INCORPORATION OF PRIVATE DEMAND INTO COST-BENEFIT ANALYSIS OF A UNIVERSAL HIB VACCINATION PROGRAM IN THAILAND

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Abstract. Conjugate Hib vaccines are costly and Hib meningitis incidence in Thailand is relatively low comparing to western countries; a decision tree model was used for cost-benefit analysis (CBA) of a universal conjugate Hib vaccination program in Thailand. Tangible and intangible costs and benefits of the program, occurring from birth to 60 years of age from the provider and client perspectives, were included in the cost analysis. With a birth cohort of 740,109, at a cost of USD 8 million (THB 288 million), the program will potentially prevent 77 deaths, 19 cases of severe disability, 135 cases of meningitis, and 628 cases of pneumonia resulting in a net benefit of about USD 70 million to society. The program is cost-effective only if intangible benefits are included in the model.

Keywords: Hib disease, Hib vaccine, cost-benefit analysis, willingness-to-pay

INTRODUCTION

The WHO recommends the *Haemophilus influenzae* type b (Hib) conjugate vaccine be included in the Expanded Programs on Immunization (EPI) (WHO 2006a). Because of the relatively high price of the vaccine and low disease incidence of Hib infection in most Asian countries, including Thailand, few countries in Asia have introduced the Hib vaccine into the EPI (Levine *et al*, 1998; WHO, 2004, 2006a). In making an appropriate Hib vaccine policy, the WHO recommended that in addition to information regarding disease burden, an economical analysis of vaccine introduction should be performed (WHO, 2006a). We found most cost-benefit studies in western countries were strongly supportive of introducing the Hib vaccine into the EPI (Brinsmead *et al*, 2004). The results are strongly affected by the incidence of Hib disease in the countries. Among countries with a low incidence of Hib disease (≤ 15/100,000), such as Thailand, the intangible benefits of the program, such as avoiding the pain and suffering caused by the disease, need to be included in the economic model to evaluate the economic benefits of the vaccination program.

From a programmatic perspective, introduction of new vaccines into the EPI is possible in Thailand. The EPI was instituted by the Ministry of Public Health

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(MoPH) in Thailand more than 30 years ago and 100% of the vaccines in the EPI are funded by the Thai government. At government hospitals and health centers, the program immunizations are free. Ninety-seven percent of children in the country receiving three doses of DTP by age 6 months (Chunsuttiwat *et al*, 1997; Tamapornpilas *et al*, 2003; WHO and UNICEF, 2005). The MoPH performed a prospective population-based surveillance of Hib meningitis in 2000 and the annual incidence of laboratory-confirmed Hib meningitis was relatively low at 3.8 per 100,000 children under age five years (Rerks-Ngarm *et al*, 2004), Thereafter, a complete economic evaluation of Hib disease burden and the private demand (willingness-to-pay or WTP) for a Hib vaccine was performed in 2006 to capture the intangible benefits (Muangchana and Bishai, 2010). In this study, we performed a CBA of a universal Hib vaccination program by incorporating tangible and intangible costs and benefits to both provider and client (Drummond *et al*, 1997; Denil *et al*, 2005). The results of this study should help in the decision making process.

MATERIALS AND METHODS

Data sources

Information used in this study was obtained from both in and outside the country (Table 1). Where possible Thai data were used. For probabilities, we used data regarding Hib disease incidence, case-fatality rates, vaccine coverage and wastage from Thailand, while disability rates were obtained from developed countries (Baraff *et al*, 1993; Chotpitayasunondh, 1994; Likitnukul, 1994; Tamapornpilas *et al*, 2003; Rerks-Ngarm *et al*, 2004). For cost, most information sources were from Thailand. The intangible benefits of the vaccination program estimated by WTP survey and the direct and indirect cost of Hib disease burden also from Thailand (Wisasa *et al*, 2002; Muangchana *et al*, 2010). The cost weighted by group was calculated for the ambulatory expense (Pannarunothai, 2003). The cost of the DTP-HB vaccination program was estimated for Hib vaccination program cost (Chunsuttiwat *et al*, 2002). GDP per capita for the country was used to estimate productivity loss (2005). For cost of treatment and disability we used the tax exemption given to families of those with severely disabled people; data obtained from Malaysia (Hussain *et al*, 1999). The results from developed country studies were used to calculate case-disability rates (Baraff *et al*, 1993; Levine *et al*, 1998). We assumed the productive life of disabled individuals was up to 50 years old, 10 years shorter than healthy individual in Thailand (Zhou *et al*, 2002) (Table 1).

Analysis

We developed a decision tree model on which to base a simulation of Hib disease in children under 5 years of age and its impact on a hypothetical cohort of Thai children born in 2006 (740,109). The cost and probability items were analyzed using the net present value (NPV), by evaluating the costs and benefits to society of the vaccine, by comparing two birth cohorts of the same size population: those with and without the Hib vaccine. Microsoft Excel and STATA version 8 were used for analyses. A three percent discount rate and general consumer price index (CPI) were used to adjust cost and benefit from the year 2006 (Drummond *et al*, 1997; Brouwer *et al*, 2001; Denil *et al*, 2005). The vaccines were assumed to be provided to the infants in the analytical birth cohort at 2, 4, and 6 months of age (Levine *et al*, 1998).

Table 1
Data source.

Variables	Probabilities (Rates)	Cost/benefit
A. Cost of Hib disease		
1. Meningitis	Findings from "Prospective population-based incidence of *Haemophilus influenzae* type b meningitis in Thailand". 1. Incidence/100,000 <1 yr old 13.7 1 yr old 4.6 2-4 yrs old 0	1. Application of the study results of "Population-based Hib burden study: Economic cost of Hib disease to Thai society" for hospitalization and home care cost. 2. Cost per relative weights by related groups for cost of ambulatory care.
2. Pneumonia	Pneumonia estimation suggested by WHO; Hib pneumonia incidence would be five times that of Hib meningitis. 1. Incidence/100,000 <1 yr old 68.5 1 yr old 23.0 2-4 yrs old 0 2. Vaccine efficacy 95%	
3. Disability	Outcomes of bacterial meningitis in children in developed countries (Baraff, 1993) Disability rate: Mental retardation 4.2% Severe hearing loss 5.1% Epilepsy 4.2% Spasticity/hemiplegia 3.5%	1. Tax exemption for disabled. Cost of disability treatment and follow-up assumed to be equal to THB 50,000 annual tax exemption given to the family with disability in Malaysia. 2. Assumption: Life expectancy of disabled 50 years. Life expectancy used to calculate productivity loss, if shorter than 60 years old. 3. Gross domestic product (GDP) per capita used to estimate productivity loss per year.
4. Premature death	Retrospective study of Hib meningitis in Thailand and WHO suggestion on case-fatality rate of Hib pneumonia based on under five mortality rate: Case-fatality rate Meningitis 11% Pneumonia 10%	1. Gross domestic product (GDP) (the description in 3. disability)

Table 1 (Continued).

Variables	Probabilities (Rates)	Cost/benefit
B. Cost of Hib vaccination program	Immunization vaccine coverage survey and estimated vaccine wastage rate in Thailand. 1. Vaccine coverage 97.6% (DTP3) 2. Vaccine wastage rate 10%	1. Application of the study results "Comparative evaluation of a combined DTP-HB vaccine in the EPI in Chiang Rai Province, Thailand" used for Hib vaccination program, cost estimated. 2. Hib initiative website for Hib vaccine price. 3. Results of A "Private demand of Hib vaccination in a probable low Hib disease incidence country: Thailand 2006", used for the estimation of intangible benefit of Hib vaccination program.

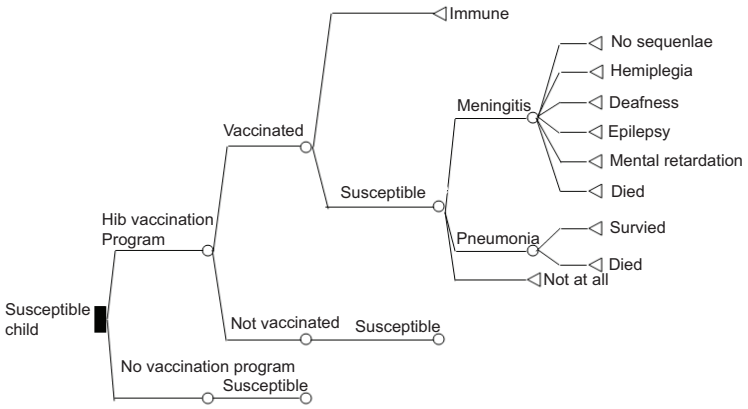

Fig 1–Decision tree diagram.

In the model it was assumed the vaccine was either given or not given. In the vaccinated children, the possible outcomes were either immunity or susceptibility to the disease. Among susceptible children, the possible outcomes were: developing meningitis, pneumonia, or neither. Of the meningitis cases, the possible outcomes were: 1) survival with no sequelae, 2) survival with sequelae, such as hemiplegia, deafness, epilepsy or mental retardation, or 3) death. For pneumonia, the possible outcomes were: 1) survival with no sequelae, or 2) death. In children without vaccination, all were susceptible to the disease and the possible outcomes were the same as susceptible children with the program (Fig 1).

Number of cases and cost of Hib disease and the vaccination program

We calculated the cumulative number of Hib disease related cases, including meningitis, pneumonia disability and death in both the pre- and post-vaccine introduction eras and number of cases prevented by Hib vaccination for the cohort over a 5-year period. The number

Table 2
Classification of costs and analysis methods.

Variables	Provider cost		Client cost	
	Direct (Capital)	Direct (Recurrent)	Direct	Indirect
A. Cost of Hib disease				
1. Meningitis	yes [a]	yes [a]	yes [a]	yes [a]
2. Pneumonia	yes [a]	yes [a]	yes [a]	yes [a]
3. Disability	yes [b]	yes [b]	yes [c]	yes [c]
4. Premature death	no	no	no	yes [d]
B. Cost of Hib vaccination program				
1. Total cost analysis using mono-valent vaccine	yes	yes	yes	yes
2. Marginal cost analysis using mono-valent vaccine	no	yes [e]	no	no
3. Marginal cost analysis using combination vaccine	no	yes [f]	no	no

[a] Acute disease treatment, including costs from both out- and in-patients.
[b] Disability treatment and follow-up, after acute phase until 50 years of age.
[c] Work impairment, between 18 and 50 years old, AND work loss, from premature death, between 51 and 60 years old.
[d] Between 18 and 60 years old.
[e] INCLUDED Hib vaccines, syringes, and staff time for vaccine injection; EXCLUDED staff time for vaccine management.
[f] INCLUDED Hib vaccines; EXCLUDED syringes, staff time for vaccine injection and staff time for vaccine management.

of cases was calculated by multiplication of the specific rates by the numbers of the relevant groups. Table 2 shows the cost classification and methods of analysis (Drummond *et al*, 1997). We assumed all institutional treatment costs were paid by provider (the government), while the client paid only for non-institutional expenses, including travel, meals and productivity loss. The cost related to Hib disease included the perspective of costs of the following clinical presentations: meningitis, pneumonia, disability caused by meningitis, and premature death from meningitis or pneumonia. The cost of the Hib vaccination program depended on the type of analyses, including: 1) total cost analysis, 2) the cost for the mono-valent vaccine, and 3) the cost for the combination vaccine. The analyses considered the additional cost of adding new vaccines into the existing vaccination service system; therefore, some items of the program were not taken into account.

For meningitis and pneumonia, the costs included both out- and in-patient care; for disability, the costs included 1) disability treatment and follow-up after the acute phase until 50 years of age, 2) productivity loss from work because of the disability, between 18 and 50 years of age, and 3) productivity loss from premature death because of disability between 51 and 60 years of age; for premature deaths the costs included productivity loss between 18 and 60 years of age. We calculated the cost of Hib disease in pre- and post-vaccine introduction eras,

Table 3
Cost of Hib disease (USD).

Cost classification	Pre-vaccine era	Vaccine era	Cost averted	%
Provider	1,642,114	119,546	1,522,568	39.9
Acute disease treatment				
Capital cost	549,280	39,988	509,292	13.4
Recurrent cost				
Labor	476,085	34,659	441,426	11.6
Material	168,120	12,239	155,881	4.1
Routine	21,176	1,542	19,635	0.5
OPD visit	53,895	3,924	49,972	1.3
Chronic disease treatment				
Disability treatment	373,557	27,195	346,362	9.1
Client	2,469,485	179,778	2,289,706	60.1
Acute disease treatment				
Direct	22,001	1,602	20,399	0.5
Indirect	24,106	1,755	22,352	0.6
Disability				
Direct	373,557	27,195	346,362	9.1
Indirect	326,805	23,791	303,014	8.0
Death				
Direct	0	0	0	0.0
Indirect	1,723,015	125,435	1,597,579	41.9
Total	4,111,599	299,324	3,812,275	100.0

therefore, cost averted could be estimated.

The total cost for the mono-valent vaccine included all perspectives, while the marginal cost analysis using the mono-valent vaccine included only some items of recurrent cost, which are provider costs. These costs were Hib vaccine, syringe, and staff time for vaccine injection, but excluded staff time for vaccine management. With marginal cost analysis using the combination vaccine, more items in the recurrent cost were excluded: the syringe and staff time for the injection.

Net present value (NPV) and sensitivity analysis

NPVs were calculated as shown in the equations below: equation (1) excluded WTP for Hib vaccines, while equation (2) included the WTP.

Equation (1) NPV = C_V-C_{AV}

Equationn(2) NPV= C_V-C_{AV}+ *Willingness-to-pay*

where, NPV = Net present value, C_V = costs of vaccination, C_{AV} = costs averted due to vaccination.

A series of sensitivity analyses were conducted to assess the uncertainty of relevant parameters. One-way and multi-way sensitivity analyses were performed. One-way sensitivity analysis was performed to assess the effect of varying one parameter, holding the other parameters constant. For threshold analysis, we de-

Table 4
Cost of Hib vaccination program.

Cost classification	Total cost (Mono-valent vaccine)		Marginal cost (Mono-valent vaccine)		Marginal cost (Combination vaccine)	
	USD	%	USD	%	USD	%
Provider	8,796,014	95.5	8,366,124	100.0	7,513,160	100.0
Capital	112,049	1.2	0	0.0	0	0.0
Recurrent						
Vaccine	7,389,604	80.2	7,389,604	88.3	7,389,604	98.4
Syringes and needles	185,523	2.0	185,523	2.2	0	0.0
Others	1,108,839	12.0	790,997	9.5	123,556	1.6
Client	414,373	4.5	0	0.0	0	0.0
Direct cost	207,187	2.3	0	0.0	0	0.0
Indirect cost	207,187	2.3	0	0.0	0	0.0
Total	9,210,387	100.0	8,366,124	100.0	7,513,160	100.0

termined the critical values beyond which the conclusions of the analysis changed. A decision change was considered when the NPV changed from negative value to positive or positive to negative. Multi-way sensitivity analysis was performed by generating random variables from the normal population given assigned means and standard deviations for N=3,000, while other variables were kept constant. The data were then analyzed for distribution, mean, standard deviation, and 95% confidence interval for the NPV. In situations in which policies had independent effects and there were no constraints on inputs, we adopted all policies that had a positive NPV (Boardman *et al*, 1996).

RESULTS

Number of cases, cost of Hib disease and vaccination program

In the pre-vaccine era, the expected cases of Hib disease were 812, which included 135 cases of meningitis (17%) and 677 cases of pneumonia (83%). Of these, the expected number of fatalities was 83 cases (10%) and the number of those severe disabled from meningitis was 20 cases (15%). If a universal immunization program included the Hib vaccine, 754 cases of Hib disease would be prevented (93%). Of these, 126 cases would be meningitis, 628 would be pneumonia, 77 would be deaths from either meningitis or pneumonia, and 19 would be severely disabled.

In the pre-vaccine era, the overall cost of Hib disease was USD 4.1 million per cohort compared to USD 0.3 million during the vaccine era (Table 3). Therefore, the cost averted by the vaccination program was USD 3.8 million. Even though the institutional costs of the cases and the disabled would be paid by the government, cost of the disease paid by the client (60%) was more than that paid by the government (40%). About half (50%) of the total cost was productivity loss from death and disability.

For the cost of Hib vaccination program (Table 4) the overall costs varied based on the types of analyses. The costs

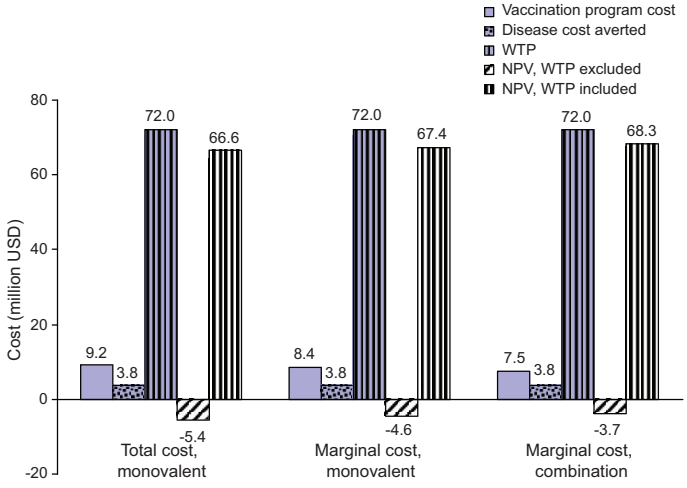

Fig 2–Net present value (NPV) of Hib vaccination program.

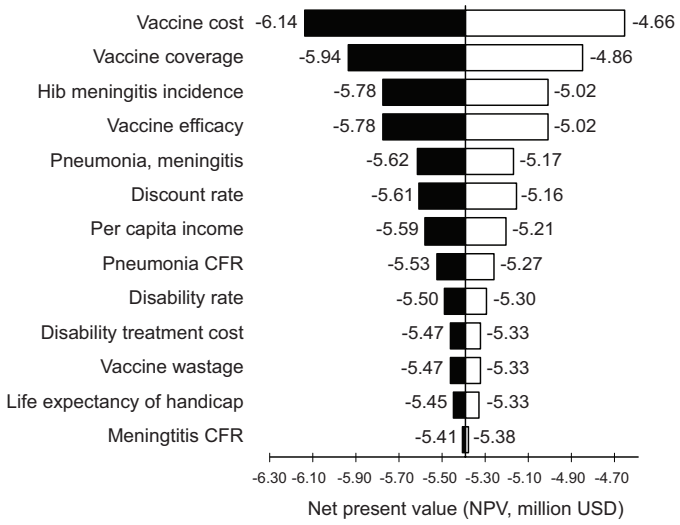

Fig 3–One way sensitivity analysis for 10% changes in selected influential values.

analyzed by marginal cost analysis were lower than those analyzed by the total cost analysis between USD 1 and USD 2 million. The overall costs, in descending order were: the total cost analysis (USD 9.2 million), the marginal cost analysis using mono-valent vaccines (USD 8.4 million), and the marginal cost analysis using combination vaccines (USD 7.5 million). The highest cost was vaccine cost, which varied from 80% to 98% of the total cost. Of the total program cost, the client paid for not more than 5% of the cost.

Net present value (NPV) and sensitivity analysis

Fig 2 shows the NPV for the base case analysis, comparing the present values of the costs of the Hib vaccination program with the disease cost averted. From the results of equation (1), with the WTP excluded, regardless of the type of vaccination program cost analysis, the NPVs were all negative (cost averted < the vaccination program cost) from -USD 5.4 million, for the total cost analysis, to -USD 3.7 million, for the marginal cost analysis using combination vaccines. In contrast to the results of equation (2), with the WTP included, regardless of the type of analysis, NPVs were all positive from USD 66.6 million, for the total cost analysis, to USD 68.3 million, for the marginal cost analysis using the combination vaccines.

Fig 3 presents the effects of changing the values of the selected variables used in equation (1), with the WTP excluded, on the NPV of the vaccination program by the total cost analysis for base case analysis. The bars show the change in the NPV (million THB) for 10% changes (either increasing or decreasing) of one variable evaluated and the other variables constant at the value used for base case analysis. The NPV was more highly sensitive to

changes in Hib vaccine cost than the other variables shown in the diagram. Reducing the cost of the vaccine by 10% increased the NPV by 14%. In contrast, if the vaccine cost increased by 10%, the NPV was reduced by 14%. The other three highly influential variables were vaccine coverage, meningitis incidence, and vaccine efficacy. Moderately influential variables were the case ratio of pneumonia to meningitis, the discount rate, and the income per capita. Variables which only influenced the NPV slightly were pneumonia CFR, disability rate among survivors of Hib meningitis, treatment costs for disabilities, vaccine wastage rate, life expectancy of disabled individuals due to meningitis, and meningitis CFR. Of the NPV for the results of equation (2), WTP was the most influential factor.

The results of threshold analysis looking at selected variables found an increasing incidence of Hib meningitis in children under five years old increased the NPV. Assuming the ratio of pneumonia to meningitis was 5:1, the benefits of the vaccination program were equal to the disease cost averted (NPV=0) when Hib meningitis incidence was approximately 9 per 100,000, or 2.5 times as high as the current incidence. When increasing the ratio of pneumonia to meningitis, the NPV increased. The NPV reached zero when the ratio of pneumonia to meningitis increased to 17:1. At this point, the Hib pneumonia incidence would be 62 per 100,000 (17 times the meningitis incidence). The vaccine cost had an inverse relationship with the NPV. When the price per dose of the vaccine was cheaper than 80 cents, or about 25% of the current price, the NPV would finally become positive. With respect to equation (2), with the WTP included, we found the critical value, when the NPV was zero, was 7.8% of the current WTP.

Results of multi-way sensitivity analysis of selected variables, including Hib meningitis incidence, the ratio of pneumonia to meningitis, and the WTP, as seen in equation (1), with the WTP excluded, was a negative amount of USD 4.77 million (95%CI -4.81, -4.72). In equation (2), with the WTP included, the result was a positive amount of USD 67.00 million (95%CI 66.47, 67.53).

DISCUSSION

This study considered the costs and benefits of adding the Hib vaccine to the current regimen. The Hib vaccination program in Thailand would prevent 126 meningitis cases per birth cohort, including 14 deaths and 19 cases of severe disability. With the assumptions used in the analysis, the vaccination program would prevent 677 pneumonia cases, including 63 deaths, per birth cohort. Other than the cost related to the disease, suffering from death and disability, would cost the parents USD 72 million. This value is 9 times higher that the additional budget needed for adding the Hib vaccine to the EPI. If we consider this cost and the intangible benefits, society would gain a net benefit of USD 68 million. Therefore, the study results with these assumptions suggest introduction of a universal Hib vaccination program would be beneficial in Thailand.

Regarding the threshold analysis, the positive net benefit of a Hib vaccination program to Thai society could be robust. On the sensitivity analysis, the NPV does not decrease to zero until the WTP for the vaccine per dose decreased to USD 2.5 or 7.7% of the WTP. The robustness of the NPV with the WTP included was also seen on multi-way sensitivity analysis,

in which the 95%CI of the NPV per birth cohort was between USD 66.47 and USD 67.53 million. When excluding the WTP, the vaccination program has a negative NPV between USD 3.7 and USD 5.4 million. Therefore, the WTP for the Hib vaccine (intangible benefit) is likely to make introduction of the conjugate Hib vaccine into the EPI cost-beneficial.

The most likely reasons for the negative NPV in the model excluding the intangible benefits are the high cost of the Hib vaccine and the low incidence of Hib disease. The one-way sensitivity analysis shows vaccine cost and Hib meningitis incidence are the two most influential factors in equation (1). The cost of the Hib vaccine is about twice as high as the DTP-HB vaccine and accounts for between 80% and 98% of the overall cost of the Hib vaccination program (Table 4). Developing countries where the Hib vaccine has been implemented have found Hib vaccine cost is the only significant cost for its addition to the existing vaccination program (Wenger *et al*, 2000). In the current situation with the WTP exluded, if the Hib vaccine cost per dose is < USD 0.80 or if the annual incidence of Hib meningitis is greater than 9/100,000 children under five years of age, introducing the Hib vaccine into the EPI is cost effective.

The high vaccine cost and low incidence are reasonable explanations for the negative NPV. When compared with the results of the evaluation of the Japanese encephalitis (JE) vaccine in Thailand, in which the NPV is positive, the annual incidence of JE in Thailand during the pre-vaccine era is 15/100,000 (comparing to 3.8 for Hib meningitis incidence) and the vaccine cost per course is USD 1.5 (compared to USD 10.2 for the Hib vaccines) (Siraprapasiri *et al*, 1997), the JE vaccination program in Thailand gives a financial benefit of USD 6 million per birth cohort. Most of the results of the economic analysis, such as the CBA, cost effectiveness analysis, and cost utility analysis, of the universal Hib vaccination program, are strongly supportive of Hib vaccine introduction. In some countries, the incidences of Hib meningitis in children are relatively high, ranging from 16/100,000 in Slovenia to 184/100,000 in Israel. One study in Spain did not support Hib vaccination; the incidence in Spain is 15/100,000, which was the lowest incidence in this review (Brinsmead *et al*, 2004).

Hib meningitis incidence from the prospective of a population-based study conducted in the country, is probably under estimated because of the limitations of the study design. A case definition of Hib meningitis in the study was laboratory-confirmed Hib identified from spinal fluid. This definition may not be sensitive enough to detect many cases, as was seen in an Indonesian study which found clinically confirmed Hib meningitis incidence was 10 times as high as laboratory-confirmed incidence (Gessner *et al*, 2005). If we assume the ratio of clinical- to laboratory-confirmed cases is similar to Thailand, the possible incidence of Hib meningitis in Thailand could be 38/100,000. This incidence is 4 times higher than the incidence threshold in our study.

The ratio of pneumonia to meningitis incidence used may have been under- or over-estimated. The ratio of 5 used in our study was recommended by the WHO for estimating Hib disease, by using available information (WHO, 2001). This ratio is based on a vaccine trial, but it is not certain if it can be applied to Thailand or not. The vaccine study conducted in Indonesia found the ratio of Hib pneumonia to meningitis was about 10, which is twice as

high as that used in this study (Gessner *et al*, 2005). The use of this higher ratio alone does not change the NPV from negative to positive because the threshold of this ratio is 17; it can be synergistic to the influence of the suspected higher incidence of Hib meningitis. The limited information regarding Hib disease incidence in Thailand and the findings of the Indonesian study, even with the intangible benefit (WTP) excluded from analysis, make it possible that a universal Hib vaccination program in Thailand could be cost-beneficial.

The budget needed to fund this Hib vaccination program is at least 37% (USD 7.5 million or THB 270 million) of the current vaccine purchasing budget for the EPI (USD 21 million). Of this amount, USD 7.4 million (99%) would be needed for vaccine purchasing. The additional budget would amount to 0.1% of the total health expenditure of the country (WHO, 2006). The high cost compared to the current vaccine budget is a major concern for policy makers in funding a Hib vaccination program. In addition to the societal benefits of a Hib vaccination program, vaccination, in general, is found to be the most cost-effective intervention in disease prevention and control (Bloom *et al*, 2005). Launching a Hib vaccination program in Thailand is probably an efficient allocation of funds.

In conclusion, even though Hib disease incidence in Thailand is relatively low, a universal vaccination program of the conjugate Hib vaccine may be beneficial because of the severity of the disease, reflected by the high WTP for the vaccine. A user fee would be a barrier to the risk group to access the vaccine (Milstein *et al*, 2005). The incidence used in the analysis is probably underestimated (WHO, 2005); underestimating the benefits of the vaccination program.

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