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Cost-effectiveness of *Haemophilus influenzae* type b vaccine in Vietnam

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Abstract

Background—With GAVI support, Vietnam introduced *Haemophilus influenzae* type b (Hib) vaccine in 2010 without evidence on cost-effectiveness. We aimed to analyze the cost-effectiveness of Hib vaccine from societal and governmental perspectives.

Method—We constructed a decision-tree cohort model to estimate the costs and effectiveness of Hib vaccine versus no Hib vaccine for the 2011 birth cohort. The disease burden was estimated from local epidemiologic data and literature. Vaccine delivery costs were calculated from governmental reports and 2013 vaccine prices. A prospective cost-of-illness study was conducted to estimate treatment costs. The human capital approach was employed to estimate productivity loss. The incremental costs of Hib vaccine were divided by cases, deaths, and disability-adjusted life years (DALY) averted. We used the WHO recommended cost-effectiveness thresholds of an intervention being highly cost-effective if incremental costs per DALY were below GDP per capita.

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Result—From the societal perspective, incremental costs per discounted case, death and DALY averted were US$ 6,252, US$ 26,476 and US$ 1,231, respectively; the break-even vaccine price was US$ 0.69/dose. From the governmental perspective, the results were US$ 6,954, US$ 29,449, and US$ 1,373, respectively; the break-even vaccine price was US$ 0.48/dose. Vietnam's GDP per capita was US$ 1,911 in 2013. In deterministic sensitivity analysis, morbidity and mortality parameters were among the most influential factors. In probabilistic sensitivity analysis, Hib vaccine had an 84% and 78% probability to be highly cost-effective from the societal and governmental perspectives, respectively.

Conclusion—Hib vaccine was highly cost-effective from both societal and governmental perspectives. However, with GAVI support ending in 2016, the government will face a six-fold increase in its vaccine budget at the 2013 vaccine price. The variability of vaccine market prices adds an element of uncertainty. Increased government commitment and improved resource allocation decision making will be necessary to retain Hib vaccine.

Introduction

Haemophilus influenza type b (Hib) is an infectious bacterium transmitted from person to person through close contact. Hib can cause meningitis, pneumonia and other less frequent diseases, primarily in children less than five years [1, 2]. In Vietnam, the incidence of Hib meningitis was estimated to be 18/100,000 (95% confidence interval, 15.1-21.6) in children less than five years [3].

Hib vaccine has been used in developed countries since the early 1990s [2]. The herd immunity effect of Hib vaccine has led to a higher vaccine effectiveness compared to efficacy and a near-elimination state in countries with high coverage [4, 5]. Thanks to global efforts in infectious disease prevention, the Global Alliance for Vaccine and Immunization (GAVI) was established and has provided new and underused vaccine support to low-income countries, including Hib vaccine, since 2000. Using GAVI funding, Vietnam introduced the combined diphtheria-tetanus-pertussis-hepatitis B-Hib (DTP-HepB-Hib or “pentavalent”) vaccine in 2010 [6].

According to the country application for GAVI, Vietnam co-financed $0.30 per dose in 2010 and increased the rate by 10% annually during 2011-2015 [6]. However, in 2012 Vietnam moved from the low-income country group to the intermediate group and was responsible for a $0.20/dose rate with a 15% annual increase. The 2013 UNICEF pentavalent vaccine procurement price (one-dose vial) for GAVI was six times more expensive than the combination price of DTP and HepB vaccines [7]. This is a significant financial burden for the Vietnamese government if it decides to cover the pentavalent vaccine in the Expanded Program for Immunization (EPI) after GAVI support ends in 2016. The objective of this study was to analyze the cost-effectiveness of the introduction of the Hib vaccine versus no Hib vaccine in Vietnam. Given that no such analysis was available before the decision of vaccine introduction was made, the study will provide a useful impact assessment to support future decision making.

Methods

Study design

A decision-tree cohort model was developed to estimate the impact of Hib vaccine on disease burden and costs for the 2011 Vietnamese birth cohort (figure 1). Two vaccine schedules in comparison were the pentavalent vaccine administered at 2, 3, and 4 months after a HepB birth dose versus 3 doses of DTP and 3 doses of HepB vaccines. Microsoft Excel 2007 was used to develop the model. Model inputs were derived from local studies and the literature. Model outputs included numbers of Hib meningitis, meningitis sequelae, and Hib pneumonia cases, deaths, and disability-adjusted life years (DALY). Disease burdens from other Hib diseases, such as epiglottitis and cellulitis which are relatively rare, were excluded due to lack of data.

The analysis was conducted from the societal and governmental perspectives. All costs were presented in 2013 US dollar (US$) (one US$ is equal to 21,125 Vietnamese Dong [8]) and adjusted for inflation [9]. Costs were discounted at 6.9% (the difference between the 2011 inflation rate and the interest rate for public lending banks [10]). Effectiveness was discounted at 5% [11]. The study was approved by the Institutional Review Board of the University of Texas in Houston, USA and the National Institute of Hygiene and Epidemiology, Vietnam.

Hib associated morbidity and mortality estimates

Table 1 presents estimates and ranges for the base-case and sensitivity analyses. Hib meningitis incidence was based on a retrospective study using the WHO Rapid Assessment Tool (RAT) [3]. We chose the RAT which reported a higher incidence estimate than that of a study conducted during 2000-2002 [12] as RAT estimates were more updated and representative. Data on children less than five years of age with a diagnosis of meningitis were collected from five hospitals in Hanoi and Ho Chi Minh City in 2004-2005 and entered into the RAT standardized worksheet for burden calculation. Hib meningitis sequelae rate and case-fatality rate (CFR) for treated cases were derived from population-based surveillance of bacterial meningitis in Hanoi [12]. Incidence of clinical pneumonia was estimated from hospital-based surveillance in Khanh Hoa during 2005- 2006 [13]. Because of the lack of hospital-based CFR data, we calculated CFR for treated pneumonia cases from the same RAT study [3].

Incidences and CFR were adjusted for limited access to care using the average reported proportion of under-five children with suspected pneumonia taken to an appropriate health provider in Vietnam according to UNICEF surveys during 1997-2011 [14, 15]. We assumed a 100% CFR for untreated meningitis and CFR of untreated pneumonia twice as that of a treated case. Due to the difficulty in estimating Hib pneumonia incidence, the number of clinical pneumonia cases was calculated, five percent of which were assumed attributable to Hib [13, 16, 17].

Vaccine coverage and effectiveness estimates

We used 91% for three-dose Hib vaccine effectiveness against meningitis from a meta-analysis of case-control studies [18]. Hib vaccine effectiveness against clinical pneumonia was estimated in two meta-analysis studies; one summarized efficacy for three doses [16] while the other used the efficacy after one dose [19]. To be consistent with the three-dose schedule, we used the three-dose effectiveness of 5% [16]. Based on government yearly reports, we averaged coverage rates for hepatitis B birth dose (48.5%), three doses of pentavalent (91.3%), hepatitis B (89.4%) and DTP vaccines (91.3%) [20].

Disability-adjusted life year estimates

DALYs were estimated as recommended in the 1996 Global Burden of Disease Study [21]. Age weighting was applied. Based on reported lengths of stay, durations of acute meningitis and pneumonia episodes were approximated at 9.5 and 8.3 days, respectively [22]. The duration of meningitis sequelae was assumed to be throughout patients' lives. The disability weight of 0.21 for a severe, acute episode of an infectious disease was used for both meningitis and pneumonia episodes [23]. We estimated the average disability weight for meningitis sequelae using weights of health states equivalent to different types of sequelae (developmental delay, hearing/vision loss, hydrocephalus, paralysis, seizure disorder, and vegetative state), adjusted for the percentage of sequelae types [12, 23]. The final weight was 0.343.

Cost estimates

Vaccine delivery costs—According to the country's application [6], no cold chain expansion or additional costs for vehicles and transportation were needed. Hence, only vaccines, injection supplies and other vaccine introduction costs were included. 2013 vaccine prices were used (US$ 2.59/pentavalent dose, US$ 0.141/DTP dose and US$ 0.29/hepatitis B dose). Vaccine wastage rates were set at 5%, 15% and 35% for the pentavalent vaccine, HepB vaccine and DTP vaccine, respectively [6]. Costs of injection supplies were the sum of costs of syringes, safety boxes and waste management, where costs of safety boxes and waste management were set at 20% of syringe costs [24]. Wastage rate of syringes was 10% and buffer stock rates for the new vaccine and syringes were 25% in the first year of introduction. Vaccine introduction costs were based on government reports, which detailed the costs of information-education-communication activities (conferences, advertisements, field trips) and training of immunization personnel [25, 26].

Disease treatment costs—These costs included direct medical costs from the governmental perspective, and both direct (medical and non-medical) and indirect costs from the societal perspective. We conducted a prospective cost-of-illness study in Bach Mai hospital to estimate mean direct medical costs (DMC), direct non-medical costs (DNMC), and caregiver's time costs among under-five pneumonia and meningitis patients [22]. 180 pneumonia patients and 15 meningitis patients were recruited. Cost categories of meningitis were between one to three times higher than those of pneumonia. Because there were no data on treatment costs of meningitis sequelae available, we based our estimate on several assumptions. Yearly, a disabled child was assumed to consume one outpatient visit at a cost

of US$ 3.16/visit [27], drugs at a cost of twice that of outpatient costs, and transportation costs estimated from the cost-of-illness study [22]. Twenty-one percent of disabled children were assumed to experience one re-hospitalization in the following year at a cost equal to that of the acute episode [28].

To estimate indirect costs, we added productivity loss of household members to care for a sick child during the acute phase and a disabled child, and future lost productivity of the disabled child. Since it has been controversial to assign a dollar value to a life, we did not include productivity loss from death in the base-case, but only in a scenario analysis. The friction human capital approach was used to estimate productivity loss, using the minimum wage rate in 2011 [29] and adjusted for the 2011 national unemployment rate of 2.22% [30].

Patients with sequelae were assumed to have the same disability-adjusted life expectancy at birth as that of patients in the other Asian Islands Region [21]. Applying the United Nation model life table, life expectancy was 55 years for a disabled child less than one year and 61 years for those from 1-5 years [31]. It was assumed that one person cared for the disabled child full time from disease onset until death [28]. To estimate productivity loss from death and disability, we subtracted 18 (the average age of starting to work and earn income) from 58 (the average age of retirement) and multiplied by productivity loss per year. Finally, costs of adverse events were ignored because of well documented safety of the vaccine.

Cost-effectiveness analysis

Incremental cost-effectiveness ratios (ICERs) were presented as the incremental costs per Hib case, death, and DALY averted. As the Vietnamese Government has not determined an official policy for using cost-effectiveness evidence for health care decision making, we used the WHO-recommended thresholds [32]. We assumed that Hib vaccine was cost-effective if incremental costs per DALY averted were less than three times the 2013 Vietnamese gross domestic product (GDP) per capita of $1,911, and highly cost-effective if incremental costs per DALY averted were less than GDP per capita.

Sensitivity analysis

Deterministic sensitivity analysis was conducted for all model inputs with ranges specified in table 1. Tornado diagram was used to present parameters of which variations changed incremental costs per DALY averted ≥10%. We conducted univariate scenario analysis for 0% discount rate for cost and effectiveness, 5% discount rate for cost, a shorter life expectancy for disabled children (30 years), and the addition of productivity loss from death. We also examined different values for Hib meningitis incidence (34/100,000 children/year [16]) and clinical pneumonia incidence (0.35 episode/child-year [33]). Break-even vaccine prices were estimated. Probabilistic sensitivity analysis with 1,000 runs of Monte Carlo simulation was employed.

Results

Impacts of Hib vaccine

Table 2 presents the impact of Hib vaccine on disease burden and vaccine delivery costs. The model predicts that Hib vaccine prevented a discounted number of 1,579 cases, 373 deaths and 8,016 DALYs in the 2011 birth cohort. The vaccine also prevented 76 meningitis sequelae cases.

The introduction of Hib vaccine has imposed an incremental vaccine delivery cost of $11.6 million. While the program actually saved resources on syringes, safety boxes and waste management, the high price of pentavalent vaccine caused a three-fold increase in vaccine delivery costs. Regarding treatment costs, after discounting the vaccine saved the society a total of $1.0 million for medical costs and $606 thousand for sequelae-related productivity loss. From the governmental perspective, the total discounted disease treatment costs saved were $703,000.

Cost-effectiveness analysis

Table 3 shows the cost-effectiveness results for the base-case. The base-case ICERs per discounted case, death and DALY prevented from the societal perspective were US$ 6,252, US$ 26,476 and US$ 1,231, respectively. The ICER per DALY averted was less than 2013 Vietnam's GDP per capita, indicating that Hib vaccine was highly cost-effective. From the governmental perspective, the base-case ICER per DALY prevented was US$ 1,370, which was also below the GDP per capita. The break-even vaccine price was US$ 0.69/dose and US$ 0.48/dose from the societal and governmental perspectives, respectively.

Sensitivity analysis

The scenario analyses (Table 3) showed that Hib vaccine remained highly cost-effective for any scenario and from any perspective. The most important variable was CFR of untreated meningitis of which variation caused incremental costs per DALY averted to increase above GDP per capita, but still below three times of the GDP (Figure 2). In probabilistic sensitivity analysis, Hib vaccine had a mean of US$ 1,279 per DALY averted (95% CI: 606-3,011) and 84% chance of being highly cost-effective from the societal perspective (Figure 3). From the governmental perspective, the Hib vaccine had a mean US$ 1,437 per DALY averted (95% CI: 725-2,840) and 78% chance of being highly cost-effective.

Discussion

Our study found that incremental costs per DALY averted of Hib vaccine compared to no vaccine was US$ 1,231 from the societal perspective and US$ 1,370 from the governmental perspective. According to the WHO thresholds, the introduction of Hib vaccine in Vietnam has been highly cost-effective. Both deterministic and probabilistic sensitivity analyses showed that our results were robust to variations in model inputs. In addition, Hib vaccine remained highly cost-effective in all scenario analyses. Our findings were consistent with other studies conducted in both lower-middle and upper-middle income countries, such as Uzbekistan, India, Indonesia, Kenya, Iran and Columbia [14, 34-39]. In high-income

countries, Hib vaccine cost-effectiveness analyses were largely conducted during the 1990s when the vaccine was first licensed. The large majority of these studies concluded that the vaccine was cost-saving. This was partly due to higher meningitis incidence rates than what has been found in Vietnam, and in particular due to considerable meningitis sequelae treatment costs, which in many instances also included special schooling [40, 41]. Our study identified another highly cost-effective vaccine for Vietnam to consider, in addition to hepatitis B, rotavirus, and HPV vaccines [42-44].

In general, a vaccine is recommended for the EPI when there is sufficient evidence on the burden of disease and the safety and efficacy of the vaccine [4]. While the safety and efficacy of Hib vaccine has been shown in various areas around the world [45], data on Hib disease burden is limited, especially in Asia. Imperfect laboratory techniques, high antibiotics use and inadequate specimen handling and transport have been suggested as possible explanations [4]. Although vaccine probe studies are able to provide better data on disease burden, only two studies have been conducted in Asia [46, 47]. In Vietnam, two epidemiologic studies estimated Hib disease burden before vaccine introduction. One study was a population-based surveillance and the other was a hospital-based surveillance [3, 12]. While both used appropriate case definitions and laboratory techniques, they failed to account for both missing cases and meningitis cases without lumbar puncture, so the reported incidence was likely underestimated. Inappropriate antibiotic use in Vietnam due to common self-medication practices and the ease of antibiotics purchase without prescription is another important issue that probably interferes with true estimates of Hib disease incidences [48]. Although Hib vaccine remained highly cost-effective in sensitivity analyses, the ICERs were especially sensitive to variations in determinants of disease burden, emphasizing the need to have a more precise disease burden estimate.

Our study has several limitations. First was the lack of local data for some model inputs, including CFRs for untreated Hib cases and costs of treatment and care for sequelae cases. However, variations in these parameters did not change our conclusion in sensitivity analyses. Secondly, the disease burden and costs might be underestimated because incidences and costs of other Hib diseases than meningitis and pneumonia were excluded. However, inclusion of other Hib diseases would make Hib vaccine more cost-effective, or even cost-saving. Thirdly, costs of vaccine adverse events were not accounted for, making the ICERs underestimated. Finally, the study did not account for herd immunity effects of Hib vaccine.

Although Hib vaccine introduction was found to be highly cost-effective in Vietnam, our study does not determine the affordability and sustainability of the program in the future. To better prepare recipient countries for self-financing, GAVI mandates a co-financing policy depending on the GNI per capita and GAVI eligibility threshold [49]. A country belongs to low-income country group if its GNI per capita is below the World Bank (WB) low-income threshold. A country is in intermediate group if its GNI per capita is above the WB low-income threshold but below GAVI threshold. A graduating country is the one with GNI per capita above GAVI threshold. The graduating country has to co-finance at a higher rate compared to the other two groups and the rate increases linearly to the full projected vaccine price after four years. Vietnam moved into the intermediate group in 2012. The 2013

Vietnam GNI was US$ 1,740 [50], which was above GAVI threshold; so GAVI has determined the country to be joining the graduating group in 2015. Therefore, the country has only one more year to apply for GAVI new vaccine support and must pay the full projected vaccine price after the next few years. Besides the issue of a six-fold increase in the vaccine budget (should the Hib vaccine remains at current 2013 GAVI-supported price), Vietnam is facing the uncertainty of market vaccine price variation after GAVI support ends. Although graduated countries can access the GAVI price for Crucell's pentavalent vaccine until 2020 [49], there is uncertainty regarding vaccine prices for different presentations (e.g. monovalent Hib vaccine) and from different manufactures after 2020. Therefore, the question of post-GAVI affordability and/or sustainability in Vietnam becomes of significance and requires a careful scrutiny into the government's EPI budget. Hopefully, adequate resources will be available to continue this highly cost-effective Hib vaccine program, which is contributing significantly to child health improvement and achievement of Millenium Development Goal 4 in Vietnam.

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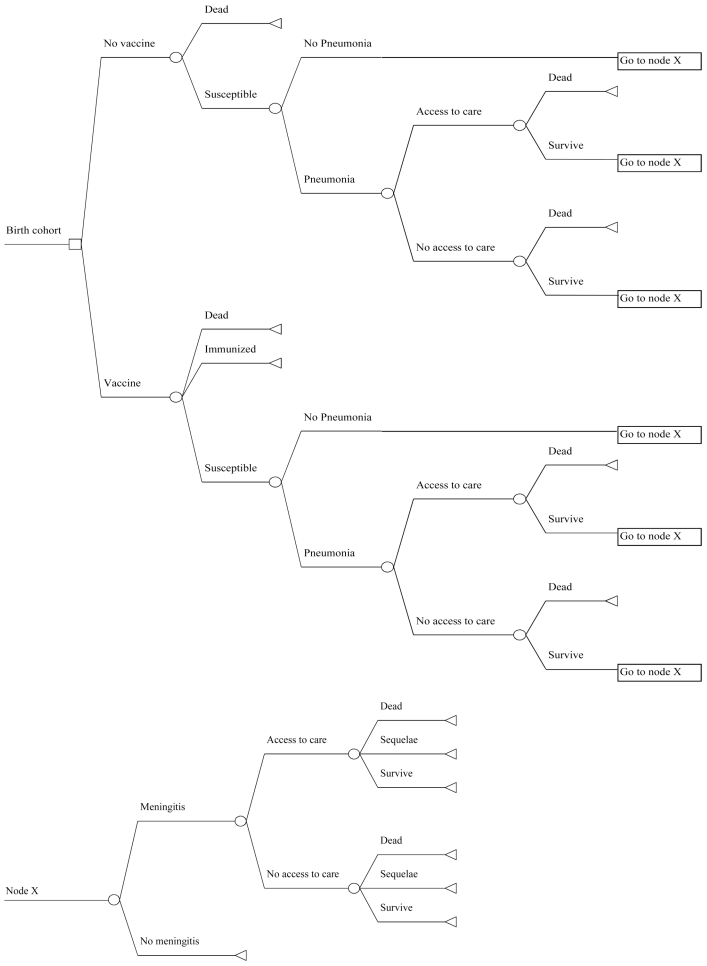
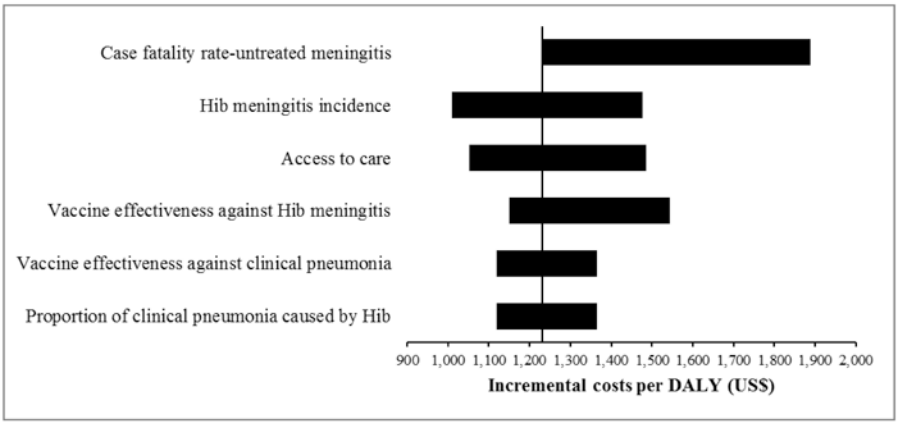


Figure 1. The decision-tree model for the 2011 Vietnamese birth cohort

a. Societal perspective



b. Governmental perspective

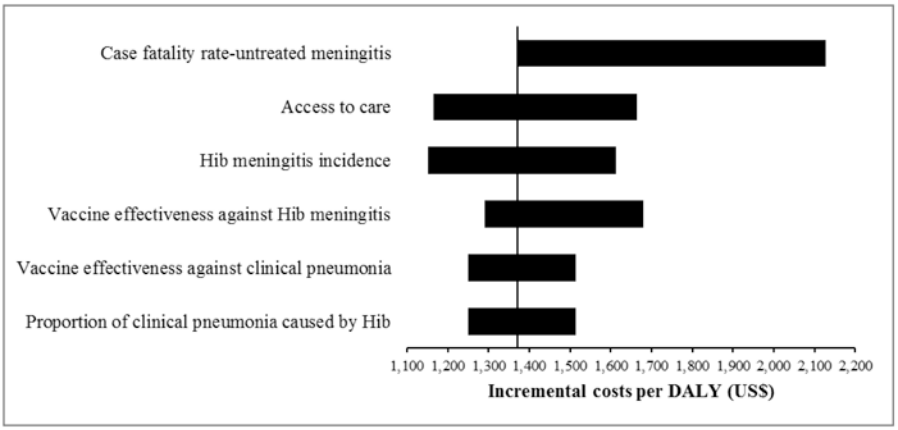
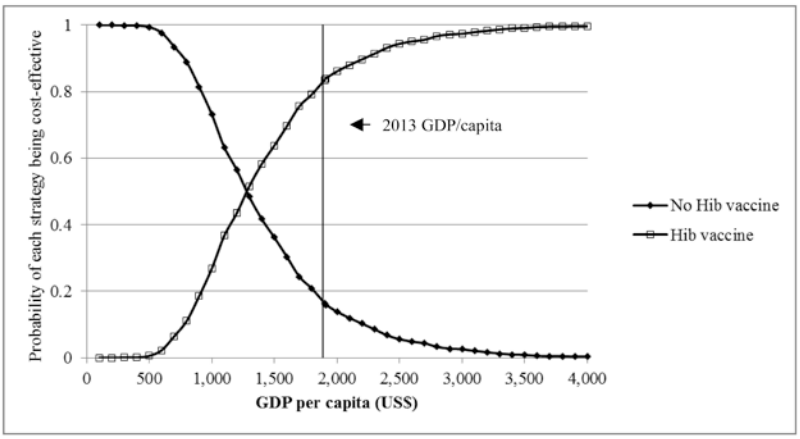


Figure 2.

Tornado diagram of influential model inputs on incremental costs per disability-adjusted life year (DALY). Hib, *Haemophilus influenzae* type b.

a. Societal perspective



b. Governmental perspective

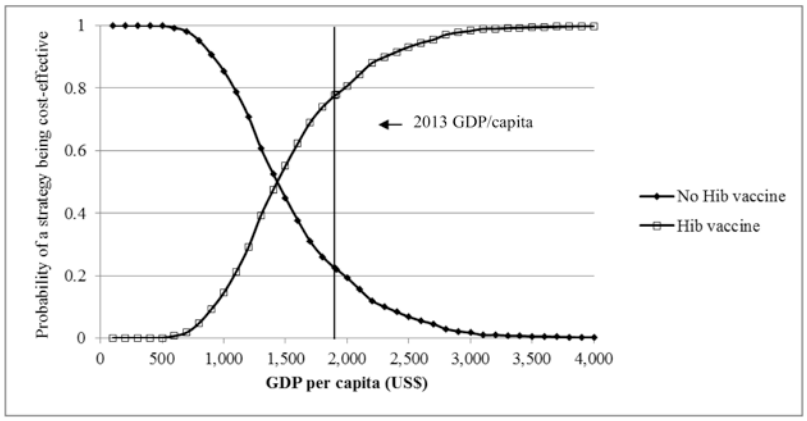


Figure 3.

Cost-effectiveness acceptability curves of Hib vaccine versus no Hib vaccine. Hib, *Haemophilus influenzae* type b; GDP, Gross Domestic Product.

Table 1

Model inputs

Parameters	Base-case value	One-way sensitivity analysis range	PSA distribution	Reference
Epidemiologic data				
2011 live birth cohort	1,444,753	N/A	N/A	
Incidence of Hib meningitis (per 100,000 children per year)	23.22	19.48-27.86	gamma	[3]
Incidence of clinical pneumonia (per child per year)	0.0293	0.0273-0.0566	gamma	[13]
Proportion of clinical pneumonia caused by Hib	0.05	0.01-0.09	beta	[16]
Hib meningitis sequelae rate	0.103	0.048-0.159	beta	[12]
Hib meningitis case fatality rate-treated	0.043	0.019-0.097	beta	[12]
Hib meningitis case fatality rate-untreated	1	0.5-1	N/A	
Hib pneumonia case fatality rate-treated	0.099	0.058-0.168	beta	[3]
Hib pneumonia case fatality rate-untreated	0.2	0.1-0.4	N/A	
Vaccine effectiveness against Hib meningitis	0.91	0.73-0.97	beta	[18]
Vaccine effectiveness against clinical pneumonia	0.05	0.01-0.09	beta	[16]
Coverage rate-HepB birth dose	0.485	0.348-0.621	beta	[20]
Coverage rate-3 doses of HepB	0.894	0.826-0.962	beta	[20]
Coverage rate-3 doses of DTP	0.913	0.86-0.966	beta	[20]
Coverage rate-3 doses of DTP-HepB-Hib	0.913	0.86-0.966	beta	[20]
Hospitalization days per Hib menigitis case	8.3	7.8-8.7	normal	[22]
Hospitalization days per Hib pneumonia case	9.5	4.5-14.5	normal	[22]
Successful rate of access to health care	0.71	0.64-0.78	beta	[15]
Cost data*				
Acute Hib diseases				
Direct medical cost per pneumonia case	189	176-202	gamma	[22]
Direct medical cost per meningitis case	316	129-502	gamma	[22]
Direct non-medical cost per meningitis case	164	44-284	gamma	[22]
Direct non-medical cost per pneumonia case	53	43-63	gamma	[22]
Time cost of caregiver per meningitis case	147	5-288	gamma	[22]
Time cost of caregiver per pneumonia case	63	47-79	gamma	[22]
Sequelae meningitis				
Rehospitalization-direct medical cost	316	129-502	gamma	Assumption & [22]
Rehospitalization-direct non-medical cost	164	44-284	gamma	Assumption & [22]
Rehospitalization-time cost of caregiver	147	5-288	gamma	Assumption & [22]
Proportion of sequelae case need rehospitalization the same year of acute case	0.213	0.096-0.33	beta	[28]
Average number of outpatient visit per year (visit)	0.99	0.06-2.55	gamma	[28]
Cost of transportation per visit	7.36	4.52-10.20	gamma	[22]
Cost per outpatient visit	3.16	N/A	N/A	[27]
Cost of medication	6.32	N/A	N/A	Assumption
Unemployment rate (%)	2.22	N/A	N/A	[30]

Parameters	Base-case value	One-way sensitivity analysis range	PSA distribution	Reference
Productivity loss per year	549	N/A	N/A	[29]

Note: PSA, probabilistic sensitivity analysis; N/A, not available; Hib, *Haemophilus influenzae* type b; DTP, diphtheria-tetanus-pertussis; HepB, hepatitis B.

* Costs are in 2013 US$ unless indicated otherwise.

Table 2

The impact of *Haemophilus influenzae* type b vaccine on discounted disease burden and program costs

	Hib vaccine	No Hib vaccine	Incremental value
Health outcome			
Case	8,756	10,334	1,579
Death	1,022	1,395	373
DALY	20,535	28,551	8,016
Costs (US$)			
Vaccine delivery cost			
Vaccine costs	14,069,633.04	2,665,366	
Program implementation cost	3,107,207.00	2,851,423	
Subtotal	17,176,840.04	5,516,789	11,660,051
Disease treatment cost			
Societal perspective	2,496,575	4,285,342	1,788,767
Governmental perspective	1,459,322	2,139,691	680,368
Total cost			
Societal perspective	19,673,415	9,802,131	9,871,284
Governmental perspective	18,636,162	7,656,480	10,979,682

Note: Hib, *Haemophilus influenzae* type b; DALY, disability-adjusted life year.

Table 3
Base-case and univariate scenario analysis (2013 US$)

	ICER/Case	ICER/Death	ICER/DALY	Break-even price
Societal perspective				
Base-case	6,252	26,476	1,231	0.69
Life expectancy of a sequelae case = 30 years	6,338	26,840	1,271	0.67
Discount rate=0% for cost and effectiveness	2,235	8,240	385	1.81
Discount rate=5% for cost	5,963	25,253	1,175	0.78
Meningitis incidence = 34/100,000 child-year	4,282	17,322	803	0.84
Clinical pneumonia incidence = 0.35/child-year	1,465	10,119	490	0.91
Productivity loss from death included	5,688	24,084	1,120	0.86
Governmental perspective				
Base-case	6,954	29,449	1,370	0.48
Life expectancy of a sequelae case = 30 years	6,953	29,444	1,394	0.48
Discount rate=0% for cost and effectiveness	5,350	19,720	923	0.72
Discount rate=5% for cost	6,883	29,147	1,356	0.5
Meningitis incidence=34/100000 child-year	5,037	20,381	945	0.54
Clinical pneumonia incidence=0.35/child-year	1,720	11,883	576	0.61

Note: ICER, incremental cost-effectiveness ratio; DALY, disability-adjusted life year.