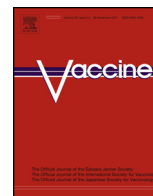




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Cost-utility analysis of 10- and 13-valent pneumococcal conjugate vaccines: Protection at what price in the Thai context?

W. Wantanee Kulpeng^{a,b,*}, Pattara Leelahavarong^a, Waranya Rattanavipapong^a, Vorasith Sornsrivichai^b, Henry C. Baggett^c, Aronrag Meeyai^{a,d}, Warunee Punpanich^e, Yot Teerawattananon^a

^a Health Intervention and Technology Assessment Program (HITAP), 6th Floor, 6th Building, Department of Health, Ministry of Public Health, Tiwanon Rd., Muang, Nonthaburi 11000, Thailand

^b Epidemiology Unit, Faculty of Medicine, Prince of Songkla University, P.O. Box 5, Kohong, Hat Yai, Songkhla 90112, Thailand

^c International Emerging Infections Program (IEIP), Global Disease Detection Regional Center, Thailand MOPH-US Centers for Disease Control and Prevention Collaboration, Department of Disease Control, Ministry of Public Health, Tiwanon Rd., Muang, Nonthaburi 11000, Thailand

^d Department of Epidemiology, Faculty of Public Health, Mahidol University, 420/1 Ratchawithi Rd., Ratchathewi District, Bangkok 10400, Thailand

^e Department of Pediatrics, Queen Sirikit National Institute of Child Health, 420/8 Rajvithi Rd., Rajthevi, Bangkok 10400, Thailand

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ABSTRACT

Objective: This study aims to evaluate the costs and outcomes of offering the 10-valent pneumococcal conjugate vaccine (PCV10) and 13-valent pneumococcal conjugate vaccine (PCV13) in Thailand compared to the current situation of no PCV vaccination.

Methods: Two vaccination schedules were considered: two-dose primary series plus a booster dose (2 + 1) and three-dose primary series plus a booster dose (3 + 1). A cost-utility analysis was conducted using a societal perspective. A Markov simulation model was used to estimate the relevant costs and health outcomes for a lifetime horizon. Costs were collected and values were calculated for the year 2010. The results were reported as incremental cost-effectiveness ratios (ICERs) in Thai Baht (THB) per quality adjusted life year (QALY) gained, with future costs and outcomes being discounted at 3% per annum. One-way sensitivity analysis and probabilistic sensitivity analysis using a Monte Carlo simulation were performed to assess parameter uncertainty.

Results: Under the base case-scenario of 2 + 1 dose schedule and a five-year protection, without indirect vaccine effects, the ICER for PCV10 and PCV13 were THB 1,368,072 and THB 1,490,305 per QALY gained, respectively. With indirect vaccine effects, the ICER of PCV10 was THB 519,399, and for PCV13 was THB 527,378. The model was sensitive to discount rate, the change in duration of vaccine protection and the incidence of pneumonia for all age groups.

Conclusions: At current prices, PCV10 and PCV13 are not cost-effective in Thailand. Inclusion of indirect vaccine effects substantially reduced the ICERs for both vaccines, but did not result in cost effectiveness.

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1. Introduction

Bacterial meningitis, pneumonia and otitis media caused by *Streptococcus pneumoniae* (*S. pneumoniae*) are serious but preventable health problems in young children. Pneumococcal conjugate vaccines (PCVs) have been proven safe and effective in children less than 5 years old to prevent both invasive (e.g., meningitis, bacteremia) and non-invasive (e.g., pneumonia, otitis media) pneumococcal diseases [1–3]. Moreover, clinical studies in the United States and Europe have demonstrated that vaccinating young children with PCV can lead to a significant decline in the incidence of pneumococcal disease among unvaccinated populations, notably older children, adults and the elderly [4–6]. Although PCV has been available for more than a decade, its use has been limited in many areas due to high cost.

Abbreviations: PCV, pneumococcal conjugate vaccine; EPI, Expanded Program on Immunization; AOM, acute otitis media; MoPH, Ministry of Public Health; SE, standard error; VE, vaccine efficacy; IPD, invasive pneumococcal disease; RCT, randomized controlled trial; THB, Thai Baht; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio.

* Corresponding author at: Health Intervention and Technology Assessment Program (HITAP), 6th Floor, 6th Building, Department of Health, Ministry of Public Health, Tiwanon Road, Muang, Nonthaburi, 11000 Thailand.
Tel.: +66 2 590 4374 5; fax: +66 2 590 4369.

E-mail addresses: wantanee.k@hitap.net, wantaney@hotmail.com (W. Kulpeng), pattara.l@hitap.net (P. Leelahavarong), waranya.r@hitap.net (W. Rattanavipapong), vorasith@msn.com (V. Sornsrivichai), Kipb@th.cdc.gov (H.C. Baggett), phamy@mahidol.ac.th, aronrag.c@hitap.net (A. Meeyai), warunee@gmail.com (W. Punpanich), yot.t@hitap.net (Y. Teerawattananon).

The cost-effectiveness of PCV has been documented in many high-income countries, and the governments in these settings have adopted the vaccine as part of their national immunization programs [7–13]. However, few economic evaluations have been conducted in low- or middle-income settings, where the burden of pneumococcal disease is at least as high [14–16]. In recent years, many low-income countries, especially in Africa, have introduced PCV programs with substantial support from the GAVI Alliance, a broad partnership that works to improve access to immunization [17]. Most middle income countries such as Thailand, which are not eligible for GAVI support and therefore face potentially substantial financial barriers to PCV implementation, have not yet implemented PCV programs. Cost-effectiveness studies are especially important to inform decision-making in these settings.

This study was conducted at the request of policy makers in Thailand to inform decisions about the adoption of PCV as part of this country's Expanded Program on Immunization (EPI). It was believed that if the vaccine is included in the EPI, its coverage would be almost 100%. Given that Thailand achieves 99% coverage with DTaP 3 dose vaccine [18], such an assumption is not unrealistic. This economic evaluation considered costs and impact of offering 10-valent PCV (PCV10), which covers 10 of approximately 90 *S. pneumoniae* serotypes, or recently licensed 13-valent PCV (PCV13), which covers 3 additional serotypes, compared to the current situation without a PCV program.

2. Methods

A model-based economic evaluation was performed to estimate costs as well as outcomes of vaccination with PCV10 and PCV13 compared to 'no vaccination'. Because there are different options for vaccination schedules [19], this study considered two commonly recommended regimens: two-dose primary series at 2 and 4 months of age plus a booster dose at age 13 months (2 + 1) and three-dose primary series at 2, 4 and 6 months of age plus a booster dose at age between 12 to 15 months (3 + 1). The study adopted a societal viewpoint using a life-time horizon with 3% discounting for both costs and outcomes beyond one year, as recommended in the by the Thai Health Technology Assessment guideline [20].

2.1. Model structure and assumptions

A Markov model was constructed based on the natural history of disease related to *S. pneumoniae* infection (Fig. 1). The model consisted of three major health states: healthy, *S. pneumoniae* infection and death. For *S. pneumoniae* infection, the model accounts for four health conditions based on their association with high case fatality or permanent disability (e.g., epilepsy, neurodevelopmental impairment or chronic lung disease): pneumococcal meningitis, pneumococcal bacteremia, all-cause pneumonia and all-cause acute otitis media (AOM). A one-year cycle was deployed in the model, and it was assumed that more than one infection is possible during a lifetime but each Markov cycle allows for only one infection.

2.2. Model input parameters

2.2.1. Epidemiological data

Estimated age-specific incidences of pneumococcal diseases in Thailand are presented (Supplementary Table 1). Pneumococcal bacteremia incidence was based on findings from active surveillance for bacteremia requiring hospitalization in two rural Thailand provinces [21] and does not include outpatient cases. All-cause meningitis and pneumonia incidence were derived from national surveillance conducted by the Bureau of Epidemiology, Ministry of

Public Health (MoPH) [22]. For this model, all hospitalized meningitis cases reported to the national surveillance system were assumed to be caused by bacteria. The proportion of pneumococcal meningitis cases among all bacterial meningitis (mean = 14.27%, standard error (SE) = 9.59) was derived from hospital databases [23,24]. AOM incidence was obtained from the Thailand Burden of Disease Project [25].

Table 1 illustrates probabilities of hospitalization and developing complications from pneumococcal disease. Mortality rate and case fatality data were acquired from the Burden of Disease Project and literature review, utilizing data from Thailand or the East Asia region whenever available [23–28].

2.2.2. Direct effects (vaccine efficacy)

For a 3 + 1 dosing schedule, vaccine efficacy (VE) against vaccine-type invasive pneumococcal disease (IPD) was considered 89% based on a 2009 meta-analysis of randomized controlled trials (RCTs) [29]. This figure was used to estimate the efficacy of PCV10 and PCV13 against vaccine-type IPD (Table 1) by assuming the same overall efficacy against vaccine-type IPD, accounting for the additional serotype coverage [30–33]. Because sufficient data on serotype coverage were not available for pneumonia and AOM, VE against all-cause pneumonia and AOM for PCV10 and PCV13 were extrapolated from the efficacy of PCV7 against all-cause pneumonia (6%) [3] and AOM (6%) [29]. It was assumed that the efficacy of PCV10 and PCV13 against pneumonia and AOM increased proportionally with the increase in serotype coverage.

VE for a 2 + 1 schedule was modified to account for reduced immunogenicity for serotypes 6B and 23F [34] compared to the 3 + 1 schedule; a 20% reduction in efficacy against these serotypes was assumed. Serotypes 6B and 23F accounted for approximately 40% of PCV7 serotypes in Thai children [30–32]. As a result, an overall reduction of 8% in VE for the 2 + 1 schedule was estimated using the following formula:

$$VE_{2-1} = VE_{3-1} \times (1 - 0.08)$$

2.2.3. Indirect effects (herd protection)

This model accounted for the indirect effect of the vaccine to prevent disease in unvaccinated populations (Supplementary Table 2). The percentage reduction in IPD incidence among unvaccinated populations was based on survey data after mass vaccination in the United States [4] with the adjustment for differences in serotype distribution between Thailand and the United States [35]. The indirect effect for IPD was based using the following formula:

$$\begin{aligned} \% \text{ IPD fall in Thailand} &= \% \text{ IPD fall in the United States} \\ &\times \text{Serotype coverage in Thailand/Serotype coverage in the United States} \end{aligned}$$

Because the indirect effects can occur in every population cohort ranging from aged 16–99 years, we manually calculated the indirect effects in each age group using the static model.

The indirect effect for pneumonia was estimated for unvaccinated populations, assuming that the protective effect would be equivalent to the decrease in IPD incidence among the same groups and adjusted for proportion of hospitalized pneumonia caused by *S. pneumoniae*. To estimate the proportion of hospitalized pneumonia cases caused by *S. pneumoniae*, we used data from Prapasiri et al. [26], who found that 11.76% (SE = 2.35) of bacteremic pneumonia cases in two Thai provinces were *S. pneumoniae*. The calculation of indirect effect of vaccine was based on the following formula:

$$\begin{aligned} \% \text{ Hospitalized pneumonia fall in Thailand} \\ &= \text{Proportion of pneumococcal pneumonia} \\ &\times \% \text{ IPD fall in Thailand} \end{aligned}$$

Table 1
Q4 Input parameters used in the model.

Parameter description	Distribution	Mean	SE	References
Epidemiological parameters				
Proportion of bacterial meningitis due to <i>S. pneumoniae</i>	Beta	0.14	0.96	Meta analysis [23,24]
Epilepsy after pneumococcal (Pnc.) meningitis	Beta	0.10	0.06	[28]
Hearing loss after Pnc. meningitis	Beta	0.03	0.03	[28]
Neurodevelopmental impairment after Pnc. meningitis	Beta	0.34	0.09	[28]
Death after Pnc. meningitis	Beta	0.03	0.03	[28]
Death after Pnc. bacteremia	Beta	0.08	0.04	[28]
Necrotizing pneumonia after Pnc. pneumonia ^a	Beta	0.18	0.05	[27]
Death after hospitalized pneumonia	Beta	0.01	0.00	[22]
Hearing loss after AOM	Beta	0.05	0.00	[25]
Risk ratio of mortality compared to general population				[25]
Epilepsy		1.01–1.14 ^b		
Hearing loss		1.00–1.01 ^b		
Neurodevelopmental impairment		5.16–7.17 ^b		
Chronic lung		1 ^b		
Baseline vaccine parameters				
Vaccine efficacy (PCV7; 3 + 1 schedule)				
IPD caused by vaccine serotype	Normal	89.00%	3.57%	[29]
Clinical pneumonia	Normal	6.00%	2.30%	[3]
AOM	Normal	6.00%	1.53%	[29]
Vaccine serotype coverage in Thais				
PCV7 serotype coverage in aged <5	Normal	67.60%	5.36%	Meta analysis [30–33]
PCV10 serotypes coverage in aged <5	Normal	70.60%	5.66%	Meta analysis [30–33]
PCV13 serotypes coverage in aged <5	Normal	86.80%	4.03%	Meta analysis [30–33]
PCV7 serotypes coverage in aged ≥5	Normal	38.09%	2.29%	Meta analysis [30–33]
PCV10 serotypes coverage in aged ≥5	Normal	43.71%	3.00%	Meta analysis [30,31,33]
PCV13 serotypes coverage in aged ≥5	Beta	60.19%	4.69%	[30]
Serotypes coverage US				
PCV7 serotypes coverage in aged 10 to 39	Not varied	71.30%		[35]
PCV7 serotypes coverage in aged 40 to 64	Not varied	65.40%		
PCV7 serotypes coverage in aged ≥65	Not varied	69.70%		
% IPD fall among unvaccinated group in US				
% fall among who aged 20 to 39	Beta	40.00%	4.59%	[4]
% fall among who aged 40 to 64	Beta	14.00%	4.59%	
% fall among who aged ≥65	Beta	29.00%	3.57%	
Cost parameters (THB)				
Vaccine costs				
PCV10 cost per dose	Not varied	1440		GlaxoSmithKline (Thailand)
PCV13 cost per dose	Not varied	1930		Pfizer (Thailand) Limited
Delivery cost per dose	Not varied	5% of vaccine price		[37]
Direct medical costs				
Cost per episode				
Meningitis aged ≤14	Gamma	63,775	20,830	[24]
Meningitis aged 15 to 59	Gamma	59,210	15,570	[24]
Meningitis aged ≥60	Gamma	31,980	15,260	[24]
Bacteremia aged ≤14	Gamma	14,120	4587	[24]
Bacteremia aged 15 to 59	Normal	22,120	743	[24]
Bacteremia aged ≥60	Gamma	22,440	5372	[24]
Hospitalized pneumonia aged ≤14	Normal	9099	46	[24]
Hospitalized pneumonia aged 15 to 59	Normal	23,952	122	[24]
Hospitalized pneumonia aged ≥60	Normal	31,948	278	[24]
Non-hospitalized pneumonia aged ≤14	Normal	39	2	[36]
Non-hospitalized pneumonia aged 15 to 59	Normal	103	5	[36]
Non-hospitalized pneumonia aged ≥60	Normal	98	5	[36]
AOM aged ≤14	Normal	350	7	[36]
AOM aged 15 to 59	Normal	520	7	[36]
AOM aged ≥60	Normal	764	17	[36]
Cost per year				
Epilepsy aged ≤14	Gamma	3962	475	[36]
Epilepsy aged 15 to 59	Normal	1600	21	[36]
Epilepsy aged ≥60	Gamma	1672	85	[36]
Hearing loss aged ≤14	Gamma	896	385	[36]
Hearing loss aged 15 to 59	Gamma	838	48	[36]
Hearing loss aged ≥60	Gamma	1312	123	[36]
Neurodevelopmental impairment aged ≤14	Gamma	3582	2333	[36]
Neurodevelopmental impairment aged 15 to 59	Gamma	936	72	[36]
Neurodevelopmental impairment aged ≥60	Gamma	5811	2892	[36]
Chronic lung aged ≤14	Gamma	1404	1404	[36]
Chronic lung aged 15 to 59	Normal	3306	62	[36]
Chronic lung aged ≥60	Normal	3636	31	[36]
Direct non-medical costs ^c				
Meningitis (per episode)		15,485		Primary data collection
Bacteremia (per episode)		9987		
Hospitalized pneumonia (per episode)		5674		
Non-hospitalized pneumonia (per episode)		527		
AOM (per episode)		527		

Table 1 (Continued)

Parameter description	Distribution	Mean	SE	References
Epilepsy (per year)		4489		
Hearing loss (per year)		868		
Neurodevelopmental impairment (per year)		17,548		
Chronic lung (per year)		7133		
Age-specific productivity loss (per day)				[38]
15-29	Not varied	196		
30-39	Not varied	409		
40-59	Not varied	571		
60-69	Not varied	246		
70-79	Not varied	98		
Utility parameters (using HUI3)				Primary data collection
Meningitis	Beta	0.96	0.00	
Bacteremia	Beta	0.99	0.00	
Pneumonia	Beta	0.99	0.00	
AOM	Beta	1.00	0.00	
Epilepsy	Beta	0.64	0.07	
Hearing loss	Beta	0.55	0.06	
Neurodevelopmental impairment				
Mild mental retardation	Beta	0.69	0.07	
Severe mental retardation	Beta	0.10	0.11	
Mental retardation + epilepsy	Normal	0.00	0.09	
Chronic lung disease	Beta	0.59	0.06	

^a Assuming all necrotizing pneumonia cases would develop chronic lung disease.

^b Risk ratio of mortality varied by age

^c Including travel costs, foods, accommodation, informal care and special education, each component is gamma distributed.

2.2.4. Costs and outcomes

The cost analysis was performed based on a societal perspective, and included both direct medical and direct non-medical costs (Table 1). Direct medical costs for outpatient and inpatient care were obtained from the Thailand's Centre for Health Equity Monitoring [36] and the Central Office for Healthcare Information [24], respectively. The cost of the vaccination program included the vaccine cost and delivery cost [37]. Direct non-medical costs, such as costs for transportation, meals, accommodation, facilities, productivity loss [38] by parents or caregivers for hospital visits or providing informal care, were derived from face-to-face interviews with caregivers of 192 ill children aged 5-14 years in seven public hospitals in five provinces throughout Thailand. All cost parameters are presented in 2010 Thai Baht (THB) (THB 31 = US\$ 1).

Outcomes were measured in quality-adjusted life years (QALYs) using the Health Utilities Index Mark 3 [39] (Table 1). Utility measures were derived from interviews with the aforementioned 192 caregivers and the results previously described [40].

2.3. Uncertainty analyses

2.3.1. One-way sensitivity analysis

One-way sensitivity analysis was performed to examine the uncertainty surrounding each parameter individually (e.g., discounting rate at 0% and 6% per annum, disease incidence, vaccine efficacy, vaccine serotype coverage, percentage incidence reduction among unvaccinated groups, utility and cost). The impact of serotype replacement and indirect vaccine effects were also examined. The former was done by adjusting the serotype coverage parameter whereas the latter was explored by varying the

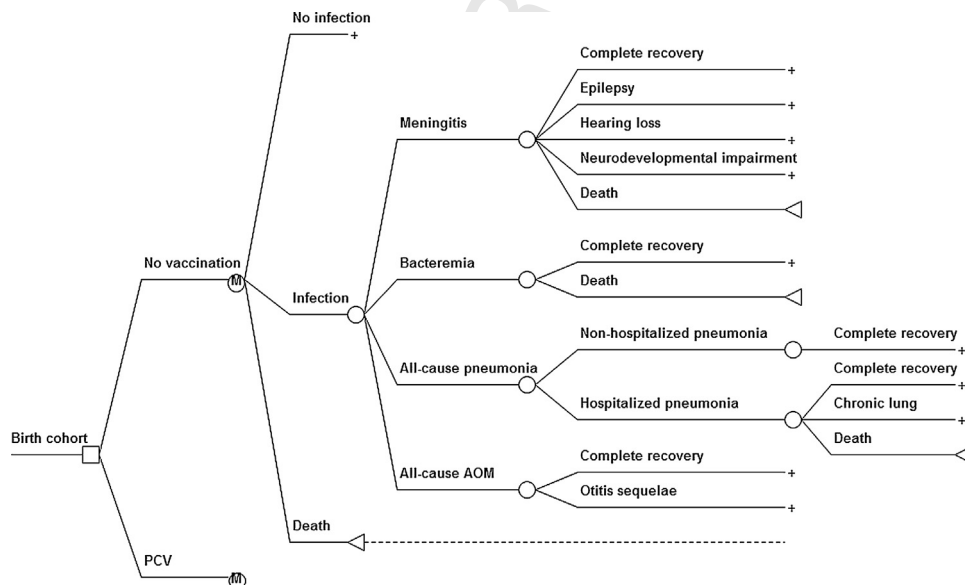


Fig. 1. Markov model used for assessing costs and outcomes of pneumococcal conjugate vaccine (PCV) vaccination compared to 'no vaccination'. The structure of the 'PCV' node is identical to the 'no vaccination' node and is thus omitted.

disease incidence reduction among unvaccinated groups in the United States [4]. For pneumonia incidence, there were two data sources in Thailand. We used data from Thailand's national surveillance (Bureau of Epidemiology, MoPH) [22] as the base-case and data from an active, population-based surveillance system operated collaboratively by MoPH and the International Emerging Infections Program (IEIP, US Centers for Disease Control and Prevention) [41] in the sensitivity analysis. We also assessed the effect of two different durations of vaccine protection: 5 and 10 years.

This analysis used the cost-effectiveness ceiling threshold of one per-capita gross domestic product or THB 100,000 (US\$ 3226) per QALY gained as recommended by the Subcommittee for Development of the National List of Essential Drugs 2007 [42]. The Subcommittee sets the threshold for considering new medicines and vaccines for public reimbursement. For PCV vaccination scenarios determined to be not cost-effective at the current price, we examined the maximum cost of the vaccine that would make it cost-effective as well as cost-saving in the Thai setting. Cost-saving implies that no additional budget would be required for vaccination, because resources saved from averted pneumococcal disease could be used to cover vaccination costs.

2.3.2. Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was conducted to examine the effect of all parameter uncertainty simultaneously using a Monte Carlo simulation using Microsoft Office Excel 2007. The simulation was run for 1000 iterations to yield a range of possible values for total costs, health outcomes, and incremental cost-effectiveness ratios (ICERs) in THB per QALY gained. The probability distributions were determined according to the range of each input parameter value. The normal distribution was used as a default. The beta distribution was used when parameter values ranged between zero and one, such as in probability and utility parameters. The gamma distribution was used when parameter values ranged between zero and positive infinity, such as costs parameters.

3. Results

Compared to 'no vaccination', the 3 + 1 dose schedule of PCV10 and PCV13 would prevent an estimated 7926 and 9747 episodes of pneumococcal disease in the vaccinated population, respectively (Fig. 2). In addition, 4510 and 6211 episodes of pneumococcal disease would be averted in unvaccinated populations due to indirect effects. It was estimated that 420 and 551 pneumococcal deaths would be avoided by introducing PCV10 and PCV13, respectively.

Table 2 shows the ICERs of different PCV vaccination schedules with and without inclusion of indirect vaccine effects. Without the indirect effects of vaccine, the 2 + 1 dose schedule produced ICERs of THB 808,933 and THB 882,291 per QALY gained for PCV10 and PCV13, respectively. The 3 + 1 dose schedule without accounting for indirect effects produced ICERs of THB 995,621 for PCV10 and THB 1,085,928 for PCV13. When the indirect effects of vaccination were included in the analysis, ICERs of PCV vaccination decreased by more than half. In one-way sensitivity analysis, the important determinants were discount rate, the change in duration of vaccine protection (5 vs. 10 years) and the incidence of pneumonia for all age groups. A 10-year protection duration including indirect effects, ICERs of PCV10 decreased to THB 287,353 and THB 363,248 for the 2 + 1 and 3 + 1 dose schedules, respectively; for PCV13, the corresponding ICERs were THB 290,420 and THB 367,339. When we used pneumonia incidence from active, population-based surveillance [41] and included indirect effects, the ICERs were reduced by almost 50% for the 3 + 1 schedule to THB 360,891 (PCV10) and THB 371,723 (PCV13) as well as by approximately 50% for the 2 + 1 schedule to THB 287,353 (PCV10) and THB 290,420 (PCV13). The model was

less sensitive to variations in direct medical and non-medical costs and serotype replacement.

At current pricing, neither PCV10 nor PCV13 would be cost-effective compared to 'no vaccination' at a ceiling threshold of THB 100,000 per QALY gained, with or without inclusion of indirect vaccine effects (Fig. 3). Including the indirect vaccine effects, PCV13 had a higher probability of being cost-effective compared to 'no vaccination' at a ceiling threshold between THB 600,000 and THB 750,000, depending on dosing schedule (Fig. 3A and 3B). Compared to PCV10, PCV13 had a higher probability of being cost-effective at a ceiling threshold between THB 550,000 and THB 600,000.

Without indirect vaccine effects, PCV10 yielded a higher probability of being cost-effective compared to 'no vaccination' at a ceiling threshold between THB 1,450,000 and THB 1,750,000, and PCV13 had a higher probability of being cost-effective compared to PCV10 at a ceiling threshold between THB 2,050,000 to THB 2,550,000 (Fig. 3C and D).

Threshold analysis demonstrated that using the 2 + 1 dosing schedule and considering indirect vaccine effects, PCV10 and PCV13 costs would have to be 76% lower (to THB 352 and THB 468), to be cost-effective; 92% cost reduction for both PCV10 and PCV13 (to THB 114 and THB 155) would be needed for either vaccine to be cost-saving (Fig. 4). Using a 3 + 1 dosing schedule, PCV10 and PCV13 costs would have to be 80% lower (to THB 287 and THB 381), to be cost-effective, and 93% and 94% lower (to THB 93 and THB 126), respectively, to be cost-saving.

When indirect vaccine effects were excluded, the maximum vaccine costs for both PCV10 and PCV13 to achieve cost-effective ranged from THB 94 to THB 141, and to be cost-saving, maximum costs ranged from THB 11 to THB 17.

4. Discussion

This study indicates that, at current pricing, neither PCV10 nor PCV13 would be considered cost-effective in Thailand at either dosing schedule examined, using Thailand's standard ceiling threshold to assess health interventions. This finding results largely from the relatively high cost of the vaccine (per dose), which is equivalent to 5–6 times Thailand's daily minimum wage. Our findings also reveal that the vaccine can become cost-effective or even cost-saving if vaccine costs were reduced by around 70–90% of current market prices.

Our findings stand in contrast to previous studies conducted in Argentina and Singapore which found PCV to be cost-effective [43,44]. The differences may be explained by differences of model structure and input parameters, especially epidemiological and economic data that vary across settings. In addition, the VE estimate used in our model was lower than that used in other studies. In this study, VE against vaccine-type IPD (89%) was derived from a systematic review and meta-analysis of RCTs [29], while other studies used 97% as reported from a single RCT conducted in the United States [1]. Difference in country specific serotype coverage may also have influenced the results. PCV10 serotype coverage for IPD among children aged less than 5 years is 75%, 81%, and 71% in Argentina, Singapore and Thailand, respectively [30–32,43,45]. This study also assumed a vaccine protection duration of 5 years, which is in line with several other economic evaluations of PCV studies [9,46], whereas some studies assumed protection lasted 10 years [7,47,48]. Our decision to use a 5-year protection duration was based on an immunogenicity study of PCV9 in South Africa [49], although this study did not follow participants beyond 5–6 years. Recognizing the limited data available, we applied a conservative assumption for the duration of vaccine protection. Furthermore, lower treatment costs in Thailand compared to other settings [12,13,43,44], contributed

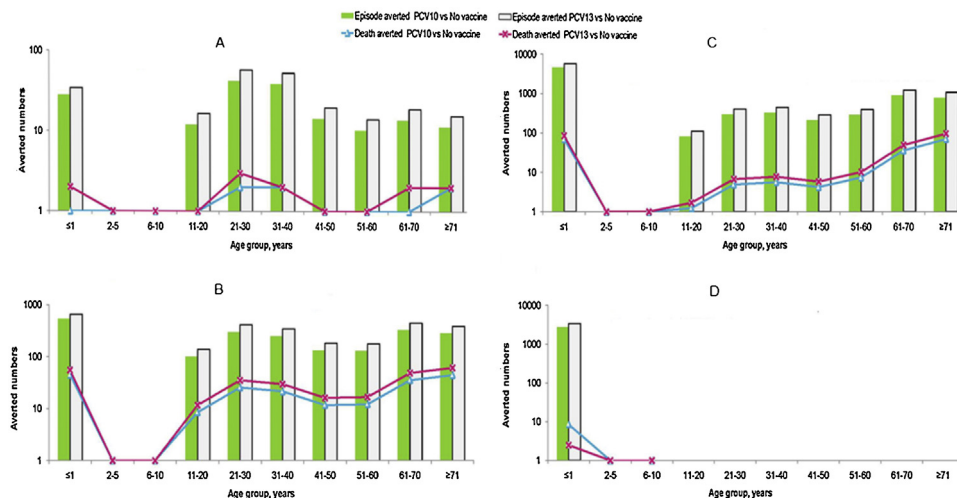


Fig. 2. Predicted numbers of life-time pneumococcal disease cases and deaths averted due to vaccination with 10- and 13-valent pneumococcal conjugate vaccines (PCV10 and PCV13) by clinical syndrome and age at entry to the cohort. (A) Pneumococcal meningitis; (B) pneumococcal bacteremia; (C) all-cause pneumonia; (D) all-cause acute otitis media.

to the different conclusions about vaccine cost effectiveness in this study.

The model was very sensitive to pneumonia incidence. The ICERs decreased significantly when the pneumonia incidence was based on active, population-based surveillance compared to Thailand's national surveillance system. However, even using the higher pneumonia incidence rate, PCV was not considered cost-effective for Thailand in our model.

4.1. Strengths and limitations

Parameters used in this model were obtained from high quality studies, including systematic reviews and meta-analyses. All parameters were contextualized for Thailand; thus, apply-

ing results of this study to other settings should be performed with caution. Our study examined two PCV formulations (10- and 13-valent) and two dosing schedules (2 + 1 and 3 + 1). Although this study adopted a static modeling rather than dynamic one, it included indirect effect of vaccination that protects infection in population who are not vaccinated. The use of static model also facilitates transparency of this study because many Thai decision makers and academics are more familiar with Markov, and the use of dynamic model in this study will require a number of assumptions given that this study considers four health conditions.

Nonetheless, this study has some limitations. First, due to the lack of local data on indirect vaccine effects, the model made assumptions based on findings from the United States [4]. Data

Table 2
Incremental cost effectiveness ratios (ICER, in THB/QALY) classified by vaccination schedules and inclusion of indirect vaccine effects.

	PCV10 vs. No vaccine	PCV13 vs. No vaccine
2 + 1 schedule with indirect effects		
Incremental cost (THB)	4178	5593
Incremental LYs	0.00674	0.00898
Incremental QALYs	0.00804	0.01061
Episode averted	0.01867	0.02501
Death averted	0.00200	0.00275
ICER per QALY gained (THB/QALY)	519,399	527,378
3 + 1 schedule with indirect effects		
Incremental cost (THB)	5658	7576
Incremental LYs	0.00726	0.00967
Incremental QALYs	0.00870	0.01147
Episode averted	0.02030	0.02723
Death averted	0.00217	0.00299
ICER per QALY gained (THB/QALY)	650,087	660,662
2 + 1 schedule without indirect effects		
Incremental cost (THB)	4492	6026
Incremental LYs	0.00212	0.00261
Incremental QALYs	0.00328	0.00404
Episode averted	0.00469	0.00577
Death averted	0.00007	0.00009
ICER per QALY gained (THB/QALY)	1,368,072	1,490,305
3 + 1 schedule without indirect effects		
Incremental cost (THB)	6001	8048
Incremental LYs	0.00229	0.00282
Incremental QALYs	0.00358	0.00440
Episode averted	0.00508	0.00625
Death averted	0.00008	0.00010
ICER per QALY gained (THB/QALY)	1,677,379	1,830,716

LY = life year, QALY = quality-adjusted life year.

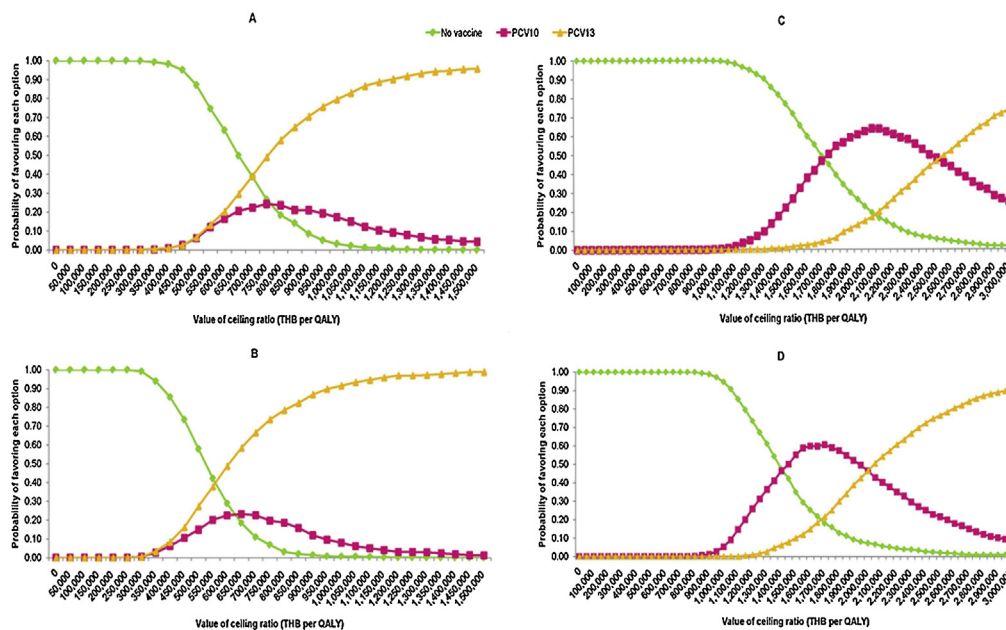


Fig. 3. Cost-effectiveness acceptability curves for 10- and 13-valent pneumococcal conjugate vaccines (PCV10 and PCV13), and 'no vaccination'. (A) 3 + 1 schedule with indirect vaccine effects; (B) 2 + 1 schedule with indirect vaccine effects; (C) 3 + 1 schedule without indirect vaccine effects; (D) 2 + 1 schedule without indirect vaccine effects.

341 from the United States showed a significant decline in IPD incidence
 342 among unvaccinated populations aged 20 years and above only.
 343 This ignored herd protection among young children (2–4 years) and
 344 teenagers, which could not be assessed in the United States, because
 345 children in this age group (2–4 years) were vaccinated as part of
 346 catch-up vaccination efforts. Second, IPD incidence rates used
 347 in this model were likely underestimates, because the available
 348 studies were conducted in public health facilities (i.e. government
 349 hospitals and health centers); thus, patients without access to public
 350 hospitals or at private hospitals were not included. Additionally,
 351 it has been shown that antibiotic use before blood culture collection
 352 in Thailand leads to underestimation of IPD incidence in hospital-
 353 based studies [21]. Perhaps more importantly, IPD rates cited for
 354 this analysis did not include outpatients because most of them were
 355 suspected and not confirmed cases. Including outpatient IPD cases
 356 in the model inputs would have resulted in lower ICERs. Lastly, the
 357 ceiling threshold used in this analysis is based on the preference of
 358 decision maker in Thailand. Decision makers in different settings
 359 may have their own preference regarding health investment, we

encourage readers to compare the results to any threshold they consider it appropriate.

4.2. Implications

In summary, based on a societal perspective with a ceiling threshold of THB 100,000 per QALY, PCV10 and PCV13 would not be considered cost-effective, whether or not indirect vaccine effects were included in the model. Therefore, it cannot be recommended that PCV be included in Thailand's EPI until prices decline to recommended values. Reduction in vaccine cost, which seems possible given the widespread introduction of PCV in many countries, could improve the feasibility of introduction in Thailand, which could result in substantial public health impact. Based on analyses that include indirect vaccine effects, PCV would become cost-effective at a price per-dose between THB 287 (PCV10, 3 + 1 schedule) and THB 381 (PCV13, 2 + 1 schedule) and cost-saving at a per-dose price between THB 93 and THB 155.

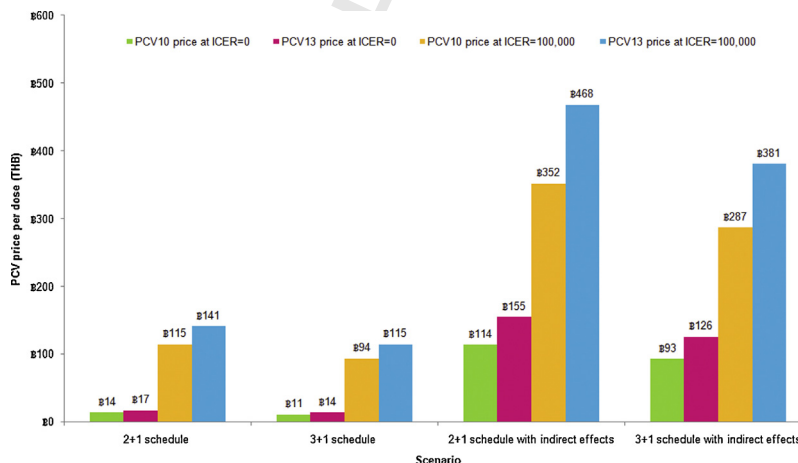


Fig. 4. Threshold analysis for maximum per-dose price for 10- and 13-valent pneumococcal conjugate vaccines (PCV10 and PCV13) to achieve cost-effective (incremental cost-effectiveness ratio (ICER) = THB 100,000) or cost-saving (ICER = THB 0). Current price per dose: THB 1440 for PCV10; THB 1930 for PCV13.

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390 **Appendix A. Supplementary data**

391 Supplementary data associated with this article can be
392 found, in the online version, at [http://dx.doi.org/10.1016/](http://dx.doi.org/10.1016/j.vaccine.2013.03.047)
393 [j.vaccine.2013.03.047](http://dx.doi.org/10.1016/j.vaccine.2013.03.047).

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