**Cost-Utility Analysis of 10- and 13-Valent Pneumococcal Conjugate Vaccines: Protection at What Price in the Thai Context?**

Wantanee Kulpeng, MSc[a,b], E-mail: wantanee.k@hitap.net, wantaney@hotmail.com

Pattara Leelahavarong, MSc[a], E-mail: pattara.l@hitap.net

Waranya Rattanavipapong, BPharm[a], E-mail: waranya.r@hitap.net

Vorasith Sornsrivichai, MD, PhD[b], E-mail: vorasith@msn.com

Henry C. Baggett, MD, MPH[c], E-mail: Kipb@th.cdc.gov

Aronrag Meeyai, PhD[a,d], E-mail: phamy@mahidol.ac.th, aronrag.c@hitap.net

Warunee Punpanich, MD, PhD[e], E-mail: waruneep@gmail.com

Yot Teerawattananon, MD, PhD[a], E-mail: yot.t@hitap.net

[a]Health Intervention and Technology Assessment Program (HITAP), 6 th Floor, 6 th 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, Khohong, 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

**Corresponding author**

Wantanee Kulpeng

Health Intervention and Technology Assessment Program (HITAP),

6th Floor, 6th Building, Department of Health, Ministry of Public Health,

Tiwanon Road, Muang, Nonthaburi, 11000 Thailand

E-mail: wantanee.k@hitap.net, wantaney@hotmail.com

Tel: +662-590-4374-5, Fax: +662-590-4369

**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 |

## 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.

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.

## 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].

### 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.

### Model Input Parameters

*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].

*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:

$$VE_{2+1} = VE_{3+1} \mathbf{x} (1\text{-}0.08)$$

*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:

% IPD fall in Thailand = % IPD fall in the United States **x** Serotype coverage in Thailand/Serotype coverage in the United States

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 base on the following formula:

% Hospitalized pneumonia fall in Thailand = Proportion of pneumococcal pneumonia **x** % IPD fall in Thailand

*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 to 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].

**Uncertainty Analyses**

*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 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$ 3,226) 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.

*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 1,000 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.

**RESULTS**

Compared to 'no vaccination', the 3+1 dose schedule of PCV10 and PCV13 would prevent an estimated 7,926 and 9,747 episodes of pneumococcal disease in the vaccinated population, respectively (Fig. 2). In addition, 4,510 and 6,211 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 3D).

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.

**DISSCUSSION**

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% to 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 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.

*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, applying 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 from the United States showed a significant decline in IPD incidence among unvaccinated populations aged 20 years and above only. This ignored herd protection among young children (2-4 years) and teenagers, which could not be assessed in the United States, because children in this age group (2-4 years) were vaccinated as part of catch-up vaccination efforts. Second, IPD incidence rates used in this model were likely underestimates, because the available studies were conducted in public health facilities (i.e. government hospitals and health centers); thus, patients without access to public hospitals or at private hospitals were not included. Additionally, it has been shown that antibiotic use before blood culture collection in Thailand leads to underestimation of IPD incidence in hospital-based studies [21]. Perhaps more importantly, IPD rates cited for this analysis did not include outpatients because most of them were suspected and not confirmed cases. Including outpatient IPD cases in the model inputs would have resulted in lower ICERs. Lastly, the ceiling threshold

used in this analysis is based on the preference of decision maker in Thailand. Decision makers in different settings may have their own preference regarding health investment, we encourage readers to compare the results to any threshold they consider it appropriate.

*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.

**ACKNOWLEDGEMENTS**

We would like to thank the Thai Health Promotion Foundation and the Thailand Research Fund under the Senior Research Scholar Program on the Development of Health Technology Assessment Capacity in Thailand (RTA5580010) for funding support through the Health Intervention and Technology Assessment Program (HITAP). We are grateful for the support from Health Utilities Inc. We wish to acknowledge the valuable information provided by Pasakorn Akarasewi from the Bureau of Epidemiology, Department of Disease Control, Julia Rhodes and Susan Maloney from the International Emerging Infections Program (IEIP). Finally, we would like to thank Virasakdi Chongsuvivatwong, Anchalee Aramtiantamrong, Supalert Netsuwan, Manit Kongpan and Anek Mungaomklang, for helpful comments.

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## FIGURES

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.

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

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

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 1,440 for PCV10; THB 1,930 for PCV13

Fig. 1

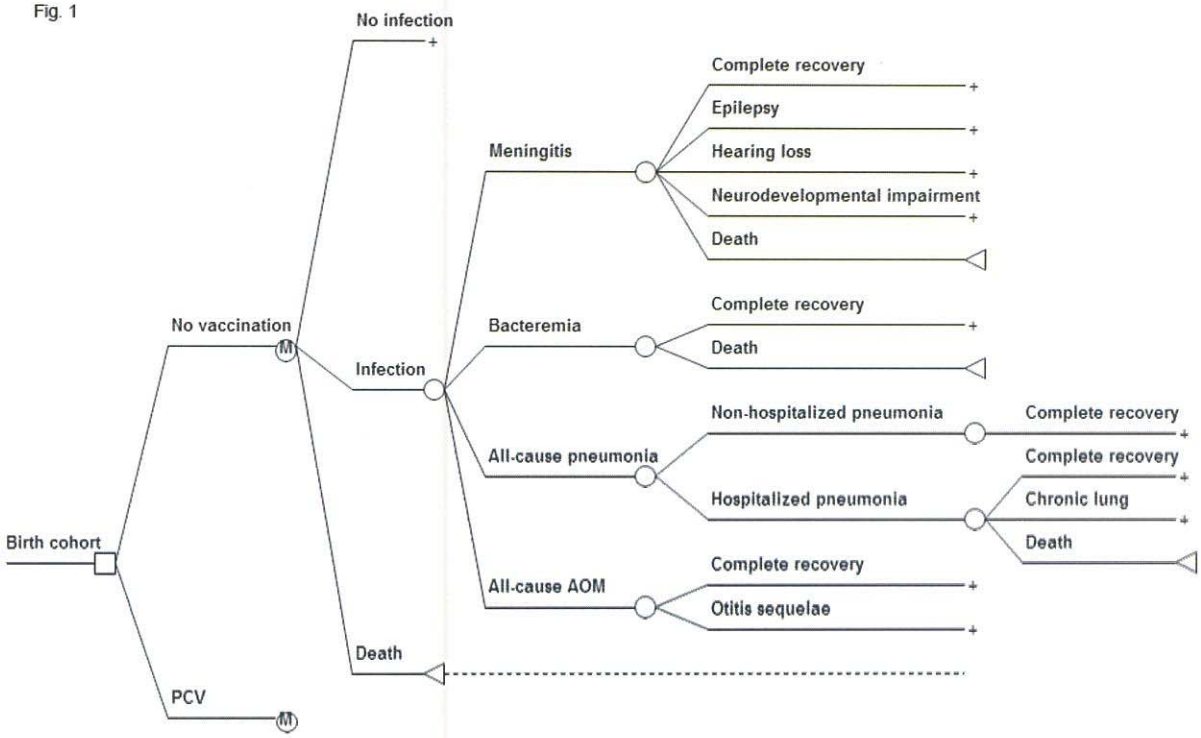
No infection
Complete recovery
Epilepsy
Hearing loss
Neurodevelopmental impairment
Death
Meningitis
No vaccination
Bacteremia
Complete recovery
Death
Infection
Non-hospitalized pneumonia
Complete recovery
All-cause pneumonia
Complete recovery
Hospitalized pneumonia
Chronic lung
Death
Birth cohort
Complete recovery
All-cause AOM
Otitis sequelae
Death
PCV

Fig. 2

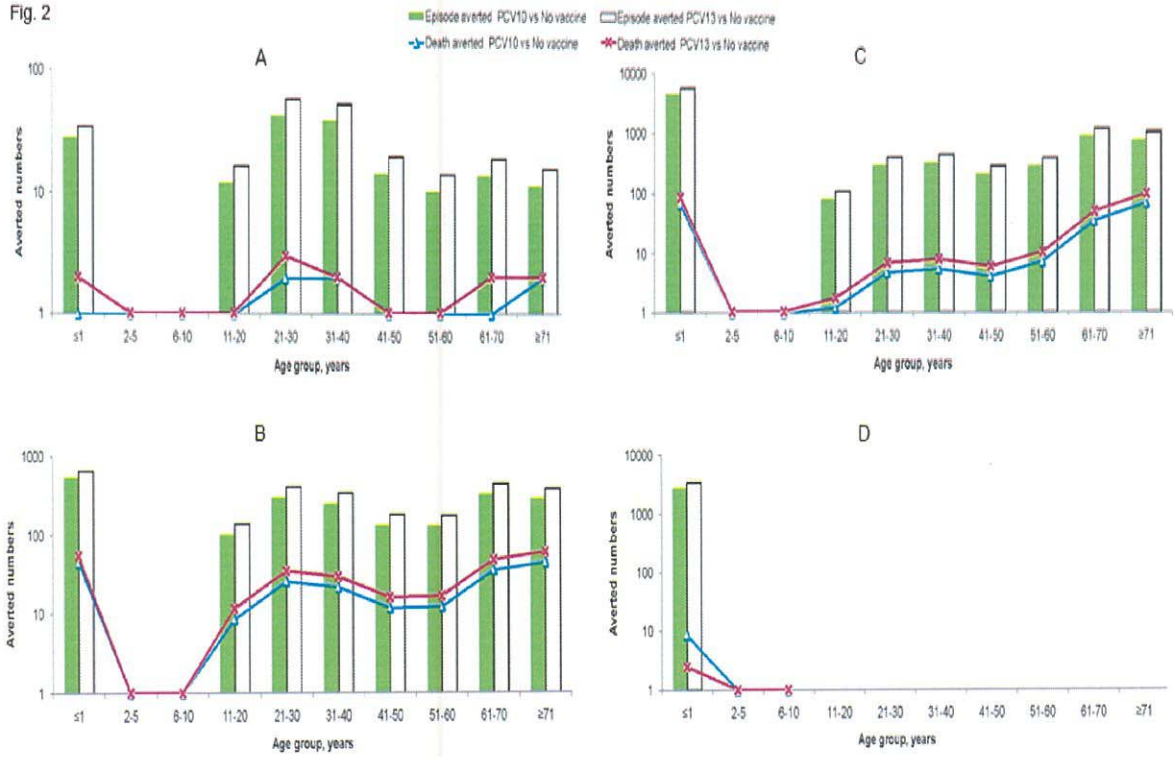
Episode averted PCV10 vs No vaccine
Episode averted PCV13 vs No vaccine
Death averted PCV10 vs No vaccine
Death averted PCV13 vs No vaccine
A
B
C
D
Averted numbers
Age group, years
≤1
2-5
6-10
11-20
21-30
31-40
41-50
51-60
61-70
≥71

Fig. 3

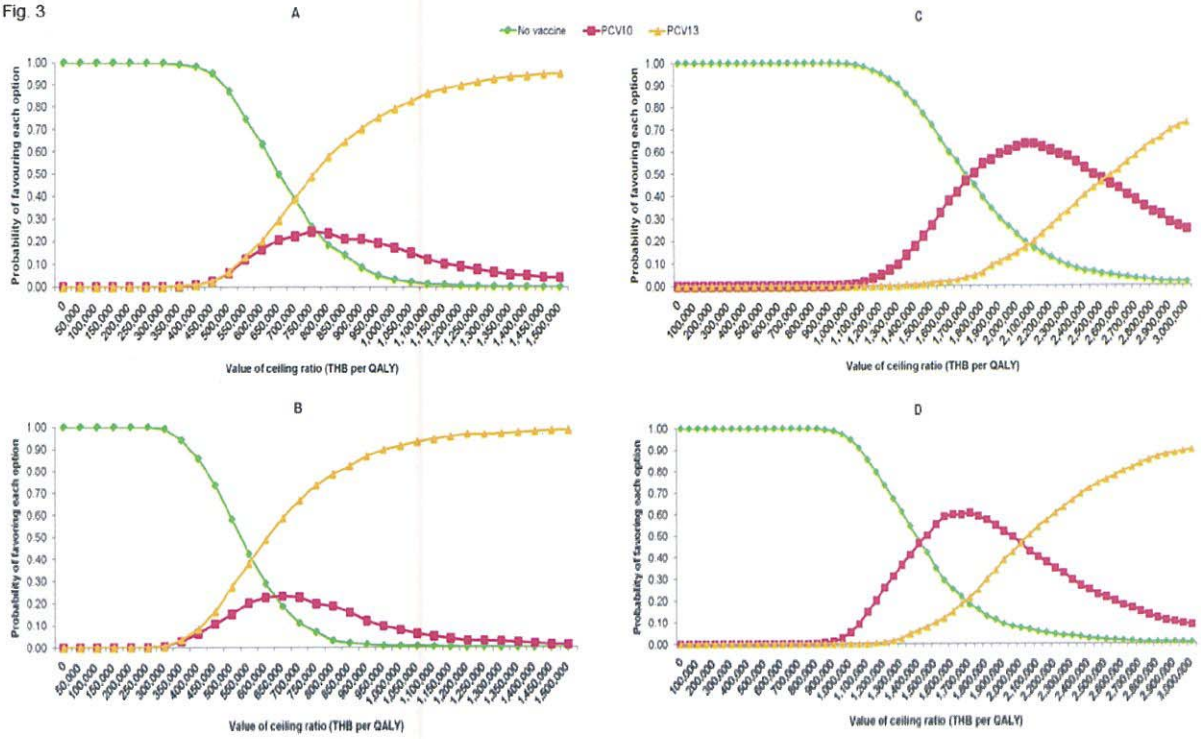
A
B
C
D
No vaccine
PCV10
PCV13
Probability of favouring each option
Value of ceiling ratio (THB per QALY)

Fig. 4

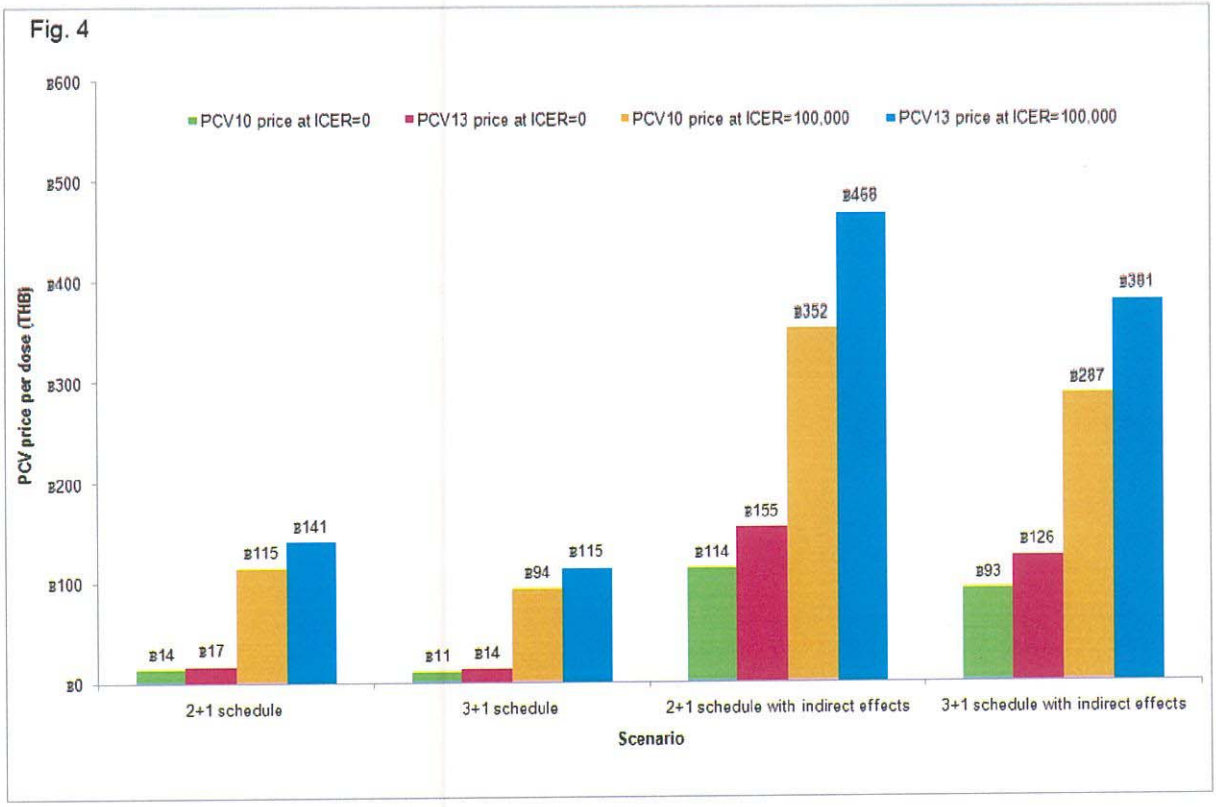
PCV10 price at ICER=0
PCV13 price at ICER=0
PCV10 price at ICER=100,000
PCV13 price at ICER=100,000
PCV price per dose (THB)
฿600
฿500
฿400
฿300
฿200
฿100
฿0
฿14
฿17
฿115
฿141
฿11
฿14
฿94
฿115
฿114
฿155
฿352
฿468
฿93
฿126
฿287
฿381
2+1 schedule
3+1 schedule
2+1 schedule with indirect effects
3+1 schedule with indirect effects
Scenario

**Table 1. Input parameters used in the model**

| Parameter description | Distribution | Mean | SE | References |
|---|---|---|---|---|
| **Epidemiological parameters** | | | | |
| Proportion of bacterial meningitis due to *S. pneumoniae* | Beta | 0.14 | 0.03 | 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 to 1.14[b] | | |
| Hearing loss | | 1.00 to 1.01[b] | | |
| Neurodevelopmental impairment | | 5.16 to 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 | Beta | 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] |

| Parameter description | Distribution | Mean | SE | References |
|---|---|---|---|---|
| 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 | | | | [35] |
| PCV7 serotypes coverage in aged 10 to 39 | Not varied | 71.30% | | |
| 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 | | | | [4] |
| % fall among who aged 20 to 39 | Beta | 40.00% | 4.59% | |
| % 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 | 1,440 | | GlaxoSmithKline (Thailand) |
| PCV13 cost per dose | Not varied | 1,930 | | Pfizer (Thailand) Limited |
| Delivery cost per dose | Not varied | 5% of vaccine price | | [37] |
| Direct medical costs | | | | |
| Cost per episode | | | | |
| Meningitis aged ≤4 | 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 ≤4 | Gamma | 14,120 | 4,587 | [24] |
| Bacteremia aged 15 to 59 | Normal | 22,120 | 743 | [24] |
| Bacteremia aged ≥60 | Gamma | 22,440 | 5,372 | [24] |
| Hospitalized pneumonia aged ≤4 | Normal | 9,099 | 46 | [24] |
| Hospitalized pneumonia aged 15 to 59 | Normal | 23,952 | 122 | [24] |
| Hospitalized pneumonia aged ≥60 | Normal | 31,948 | 278 | [24] |

| Parameter description | Distribution | Mean | SE | References |
|---|---|---|---|---|
| Non-hospitalized pneumonia aged ≤4 | 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 ≤4 | 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 ≤4 | Gamma | 3,962 | 475 | [36] |
| Epilepsy aged 15 to 59 | Normal | 1,600 | 21 | [36] |
| Epilepsy aged ≥60 | Gamma | 1,672 | 85 | [36] |
| Hearing loss aged ≤4 | Gamma | 896 | 385 | [36] |
| Hearing loss aged 15 to 59 | Gamma | 838 | 48 | [36] |
| Hearing loss aged ≥60 | Gamma | 1,312 | 123 | [36] |
| Neurodevelopmental impairment aged ≤4 | Gamma | 3,582 | 2,333 | [36] |
| Neurodevelopmental impairment aged 15 to 59 | Gamma | 936 | 72 | [36] |
| Neurodevelopmental impairment aged ≥60 | Gamma | 5,811 | 2,892 | [36] |
| Chronic lung aged ≤4 | Gamma | 1,404 | 1,404 | [36] |
| Chronic lung aged 15 to 59 | Normal | 3,306 | 62 | [36] |
| Chronic lung aged ≥60 | Normal | 3,636 | 31 | [36] |
| Direct non-medical costs[c] | | | | Primary data collection |
| Meningitis (per episode) | | 15,485 | | |
| Bacteremia (per episode) | | 9,987 | | |
| Hospitalized pneumonia (per episode) | | 5,674 | | |
| Non-hospitalized pneumonia (per episode) | | 527 | | |
| AOM (per episode) | | 527 | | |
| Epilepsy (per year) | | 4,489 | | |
| Hearing loss (per year) | | 868 | | |

| Parameter description | Distribution | Mean | SE | References |
|---|---|---|---|---|
| Neurodevelopmental impairment (per year) | | 17,548 | | |
| Chronic lung (per year) | | 7,133 | | |
| 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.

**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) | 4,178 | 5,593 |
| 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) | 5,658 | 7,576 |
| 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) | 4,492 | 6,026 |
| 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) | 6,001 | 8,048 |
| 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

**Supplementary Table 1. Annual incidence per 100,000 population by syndrome used for model inputs**

| Age | Pneumococcal disease | | Non-specific pathogen | | |
|---|---|---|---|---|---|
| | Meningitis[a] | Bacteremia [21] | Hospitalized pneumonia [22] | Non-hospitalized pneumonia [22] | AOM [25] |
| 0-4 | 0.88 | 11.95 | 934.11 | 1000.67 | 601.08 |
| 5-9 | 0.26 | 1.38 | 121.34 | 101.20 | 1139.97 |
| 10-14 | 0.45 | 1.38 | 39.66 | 32.56 | 1139.97 |
| 15-19 | 0.33 | 1.38 | 22.81 | 16.73 | 0 |
| 20-24 | 0.33 | 1.87 | 22.81 | 16.73 | 0 |
| 25-34 | 0.40 | 1.87 | 31.14 | 21.51 | 0 |
| 35-44 | 0.44 | 1.87 | 41.39 | 28.35 | 0 |
| 45-49 | 0.38 | 1.87 | 68.57 | 50.40 | 0 |
| 50-54 | 0.38 | 4.77 | 68.57 | 50.40 | 0 |
| 55-64 | 0.42 | 4.77 | 137.26 | 114.55 | 0 |
| ≥65 | 0.60 | 13.89 | 373.78 | 425.45 | 0 |

[a]Pneumococcal meningitis = hospitalized meningitis [22] x proportion of bacterial meningitis due to *S.pneumoniae* [23, 24]. All hospitalized meningitis cases were assumed to be bacterial.

**Supplementary Table 2. Expected efficacy of pneumococcal conjugate vaccine (3+1 schedule) among vaccinated groups and decreased disease incidence among unvaccinated groups through indirect vaccine effects**

| | PCV10 | | | PCV13 | | |
|---|---|---|---|---|---|---|
| | **IPD (vaccine serotype)** | **Pneumonia** | **AOM** | **IPD (vaccine serotype)** | **Pneumonia** | **AOM** |
| Vaccinated group | 89.00% | 6.27% | 6.27% | 89.00% | 7.70% | 7.70% |
| Unvaccinated groups | | | | | | |
| Age 2-4 | 0% | 0% | 0% | 0% | 0% | 0% |
| Age 5-19 | 0% | 0% | 0% | 0% | 0% | 0% |
| Age 20-39 | 26.73% | 1.59% | 0% | 36.81% | 2.19% | 0% |
| Age 40-64 | 9.36% | 0.56% | 0% | 12.88% | 0.77% | 0% |
| Age ≥65 | 18.19% | 1.08% | 0% | 25.04% | 1.49% | 0% |

Vaccine benefits from a 2+1 schedule were set to 92% of benefits produced by a 3+1 schedule