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# An updated cost-effectiveness analysis of pneumococcal conjugate vaccine among children in Thailand

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ABSTRACT

*Background:* A previous cost-effectiveness analysis (CEA) showed that Pneumococcal Conjugate Vaccine (PCV) 10 and PCV13 were not cost-effective for universal immunization among children in Thailand. Given recent changes in the evidence of efficacy, herd effects and price, a CEA of PCVs should be revisited. This study aimed to determine the cost-effectiveness of PCV10 and PCV13 compared to no PCV vaccination in Thai children.

*Material and methods:* A Markov model was developed under a societal perspective with a lifetime horizon. Inputs were derived from a comprehensive literature review. Costs were calculated using the Thai National Electronic Database and converted to the year 2017 value. All costs and outcomes were discounted at a rate of 3%. The findings were reported as incremental cost-effectiveness ratios (ICERs) in Thai Baht (THB) per quality-adjusted life year (QALY) gained. Sensitivity analyses were performed. A cost-effectiveness acceptability curve was generated with the cost-effectiveness threshold of 160,000 THB/QALY.

*Results:* Base-case analysis of 2 + 1 dose schedule and five-year protection, with no consideration of herd effect showed that ICER for PCV10 was 170,437 THB/QALY, while ICER for PCV13 was 73,674 THB/QALY. With consideration of herd effect, both PCV10 and PCV13 had lower costs and higher QALYs compared to no PCV vaccination. Based on our probabilistic sensitivity analysis at willingness-to-pay of 160,000 THB/QALY, PCV13 had 93% of being cost-effective, while 4.7% and 2.3%, for PCV10 and no PCV vaccination, respectively.

*Conclusion:* At current prices, PCV13 is cost-effective, while PCV10 is not cost-effective in Thailand. When considering herd-effect, both PCV10 and PCV13 are cost-effective.



## 1. Introduction

*Streptococcus pneumoniae* (*S. pneumoniae*) causes invasive pneumococcal diseases (IPD) such as meningitis and bacteremia, and non-invasive diseases such as pneumonia and acute otitis media (AOM) [1]. The World Health Organization (WHO) estimated that 1.6 million deaths were caused by pneumococcal infections, particularly in children aged under 5 years in 2008 [2]. In Thailand, the incidence rate of pneumonia and IPD in children aged under 5 years was 11.1 and 1.3 per 100,000 populations [3,4]. The high morbidity and mortality in infants and elderly in Asia including Thailand thus were translated into high economic burden [5].

Pneumococcal conjugate vaccine (PCV) has been demonstrated effective and safe in preventing *S. pneumoniae* related diseases in young children [6]. Routine use of PCV7 in children less than 5 years has markedly decreased the incidence of IPD, pneumonia, and otitis media due to vaccine serotype pneumococcus in several countries where it has been used [7–9]. In addition to this direct

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vaccine effect, indirect vaccine effects, in particular herd protection, have also been documented. In the United States, more cases of IPD and hospitalized pneumonia have been prevented by the herd effect, than in vaccinated children [10,11].

Two types of PCV have been developed which expanded serotype coverage from seven serotype covered by PCV7. A 10-Valent pneumococcal conjugate vaccine (PCV10), includes the 7 serotypes in PCV7 (4, 14, 6B, 9V, 18C, 19F, 23F) plus additional three serotypes (1, 5, and 7F), and is conjugated to three protein carriers (protein D derived from non-typeable *Haemophilus influenzae*, tetanus toxoid, and diphtheria toxoid) [12]. A 13-Valent pneumococcal conjugate vaccine (PCV13) includes all serotypes covered by the PCV7 and PCV10 vaccines plus additional three serotypes (3, 6A, and 19A). All serotypes in PCV13 are conjugated to CRM197, the same protein carrier used in PCV7 [13].

As of Jun 2018, PCVs have been introduced into the National Immunization Program (NIP) in 142 countries worldwide [14]. The incidence of pneumococcal diseases among all unvaccinated age groups has been continuously declined after PCV introduction as the NIP in these countries [11,15]. In Thailand, PCV has not been adopted as a part of the NIP due to several key reasons. One important reason is the limited economic evaluation evidence supporting government decision-making. Even though there are economic evaluations from many countries especially in developing countries, the generalizability of their results should be cautious and it requires country-specific data including burden of diseases, healthcare resource used, cost, cost-effectiveness threshold and budget impact analyses [16].

In Thailand, Kulpeng et al. conducted an economic evaluation of PCVs in 2010 and it was shown that none of PCVs was cost-effective for NIP among children compared with no vaccination [17]. Given recent changes in evidence of efficacy, herd effect and prices of PCV, an updated CEA should be revisited. This study aimed to update the current evidence of economic evaluation of the both PCV10 and PCV13 compared to no vaccine in NIP by applying the current local epidemiological and economic data to access cost-effectiveness among children less than 6 months old in Thailand.

## 2. Methods

### 2.1. Overall description

A cost-effectiveness analysis was undertaken to estimate cost and health outcomes of PCV10 and PCV13 compared to no vaccine among children less than 6 months old. No vaccine was selected to be the common comparator because PCV has not been listed in NIP in Thailand (status quo). The intervention of interest was PCV10 or PCV13 with two-dose and one-booster dose (2 + 1 schedule) and three-dose and one-booster dose (3 + 1 schedule). Since some cases of invasive pneumococcal disease (IPD), such as meningitis, have long-term sequelae including hearing loss, epilepsy, and neurodevelopmental impairment, the lifetime time horizon was chosen. The discount rate of 3% was applied to both cost and health outcomes [18]. Results were presented as incremental cost-effectiveness ratio (ICER) in Thai Baht (THB) per quality-adjusted life year (QALY) gained. This study was undertaken under a societal perspective as recommended by Thailand's Health Technology Assessment (HTA) Guideline [19].

A hybrid model consisting of a decision tree and a Markov model was built based on the natural history of diseases from pneumococcal infection (Fig. 1). A hypothetical of 100,000 birth cohort was assumed to be eligible for vaccination. The cohort could be vaccinated (or not vaccinated). The consequences of vaccination or non-vaccination included pneumococcal meningitis, pneumo-

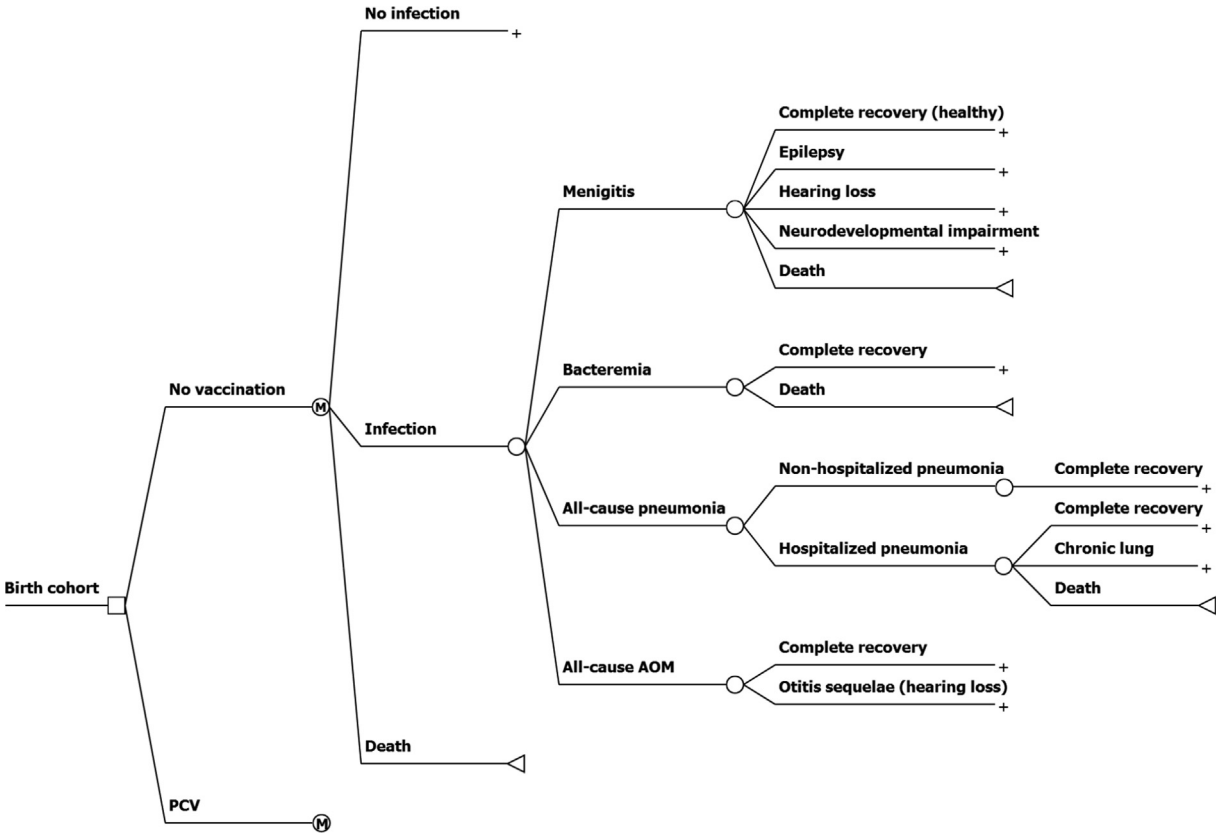


**Fig. 1.** Schematic diagram representing the decision tree for assessing the cost-effectiveness of Pneumococcal vaccination among children.

**Table 1**
Annual incidence per 100,000 populations by consequences.

| Age | Pneumococcal disease | | Non-specific pathogen | | |
|---|---|---|---|---|---|
| | Meningitis [2,4,20] | Bacteremia [21] | Hospitalized pneumonia [3] | Non-hospitalized pneumonia [3] | AOM [22] |
| 0–4 | 1.36 | 11.10 | 2445.00 | 1182.00 | 601.08 |
| 5–9 | 0.46 | 1.40 | 271.00 | 560.00 | 1139.97 |
| 10–14 | 0.42 | 1.40 | 271.00 | 560.00 | 1139.97 |
| 15–19 | 0.24 | 1.40 | 184.00 | 89.00 | 0 |
| 20–24 | 0.24 | 1.90 | 184.00 | 89.00 | 0 |
| 25–34 | 0.27 | 1.90 | 184.00 | 89.00 | 0 |
| 35–44 | 0.28 | 1.90 | 184.00 | 89.00 | 0 |
| 45–49 | 0.32 | 1.90 | 184.00 | 89.00 | 0 |
| 50–54 | 0.62 | 4.60 | 184.00 | 89.00 | 0 |
| 55–64 | 1.36 | 4.60 | 184.00 | 89.00 | 0 |
| ≥65 | 0.46 | 13.60 | 1466.00 | 3032.00 | 0 |

*Abbreviations:* Acute Otitis Media: AOM.

coccal bacteremia, all-cause pneumonia, and all-cause acute otitis media (AOM). The likelihood of getting the consequences was based on the incidence of each consequence (Table 1) and vaccine effectiveness (Table 2).

The Markov model was developed on top of the decision tree to capture long-term cost and consequences. First, subjects who experienced pneumococcal meningitis could have clinical consequences including full recovery, recovery with sequelae, and death. The sequelae included hearing loss, epilepsy, and neurodevelopmental impairment. Second, subjects with pneumococcal bacteremia could have complete recovery or death. Third, subjects with pneumonia could have hospitalized or non-hospitalized pneumonia. Subjects who were hospitalized with pneumonia could become complete recovery, getting chronic lung diseases, or death. In addition, subjects with AOM could have complete recovery or hearing loss. The probabilities of getting each sequelae were also presented in Table 2. The vaccine herd effect was not captured in our base-case analysis but it was considered in our sensitivity analysis.

The model structure and model assumptions were validated through a consultation in stakeholder meeting (Appendix). Pneumococcal infection occurring only once for each subject was primarily assumed with one-year cycle length [28].

### 2.2. Model inputs

Inputs were obtained published literature or electronic healthcare utilization databases obtained from the National Health Security Office (NHSO) (Table 1).

### 2.3. Epidemiological data

As shown in Table 1, the incidence of pneumococcal meningitis was derived from the updated report from Bureau of Epidemiology of Thailand [2]. Proportions of bacterial meningitis due to *S. pneumoniae* were 26.1% in children [4] and 11.6% in adults [20]. The incidence of pneumococcal bacteremia was from a population-based surveillance in Thailand [21]. For all-cause pneumonia, data were from a hospital-based surveillance in Thailand [3], while the incidence of all-cause AOM was based on a report from Burden of Disease and Injuries in Thailand [22].

Probabilities of developing sequelae after pneumococcal meningitis were estimated from the NHSO databases. The databases contained longitudinal data of medical diagnoses, date of admission and discharge, and discharge status. Patients from 2011 to 2016 diagnosed with pneumococcal meningitis (N = 1203), bacteraemia (N = 1874), pneumonia (N = 1956), and AOM (n = 262,688) were included. Case-fatality rates associated with meningitis, bacteraemia, and pneumonia were captured from a previous study [17] (Table 2).

## 3. Vaccine effectiveness and coverage rate

### 3.1. Direct effect

Vaccine effectiveness against IPD, all-cause pneumonia, and all-cause AOM were estimated from previous scientific literature (Table 2). The relative vaccine efficacy for 3 + 1 and 2 + 1 schedule was based on a previous study [23].

### 3.2. Indirect effect

Herd effect was applied in our sensitivity analysis for all population cohorts ranging from aged 16–99 years. Herd effect of PCV10 and PCV13 against IPD were based on a recently published systematic review and meta-analysis [11], while herd effect of PCV10 and PCV13 against pneumonia were calculated from the effect of PCV7 with a serotype coverage adjustment [24]. The percentage of pneumonia reduction in Thailand was adjusted using the following equation.

$$\%\text{Pneumonia reduction in Thailand} = \frac{\%\ \text{Hospitalized pneumonia reduction in the US} \times \text{Serotype coverage in Thailand}}{\text{Serotype coverage in the US}}$$

Serotype coverage for Thailand was based on two recent reports [25 26]. The wastage rate was 1.1% according to a previous study in Thai setting [27].

### 3.3. Costs and outcomes

Direct medical cost and direct non-medical cost were included in this study, while productivity cost was omitted based on a recommendation from the Thai cost-effectiveness guideline [28] Prices of PCV10 (1440 THB/vial) and PCV13 (1146 Thai baht (THB)/vial) were based on the proposed prices from

**Table 2**
Input parameters.

| Parameter description | Mean | SE | Distribution | References |
|---|---|---|---|---|
| **Epidemiology/efficacy parameters** | | | | |
| Epilepsy after pneumococcal meningitis | 0.0821286 | 0.0048154 | Beta | NHSO |
| Hearing loss after pneumococcal meningitis | 0.0163027 | 0.002221 | Beta | NHSO |
| Neurodevelopmental impairment pneumococcal meningitis | 0.0018456 | 0.0007528 | Beta | NHSO |
| Hearing loss after AOM | 0.0065826 | 0.000957 | Beta | NHSO |
| Death after pneumococcal meningitis | 0.032258 | 0.031234 | Beta | [17] |
| Death after pneumococcal bacteremia | 0.080000 | 0.036693 | Beta | [17] |
| Death after hospitalized pneumonia | 0.014241 | 0.000408 | Beta | [17] |
| Vaccine efficacy (PCV7; 3 + 1 schedule) | | | | |
| IPD caused by vaccine serotype | 89.00% | 5.87% | Beta | [50] |
| Clinical pneumonia | 25.50% | 8.72% | Beta | [51] |
| AOM | 6.00% | 1.28% | Beta | [50] |
| Vaccine efficacy (PCV10; 3 + 1 schedule) | | | | |
| IPD caused by vaccine serotype | 100.00% | 0.18% | Beta | [23,52] |
| Clinical pneumonia | 21.80% | 6.63% | Beta | [52] |
| AOM | 6.00% | 1.28% | Beta | [50] |
| Vaccine efficacy (PCV13; 3 + 1 schedule) | | | | |
| IPD caused by vaccine serotype | 89.00% | 5.87% | Beta | [50] |
| Clinical pneumonia | 25.50% | 8.72% | Beta | [51] |
| AOM | 6.00% | 1.28% | Beta | [50] |
| Vaccine efficacy of PCV10; 2 + 1 schedule against IPD | 92.00% | 10.71% | Beta | [23] |
| Vaccine serotype coverage in Thai | | | | |
| PCV7 serotype coverage in Thai <5 | 74.11% | N/A | Beta | MA [25,26] |
| PCV7 serotype coverage in Thai 5–64 | 47.82% | N/A | Beta | MA [25,26] |
| PCV7 serotype coverage in Thai ≥ 65 | 48.11% | N/A | Beta | MA [25,26] |
| PCV10 serotype coverage in Thai <5 | 78.72% | N/A | Beta | MA [25,26] |
| PCV10 serotype coverage in Thai 5–64 | 54.73% | N/A | Beta | MA [25,26] |
| PCV10 serotype coverage in Thai ≥65 | 55.30% | N/A | Beta | MA [25,26] |
| PCV13 serotype coverage in Thai <5 | 91.73% | N/A | Beta | MA [25,26] |
| PCV13 serotype coverage in Thai 5–64 | 76.04% | N/A | Beta | MA [25,26] |
| PCV13 serotype coverage in Thai ≥65 | 77.60% | N/A | Beta | MA [25,26] |
| Serotype coverage the US | | | | |
| PCV7 serotype coverage in aged 10–39 | 71.30% | N/A | Beta | [25] |
| PCV7 serotype coverage in aged 40–64 | 65.40% | N/A | Beta | [25] |
| PCV7 serotype coverage in aged ≥65 | 69.70% | N/A | Beta | [25] |
| % Reduction in IPD (herd effects) from PCV7 | | | | |
| % Herd effects in aged 0–4 | 38.00% | 3.83% | Beta | [11] |
| % Herd effects in aged 5–18 | 19.00% | 4.85% | Beta | [11] |
| % Herd effects in aged 19–49 | 15.00% | 2.80% | Beta | [11] |
| % Herd effects in aged 50–64 | 22.00% | 1.79% | Beta | [11] |
| % Herd effects in aged ≥65 | 23.00% | 1.28% | Beta | [11] |
| % Reduction in pneumonia from PCV7 | | | | |
| % Herd effects in aged 0–4 | 43.2% | 4.26% | Beta | [24] |
| % Herd effects in aged 5–18 | 4.50% | 5.40% | Beta | [24] |
| % Herd effects in aged 19–49 | 7.80% | 3.69% | Beta | [24] |
| % Herd effects in aged 50–64 | 0.00% | N/A | Beta | [24] |
| % Herd effects in aged ≥65 | 6.60% | 3.11% | Beta | [24] |
| % Reduction in IPD (herd effects) from PCV13 | | | | |
| % Herd effects in aged 0–4 | 42.34% | N/A | Beta | [11] |
| % Herd effects in aged 5–18 | 36.82% | N/A | Beta | [11] |
| % Herd effects in aged 19–49 | 37.10% | N/A | Beta | [11] |
| % Herd effects in aged 50–64 | 37.10% | N/A | Beta | [11] |
| % Herd effects in aged ≥65 | 40.71% | N/A | Beta | [11] |
| **Cost parameters** | | | | |
| Vaccine cost | | | | |
| PCV10 (THB/vial) | 1440 | – | Fixed | [53] |
| PCV13 (THB/vial) | 1146 | – | Fixed | [53] |
| Direct medical cost | | | | |
| *Cost per episode* | | | | |
| Meningitis aged ≤14 | 88,863.7 | 5576.88 | Gamma | NHSO |
| Meningitis aged 15–59 | 83,063.84 | 4728.69 | Gamma | NHSO |
| Meningitis aged ≥60 | 110,488.07 | 6313.6 | Gamma | NHSO |
| Bacteremia aged ≤14 | 53,424.67 | 6526.55 | Gamma | NHSO |
| Bacteremia aged 15–59 | 65,466.53 | 4334.92 | Gamma | NHSO |
| Bacteremia aged ≥60 | 76,565.08 | 3833.83 | Gamma | NHSO |
| Hospitalized pneumonia aged ≤14 | 26,923.18 | 9099 | Gamma | NHSO |
| Hospitalized pneumonia aged 15–59 | 76,660.64 | 23,952 | Gamma | NHSO |
| Hospitalized pneumonia aged ≥60 | 91,201.38 | 31,948 | Gamma | NHSO |
| Non-hospitalized pneumonia aged ≤14 | 333.78 | 54.19 | Gamma | NHSO |
| Non-hospitalized pneumonia aged 15–59 | 771.58 | 169.09 | Gamma | NHSO |
| Non-hospitalized pneumonia aged ≥60 | 640.76 | 84.81 | Gamma | NHSO |
| AOM aged ≤14 | 379.33 | 4.53 | Gamma | NHSO |
| AOM aged 15–59 | 254.7 | 3.69 | Gamma | NHSO |
| AOM aged ≥60 | 500.12 | 11.51 | Gamma | NHSO |

**Table 2** (*continued*)

| Parameter description | Mean | SE | Distribution | References |
|---|---|---|---|---|
| *Cost per year* | | | | |
| Epilepsy aged ≤14 | 5589.81 | 64.15 | Gamma | NHSO |
| Epilepsy aged 15–59 | 7702.81 | 47.18 | Gamma | NHSO |
| Epilepsy aged ≥60 | 14,288.80 | 127.57 | Gamma | NHSO |
| Hearing loss aged ≤14 | 892.19 | 33.82 | Gamma | NHSO |
| Hearing loss aged 15–59 | 957.80 | 14.81 | Gamma | NHSO |
| Hearing loss aged ≥60 | 877.37 | 9.93 | Gamma | NHSO |
| Neurodevelopmental impairment aged ≤14 | 1796.98 | 37.23 | Gamma | NHSO |
| Neurodevelopmental impairment aged 15–59 | 4940.03 | 60.83 | Gamma | NHSO |
| Neurodevelopmental impairment aged ≥60 | 1312.17 | 76.93 | Gamma | NHSO |
| Chronic lung ≤14 | 1519 | 1404 | Gamma | [17] |
| Chronic lung 15–59 | 3576 | 62 | Gamma | [17] |
| Chronic lung ≥60 | 3933 | 31 | Gamma | [17] |
| **Utility parameters** | 0.9638 | 0.0046 | | |
| Utility for meningitis | 0.9852 | 0.0025 | Beta | [17] |
| Utility for bacteremia | 0.9910 | 0.0020 | Beta | [17] |
| Utility for pneumonia | 0.9984 | 0.0001 | Beta | [17] |
| Utility for acute otitis media | 0.6400 | 0.0737 | Beta | [17] |
| Utility for epilepsy | 0.5500 | 0.0554 | Beta | [17] |
| Utility for hearing loss | 0.6900 | 0.0707 | Beta | [17] |
| Utility for neurodevelopmental impairment- mild mental retardation | 0.1000 | 0.1085 | Beta | [17] |
| Utility for neurodevelopmental impairment-severe mentalretardation | 0.0001 | 0.0943 | Beta | [17] |
| Utility for neurodevelopmental impairment- mental retardation plus epilepsy | 0.5900 | 0.0575 | Beta | [17] |
| Utility for chronic lung disease | | | Beta | [17] |

*Abbreviations:* National Health Security Office: NHSO, Pneumococcal Conjugated Vaccine: PCV, Invasive Pneumococcal Disease: IPD, Acute Otitis Media: AOM, Two-dose and one-booster dose schedule: 2 + 1, Three-dose and one-booster dose schedule: 3 + 1. MA: Meta-analysis.

pharmaceutical companies. The cost of the vaccination program including vaccine acquisition cost and wastage cost was a Thailand's survey study [27]. Direct medical costs for a hospitalized episode of meningitis, bacteremia, pneumonia, and non-hospitalized pneumonia and AOM, were estimated using the NHSO database (2011–2016). All costs were calculated from charges using a cost-to-charge ratio of 1.63 [29]. Consumer price index in medical care section was used to convert the value of the costs to the Year 2018 value. Direct non-medical costs, including transportation, meals, accommodation, facilities, productivity loss by parents or caregivers for hospital visits or providing informal care, and utilities were derived from a previous cost-effectiveness study [17]. All inputs are summarized in Table 2.

## 4. Cost-effectiveness analysis

### 4.1. Base-case analysis

Primary outcomes of interest were the number of pneumococcal infections, incremental costs, life year gained, QALYs gained, and incremental cost-effectiveness ratio (ICER). For base-case analysis, the expected lifetime cost and outcomes for all options compared to no vaccination as a reference were calculated. The willingness-to-pay (WTP) of 160,000 Thai baht (THB)/QALY gained was used to determine the cost-effectiveness ceiling threshold based on a recommendation of the Thai Health Economic Working Group (HEWG) for drug listing in NLEM year 2012 [30,31].

### 4.2. Scenario analysis

We assessed how the results were changed when we altered a parameter in our sensitivity analyses. We incorporated herd effect in our sensitivity analysis. We also performed analyses for 3 + 1 dose of PCVs. Vaccine efficacy of PCV10 against AOM was varied, giving a significant (33·6% [95% CI 20·8–44·3]) reduction in the overall incidence of AOM from POET study, [32] and extrapolated vaccine efficacy of PCV13 against pneumonia from PCV7's data. We replaced the serotype coverage for 10% in both PCV10 and PCV13. We also added cross-protection for serotype 19A for PCV10.[33,34] We changed the vaccine protection from 5 years to 8 years in both PCV10 and PCV13. Threshold analyses were also performed to estimate the acceptable cost of the vaccines which were reduced to the threshold that set in two aspects. First is to be cost-saving by reducing the cost of the vaccines per vial till ICER was ≤0 THB/QALY. Second is to be cost-effective by reducing the cost of the vaccines per vial till ICER was ≤160,000 THB/QALY. The threshold analyses were performed for both 2 + 1 and 3 + 1 schedules.

In addition, a probabilistic sensitivity analysis (PSA) was conducted to simultaneously examine the effect of all parameter uncertainty using a Monte Carlo simulation performed by Microsoft Excel 2013 (Microsoft Corp., Redmond, WA). [35] The Monte Carlo simulation was run for 10,000 iterations to give a range of values for total cost, outcomes, and ICERs. Results of the PSA were presented as cost-effectiveness acceptability curve. The expected net monetary benefit (NMB) was calculated for WTP of NLEM 2012 threshold (160,000 THB/QALY) in Thailand in order to show the probability that PCV10 and PCV13 were cost-effective for monetary values that a decision-maker might be willing to pay.

### 4.3. Budget impact analysis

The budget impact analysis was also analysed to estimate the whole budget required for implementing national PCV10 and PCV13 vaccination program compared to no vaccination among Thai children in year 2017–2021. The estimated numbers of Thai children were estimated using linear trend relationship from data of the year 2007–2017. As a result, the estimated numbers of Thai children were 675,893, 668,470, 653,624, 631,355, and 601,663 individuals for the year 2017–2021, respectively. The wastage rate of 1.1% was also applied based on a previous study in Thai setting [27]. All costs were presented in the year 2018 and readers can convert to US dollar ($) using the exchange rates THB 31.4 = 1 US dollar in order to compare across countries. Because PCV10 and PCV13 vaccination could prevent future cost due to the prevention of pneumococcal infected diseases, cost offset was also considered

to estimate the budget impact in addition to the whole required budget. To calculate the cost offset, the cost incurred in the non-vaccinated population was subtracted by the cost incurred in the vaccinated population.

## 5. Results

### 5.1. Base-case analysis

For the use of 2 + 1 PCV10 among a hypothetical cohort of 100,000 Thai children was expected to avert, a total of 3757 cases which includes 5 pneumococcal meningitis, 42 pneumococcal bacteremias, 3560 all-cause pneumonias, and 150 all-cause AOM compared to no vaccination. For the use of 2 + 1 PCV13, the expected number of averted cases was 5829 cases which include 6 pneumococcal meningitis, 46 pneumococcal bacteremias, 5596 all-cause pneumonias, and 180 all-cause AOM. Implementing of 2 + 1 schedule, PCV10 and PCV13 increases both cost and QALYs compared to no vaccination. PCV10 would increase 0.0228 QALYs/individual and 3881 THB/individual. Therefore, the ICER of PCV10 was 170,437 THB/QALY. Similarly, PCV13 would increase 0.0349 QALYs/individual and 2571 THB/individual. Thus, the ICER of PCV13 was 73,674 THB/QALY. Based on the Thai ceiling threshold of cost-effectiveness intervention (160,000 THB/QALY gained), Only PCV13 was considered as a cost-effectiveness intervention (Table 3).

### 5.2. Multivariate probabilistic sensitivity analysis

Results of the PSA based on 1000 Monte Carlo simulations were presented in cost-effectiveness scatter plot (Fig. 2). Despite variation in base-case inputs, all simulated incremental cost-effectiveness ratios were in the upper-right quadrant indicating that implementing national PCV13 vaccination program was the higher cost but better QALYs.

The cost-effectiveness acceptability curve indicated that national 2 + 1 PCV13 vaccination program will have 93.0% chance of being cost-effective at all willingness-to-pay (WTP) and reduced to 87.6%, 89.2%, and 86.9% (Fig. 3), if changed schedule to 3 + 1, 3 + 1 schedule with herd-effect, and 2 + 1 schedule with herd-effect, respectively. While the national 2 + 1 PCV10 vaccination program will only have 4.7% chance of being cost-effectiveness at all WTP and increased to 9.3%, 10.8%, and 13.1%, if changed schedule to 3 + 1, 3 + 1 schedule with herd-effect, and 2 + 1 schedule with herd-effect, respectively.

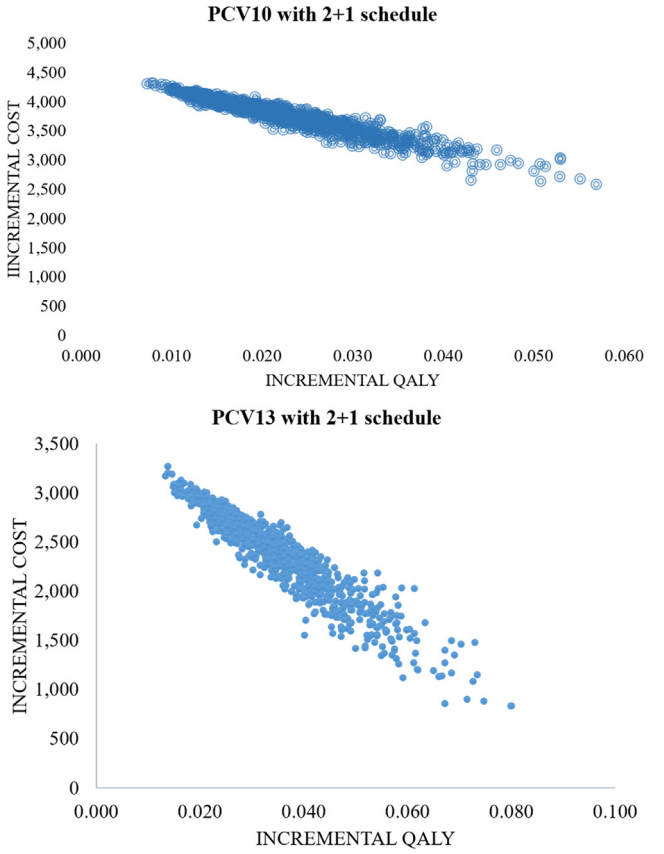


**Fig. 2.** A graphical presentation showing the finding of probabilistic sensitivity analysis (Cost-effectiveness scatter plot).

**Table 3**
Base-case analysis.

| Treatment | Total cost | LYs | QALYs | Incremental cost | Incremental QALY | ICER |
|---|---|---|---|---|---|---|
| Base-case analysis (no herd effect) | | | | | | |
| Dose: 3 + 1 | | | | | | |
| No vaccine | 1,047,360 | 1,718.40 | 1717.42 | *Ref* | *Ref* | *Ref* |
| PCV10 | 1,052,709 | 1,718.42 | 1717.44 | 5348 | 0.0248 | 215,948 |
| PCV13 | 1,051,054 | 1,718.43 | 1717.46 | 3693 | 0.0380 | 97,269 |
| Dose: 2 + 1 | | | | | | |
| No vaccine | 1,047,360 | 1,718.40 | 1717.42 | *Ref* | *Ref* | *Ref* |
| PCV10 | 1,051,242 | 1,718.42 | 1717.44 | 3881 | 0.0228 | 170,437 |
| PCV13 | 1,049,932 | 1,718.43 | 1717.45 | 2571 | 0.0349 | 73,674 |
| Analysis with herd effect | | | | | | |
| Dose: 3 + 1 | | | | | | |
| No vaccine | 1,047,360 | 1,718.40 | 1717.42 | *Ref* | *Ref* | *Ref* |
| PCV10 | 1,044,208 | 1,718.46 | 1717.48 | −3152 | 0.0672 | Cost-saving −46,918 |
| PCV13 | 1,039,091 | 1718.48 | 1717.51 | −8270 | 0.0976 | Cost-saving −84,770 |
| Dose: 2 + 1 | | | | | | |
| No vaccine | 1,047,360 | 1,718.40 | 1717.42 | *Ref* | *Ref* | *Ref* |
| PCV10 | 1,042,741 | 1,718.46 | 1717.48 | −4619 | 0.0652 | Cost-saving −70,854 |
| PCV13 | 1,037,969 | 1,718.48 | 1717.51 | −9392 | 0.0945 | Cost-saving −99,394 |

*Abbreviations:* Life Years: LYs, Quality-adjusted life years: QALYs, Incremental Cost Effectiveness Ratio: ICER, Pneumococcal Conjugated Vaccine: PCV, Two-dose and one-booster dose schedule: 2 + 1, Three-dose and one-booster dose schedule: 3 + 1.

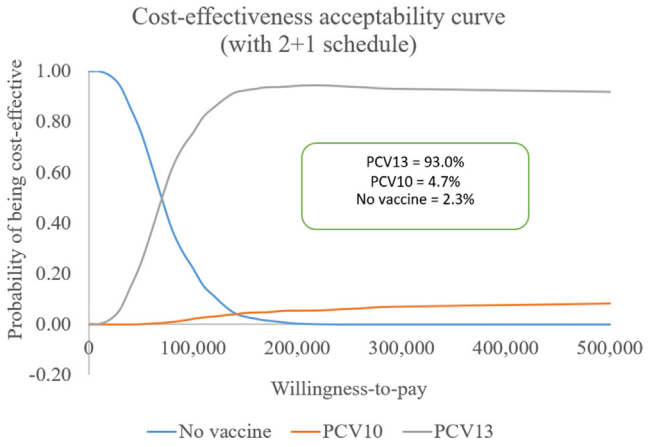


**Fig. 3.** A graphical presentation showing the probability of being cost-effective (Cost-effectiveness acceptability curve).

## 6. Scenario analyses

A scenario analysis by changing PCV10 and PCV13 schedule from 2 + 1 to 3 + 1 indicated that PCV13 was still a cost-effective strategy. It increased the total healthcare cost of 3693 THB/individual and increases 0.0380 QALYs compared to no vaccination. Scenario analyses by using POET's data for PCV10 against AOM shown that PCV10 was possibly cost-effective in 2 + 1 schedule that the ICER was 141,202 THB/QALY. For 10% serotype replacement scenario analyses, it was found that PCV13 was a cost-effective strategy in both 2 + 1 and 3 + 1. Scenario analyses by adding cross-protection for PCV10 reveal that PCV10 was still not cost-effective. Changing vaccine protection from 5 years to 8 years indicated that PCV10 could be cost-effective in 2 + 1 schedule with the ICER of 142,925 THB/QALY (Table 4) . All of the scenario analyses were incorporated with herd-effect and indicated that both PCV10 and PCV13 were cost-saving in every changing and schedule (Appendix Table 1).

Another scenario analysis by incorporating herd-effect of PCV10 and PCV13 indicated that both PCV10 and PCV13 had lower total cost and higher QALYs compared to no PCV vaccination. PCV10 would increase 0.0672 QALYs/individual and save 4619 THB/individual. Therefore, the ICER of PCV10 was cost-saving for 70,854 THB/QALY. Likewise, PCV13 would increase 0.0945 QALYs/individual and save 9392 THB/individual. Thus, the ICER of PCV13 was cost-saving for 99,394 THB/QALY (Table 3).

### 6.1. Threshold analysis

In terms of cost-saving, cost of PCV10 needed to be reduced by 87.47% and 84.64% in 3 + 1 and 2 + 1 schedules, respectively. Cost of PCV13 needed to be reduced by 75.90% and 70.46% in 3 + 1 and 2 + 1 schedules, respectively (Table 4). In terms of cost-effective, cost of PCV 10 needed to be reduced by 22.68% and 5.19% in 3 + 1 and 2 + 1 schedules, respectively and PCV13 was considered to be cost-effective at unreduced cost (Table 5).

## 7. Budget impact analysis

Budget impact analysis indicated that Thai government should invest approximately 2755–3095 million THB for implementing national 2 + 1 PCV10 vaccination program and 2192–2463 million THB for implementing national 2 + 1 PCV13 vaccination program for the year 2017–2021. However, when considering the cost offset from cases prevented by 2 + 1 PCV10 and PCV13 vaccination program, Thai government could save approximately 724 and 1100 million THB, respectively. Implementing national 3 + 1 PCV10 and PCV13 vaccination program required more investment but when considering offset cost, Thai government could save approximately 788 million THB in PCV10 vaccination program and 1196 million THB in PCV13 vaccination program (Tables 6 and 7).

## 8. Discussion

We developed a decision tree model together with a Markov model to forecast and compare the economic impact of sustained use of PCV10 and PCV13 with no vaccination in the children vaccination program in Thailand using the most updated and comprehensive data. The analysis estimated that implementing the PCV13 program would be cost-effective, while PCV10 is not cost-effective in Thailand. However, when considering herd-effect both PCV10, and PCV13 are cost-effective. Using current vaccine prices, the estimated budget impact for implementing PCV10, and PCV13 are still high since Thai government should invest more than 2000 million THB per year for either PCV10 or PCV13. Therefore, implementing the vaccine may lead to a substantial burden on public health and costs to the health care system.

The model used is similar to other models in the literature in terms of the model structure and diseases considered, including meningitis and its sequelae, bacteremia, pneumonia, and acute otitis media. The results found in this analysis are similar to some of the earlier published cost-effectiveness studies in low-and-middle-income countries (LMIC). The evidence shows that both PCV10 and PCV13 are probably cost-effective in a comparison with PCV7 or no vaccination [16]. In South East Asian countries, the results from our study were also consistent with previous studies. In Singapore which evaluated the cost-effectiveness of PCV7, PCV10, and PCV13, it was shown that PCV13 was cost-effective compared to PCV10 and PCV7 [36]. In Malaysia and Hong Kong, PCV13 would be cost-saving when compared to a similar program with PCV10, under both payer and societal perspectives [37]. Contrary to our findings, a prior study in Thailand indicated that both PCV10 and PCV13 were not cost-effective even the inclusion of indirect vaccine effects [17]. They proposed that PCVs to be cost-effective,

**Table 4**
Sensitivity analysis (without considering herd effect).

| Sensitivity analysis | ICER | | | |
|---|---|---|---|---|
| | PCV10 | | PCV13 | |
| Schedule | 3 + 1 | 2 + 1 | 3 + 1 | 2 + 1 |
| PCV10 with POET data for PCV10 against AOM | 179,538 | 141,202 | – | – |
| 10% serotype replacement | 217,389 | 171,623 | 97,839 | 74,148 |
| Cross-protection for PCV10 | | | – | – |
| Vaccine protection (8 years) | 182,182 | 142,925 | 80,380 | 59,912 |

*Abbreviations:* Incremental Cost Effectiveness Ratio: ICER, Pneumococcal Conjugated Vaccine: PCV, Two-dose and one-booster dose schedule: 2 + 1, Three-dose and one-booster dose schedule: 3 + 1, Acute Otitis Media: AOM.

**Table 5**
Threshold analysis.

| Treatment | Actual cost per vial | Reduced cost per vial | % reduction | ICER after reduction |
|---|---|---|---|---|
| *To be cost-saving strategies* | | | | |
| Base-case (3 + 1) | | | | |
| PCV10 | 1440 | 180.43 | 87.47% | 0 |
| PCV13 | 1146 | 276.19 | 75.90% | −4 |
| Base-case (2 + 1) | | | | |
| PCV10 | 1440 | 221.18 | 84.64% | −4 |
| PCV13 | 1146 | 338.53 | 70.46% | −2 |
| *To be cost-effective strategies (WTP = 160,000 THB/QALY)* | | | | |
| Base-case (3 + 1) | | | | |
| PCV10 | 1440 | 1113.40 | 22.68% | 159,955 |
| PCV13 | 1146 | 1146.00 | 0% | 97,269 |
| Base-case (2 + 1) | | | | |
| PCV10 | 1440 | 1365.26 | 5.19% | 159,986 |
| PCV13 | 1146 | 1146.00 | 0% | 73,674 |

*Note:* Both PCV10 and PCV13 are cost-effective when herd effect is considered.
*Abbreviations:* Incremental Cost Effectiveness Ratio: ICER, Pneumococcal Conjugated Vaccine: PCV, Two-dose and one-booster dose schedule: 2 + 1, Three-dose and one-booster dose schedule: 3 + 1, Willingness-to-pay: WTP, Quality-adjusted life years: QALYs.

**Table 6**
Costs of vaccinating Thai children, without considering disease costs in millions bath (Budget impact analysis).

| Budget impact | 2017 | 2018 | 2019 | 2020 | 2021 |
|---|---|---|---|---|---|
| Number of newborn babies | 675,893 | 668,470 | 653,624 | 631,355 | 601,663 |
| Schedule 3 + 1 | | | | | |
| PCV10 | | | | | |
| Without management cost | 3893 | 3850 | 3765 | 3637 | 3465 |
| With management cost | 4127 | 4081 | 3991 | 3855 | 3674 |
| PCV13 | | | | | |
| Without management cost | 3098 | 3064 | 2996 | 2894 | 2758 |
| With management cost | 3284 | 3284 | 3176 | 3068 | 2924 |
| Schedule 2 + 1 | | | | | |
| PCV10 | | | | | |
| Without management cost | 2919 | 2888 | 2824 | 2727 | 2559 |
| With management cost | 3095 | 3061 | 2993 | 2891 | 2755 |
| PCV13 | | | | | |
| Without management cost | 2324 | 2298 | 2247 | 2170 | 2068 |
| With management cost | 2463 | 2436 | 2382 | 2300 | 2192 |

*Note:* Management cost included 5%delivery cost and 1%wastage.
*Abbreviations:* Pneumococcal Conjugated Vaccine: PCV, Two-dose and one-booster dose schedule: 2 + 1, Three-dose and one-booster dose schedule: 3 + 1.

**Table 7**
Costs of vaccinating Thai children in the Year 2017 birth cohort, with considering disease costs in millions bath (Budget impact analysis).

| Intervention | Incurred cost | Offset cost | Vaccine cost (no management cost) | Budget impact (no management cost) | Vaccine cost (with management cost) | Budget impact (with management cost) |
|---|---|---|---|---|---|---|
| No vaccination | *Ref* | *Ref* | *Ref* | 24,376 | *Ref* | *Ref* |
| Schedule 3 + 1 | | | | | | |
| PCV10 | 23,588 | 788 | 3893 | 3105 | 4127 | 3339 |
| PCV13 | 23,180 | 1196 | 3098 | 1902 | 3284 | 2088 |
| Schedule 2 + 1 | | | | | | |
| PCV10 | 23,652 | 724 | 2919 | 2195 | 3095 | 2371 |
| PCV13 | 23,277 | 1100 | 2324 | 1224 | 2463 | 1363 |

*Abbreviations:* Pneumococcal Conjugated Vaccine: PCV, Two-dose and one-booster dose schedule: 2 + 1, Three-dose and one-booster dose schedule: 3 + 1.

the vaccine price per vial would have to be reduced from US$46.2 to US$9.8 (for PCV10) or from US$61.9 to US$15.9 (for PCV13) [17].

Our model did not include the incidence of adverse events for both PCV10 and PCV13 because adverse events of the vaccines are usually non-serious and their incidence is minimal. A study from Australia [38] indicated that the adverse event following immunization (AEFI) of PCV13 was approximately 128.7 per 100,000 doses. It was a little higher than PCV7 which was the status quo of Australia. However, the most common AEFIs were fever, diarrhea, irritability, vomiting, and rash. For PCV10, a study from Finland [39] showed no AEFI increased when PCV10 was introduced into the Finnish National Vaccination Program except rash which was the most common AEFI of pneumococcal vaccine. Comparing between PCV10 and PCV13, a previous RCT [40] indicated

no significant difference of serious adverse events between the vaccines including any morbidity, hospitalization, and acute lower respiratory tract infection. As the adverse events are not serious, we decided to not include them into our model. Our approach is similar to previous cost-effectiveness studies which did not include adverse events in the models [16,41].

There are several strengths that should be highlighted in this study. First, inputs used in the model were considered as the most updated data at the time of the analysis in which incidence, mortality, serotype coverage, and costs were country-specific and obtained from high-quality sources, including national-level data, systematic reviews and meta-analyses. We used incidence, utility, and cost from local studies. We used the most updated vaccine efficacy, coverage to reflect vaccine effectiveness that would be applicable to Thailand. We believed that we generated more realistic findings because we obtained data from real-world evidence. Second, with the use of local inputs in the current analysis, along with comprehensive sensitivity analyses, threshold analysis, and estimated budget impact analysis, it enables health authorities to be better informed in the decision-making process.

There are some important considerations in the interpretation of our results. First, the projections used in this work are simple and illustrative. They are, however, not based on a dynamic transmission model to predict the contribution of the different vaccine-serotypes in the future, the static model also is unable to estimate the herd effect of vaccination. However, we indirectly adjust the herd effect from literature and present it in our sensitivity analysis. The results of sensitivity analysis showed higher cost-saving of both PCV10 and PCV13. Second, we assumed that pneumococcal infection could occur only once for each individual which might not reflect the real-life situation. However, most static models used this approach for the estimation of cost-effectiveness analysis [16]. Third, we did not incorporate serotype replacement in our study, which could lead to the overestimation of the benefit of the vaccines. However, we used evidence of the indirect effect of PCVs from various sources where PCVs has been implemented a certain period of time. The indirect effect observed could be a combination of herd effect and serotype replacement. Last, we did not incorporate adverse events of the vaccine. It might overestimate the cost-effectiveness of our findings.

In terms of vaccine introduction, the Strategic Advisory Group of Experts (SAGE) that advises WHO on vaccines recommends the use of pneumococcal conjugate vaccine worldwide, and particularly in countries with high child mortality rates (>50 deaths/1000 births). As of July 2017, there are 141 countries (72% of all countries in the world) that have introduced PCV [42]. However, a comprehensive review found a significant difference in the uptake of PCV in lower-middle-income countries (LMICs) (71%) and upper-middle-income countries (UMICs) (48%). These are largely due to an unsuccessful process of ‘‘graduation” of MICs from GAVI assistance, a lack of country-specific data on disease burden, a lack of local expertise in economic evaluation, and the price of PCV were identified as the leading causes of the slow uptake of PCVs in MICs [8,43]. Even in LMICs, the major obstacles of PCV implementation in some countries are also related to vaccine price which influences the national budget impact.[16] Saokaew et al. [16] found that only 1 study of PCV10/PCV13 in Thailand, out of 22 studies from LMICs, is not cost-effective. The key influential parameter is the vaccine price which is largely higher than average price of other studies around 4–6 folds. This would result in a substantial budget impact. Therefore, to implement PCV10 or PCV13 into NIP, vaccine price negotiation to meet the affordable budget threshold (around 200 million THB per year [44]) is needed. However, based on the number of newborn babies shown in Table 6, it is unlikely to achieve such affordable budget threshold unless vaccine price is less than 90 THB (US$ 3) per vial (current price >1100 THB/vial).

Even though, our cost-effectiveness analysis indicates that PCV13 is a cost-effective alternative, there remains a challenge to adopt PCV program in Thailand given the high budget impact incurred. Thai government needs to invest more than 2000 million THB per year for the vaccine. Based on previous BIA studies, interventions which are listed for full reimbursement in Thailand usually had budget impacts of less than 150 million THB per year [45–49]. Therefore, Thai government might be hesitant to invest the amount of money for only one vaccination program. However, our budget impact analysis did not incorporate the percentages of vaccine uptake, vaccine coverage. Thus, the budget impact might be less than what we have found in our analysis. Thai government should consider this factor once PCV vaccination program is in a consideration.

In conclusion, the use of PCV10 or PCV13 in the NIP for Thai children would be a cost-saving intervention when considered herd effect, but is unlikely to produce budget impact affordable to government. Our analyses may help inform policy makers of the potential benefits of vaccinating children in Thailand, thereby reducing cases of preventable disease.

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.06.015.

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