Research Proposal

The Cost-Utility Analysis of 7-, 10- and 13-valent Pneumococcal Conjugate Vaccine in Thailand

Contents

Contents (Continued)

List of Tables

List of Figures

1. Summary

This study aims to determine the cost-utility of the 7-, 10- and 13-valent pneumococcal conjugate vaccine (PCV7, PCV10 and PCV13) for children aged less than 5 years using a societal perspective. A Markov model will be used to estimate the relevant costs and health outcomes for a lifetime horizon. Costs will be collected and calculated in 2009 value. The health outcome will be the quality adjusted life years (QALYs). The results will be expressed as the incremental cost-effectiveness ratio (ICER) in Thai Baht per QALY gained, with future costs and outcomes being discounted at 3% per annum, as recommended by the Guidelines for Economic Evaluation in Thailand. One-way and probabilistic sensitivity analyzes using a Monte Carlo simulation will be carried out in R statistical software to assess uncertainty in the results, and presented as a tornado diagram and cost-effectiveness acceptability curves, respectively.

The results from this study will be used for informing policy decisions regarding the adoption of pneumococcal conjugate vaccine (PCV) in the Expanded Program of Immunization (EPI) for the prevention of pneumococcal disease.

2. Background

Streptococcus pneumoniae (*S. pneumoniae*) are etiology of invasive pneumococcal disease (IPD), pneumonia and otitis media in children worldwide, which lead to morbidity and mortality among children, especially at young ages. The World Health Organization (WHO) estimated that 1.6 million people die of pneumococcal disease annually. This estimate includes the deaths of children younger than 5 years, most of whom live in developing countries [1]. In Thailand, the incidence rate of IPD among this age group in two rural provinces in years 2005-2007 has been reported at 10.6 and 28.9 cases per 100,000 persons per year [2].

Pneumococcal conjugate vaccine (PCV), a vaccine developed to provide immunity from *S. pneumoniae* and made from inactivated bacteria, has been approved for infants and toddlers, and is considered safe and effective. PCV has been tested in trials in the US and Europe, the results indicating that the vaccine is very safe and highly effective in preventing IDP. It has also been shown to decrease the incidence of pneumonia and otitis media episodes [3-5].

PCV is designed to cover the serotypes most commonly associated with severe pneumococcal disease. Nevertheless, it will not protect against other groups of pneumococcal bacteria. Presently, the vaccination is marketed internationally. PCV has been widely used in several countries, and is recommended as a routine vaccination for infants and young children in many countries worldwide. Currently, PCV7 has been available in the Thai market.

3. Rationale

In Thailand, PCV is not included in the Expanded Program of Immunization (EPI). It is considered safe but its worthiness is unknown. Hence, economic evaluation (EE) is necessary. The cost-utility analysis (CUA) is the method of choices for informing policy decisions because it accounts both the quantity and quality of health outcomes.

Results from this study can provide more insightful information for policy decision making whether to adopt PCV in the EPI for the prevention of pneumococcal disease.

4. Objectives

- To determine the cost-utility of vaccination with PCV7, PCV10 and PCV13 compared with no vaccination in Thailand.
- To estimate the government budget in including the PCV in the EPI program, if the PCV vaccination program is found to be cost-effective.

5. Analytical Framework

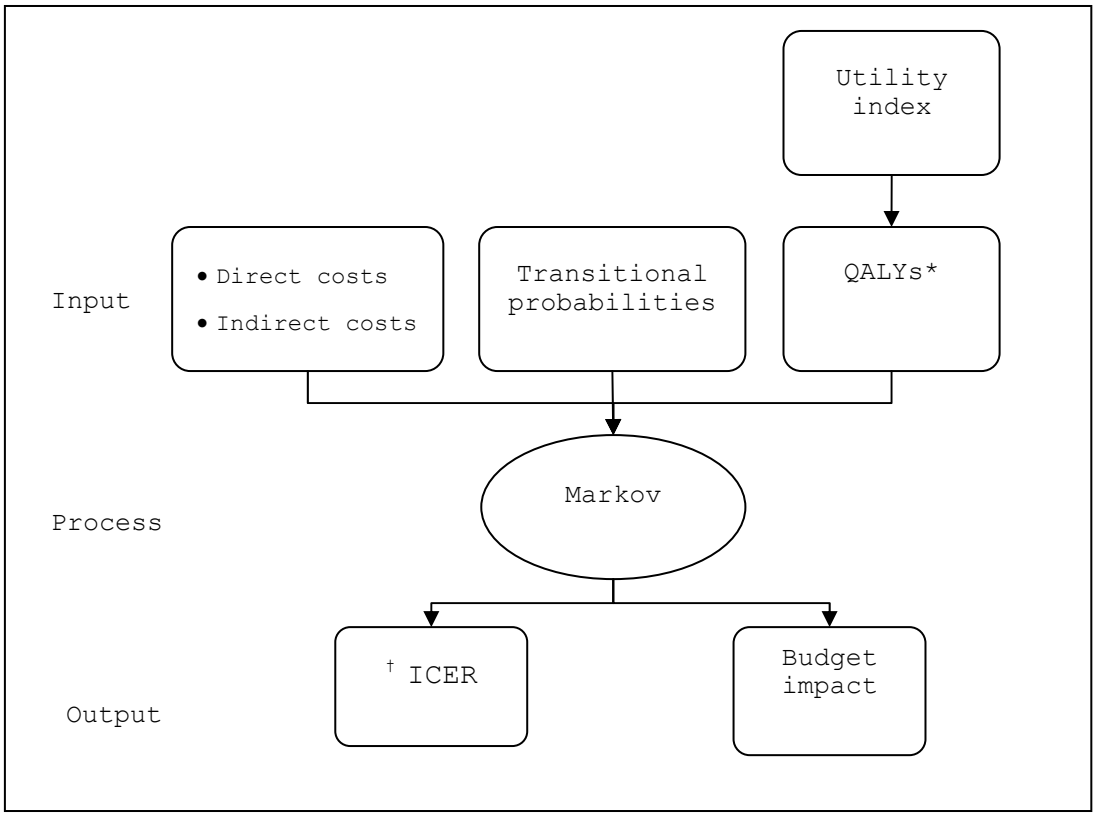

Figure 1 : The analytical framework of the cost-utility and budget impact analysis

*QALYs: quality adjusted life years

† ICER: Incremental cost-effectiveness ratio

6. Literature Review

6.1 Pneumococcal Infections

6.1.1 Clinical Manifestations

S. pneumoniae are the common bacterial cause of invasive infections in children and a cause of meningitis, bacteremia, pneumonia, and otitis media. More detailed information about these is shown below:

- Meningitis is an inflammation of the membranes that cover the brain and spinal cord. The severity of illness and the treatment for meningitis differ depending on the cause, particularly pneumococcal meningitis, which is a very serious problem and requires emergency treatment [6]. Meningitis can progress rapidly, and can cause severe brain damage which can lead to learning disabilities, hearing loss, or death.

- Bacteremia is the presence of bacteria in the bloodstream which can spread to other parts of body, producing abscesses, peritonitis, endocarditis, or meningitis. Bacteremia may lead to sepsis or shock, causing a systemic illness with high fever, blood coagulation, and eventually organ failure. Most episodes of occult bacteremia spontaneously resolve, and serious sequelae are increasingly uncommon [7].

- Pneumonia, an infection of the lung, is the one of the leading cause of death in young children. Pneumonia caused by *S. pneumoniae* remains the most common cause of all bacterial pneumonias. Empyema and lung abscess may occur as direct complications of bacterial pneumonia. Bronchiectasis may be the sequelae of bacterial pneumonia [8].

- Otitis media is an ear infection of the middle ear which can consequently reduce a child's hearing ability. Children who get ear infection are likely to have speech and language impairments. The rate of recurrence of otitis media is high. Almost 50% of children will have suffered from grater than or equal to 3 episodes of acute otitis media [9].

6.1.2 *Etiology*

S. pneumoniae organisms are lancet-shaped, gram-positive catalase-negative diplococci. Although, there are about 90 different serotypes, and 42 separate serogroups of *S. pneumoniae*, only about 10 of which account for invasive infections [10].

6.1.3 Epidemiology

S. pneumoniae are ubiquitous, with many people having transient colonization of their upper respiratory tract. Transmission is from person to person by respiratory droplet contact. Pneumococcal infections are most prevalent during winter months. All age groups have the risk of being infected, especially in infants, young children, and elderly. In addition, the incidence and severity of infections are increased in people with congenital or immunity deficiency, HIV infection, absent or deficient splenic function (e.g. sickle cell disease, congenital or surgical asplenia), or abnormal innate immune response [11] .

- Global situation

Pneumococcal disease has been one of the major causes of morbidity and mortality among children in developed countries, and considered the leading cause of mortality in developing countries, especially in young children. WHO estimated that 1.6 million people die of

pneumococcal disease, this estimate includes, most of whom live in developing countries [1]. Similarly, a study on the burden of disease caused by *S. pneumonia*e in children younger than 5 years [12], found that the highest mortality rates were in sub-Saharan Africa and south Asia. Figure 2 shows the pneumococcal mortality rate in children aged less than 5 years (HIV negative only) by country.

Additionally, *S. pneumoniae* is the most common cause of pneumonia which is the leading cause of death in young children. The United Nation (UN) reported that pneumonia caused death in Asian children at a rate of 98 per hour, of which 49 (50%) were attributable to *S. pneumonia*e.

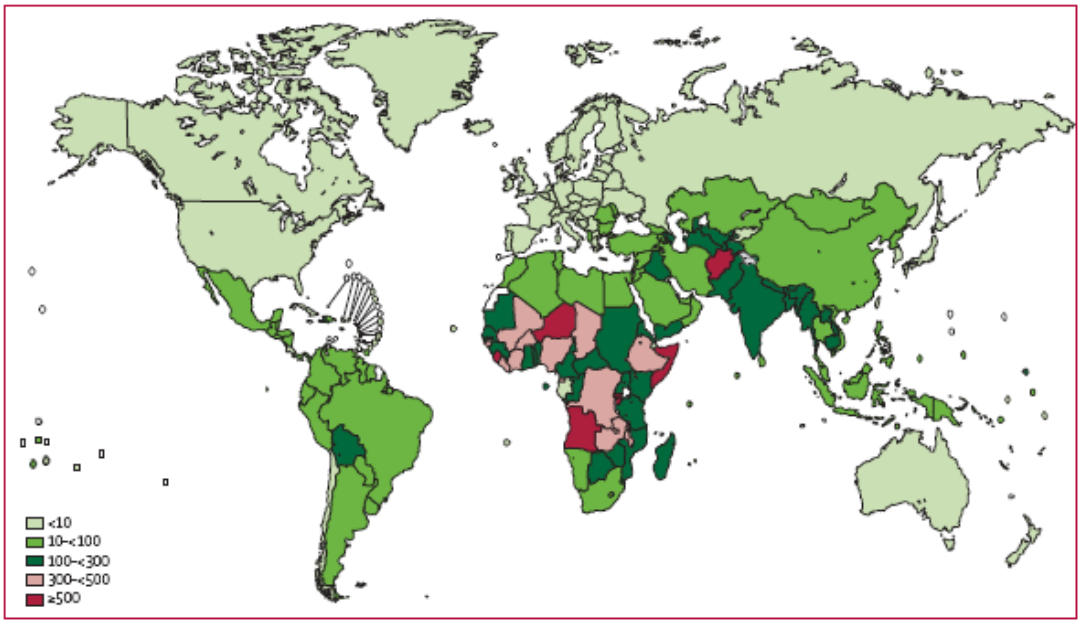

Figure 2 : Pneumococcal mortality rate (per 100,000) in children aged 1–59 months [12].

- Situation in Thailand

A retrospective study of childhood meningitis [13] among children admitted to Queen Sirikit National Institute of Child Health during

1980-1990 found that *S.pneumoniae* was the second most common causative organism (22%).

A prospective study of invasive *S.pneumoniae* infection in children at Chiang Mai University Hospital during 1997-1999 [14] showed 51 episodes of invasive *S.pneumoniae* in 50 patients; including pneumonia (25), bacteremia (17), meningitis (6), soft issue infection/sepsis (2), and endrocaditis (1). A HIV-infected girl had 2 episodes of pneumococcal pneumonia.

A retrospective study of children aged less than 5 years admitted to Bangkok Metropolitan Administration Medical College and Vajira Hospital during 2002-2005 showed that among 664 children diagnosed with pneumonia, 67 of them (9.1%) had recurrent pneumonia. (Udomsak P, unpublished 2005)

Results from a population-based survey during 2005-2007 [2] found that the incidence rates of hospital admissions of children aged less than 5 years with pneumococcal bacteremia in Sakeaw and Nakorn Panom provinces were 10.6 and 28.9 cases per 100,000 persons per year, respectively [2].

The Annual Epidemiological Surveillance Report published by the Bureau of Epidemiology, Thai Ministry of Public Health, revealed that in 2008, the incidence rate of pneumonia due to all causes among children less than 5 years of age was 1,640 cases per 100,000 persons [15].

Previous studies in Thai people were mostly conducted in hospitals, and might have underestimated the incidence of the disease among young Thai children. Information on epidemiological incidence and burden of pneumococcal disease in Thailand is limited.

6.1.4 Serotype Distribution of S. pneumoniae in Thailand

Three studies have been conducted on *S. pneumoniae* in young Thai children. Phongsamart W *et al.* (2007), examined serotype coverage of PCV among the isolates causing IPD in children aged less than 5 years during 2000-2005. The 4 most common serotypes isolated were 6B, 23F, 14 and 19F, in descending order. Of all the isolated serotypes, 74%, 77%, 77% and 89% of the serotypes could be covered by PCV7, PCV9, PCV11 and PCV13, respectively. (Figure 3) The coverage of PCV13 was significantly higher than that of PCV7 ($P<0.001$). It was found that also the majority of the bacteria were penicillin-resistant strains [16].

A similar study by Levine S *et al.* (2006), showed that 6B, 23F and 19F were the most common serotypes isolated from patients with respiratory illness in rural areas. Among serotypes found in young children, 55% of serotypes were covered by PCV7 and 68% were non-susceptible to penicillin [17].

Another study by Baggett HC *et al.* (2009), found that the 4 most common serotypes isolated from rural children aged less than 5 years with pneumococcal bacteremia were 14, 6B, 19F, and 23F, in descending order. Seventy nine percent, 84% and 95% of serotypes were covered by PCV7, PCV10 and PCV13, respectively, and 41% were non-susceptible to penicillin [2]. (Figure 4)

In conclusion, the most common serotypes isolated in previous studies were 6B, 23F, 14 and 19F. The overall coverage of PCV7, PCV10 and PCV13 for isolated serotypes of pneumococcal bacteria was between 55% to 79%, 77% to 84% and 89 to 95%, respectively, and 41% to 70% were non-susceptible to penicillin.

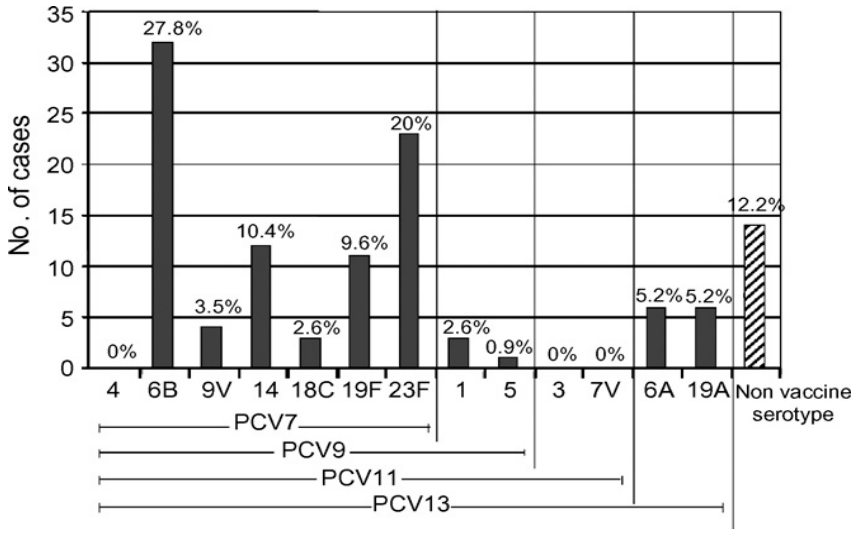

Figure 2 : Serotype distribution of pneumococcal isolates causing invasive infection in children < 5 years. (N=115) [16]

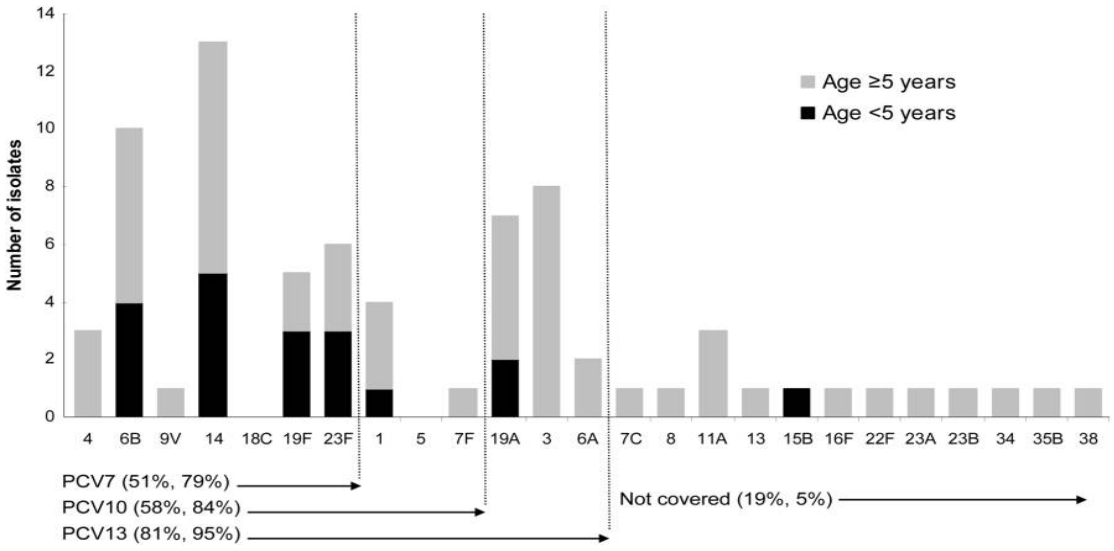

Figure 3 : Serotype distribution of pneumococcal isolates, where the percentage of vaccine serotypes among all invasive isolate and among children<5 years are shown in parentheses. (N=74) [2]

6.1.5 Burden of Disease

Pneumococcal disease is a major public health problem. IPD is a major cause of mortality, and remains an important cause of serious illness and death in children worldwide. Non-IPD causes a high burden and cost to society due to the high incidence of diseases such as pneumonia [10, 18]. Additionally, *S. pneumoniae* has become resistant against many antibiotics [10, 14, 19]. The treatment of pneumococcal disease in these cases is complicated and costly.

6.2 Pneumococcal Conjugate Vaccine

6.2.1 Current Pneumococcal Conjugate Vaccine

PCV, a vaccine against *S. pneumoniae*, is made from inactivated bacteria. The first PCV was licensed in 2000. It includes purified capsular polysaccharide of 7 types of bacteria, and is commonly known as a 7-valent pneumococcal conjugate vaccine (PCV7) or Prevnar, which is its trade name. PCV7 is designed to cover the 7 serotypes most commonly associated with severe pneumococcal disease, consisting of 4, 6B, 14, 18C, 19F and 23F serotypes. It is recommended for infants and young children aged from 2 months to 5 years. Those who are vaccinated will be protected when they are at risk of serious disease. PCV7 is widely used in several countries. Currently, 9-valent (PCV9), 10-valent (PCV10), 11-valent (PCV11), and 13-valent (PCV13) are designed to cover 9, 10, 11, and 13 serotypes, respectively. See table 1. Among these, PCV9 and PCV11 are not expected to enter the market [20, 21].

Table 1 : Serotype composition of pneumococcal conjugate vaccine

Manufacturer	Serotype composition												
	4	6B	9V	14	18C	19F	23F	1	5	7F	3	6A	19A
Wyeth	PCV7												
	PCV9*												
GSK	PCV10												
	PCV11*												
Wyeth	PCV13												
	4	6B	9V	14	18C	19F	23F	1	5	7F	3	6A	19A

* Not expected to reach the market.

In the USA, PCV7 has been recommended for routine childhood immunization since 2000 for all children aged 2 to 23 months and for at-risk children aged 24 to 59 months. The UK government introduced PCV7 in year 2006. Additionally, PCV7 is recommended for routine national childhood immunization in at least 40 countries worldwide, including Canada, Mexico, Peru, Germany, Greece, Australia, South Africa, Kuwait, UAE, Israel, Hong Kong and Macau.

In 2009, PCV10 was approved by the European Medicines Agency (EMEA) for use in Europe. In the US, PCV13 was licensed by the Food and Drug Administration (FDA) on February 4, 2010 [22].

Currently, PCV7 is available in the Thai market. PCV10 will be launched later in the year 2010. However, PCV7 is not included in the EPI. The cost of PCV7 in Thailand is approximately 3,100 Baht per dose.

6.2.2 Vaccine Dosage Schedules

The routine schedule for PCV is 3- or 4-dose, however most countries have implemented a 2-dose or 3-dose schedule with an additional dose

given between the ages of 11 and 18 months. In the US, the first country to introduce PCV7 into the childhood immunization schedule, doses are given at 2, 4, 6 and 12-15 months of age. The UK subsequently introduced a 3-dose schedule in year 2007, which is given at ages 2, 4 and 13 months. For developing countries in Africa and Asia, WHO recommends scheduled doses at 6, 10 and 14 weeks of age [20].

6.2.3 Vaccine Impact and Safety

- Direct effect of vaccination

PCV has been tested in several trials in the US, Europe, Africa and Asia, with results indicating that the vaccine is very safe and is highly effective in prevention of IDP due to vaccine serotype (72% to 94%), It has also been shown the significant reduction of incidence of pneumonia and otitis media. (See table 2)

Recently, PCV13 has been tested in randomized controlled trials (RCTs) which were conducted in UK, Poland and France, involving more than 7,000 infants and young children. These studies indicate that PCV13 is as effective as PCV7 and also effective in prevention of IPD due to six additional serotypes [23].

However, PCV will not protect against other groups of pneumococcal bacteria. The side effects of PCV are mild and include: redness, irritability, drowsiness, decreased appetite and slight fever.

- Indirect effect of vaccination (herd immunity)

Giving vaccine to all children may lead to a decline in pneumococcal disease among those unvaccinated e.g. older children, adults and the elderly. A study in USA by Whitney CG *et al.* (2003), showed that 1 year after the introduction of PCV7 in infants in the US in 2000, there were significant reductions in the incidence of IPD, both in the

vaccinated age groups and unvaccinated adults. The reductions in IPD incidence in unvaccinated age groups were: 32% (95%CI: 23 to 39%) among those aged 20 - 39 years, 8% (95%CI: 1 to 15%) among those aged 40 - 64 years, and 18% (95%CI: 11 to 24%) among those aged 65years and above [24].

Table 2 : PCV efficacy trials

Age	Setting	Type of vaccine	Type of infection	Vaccine efficacy(95%CI)	Reference
< 2 yrs	USA	PCV7	IPD	93.9%(76.6 to 98.5)*	Black S *et al.*(2000)[3]
American Indian < 2 yrs	USA	PCV7	IPD	82.6%(21.4 to 96.1)*	O'Brien KL *et al.* (2003)[25]
< 2 yrs	South Africa	PCV9**	IPD	72%(46 to 87)*	Klugman KP *et al.* (2003)[26]
< 2 yrs	Gambia	PCV9**	IPD	77%(51 to 90)	Cutts FT *et al.* (2005)[27]
< 5 yrs	USA	PCV7	Radiologically confirmed pneumonia	17.7%(4.8 to 28.9)*	Black SB *et al.* (2002)[4]
< 2 yrs	South Africa	PCV9**	Radiologically confirmed pneumonia	17%(4 to 28)*	Klugman KP *et al.* (2003)[26]
< 2 yrs	Gambia	PCV9**	Radiologically confirmed pneumonia	33%(27 to 45)	Cutts FT *et al.* (2005)[27]
< 2 yrs	The Philippines	PCV11**	Radiologically confirmed pneumonia	16.0%(-7.3 to 34.2)*	Lucero MG *et al.* (2009)[28]
< 2 yrs	USA	PCV7	All cause otitis media	7% , p <0.04	Black S *et al.* (2000)[3]
< 2 yrs	Finland	PCV7	All cause AOM	6%(-4 to16)	Eskola J *et al.* (2001)[5]
< 2 yrs	Czech and Slovakia	PCV11	All cause AOM	33.6%(20.8 to 44.3)*	Prymula R *et al.* (2006)[29]

*Intention-to-treat

** 3-dose series

6.3 Economic Evaluation

Economic evaluation (EE) is defined as a comparative analysis of alternatives in terms of both their costs and outcomes. The cost component is always measured in monetary unit, while the outcome component can be measured in various ways. Based on different outcome measurements, the full economic evaluation is divided into four types of analysis. They are cost-benefit analysis, cost-minimization analysis, cost-effectiveness analysis, and cost-utility analysis.

6.3.1 Cost-Benefit Analysis

Cost-benefit analysis (CBA) compares costs and consequences of two or more alternatives that have similar of different outcomes. Costs and outcomes are measured in monetary unit. The benefit from a program and all the costs of providing a program are identified and converted into monetary unit in the year in which they occur. The objective of CBA is to find the alternative with the most favorable cost- to-benefit ratio. The limitation of CBA is valuation of outcome in monetary units. Many outcomes such as years of life saved or quality of life are difficult to value in monetary terms.

6.3.2 Cost-Minimization Analysis

Cost-minimization analysis (CMA) compares costs of two or more alternatives that have equivalent outcomes. The outcomes of the alternatives are assumed to be equal, only costs of each alternative have been estimated. CMA shows only cost savings of one program or treatment over another.

6.3.3 Cost-Effectiveness Analysis

Cost-effectiveness analysis (CEA) is the tool that is used to address the limitations of CBA by using a single, common natural unit as outcome measures e.g. mmHg, cure rate, life-years gained, case treated, etc.

6.3.4 Cost-Utility Analysis

Cost-utility analysis (CUA) is similar to CEA, except the outcomes are measured in terms of utility. CUA provides more complete information because both the quantity and quality of the outcomes are accounted. CUA can be viewed as the extended analysis of CEA while the outcomes in CEA are being quantified; outcomes in CEA are adjusted by quality for CUA. For instance, each life-year gained is adjusted by utility index of health states. As a result, the outcome is reported as quality-adjusted life years (QALYs), which is a one of generic outcome measures for CUA. Additionally, CUA should be applied when alternatives affect both morbidity and mortality and a common unit of outcome is required for a combination of both effects.

Currently, CUA and CEA were more likely to be recommended in both Thai and international EE guidelines. The selection between CUA and CEA depends on the nature of clinical problem addressed.

6.4 Cost

Generally, cost refers to the amount paid to produce a good or service. Cost is always measure in monetary unit. For health care planning, cost is the one of information used for setting priorities.

6.4.1 Perspective

Perspective or viewpoint is an important issue of a health economic study. Perspective determines the type of cost that should be taken into account. The analysis can be conducted from various perspectives. Perspectives can be classified as patient, provider or hospital, payer, government, and societal perspective.

6.4.2 Time Horizon

For economic evaluation, the time horizon must be long enough to capture all effects of the interventions.

6.4.3 Types of Costs

Cost to be included will be depended on study perspective. Cost category is composed of;

- Direct medical costs refer to those resources whose consumption is whole attributable to the use of health care intervention in the study. These include costs of diagnosis, treatment, follow-up, rehabilitation, and terminal care.
- Direct non-medical costs are out-of-pocket expenses for goods or services outside the medical care sector. These include costs of transportation, meals, accommodation, facilities, services, and informal care.
- Indirect costs refer to lost productivity resulting from morbidity and mortality i.e. cost of productivity loss due to sick leave, permanent disability or premature death.

6.4.4 Cost of Informal Care

Informal care is care provided by family member, friends or neighbors of patients without financial compensation. The study which related to

people with disable or chronic illnesses, cost of informal care is important and should be considered. Valuation methods for informal care should be conducted using both opportunity cost and replacement cost.

Opportunity cost calculation of informal care should correspond to that of the indirect costs of the patient.

Replacement cost is valued time spent on informal care at (labor) market prices of a closed market substitute. Informal care is classified as follow;

- Household activities of daily living (HDL) includes prepare food and drink, shopping, doing chores and taking care of children.
- Health care activities (HCA) include preparing medication, doing rehabilitation, contacting health care providers and organizing home facilities for the patient.
- Activities of daily living (ADL) includes assistance such as toilet activities, moving around the house
- Instrumental activities of daily living (IADL) includes management matters, e.g. banking, shopping or travelling.

Table 3 : Description of costs classified by study perspective

Cost	Source of services/ information	Resource identification	Valuation by perspective				
			Patient	Provider/hospital	Third-party payer	Health system	Societal
Direct medical							
Treatment/ health care	Study health setting	Medical service	Charge	Cost	Reimbursement	Cost	Cost
	Other health facilities	Medical service	Charge	-	Reimbursement	Charge (Cost if available)	Charge (Cost if available)
Direct non-medical							
Personal facilities	Patient or family	Home modification/special devices/social service	Charge	-	-	-	Charge (Market price)
Travel	Public/own transportation	Travel distance, vehicle type	Charge or estimated cost	-	-	-	Charge (Market price) or estimated cost
Food	Patient or family	Extra food	Charge	-	-	-	Charge (Market price)
Accommodation	Hotel	Day of stay	Charge	-	-	-	Charge (Market price)

Table 3 : Description of costs classified by study perspective (Continued)

Cost	Source of services/ information	Resource identification	Valuation by perspective				
			Patient	Provider/hospital	Third-party payer	Health system	Societal
Time loss while receiving treatment	Time loss of patient	Hours or days	Income loss	-	-	-	Productivity cost
Informal care	Time loss of caregiver	Hours or days	Income loss	-	-	-	Productivity cost
Personal care/ assistance	Paid helpers	Person-day/month	Charge	-	-	-	Charge (Market price)
Indirect							
Morbidity cost	Working time loss	Day of illness	Income loss	-	-	-	Productivity cost
Mortality cost	Working time loss	Work-absence years from death to retired age	Income loss	-	-	-	Productivity cost
Other sectors							
Welfare	Occupation rehabilitation	Services	Fee/travel/ food/material	-	Reimbursement	-	Cost
Education	Special education	Services	Fee/travel/ food/material	-	Reimbursement	-	Cost

Source: Riewpaiboon A., J Med Assoc Thai Vol.91 Suppl. 2 2008 [30]

6.5 Utility

The utility is a value placed on a level of health status, as weighted by the preferences (How good or bad people thinks his/her health status is?) The utility measurement is used for the calculation of QALYs to determine the health outcome in CUA. Utility index ranges from 0 to 1, 1 is equivalent to full health, while 0 is equivalent to dead.

To measure patient's utility, the questionnaires can be completed by patients, or by their proxies, such as parents or paediatricians in case of young children. Previous studies showed that the Visual Analogue scale (VAS), Health Utility Index Mark 2 version (HUI2), Health Utility Index Mark 3 version (HUI3), and EuroQol (EQ-5D) have been used for evaluating the utility index in young children, even though those instruments have not been validated for young age-groups.

In addition, a critical review of published cost-utility studies in child health by Griebsch I *et al.* (2005) found that a generic instrument was used for calculating QALYs in 22 articles, of these, 12 and 5 articles using HUI and EQ-5D, respectively [31].

6.5.1 EQ-5D

The EQ-5D, developed by the EuroQol Group, includes 5 dimensions (mobility, self-care, usual activities, pain, and mood) with 3 ordered levels of severity for each dimension. The ED-5D can be summarized into a utility index by a scoring rule, based on time trade-off (TTO) [32, 33]. The self-administered version of EQ-5D has been considered suitable for people aged 12 years and above, and has been translated into the Thai language. Currently, EQ-5D youth (EQ-5D-Y) versions for

children aged between 8 to 11 years are currently available in UK, Swedish, Italian, Spanish and German but not in Thailand [34].

6.5.2 Health Utility Index

The health utility index (HUI) has been developed at the McMaster University in Hamilton, Canada. The HUI2 and HUI3 are much more frequently used as compared to the HUI1. The HUI2 was originally applied to childhood cancer. The HUI2 includes 6 dimensions (sensation, mobility, emotion, cognition, self-care, and pain and fertility) with 4 or 5 ordered levels of severity for each dimension. The fertility dimension is optional. The HUI2 was originally applied to childhood cancer. The HUI3 consists of 8 dimensions (vision, hearing, speech, cognition, pain, emotion, ambulation, and dexterity) with 5 or 6 ordered levels of severity for each dimension. The dimensions of the HUI3 were based on the HUI2. The fertility dimension was excludes, whereas sensation dimension was split into vision, hearing and speech dimensions. There is only one version in Thai namely 'HUI23SUTH'. The interviewer-administered version of it has been considered suitable for people aged 8 years and above [35]. Additionally, the HUI can be summarized into the utility index by a scoring rule, are based on Standard Gamble (SG) and VAS [36, 37].

6.5.3 Utility in Pneumococcal Infected Patient

Stouthard MEA *et al.* (1997) investigated Dutch disability weights for patients with pneumococcal disease. The utility was defined by the original five dimensions of EuroQol plused the sixth dimension on "cognitive functioning", (and was labelled as EQ5D+C), They found that the weights were 0.09 for invasive pneumonia, 0.75 for mental retardation, 0.083 for spasticity, 0.89 for seizures and unilateral hearing loss, and 0.77 for bilateral hearing loss [38].

Bennett JE *et al.* (2000) assessed the parent's utilities for outcomes of occult bacteremia, investigated in parents presenting with a child aged between 3 to 36 months using VAS. They found that mean utilities were 0.9971±0.02 for blood drawing, 0.9941±0.03 for local infection, 0.9921±0.03 for hospitalization, 0.9768±0.08 for meningitis with recovery, 0.8611±0.22 for deafness, 0.7393±0.29 for minor brain damage, 0.3903±0.37 for severe brain damage, and 0.0177±0.07 for death [39].

Oostenbrink R *et al.* (2002) evaluated the quality weights for permanent sequelae after childhood bacterial meningitis using the EQ-5D, and HUI. The paediatricians were asked to imagine a child aged 6 years with the specified sequel on the basis of the descriptions provided, and to complete the questionnaires [40]. Mean preference scores are shown in table 4.

Table 4 : Mean preference scores and standard deviation per case description for EQ-5D, HUI2, and HUI3

Case description	EQ-5D	HUI2	HUI3A[a]	HUI3B[b]
Deafness	0.81 (0.15)	0.79 (0.06)	0.47 (0.10)	0.28 (0.14)
Mild hearing loss	0.91 (0.08)	0.84 (0.07)	0.74 (0.11)	0.65 (0.14)
Epilepsy	0.83 (0.08)	0.88 (0.06)	0.78 (0.11)	0.70 (0.14)
Mild mental retardation (MR)	0.62 (0.11)	0.55 (0.03)	0.44 (0.14)	0.24 (0.18)
Severe retardation and tetraplegia	-0.15 (0.13)	0.12 (0.03)	0.02 (0.02)	-0.33 (0.02)
Leg paresis	0.67 (0.12)	0.80 (0.10)	0.64 (0.10)	0.51 (0.14)
Epilepsy, MR, and leg paresis	0.47 (0.25)	0.46 (0.07)	0.28 (0.10)	0.02 (0.14)

a HUI3A : quality weights of HUI Mark 3 computed by the algorithm with anchor points "Pits" and "Healthy."

b HUI3B : quality weights of HUI Mark 3 computed by the algorithm with anchor points "Dead" and "Healthy."

Source: Oostenbrink R et al. (2002) [40]

6.6 Related Study

Based on the Pubmed search, there are 12 published studies accessed the economic evaluation of PCV7 compared with no vaccination program in children. These studies were internationally published between 2003 and 2008. In addition, all studies were only conducted in developed countries (9 studies in Europe, 2 studies in US and 1 study in Australia)

Nine studies were conducted using the societal perspective, and 3 studies based on a health care payer/provider perspective. Regarding the time horizon, 5 studies estimated the relevant costs and health outcomes for lifetime, 3 studies using a 5-year horizon and 3 studies using a 10-year horizon.

Results were mostly expressed as ICER per life-year and QALY gained, and rarely expressed as cost per episode of illness avoided. Some studies reported the net present costs (NPC) per case of infection averted and death averted. Additionally, costs and outcomes were discounted at 1.5%, 3%, 3.5%, 4% and 5% per annum. The discount rate depends on the guidelines of each country. With regard to the method approach to the parameter uncertainty, univariate, multivariate, and probabilistic sensitivity analysis were used to assess uncertainty in the results.

Both direct and indirect costs were used in these studies. Direct costs were those associated with the health care interventions such as vaccination, physician visits, hospital days, diagnostic test and transportation. Indirect costs were the cost of productivity loss by parents or care givers [18, 41-46], the cost of care for long-term disabilities [44], lifetime care cost and the cost of special education as sequelae of meningitis [18]. Both costs were measured in several

monetary units. The cost of vaccine per dose had varied by counties when vaccine price was converted into the same unit as presented as the international US dollar (using purchasing power parity (PPP) exchange rate), available from International Monetary Fund, World Economic Outlook Database, April 2008. Of them, the vaccine price was likely to be between 109 PPP$ to 202 PPP$ which is shown in table 5.

Table 5 : The price per dose of vaccine by countries

Country	Vaccine price in monetary unit (year)	Vaccine price in year 2008	
		Baht	PPP$
Canada	Can$67.5 (2000)	2,029.52	127.21
Spain	€48.56 (1999), ESP8,080	2,218.98	139.09
Canada	Can$58 (2000)	1,743.88	109.31
Norway	€54 (2004)	2,789.16	175.39
Sweden	€55.3 (2006)	2,558.38	166.38
England and Wales	£39.25 (2002)	2,722.08	170.62
Germany	€62 (2004)	3,212.70	201.37
Ireland	€63.18 (2005)	3,223.32	202.04
Finland	€50.5 (1999)	2,307.63	144.64
The Netherlands	€50 (2004)	2,590.88	162.4
The Netherlands	€40 (1999)	1,827.83	114.57
Australia	Aus$90 (1998)	2,726.29	170.88

Concerning vaccine efficacy (VE), a systematic review and meta-analysis was not used for consideration of a vaccine efficacy parameter. Nevertheless, all models in these studies considered vaccine efficacy rates as observed in trials, mostly based on the randomized control trials (RCTs), such as the Northern California Kaiser Permanente Efficacy Study (NCKPES) [3, 4, 47] and the Finnish Otitis Media Vaccine trial [5]. In conclusion, the investigators considered VE

rates of 63% to 97.4% for the reduction in IPD, 6% to 33% for reduction in pneumonia, 5.8% to 7% for reduction in otitis media, and 6% to 10.6% for reduction in AOM. Furthermore, VE was mostly assumed to decline 3% per year when after 6 year of first dosage [18, 41, 44, 48]. See table 6.

Based on these findings, a half of these studies indicated that PCV7 was cost-effective, consisting of the study from Spain, Sweden, Germany, Ireland and the Netherlands, and although the results from a study in Norway was not cost-effective, ICER was close to the ceiling threshold. After this study the Norwegian government decided to include PCV7 in the vaccination program in the autumn of 2005 [49]. In addition, studies which indicated PCV7 was cost-effective, included herd immunity in their models. It is noted that there are two studies from the Netherlands [18, 46] yielded different results and conclusions. This may because of the fact that they applied different, vaccine prices and models, See table 7.

Table 6 : Summary of PCV7 efficacy parameter

Reference	IPD	Clinical pneumonia	Radiologically confirmed pneumonia	All-cause otitis media	AOM
[48]	89.1%	11.4%	33%	5.8%	**10.6%
[41]	97.4% (82.7 to 99.9)	11.4%	33%	5.8%	**10.6%
[42]	97%	10.7%	NA	NA	8.2%
[49]	93.9% (79.6 to 98.5)	NA	17.7% (4.8 to 28.9)	NA	6% (-4 to 16)
[43]	93.9% (79.6 to 98.5)	NA	25.5% (6.5 to 40.7)	NA	6% (-4 to 16)
[50]	63% to 87%	NA	17.7% (4.8 to 28.9)	7% (-5 to 17)	NA
[44]	92% (82.7 to 99.9)	6 (-1.5 to 11)	17.7% (4.7 to 28.9)	NA	6% (3.9 to 8.7)
[51]	93.9% (79.9 to 98.5)	NA	17.7% (4.8 to 28.9)	NA	7% (-5 to 17)
[45]	89.1%	NA	17.7%	NA	6% and 6.4%
[18]	85.7% and 93.9%	6	NA	6.4%	NA
[46]	*0, 86, 90 and 95%	11.4	NA	5.8%	NA
[52]	93.9% (79.6 to 98.5)	6%(-1.15 to 11)	17.7% (4.8 to 28.9)	6.4% (3.9 to8.7)	NA

Remark: Vaccine efficacy was shown in percent reduction

NA=not available. *=vaccine efficacy of 1, 2, 3 and 4 doses, respectively. **=recurrent AOM

Table 7 : Summary of the results by study setting

Country (year)	ICER	Ceiling threshold	Conclusion
Canada (2003) [48]	Can$79,000 per LYG		If vaccine cost <= Can$50 per dose, vaccination would result in net saving
Spain (2004) [41]	€22,500 per LYG		Cost-effective
Canada (2003) [42]	Can$125,000 per LYG		If vaccine cost <= Can$30 per dose, vaccination would result in net saving
Norway (2006) [49]	€ 58,000 per LYG (Including herd immunity)	€ 54,000 per LYG	Not cost-effective, but the Norwegian government decided to include PCV7 in the vaccination program in 2005
Sweden (2008) [43]	€29,200 per QALYs gained and €51,400 per LYG. €5,500 per QALYs gained and €6,600 per LYG. (Including herd immunity)	No explicit threshold, a reasonable value vary from €43,000 to €70,000 per QALY gained	Cost-effective
England and Wales (2004) [50]	£113,231 per LYG and £ 59,945 per QALY gained		Not cost-effective in base case

Table 7 : Summary of the results by study setting (Continued)

Country (year)	ICER	Ceiling threshold	Conclusion
Germany (2008) [44]	€100,636 per LYG €38,222 per LYG (children at high risk)		Cost-effective in children at high risk
Ireland (2008) [51]	€249,591 per LYG €5,997 per LYG (Including herd immunity)		Cost-effective when herd immunity included
Finland (2005) [45]	€134,986 per LYG		To achieve cost savings, the price of PCV7 should be 70% of the price used in the base case.
The Netherlands (2007) [18]	€14,000 per QALY gained and €15,600 per LYG	€ 20,000 per LYG or QALY gained	Cost-effective
The Netherlands (2003) [46]	€71,250 per QALY gained and €82,700 per LYG	€ 20,000 per LYG or QALY gained	Not cost-effective
Australia (2004) [52]	Aus$ 230,130 per LY saved and Aus$ 121,100 per DALY averted		Would not result in net cost savings.

7. Methodology

7.1 Study Design

A model-based economic evaluation will be constructed to compare long-term outcomes and to estimate the cost-utility of PCV7, PCV10 and PCV13 compared with no vaccination.

7.2 Study Population

The study population will be 1) healthy Thai children aged less than 5 years and 2) special subgroups i.e. children aged less than 5 years with HIV/AIDS and children aged less than 5 years with severe thalassemia.

7.3 Economic Model

The decision tree and Markov model will be used to simulate the relevant costs and health outcomes of pneumococcal vaccine program for newborns.

Decision tree will be constructed based on the natural history of pneumococcal disease, consisting of the initial diseases (meningitis, bacteremia, pneumonía and otitis media) in children aged less than 5 years, with no infection and death from other causes. The structure of the decision tree is shown in figure 4.

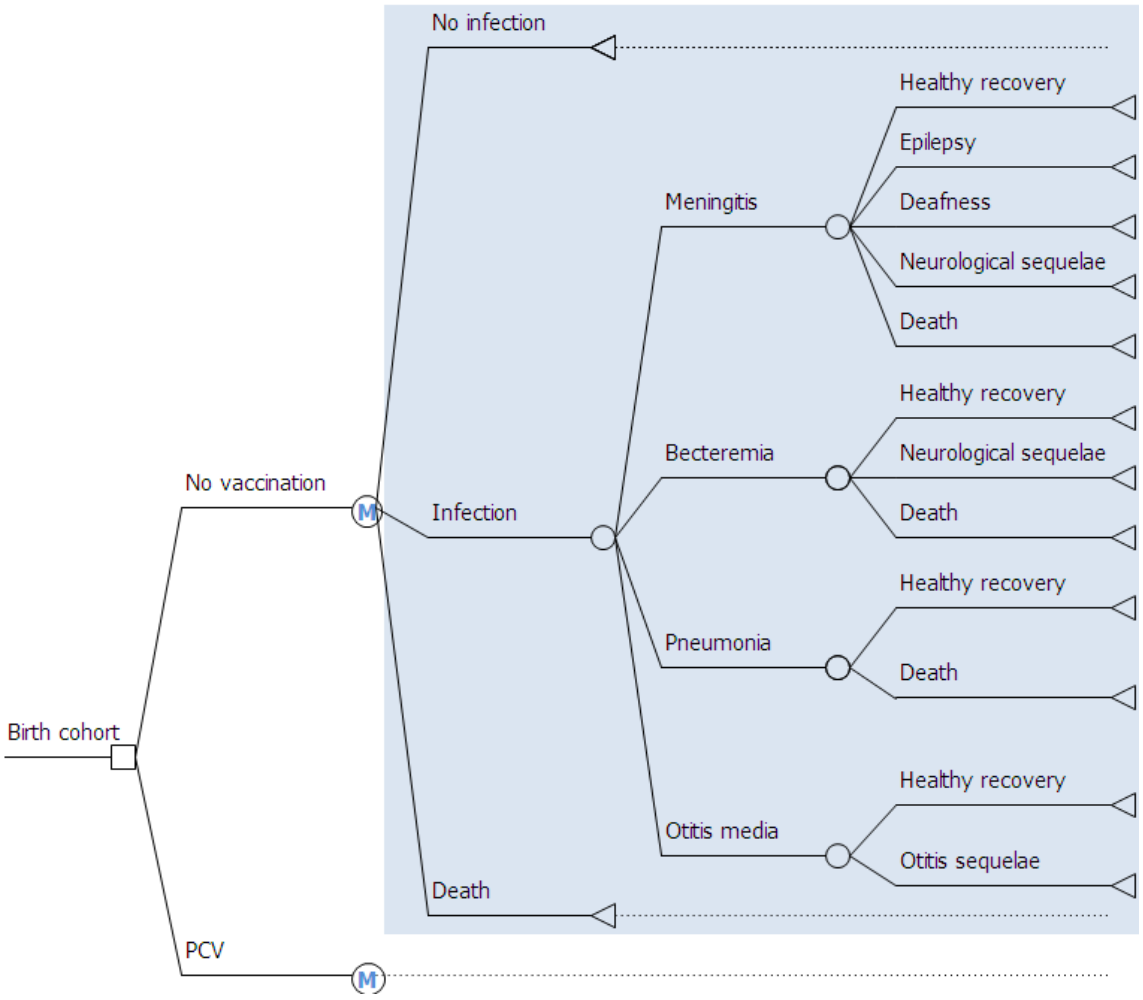

Figure 4 : Illustration of the decision analytic model, to be used for assessing costs and outcomes of vaccination comparing to no vaccination. The structure of node 'PCV' is identical to node 'No vaccination' but the disease incidence is reduced due to vaccination.

Remark: (M) = Markov model

In the Markov model, a cohort of children is followed from birth until death at the estimated age of 100, with a one year cycle length. More than one pneumococcal infection is possible during one lifetime. The Markov model demonstrated in figure 5. It describes potential health states, namely 1) no infection, 2) infection, 3) several sequelae, and 4) death. The possible transitions from one health state to another

are represented in arrows. For every 1 year (Markov cycle), the pneumococcal-infected patient will have a probability of developing several sequelae (arrow 1), being cured (arrow 2), dying (arrow 3), or developing complications (arrow 4). The patient with several sequelae will have a probability of being cured (arrow 5), being infected (arrow 6), staying at the same stage (arrow 7) or dying (arrow 8). For fully recovered persons, there will be probabilities of pneumococcal relapse (arrow 9), being free from pneumococcal infection (arrow 10) or dying (arrow 11).

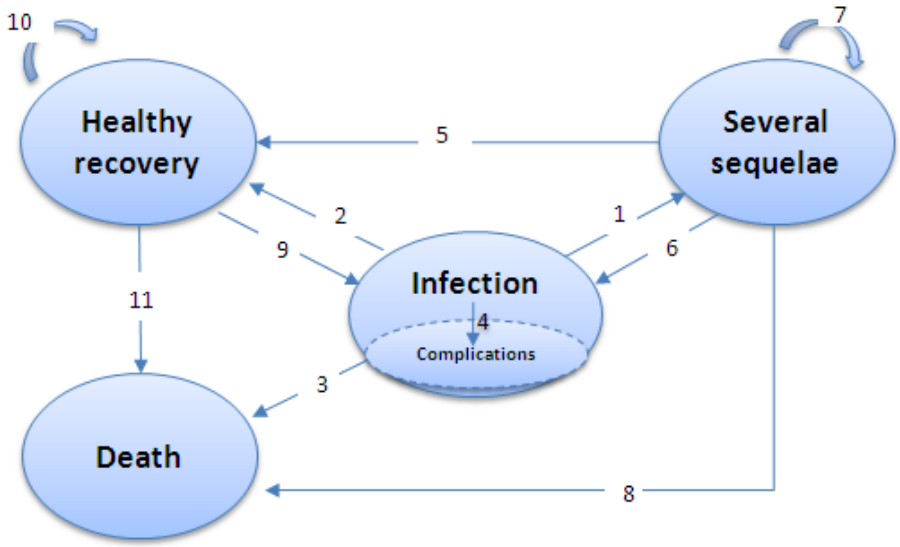

Figure 5 : Markov model represents disease progression of pneumococcal-infected patients in each state, while the arrows represent the transitional probability of state-shifting

7.4 Model Input Parameters

Most input parameters will be obtained from literature review. Two parameters (direct non-medical costs and utility index) will be obtained from primary data collection. Vaccine efficacy will be obtained from systematic review and meta-analyses of publications. See table 8.

Table 8: Data source

Parameters	Data source
Transitional probability	
Transitional probability of children developing pneumococcal infection	Literature reviews
Transitional probability of patients developing complications	Literature reviews
Transitional probability of patients developing sequelae	Literature reviews
Transitional probability of patients being cured from pneumococcal infection	Literature reviews
Transitional probability of patients being cured from sequelae	Literature reviews
Transitional probability of re-infection or relapse (patients developed pneumococcal again)	Literature reviews
Incidence of pneumococcal diseases	
Age-specific incidence rate of pneumococcal infected patients	Literature reviews
Mortality	
Baseline mortality of Thai population	Burden of Disease project
Mortality due to pneumococcal infection	Literature reviews
Intervention effect	
Vaccine efficacy of PCV7, PCV10 and PCV13	Systematic reviews and meta-analyses of international publications
Covered serotypes by PCV7, PCV10 and PCV13	Literature reviews
Costs	
Direct medical costs	Literature reviews
Direct non-medical costs	Primary data collection
Indirect costs	Literature reviews
Outcomes	
Health utility of pneumococcal infected patients in each state	-Primary data collection

7.4.1 Vaccine Efficacy

Summary mean estimates from systematic review and meta-analysis will be used and derived from the published articles.

7.4.2 Costs

The cost analysis will be performed based on societal perspective. It will include both direct costs and indirect costs.

- Direct medical costs will include vaccination, physician visits, hospital stay, medications (antibiotics and other supportive medications), x-ray investigation, laboratory test and costs related to treatment of pneumococcal sequelae, rehabilitation, etc. In special groups (children with HIV/AIDS and children with severe thalassemia), there is an additional cost in identifying target population for vaccination.
- Direct non-medical costs will include transportation expense, meals, accommodation, facilities, productivity loss by parents or care-givers (time spent due to attending physician visits), cost of informal care, special education and child developmental services due to pneumococcal sequelae.
- Indirect costs will include lifetime productivity loss due to sick leave and permanent disability. Cost of premature death (mortality cost) is not included because QALYs are the measure of effectiveness. This is to avoid double counting since QALYs have included both quality of life (Qol) and life year effects.

Direct medical costs and indirect costs will be derived from literature reviews, while direct non-medical will be derived from primary data collection. All cost parameters will be presented in 2009

Thai Baht as well as 2009 international US Dollars (using purchasing power parity (PPP) exchange rates of the International Monetary Fund).

7.4.3 Utility

To measure health-related quality of life, a cross-sectional survey will be conducted by interviewing patients aged 7 to 14 years with the assumption that the health state utility among older and young children is similar. Whereas, health state utility among other age-group (aged 15 years and above) will be obtained from literature review.

7.5 Health Outcome

Health outcomes in this study will be the quality adjusted life years (QALYs), which refer to the number of years lived, adjusted by the utility index.

$$\text{QALYs} = \text{Utilty index} \times \text{Life years}$$

7.6 Time Horizon and Discounting

The relevant costs and health outcomes will be estimated throughout patients' lifetime, which is estimated to be at a maximum of 100 years, with one year cycle length. In addition, due to time horizon of more than 1 year, future costs and outcomes will be discounted at 3% per annum, as recommended by the Guidelines for Economic Evaluation in Thailand [53] . The present value of costs and outcomes (ΔCE) can be calculated using the following formula.

$$\Delta CE = \sum_{1}^{time} \frac{\text{Incremental cost } or \text{ effectiveness}}{(1 + \text{Discount rate of cost } or \text{ effectiveness})^{time-1}}$$

7.7 Results

The results will be expressed as the incremental cost-effectiveness ratio (ICER) in Thai Baht per QALY gained.

$$ICER = \frac{\text{Incremental cost}}{\text{Incremental effectiveness}}$$

$$= \frac{\text{Cost}_{PCV} - \text{Cost}_{\text{no vaccination}}}{\text{QALY}_{PCV} - \text{QALY}_{\text{no vaccination}}}$$

7.8 Sensitivity Analysis

One-way sensitivity analysis and probabilistic sensitivity analysis (PSA) using a Monte Carlo simulation will be carried out in the R statistical software to assess uncertainty in the results. The simulation will then draw one value from each distribution simultaneously and calculate cost and effectiveness pairs. This process will then be repeated 1,000 times. One-way sensitivity analysis will be performed at discount rates of 0% and 6%. The results of one-way sensitivity analysis and PSA will be presented as a tornado diagram and cost-effectiveness acceptability curves, respectively.

7.9 Primary Data Collection

There are two parameters which will be obtained from primary data collection, i.e. direct non-medical costs and utility index.

7.9.1 Study Design

This study will be a cross-sectional survey.

7.9.2 Study Settings

The population included in this study will be obtained from 5 hospitals. Three of the hospitals are selected due to the high number of cases[a], where 2 hospitals are recommended by the experts.

Hospital	Province
Queen Sirikit National Institute of Child Health*	Bangkok
Had Yai Hospital*	Songkhla
Maharat Nakhonratchasima Hospital	Nakhon Ratchasima
Udonthani Hospital	Udon Thani
Chaingrai Regional Hospital	Chaingrai

Remark: *=recommended by the experts

7.9.3 Primary Data Collection Period

Primary data will be collected from July to October, 2010.

7.9.4 Study Sample

Patients with meningitis, becteremia, pneumonia and otitis media from all causes, aged between 7 - 14 years in the 5 selected hospitals, will serve as the study population. The study samples will be randomly selected from patients in the selected hospitals who meet the eligibility criteria.

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[a] Source: Reported cases by province and by age group: Thailand 2552 (2009). Center of Epidemiological Information, Bureau of Epidemiology, Ministry of Public Health

- ***Inclusion criteria***

Thai children with meningitis, becteremia, pneumonia and otitis media from all causes, aged between 7 – 14 years, who are able to communicate or are literate, and willing to participate in the study.

- ***Exclusion criteria***

Children who refuse or are unable to answer a series of questions.

7.9.5 Sample Size Calculation

The sample size for collecting costs and utility index has been calculated. The total number of patients required for measuring health state utility has been calculated by using the formula below.

$$n = \frac{Z^2_{1-\alpha/2}\,\sigma^2}{d^2}$$

Where

n	Sample size
$Z_{1-\alpha/2}$	Level of statistical significance (α = 0.05)
σ	Standard deviation (0.2)
d	Precision of estimate (0.1)

In order to estimate the sample size required for determining health state utility of our study population, a literature review of studies examining utilities of patients with pneumococcal sequelae was conducted. The standard deviations (SD) of health utility ranged from 0.02-0.37 for meningitis group. The mean standard deviation of 0.2 was used for the meningitis group. A precision of estimate of 10% and a significance level α = 0.05 was used for sample size estimation. The

result was that at least 16 subjects were required for meningitis group.

As the purpose of this study is also to examine utilities in children with pneumococcal disease and children with pneumococcal sequelae, the SD of 0.2 was estimated for each type of disease and sequelae, the same level as in meningitis group. Hence, the total sample size for the 8 sub-groups is 128 subjects. The estimated numbers of participants in each study site with each disease are presented in Table 9.

Table 94: Estimated number of participants

Group of patient	**Total number**	**Study site**				
		Site 1	**Site 2**	**Site 3**	**Site 4**	**Site 5**
Disease						
Meningitis	20	4	4	4	4	4
Bacteremia	20	4	4	4	4	4
Pneumonia	20	4	4	4	4	4
Otitis media	20	4	4	4	4	4
Sequelae						
Deafness	20	4	4	4	4	4
Epilepsy	20	4	4	4	4	4
Neurological sequelae	20	4	4	4	4	4
Otitis sequelae	20	4	4	4	4	4
Total	**160**	**32**	**32**	**32**	**32**	**32**

Remark: Patients are classified into each group according to physician’s diagnosis, regardless of diagnosis method.

7.9.6 Study Instrument

A questionnaire will be used as the study instrument. The developed questionnaire consists of 3 main parts as follow:

Part	Information to be collected	Respondent
I	Ddemographics data and general information of patient e.g. age, gender, insurance, etc	Parent or care-giver
II	Utility measure by using Health Utility Index and EQ-5D	Patient
III	Direct non-medical costs	Parent or care-giver

7.9.7 Data Collection

Health personnel from the study sites will identify the eligible patients based on the inclusion and exclusion criteria. These patients will then be invited to participate in this study.

Prior to data collection, the questionnaires will be pilot tested by the researcher. The pilot test will include every group of patient mentioned above on a voluntary basis. There will be 20 samples for pilot testing. Written consent for interviews and for access to the clinical records will be obtained from all participants. These participants will be interviewed face-to-face by trained interviewers. Once the questionnaire is modified based on comments received from the pilot test, data collection will be conducted at 5 hospitals. The number of patients required is shown in table 9. Completeness of the questionnaire will be examined after data collection. All data will be analysed using R statistics software.

7.9.8 Quality Control/Assurance

The pilot study will be undertaken to assure that the questionnaire is practicable. Before the pilot study, the questionnaire will be

reviewed by the experts. After the pilot, the adjustments will be made before the field data collection.

7.9.9 Limitation of Primary Data Collection

The samples that are included in this study will be from 5 hospitals. Three of the hospitals are selected due to the high number of cases, where other hospitals are recommended by the experts. The study samples might not represent the entire population of Thai children and there may be bias, particularly selection bias, since convenient sampling will be used for sample selection.

7.10 Study Procedure

- Developing the analytical model structure from relevant clinical and economic literatures of children aged less than 5 years with pneumococcal disease.
- Developing the instrument for data collection on costs and utility index.
- Submitting to the Ethics Committee of MoPH for approval. If the study is approved, the data on costs, utility index, and clinical data of patients will be collected.
- Reviewing the literature and pooling estimate by meta-analysis method for vaccine efficacy parameters.
- Estimating the cost and utility index and analyze clinical data for input parameters of economic model.
- Estimating the expected costs and health outcomes during life-time horizon for intervention.
- Estimating the incremental cost-effectiveness ratio (ICER).

- Conducting the probabilistic sensitivity analysis and presenting the results in terms of a cost-effectiveness acceptability curve.

7.11 Expected Outcomes and Benefits

The results from this study can be used as the evidence-based information for policy decision-making on whether or not to adopt PCV into the Expanded Program of Immunization (EPI) or special subpopulation e.g. HIV/AIDS or severe thalassemia for the prevention of pneumococcal diseases in Thailand.

7.12 Plan of Study

Activities in each month	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th
Developing economic models	√	√										
Expert meeting for investigation of the methodological methods		√										
Develop questionnaires or survey tools for data collection of some parameters, e.g. costs and utility index			√	√								
Expert meeting for investigation of the questionnaire				√								
Pilot study for testing of the data collection tool					√							
Data collection for costs and utility index					√	√	√	√				
Analysis of primary data and review of literature to identify all model parameters				√	√	√	√	√	√			
Data analysis										√	√	
Expert meeting for investigation and discussion of the results											√	
Reporting											√	√

7.13 Budget

Expenditure	unit/unit cost	Expenses(Baht)
Expert meeting (12 persons)	12 experts X 2,000 Baht X 3 times	72,000
Pilot test	10,000 Baht	10,000
Collecting cost data from hospitals	30,000 Baht	30,000
Collecting cost and utility index from patients	200 units X 500 Baht	100,000
Transportation and accommodation	6,000 Baht X 5 sites X 2 times	60,000
Document preparation and stationery	20,000 Baht	20,000
Total		**292,000**

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Reference List

[1] World Health Organization. Pneumococcal conjugate vaccines. 2009 [cited 2009 October 30]; Available from: http://www.who.int/biologicals/areas/vaccines/pneumo/en/

[2] Baggett HC, Peruski LF, Olsen SJ, Thamthitiwat S, Rhodes J, Dejsirilert S, et al. Incidence of pneumococcal bacteremia requiring hospitalization in rural Thailand. Clin Infect Dis. 2009 Mar 1;48 Suppl 2:S65-74.

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

[4] Black SB, Shinefield HR, Ling S, Hansen J, Fireman B, Spring D, et al. Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than five years of age for prevention of pneumonia. Pediatr Infect Dis J. 2002 Sep;21(9):810-5.

[5] Eskola J, Kilpi T, Palmu A, Jokinen J, Haapakoski J, Herva E, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. N Engl J Med. 2001 Feb 8;344(6):403-9.

[6] Centers of Disease Control and Prevention. Meningitis. [cited 2010 April 8]; Available from: http://www.cdc.gov/meningitis/index.html

[7] Bennett NJ, Domachowske J, Holland BJ. Bacteremia. 2010 Mar 18, 2010 [cited 2010 April 8]; Available from: http://emedicine.medscape.com/article/961169-overview

[8] Stephen JM. Bacterial Pneumonia. 2010 [cited 2010 April 8]; Available from: http://emedicine.medscape.com/article/807707-overview

[9] Teele DW, Klein JO, Rosner B. Epidemiology of otitis media during the first seven years of life in children in greater Boston: a prospective, cohort study. J Infect Dis. 1989 Jul;160(1):83-94.

[10] World Health Organization. Immunization, Vaccines and Biologicals 1999 [cited 2009 October 25]; Pneumococcal vaccines]. Available from: http://www.who.int/vaccines/en/pneumococcus.shtml

[11] Committee on Infectious Dieases, American Academy of Pediatrics. Red Book. 28 ed. Bangkok: iGroup Press Co.,Ltd. 2009.

[12] O'Brien KL, Wolfson LJ, Watt JP, Henkle E, Deloria-Knoll M, McCall N, et al. Burden of disease caused by Streptococcus pneumoniae in children younger than 5 years: global estimates. Lancet. 2009 Sep 12;374(9693):893-902.

[13] Chotpitayasunondh T. Bacterial meningitis in children: etiology and clinical features, an 11-year review of 618 cases. Southeast Asian J Trop Med Public Health. 1994 Mar;25(1):107-15.

[14] Sirisanthana V, Chatborairak P, Baosoung V, Khantawa B. Invasive Cefotaxime-nonsusceptible Strepto- coccus pneumoniaeInfection in Children in Northern Thailand. J Infect Dis Antimicrob Agents 2001;18:8-14.

[15] The Bureau of Epidemiology, MOPH, Thailand. Annual Epidemiological Surveillance Report 2008. *Pneumonia*:122-3.

[16] Phongsamart W, Srifeungfung S, Dejsirilert S, Chatsuwan T, Nunthapisud P, Treerauthaweeraphong V, et al. Serotype distribution and

antimicrobial susceptibility of S. pneumoniae causing invasive disease in Thai children younger than 5 years old, 2000-2005. Vaccine. 2007 Jan 26;25(7):1275-80.

[17] Levine S, Dejsirilert S, Sangsuk L, Chantra S, Feikin DR, Dowell SF, et al. Serotypes and antimicrobial resistance of streptococcus pneumoniae in Thailand 2002-2004. Pediatr Infect Dis J. 2006 Feb;25(2):176-8.

[18] Hubben GA, Bos JM, Glynn DM, van der Ende A, van Alphen L, Postma MJ. Enhanced decision support for policy makers using a web interface to health-economic models--illustrated with a cost-effectiveness analysis of nation-wide infant vaccination with the 7-valent pneumococcal conjugate vaccine in the Netherlands. Vaccine. 2007 May 4;25(18):3669-78.

[19] Pilishvili T. Manual for the Surveillance of Vaccine-Preventable Diseases (4th Edition), Chapter 11: Pneumococcal 2008.

[20] World Health Organization. Target Product Profile for the Advance Market Commitment for Pneumococcal Conjugate Vaccines. 2008 Febuary 22.

[21] Detailed Review Paper on Pneumococcal Conjugate Vaccine - presented to the WHO Strategic Advisory Group of Experts (SAGE) on Immunization November 2006.

[22] Licensure of a 13-valent pneumococcal conjugate vaccine (PCV13) and recommendations for use among children - Advisory Committee on Immunization Practices (ACIP), 2010. MMWR Morb Mortal Wkly Rep. Mar 12;59(9):258-61.

[23] Wyeth Pharmaceuticals. Approval sought for investigational vaccine for protection against the 13 most prevalent serotypes associated with serious pneumococcal disease; 2008 December 3.

[24] Whitney CG, Farley MM, Hadler J, Harrison LH, Bennett NM, Lynfield R, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. N Engl J Med. 2003 May 1;348(18):1737-46.

[25] O'Brien KL, Moulton LH, Reid R, Weatherholtz R, Oski J, Brown L, et al. Efficacy and safety of seven-valent conjugate pneumococcal vaccine in American Indian children: group randomised trial. Lancet. 2003 Aug 2;362(9381):355-61.

[26] Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. N Engl J Med. 2003 Oct 2;349(14):1341-8.

[27] Cutts FT, Zaman SM, Enwere G, Jaffar S, Levine OS, Okoko JB, et al. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. Lancet. 2005 Mar 26-Apr 1;365(9465):1139-46.

[28] Lucero MG, Nohynek H, Williams G, Tallo V, Simoes EA, Lupisan S, et al. Efficacy of an 11-valent pneumococcal conjugate vaccine against radiologically confirmed pneumonia among children less than 2 years of age in the Philippines: a randomized, double-blind, placebo-controlled trial. Pediatr Infect Dis J. 2009 Jun;28(6):455-62.

[29] Prymula R, Peeters P, Chrobok V, Kriz P, Novakova E, Kaliskova E, et al. Pneumococcal capsular polysaccharides conjugated to protein D for prevention of acute otitis media caused by both Streptococcus pneumoniae and non-typable Haemophilus influenzae: a randomised double-blind efficacy study. Lancet. 2006 Mar 4;367(9512):740-8.

[30] Riewpaiboon A. Measurement of Cost. J Med Assoc Thai. 2008 June;91(Suppl 2):S28-37.

[31] Griebsch I, Coast J, Brown J. Quality-adjusted life-years lack quality in pediatric care: a critical review of published cost-utility studies in child health. Pediatrics. 2005 May;115(5):e600-14.

[32] Dolan P. Modeling valuations for EuroQol health states. Med Care. 1997 Nov;35(11):1095-108.

[33] Dolan P, Gudex C, Kind P, Williams A. The time trade-off method: results from a general population study. Health Econ. 1996 Mar-Apr;5(2):141-54.

[34] EuroQol Group. EQ-5D versions. 2010 [cited 2010 March 2]; Available from: http://www.euroqol.org/eq-5d/eq-5d-versions.html

[35] HEALTH UTILITIES INC. Self or Interviewer Administered? Paper&Pencil or Web-based Format? 2008 September 2 [cited 2010 March 2]; Available from: http://www.healthutilities.com/

[36] Torrance GW, Feeny DH, Furlong WJ, Barr RD, Zhang Y, Wang Q. Multiattribute utility function for a comprehensive health status classification system. Health Utilities Index Mark 2. Med Care. 1996 Jul;34(7):702-22.

[37] Feeny D, Furlong W, Torrance GW, Goldsmith CH, Zhu Z, DePauw S, et al. Multiattribute and single-attribute utility functions for the health utilities index mark 3 system. Med Care. 2002 Feb;40(2):113-28.

[38] Stouthard MEA, Essink-Bot M-L, Bonsel GJ, Barendregt JJ, Kramers PGN, van de Water HPA, et al. Disability weights for diseases in the Netherlands. Rotterdam: Department of Public Health, Erasmus University. 1997.

[39] Bennett JE, II WS, Downs SM, Jaffe DM. Parents' Utilities for Outcomes of Occult Bacteremia. Arch Pediatr Adolesc Med. 2000 Jan;154:43-8.

[40] Oostenbrink R, HA AM, Essink-Bot ML. The EQ-5D and the Health Utilities Index for permanent sequelae after meningitis: a head-to-head comparison. J Clin Epidemiol. 2002 Aug;55(8):791-9.

[41] Asensi F, De Jose M, Lorente M, Moraga F, Ciuryla V, Arikian S, et al. A pharmacoeconomic evaluation of seven-valent pneumococcal conjugate vaccine in Spain. Value Health. 2004 Jan-Feb;7(1):36-51.

[42] De Wals P, Petit G, Erickson LJ, Guay M, Tam T, Law B, et al. Benefits and costs of immunization of children with pneumococcal conjugate vaccine in Canada. Vaccine. 2003 Sep 8;21(25-26):3757-64.

[43] Bergman A, Hjelmgren J, Ortqvist A, Wisloff T, Kristiansen IS, Hogberg LD, et al. Cost-effectiveness analysis of a universal vaccination programme with the 7-valent pneumococcal conjugate vaccine (PCV-7) in Sweden. Scand J Infect Dis. 2008;40(9):721-9.

[44] Lloyd A, Patel N, Scott DA, Runge C, Claes C, Rose M. Cost-effectiveness of heptavalent conjugate pneumococcal vaccine (Prevenar) in Germany: considering a high-risk population and herd immunity effects. Eur J Health Econ. 2008 Feb;9(1):7-15.

[45] Salo H, Sintonen H, Nuorti JP, Linna M, Nohynek H, Verho J, et al. Economic evaluation of pneumococcal conjugate vaccination in Finland. Scand J Infect Dis. 2005;37(11-12):821-32.

[46] Bos JM, Rumke H, Welte R, Postma MJ. Epidemiologic impact and cost-effectiveness of universal infant vaccination with a 7-valent conjugated pneumococcal vaccine in the Netherlands. Clin Ther. 2003 Oct;25(10):2614-30.

[47] Hansen J, Black S, Shinefield H, Cherian T, Benson J, Fireman B, et al. Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than 5 years of age for prevention of pneumonia: updated analysis using World Health Organization standardized interpretation of chest radiographs. Pediatr Infect Dis J. 2006 Sep;25(9):779-81.

[48] Lebel MH, Kellner JD, Ford-Jones EL, Hvidsten K, Wang EC, Ciuryla V, et al. A pharmacoeconomic evaluation of 7-valent pneumococcal conjugate vaccine in Canada. Clin Infect Dis. 2003 Feb 1;36(3):259-68.

[49] Wisloff T, Abrahamsen TG, Bergsaker MA, Lovoll O, Moller P, Pedersen MK, et al. Cost effectiveness of adding 7-valent pneumococcal conjugate (PCV-7) vaccine to the Norwegian childhood vaccination program. Vaccine. 2006 Jul 17;24(29-30):5690-9.

[50] Melegaro A, Edmunds WJ. Cost-effectiveness analysis of pneumococcal conjugate vaccination in England and Wales. Vaccine. 2004 Oct 22;22(31-32):4203-14.

[51] Tilson L, Usher C, Butler K, Fitzsimons J, O'Hare F, Cotter S, et al. Economic evaluation of a universal childhood pneumococcal conjugate vaccination strategy in Ireland. Value Health. 2008 Sep-Oct;11(5):898-903.

[52] Butler JR, McIntyre P, MacIntyre CR, Gilmour R, Howarth AL, Sander B. The cost-effectiveness of pneumococcal conjugate vaccination in Australia. Vaccine. 2004 Mar 12;22(9-10):1138-49.

[53] Guidelines Development Working Group. Thai Health Technology Assessment Guideline. Bangkok 2008.