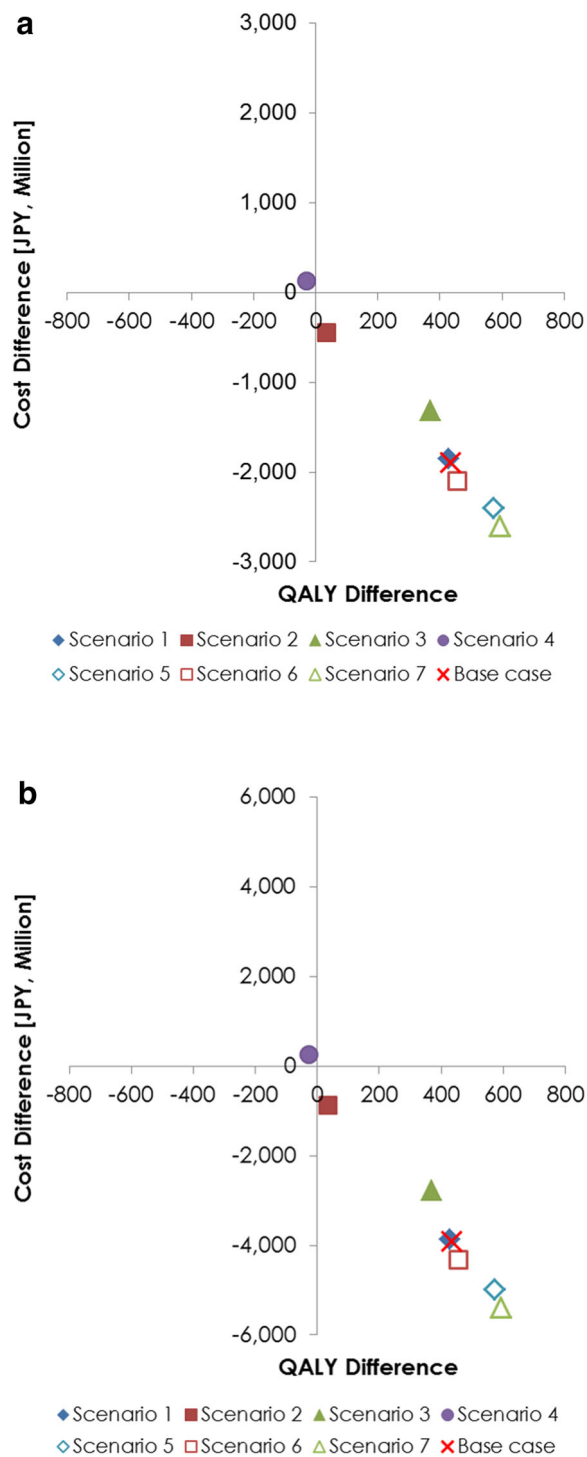
a

◄ **Fig. 2** Scenario analyses. **a** Healthcare provider perspective, **b** societal perspective. *1* No protection for PHiD-CV against cross-reactive types 6A and 19A; *2* no efficacy of PHiD-CV against NT*Hi*-AOM; *3* decreased VE for reduction of myringotomy; *4* no efficacy of PHiD-CV against NT*Hi*-AOM and decreased VE for reduction of myringotomy; *5* decreased efficacy of PCV-13 against *Sp*-AOM; *6* decreased VE for reduction of myringotomy; *7* decreased efficacy of PCV-13 against *Sp*-AOM and decreased VE for reduction of myringotomy. *AOM* acute otitis media, *JPY* Japanese yen, *PCV-13* 13-valent pneumococcal conjugate vaccine, *PHiD-CV* 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine, *QALY* quality-adjusted life-years, *Sp* *Streptococcus pneumonia*

b

dominance of vaccination with PHiD-CV over PCV-13 (Fig. 2). One-way sensitivity analyses substantiated AOM/TTP-related parameters as consistent influential drivers of model outcome. Sensitivity analyses also demonstrated the robustness of the base case model outcome to changes in key model parameters and assumptions. Specifically, the one-way sensitivity analyses showed that the ICERs were most sensitive to PHiD-CV efficacy against NT*Hi*-AOM, percentage reduction in myringotomy/TTP procedures and changes in other AOM-related parameters from both the provider and societal perspectives. Despite varying these parameters, PHiD-CV vaccination was either cost saving or cost-effective compared to PCV-13 vaccination (Fig. 3).

In the PSA, vaccination PHiD-CV is shown to dominate PCV-13 in terms of QALYs gained and cost savings (89% and 90% of the simulations in provider and societal perspectives, respectively). In contrast, only 4% of the simulations indicated that vaccination with PCV-13 was expected to dominate PHiD-CV in both perspectives. The probability that PHiD-CV vaccination was cost-effective compared to

expected to generate larger QALYs gains and lower costs from both the healthcare provider and societal perspectives, which translated into

PCV-13 vaccination was estimated to be 93% from both perspectives (Fig. 4).
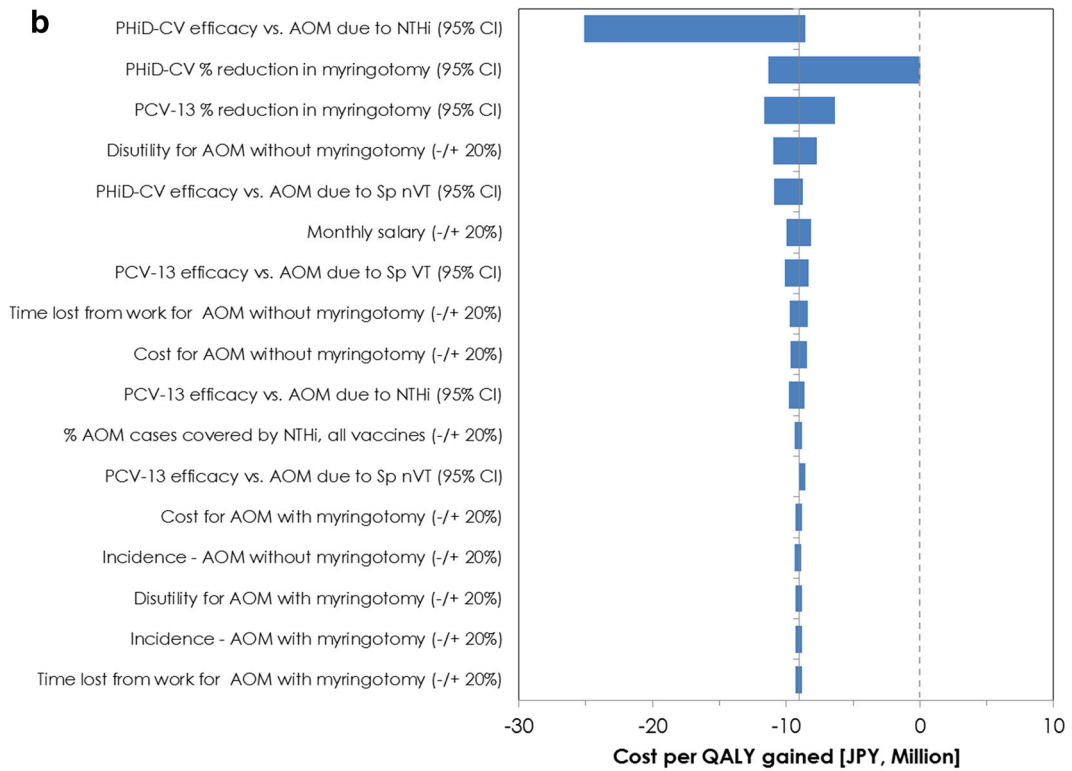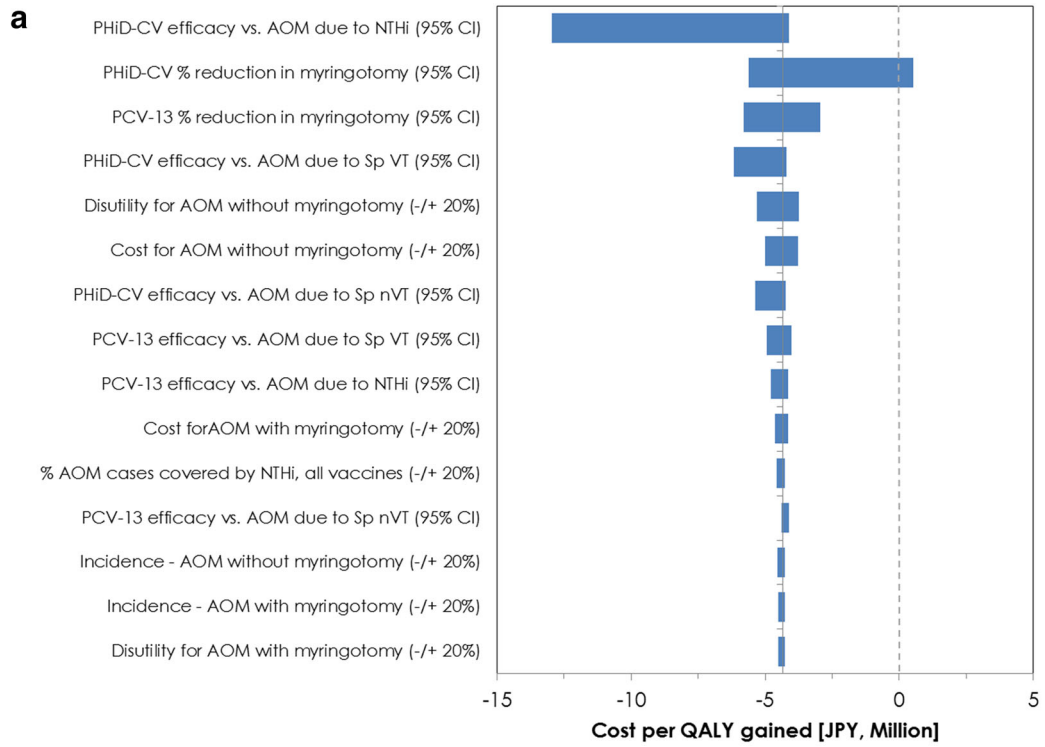
DISCUSSION

A recent study indicates that both, the disease burden and costs associated with highly prevalent AOM outweigh IPD due to the high volume of outpatient consultations, myringotomy/TTP procedures and utilization of antibiotics [45]. A vaccine that confers significant protection against AOM and the associated frequent use of antibiotics could be advantageous in settings with highly prevalent AOM disease. PHiD-CV may help in the control of NTHi-related AOM in addition to Sp-related AOM [17, 18, 40, 45–49].

The potential impact of PHiD-CV and PCV-13 on IPD and AOM incidence was compared in children aged <5 years using a previously published age-stratified Markov model [24, 25] that was populated with epidemiological, resource use and cost data specific for Japan. The model findings demonstrate a similar impact on overall IPD outcomes with either vaccine. In terms of IPD incidence and associated deaths, a similar impact was predicted for either of the formulations, in line with likely marginal, if any at all, differences in protection reflected by serotype-specific VE for vaccine and vaccine-related serotypes 6A [19] and 19A [19–21]. Similarly, identical VE against pneumonia was assumed which resulted in equivalent impact on pneumonia-related outcomes. However, PHiD-CV is projected to have a larger public health and economic impact owing to the high disease incidence of AOM in Japan [12] and its likely larger effects against this clinical syndrome compared to PCV-13. Although, a large body of evidence, including both preclinical and clinical research, points to the potential NTHi-

related impact of PHiD-CV in AOM [17, 18, 46, 48, 50], rather conservative assumptions have been made in this cost-effectiveness model with respect to the magnitude of its NTHi-effect in AOM. Nonetheless, an incremental benefit with PHiD-CV over PCV-13 is observed for NTHi-related AOM outcomes.

Given the current epidemiological landscape in Japan and our model findings regarding impact on disease outcomes, it is likely that childhood immunization with PHiD-CV in Japan will result in better cost-offsets and health gain compared to PCV-13. Under base case assumptions, PHiD-CV vaccination of infants is a cost-saving modality compared with PCV-13 vaccination from both the healthcare provider and societal perspectives. Sensitivity analyses showed that ICER was robust to changes in key model parameters and confirmed a consistent impact of AOM prevention on model outcome. The model outcome was driven by the incremental benefit of PHiD-CV in terms of preventing highly prevalent AOM disease and myringotomy/TTP procedures. In the light of the publications of [45] which has shown that PHiD-CV vaccination reduced the rates of antibiotic prescriptions in outpatient settings, one may therefore expect that the introduction of PHiD-CV in Japan will reduce the frequency of antibiotic use in conjunction with highly prevalent AOM and consequently likely contribute to the control of increasing antibiotic resistance of NTHi bacteria in addition to Sp [10, 12].

While the cost-effectiveness profiles of different pneumococcal vaccination strategies in several countries have been previously described using similar tools such as Markov cohort models [24, 25], a direct comparison of results and, therefore, generalizability are limited due to the differences in the local epidemiology of the disease under

a

PHiD-CV efficacy vs. AOM due to NTHi (95% CI)
PHiD-CV % reduction in myringotomy (95% CI)
PCV-13 % reduction in myringotomy (95% CI)
PHiD-CV efficacy vs. AOM due to Sp VT (95% CI)
Disutility for AOM without myringotomy (-/+ 20%)
Cost for AOM without myringotomy (-/+ 20%)
PHiD-CV efficacy vs. AOM due to Sp nVT (95% CI)
PCV-13 efficacy vs. AOM due to Sp VT (95% CI)
PCV-13 efficacy vs. AOM due to NTHi (95% CI)
Cost forAOM with myringotomy (-/+ 20%)
% AOM cases covered by NTHi, all vaccines (-/+ 20%)
PCV-13 efficacy vs. AOM due to Sp nVT (95% CI)
Incidence - AOM without myringotomy (-/+ 20%)
Incidence - AOM with myringotomy (-/+ 20%)
Disutility for AOM with myringotomy (-/+ 20%)

Cost per QALY gained [JPY, Million]

b

PHiD-CV efficacy vs. AOM due to NTHi (95% CI)
PHiD-CV % reduction in myringotomy (95% CI)
PCV-13 % reduction in myringotomy (95% CI)
Disutility for AOM without myringotomy (-/+ 20%)
PHiD-CV efficacy vs. AOM due to Sp nVT (95% CI)
Monthly salary (-/+ 20%)
PCV-13 efficacy vs. AOM due to Sp VT (95% CI)
Time lost from work for AOM without myringotomy (-/+ 20%)
Cost for AOM without myringotomy (-/+ 20%)
PCV-13 efficacy vs. AOM due to NTHi (95% CI)
% AOM cases covered by NTHi, all vaccines (-/+ 20%)
PCV-13 efficacy vs. AOM due to Sp nVT (95% CI)
Cost for AOM with myringotomy (-/+ 20%)
Incidence - AOM without myringotomy (-/+ 20%)
Disutility for AOM with myringotomy (-/+ 20%)
Incidence - AOM with myringotomy (-/+ 20%)
Time lost from work for AOM with myringotomy (-/+ 20%)

Cost per QALY gained [JPY, Million]

◀ **Fig. 3** One-way sensitivity analyses. **a** Healthcare provider perspective, **b** societal perspective. *AOM* acute otitis media, *JPY* Japanese yen, *NTHi* non-typeable *Haemophilus influenza*, *nVT* non-vaccine type, *PCV-13* 13-valent pneumococcal conjugate vaccine, *PHiD-CV* 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine, *QALY* quality-adjusted life-years, *Sp Streptococcus pneumoniae*, *VT* vaccine type

investigation and healthcare systems specific to each country. Apart from generalizability, there are several study limitations that need to be addressed. Reliable epidemiological data such as incidence in individuals aged >5 years are not available for Japan; hence, a time horizon of 5 years was used in the base case analysis. While waning of VE is usually assumed from 2 years after vaccination, however, due to the short time horizon this factor was not considered in the analysis. In addition, while productivity losses due to the treatment of acute disease were evaluated, productivity losses due to long-term sequelae were not estimated due to lack of data. The incidence of pneumonia was based on information for the time period prior to PCV-7 implementation due to limited data from post-PCV-7 vaccination implementation in Japan, implying that there is a need for up-to-date epidemiological data for future epidemiological and cost-effectiveness studies. In our analysis, herd protection was not assumed given that the analytical time horizon was restricted to child age cohorts. To our knowledge, the implications of herd protection have not been addressed in any of the cost-effectiveness analyses published for Japan [51, 52]. Previous studies have examined the potential magnitude of such indirect effects including herd protection and serotype replacement [38]. The findings varied considerably, therefore providing the rationale for not including herd protection in the current model [53]. To assess the true cost-effectiveness profiles of PCV vaccination modalities and explore sustainability of the selected PCV in
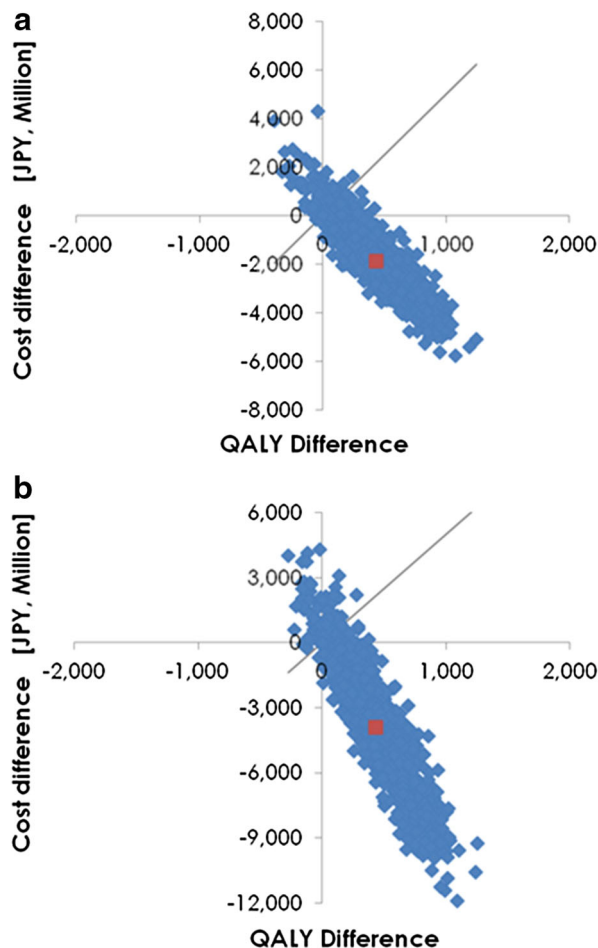

Fig. 4 Probabilistic sensitivity analysis. **a** Healthcare provider perspective, **b** societal perspective. *JPY* Japanese yen, *QALY* quality-adjusted life-years, *filled square* point estimate of base case analysis, the inclination of the line passing a point (0, 0) represents the cost-effectiveness threshold for Japan (5 million JPY per QALY gained)

Japan, it is suggested to investigate the importance of these factors in the overall impact of vaccination.

CONCLUSIONS

This cost-effectiveness analysis shows that a 3 + 1 universal childhood vaccination program using PHiD-CV, priced at parity with PCV-13, is expected to be cost saving compared to an identical vaccination program involving PCV-13, specifically in providing incremental

benefits with AOM, translating into fewer cases of AOM and myringotomy/TTP procedures, as well as associated costs, both from healthcare provider and societal perspectives. Given the importance of pneumococcal serotype coverage and associated serotype-specific VE levels including protection against cross-reactive serotypes, modeling exercises accommodating these aspects adequately provide valuable insights into how these factors may play out in the context of local epidemiology. Nonetheless, it is important to continuously and actively monitor epidemiological changes effected by pneumococcal vaccination to inform future decision making and healthcare policy in Japan.

ACKNOWLEDGMENTS

Compliance with ethics guidelines. This article does not contain any new studies with human or animal subjects performed by any of the authors. Where applicable, data were obtained from previously conducted studies.

APPENDIX

See Tables 6 and 7.

Table 6 Retrospective survey

	Meningitis	Bacteremia	All-cause pneumonia	AOM[a]
Data source	Medical Data Vision	Medical Data Vision	Medical Data Vision	Japan Medical Data Centre
ICD-10 diagnosis[b]	G001: Pneumococcal meningitis	A403: Sepsis due to *Sp*	J13: Pneumonia due to *Sp*	H660: Acute Suppurative otitis media
	G009: Bacterial meningitis	A419: Sepsis	J14: Pneumonia due to *Haemophilus influenzae*	H664: Suppurative otitis media
	G009: Acute bacterial meningitis	A499: Bacteremia		H669: AOM
			J189: Pneumonia	H669: Otitis media
Age	<5 years old	<5 years old	<5 years old	<5 years old
Analysis period	Apr 01, 2010–Mar 31, 2013	Apr 01, 2010–Mar 31, 2013	Apr 01, 2012–Mar 31, 2013	Apr 01, 2012–Mar 31, 2013
Department visited	All	All	Including pediatrics	Pediatrics or otorhino-laryngology

AOM acute otitis media, *ICD-10* the international statistical classification of diseases and related health problems 10th revision

[a] One episode was defined as a series of treatment with a visit interval of less than 1 month from the initial diagnosis. When the treatment was restarted after the visit interval of 1 month or more, it was regarded as a different episode

[b] Codes have been used to extract cost information

Table 7 Scenario analyses

	PHiD-CV	PCV-13
Scenario		
(1) Efficacy of IPDs	6A and 19A: 0.0%	Base case
(2) Efficacy of NT*Hi*-AOM	0.0%	Base case
(3) % reduction in myringotomy	26.1%[a]	Base case
(4) = (2) + (3)	NT*Hi*-AOM efficacy: 0.0%	Base case
	% reduction in myringotomy: 26.1%	
(5) Efficacy of *Sp*-AOM	Base case	Common vaccine serotypes, 6A, and 19A: 57.0% (Eskola et al.) [39]
(6) % reduction in myringotomy	Base case	22.0%[b]
(7) = (5) + (6)	Base case	Common vaccine serotypes, 6A and 19A: 57.0%
		% reduction in myringotomy/TTP: 22.0%

AOM acute otitis media, *IPD* invasive pneumococcal disease, *PCV-13* 13-valent pneumococcal conjugate vaccine, *PHiD-CV* 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine, *Sp Streptococcus pneumoniae*

[a] Calculated value in case of no efficacy of PHiD-CV against NT*Hi*-AOM

[b] Calculated value in case of the efficacy of PCV-13 against *Sp* vaccine serotype AOM taken from FIN-OM study [39]

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