Economic evaluation of *Haemophilus influenzae* type B vaccination in Indonesia: a cost-effectiveness analysis

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ABSTRACT

**Background** *Haemophilus influenzae* type B (Hib) causes significant morbidity and mortality in children under five years of age. A safe and effective vaccine is available but is not in general use in developing countries. This paper evaluates the cost-effectiveness of introducing Hib vaccine in Indonesia as an addition to the country's current DTP–Hepatitis B vaccination program.

**Methods** The economic analysis uses a societal perspective and is based on a 1-year birth cohort of 4.234 million. The disease status of children with and without Hib vaccination is modeled for the year, and health consequences are modeled over the expected life of the child. One-way, two-way, probabilistic and worst-case sensitivity analyses were performed to evaluate the robustness of the results.

**Results** Implementation of Hib vaccination in Indonesia would avert ~76,700 cases of invasive infection, more than 7,150 deaths and 273,000 disability-adjusted life years (DALYs). Compared to no vaccine, the incremental cost-effectiveness ratio (ICER) is US $67 per DALY averted based on UNICEF pricing, whereas the program would save US $3.7 million with GAVI pricing. The result is not sensitive to uncertainty in disease incidence, costs of treatment or the probability of developing immunity.

**Conclusion** The model demonstrates significant cost-effectiveness of implementation of a Hib vaccination program for Indonesian society.

**Keywords** Hib (Haemophilus influenza B), vaccine, Indonesia, cost-effectiveness, immunization, meningitis, pneumonia, childhood

Introduction

Invasive *Haemophilus influenzae* type b (Hib) infection is associated with significant morbidity and mortality in children under five years of age, particularly in developing countries.¹,² Safe and effective vaccines protecting infants from Hib infection have been available for many years and are routinely administered in most high-income countries. However, the vaccines are not widely available in resource-poor settings due to their cost and a paucity of data in developing countries.

A number of economic evaluations of Hib vaccination programs have been performed in low-income countries. Although a cost-effective analysis has been completed for the island of Lombok, Indonesia, none have been completed for the nation as a whole.¹ Evaluations are particularly important for countries such as Indonesia that are eligible for financial support for immunization programs from the GAVI Alliance.³ This paper presents a cost-effective evaluation of introduction of the pentavalent childhood vaccine, including Hib, implemented as an extension to ongoing DTP–Hepatitis B vaccination. This paper used a societal perspective in order to provide decision-makers with information crucial to determining the strength of the case for adding Hib vaccines to Indonesia's national program.

Methods

**Model**

The state of health of the theoretical birth cohort was modeled using Microsoft Excel⁴ and TreeAge Pro software.⁵ A simplified decision tree diagram is presented in Fig. 1A and 1B. Decision tree branches distal to the vaccination/no vaccination node are identical and attached to the distal nodes on the small tree in Fig. 1A.

In the Hib vaccination branch, the model accounts for the proportions receiving the vaccine, those developing immunity and those with no immunity who develop invasive...
Fig. 1  (A) Simplified decision tree: proximal branches  (B) Simplified decision tree: proximal branches
Hib infection with or without long-term sequelae. This paper modeled the surviving birth cohort for one year passing through the decision tree. Consequences of disease are considered over the lifetime of individuals in the cohort.

Epidemiologic data
A surviving birth cohort of 4,234,000 as reported by the WHO in 2005 was used to determine total costs, disability-adjusted life years (DALYs) and cases averted comparing the vaccination program with the status quo of DTP–Hep B tetravalent vaccination. Coverage of 93% was based on the level achieved in the current DTP–Hep B program. Several epidemiological studies were used in the absence of country-specific data for Hib disease and consequences (Table 1). Reports from studies in Lombok were particularly useful as they report data from observations and a hamlet-randomized trial of Hib vaccine. Incidence of bacterial meningitis from that study was lower than that reported previously so the more recent lower estimate was used.2 Studies from Abdullah et al.7 and Al Khorasani and Banajeh8 reported case fatality in Saudi Arabia and Yemen, respectively, and it was assumed that these figures are comparable to those in Indonesia. Case fatality in untreated cases was assumed to be 75%. The incidence of sequelae reported by Thomas9 based on Australian data was used, assuming that occurrence of permanent disability among those who develop invasive infections is similar in different settings. Incidence data were assigned wide variation for sensitivity analysis to account for generalizations made from studies outside Indonesia.

Adverse events associated with Hib pentavalent vaccine do not occur in a significantly higher proportion compared to DTP–Hep B vaccine alone.10 Side effects specifically attributable to the Hib vaccine are generally trivial, and therefore associated costs were not included.

This paper considered the pentavalent vaccine administered at 6, 10 and 14 weeks according to the WHO schedule for DPT. Vaccine effectiveness determined by antibody radioimmunooassay has been reported as high as 99.7% in clinical trials of three doses in Lombok10 and 89–90% with at least one dose for meningitis in Bangladesh.11 However, effectiveness measured by cases averted in randomized trials is reported elsewhere at 80% with plausible variation between 46 and 93%.12 Effectiveness for this evaluation was determined at 95% with variation between 46 and 99%, used in sensitivity analyses. A high estimate was used to partially account for herd immunity, which is known to decrease carriage of infection among those with no immunity.13 This paper also considered the possibility of no herd immunity in sensitivity analyses to account for the slow build-up of herd immunity that occurs when older siblings are unprotected by vaccination.

The proportion of those who receive active treatment among those who develop invasive disease was taken from the Global Burden of Disease ‘Other Asian Islands Region’, which includes Indonesia.14

Cost data
The cost of vaccine purchase was determined by the difference between UNICEF pricing for the Hib pentavalent vaccine and the tetravalent vaccine, currently that does not include Hib.15 A combination of single- and ten-dose vials would be used to keep wastage to 5%. Additional training, waste disposal and increased use of syringes were all factored into the vaccine cost at levels comparable to other studies in similar settings.16, 17 The time cost and transportation of caregivers were not included, because Hib vaccination visits were no more expensive than those for DTP–Hep B vaccination. Limits for sensitivity analyses ranged from the minimum GAVI co-financing amount, for which Indonesia is eligible, to 10% more than UNICEF’s incremental 2006 price.18 Costs were reported in 2005 US dollars and based on completion of a three-dose schedule: US $6.68 with UNICEF pricing and US $1.10 with GAVI pricing.

<table>
<thead>
<tr>
<th>Table 1 Incidence data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive Hib condition</td>
</tr>
<tr>
<td>Meningitis (per 100 000)</td>
</tr>
<tr>
<td>Severe pneumonia (per 100 000)</td>
</tr>
<tr>
<td>Non-severe pneumonia (per 100 000)</td>
</tr>
<tr>
<td>Other invasive disease (per 100 000)</td>
</tr>
</tbody>
</table>

Case fatality rate (%)

- Meningitis (treated) | 20 | Al Khorasani and Banajeh8 |
- Pneumonia (treated) | 1.0 | 0.5–1.5 | Al Khorasani and Banajeh8 |
- Other (treated) | 10 | Al Khorasani and Banajeh8 |

Incidence of sequelae (%)

- Visual impairment | 10 | 5–15 | Thomas9 |
- Hearing impairment | 25 | 20–30 | Thomas9 |
- Paralysis | 19 | 14–24 | Thomas9 |
- Seizures | 17 | 11–23 | Thomas9 |
The estimate is considered high given the fact that significant development of vaccine production capacity is occurring in Indonesia that will likely reduce prices significantly.19

The cost of acute illness from invasive Hib infection was divided into hospitalization, drug and laboratory tests, and one caregiver’s transportation, lodging and time. The average number of days of hospitalization by ward type was estimated from primary data from meningitis and pneumonia cases in Bangladesh (unpublished data) under the assumption that Indonesia would have a comparable protocol of clinical care. Costs for hospital stays were calculated from the WHO20 and corresponded to hospital bed costs reported by Suwandono et al.21 Drug and laboratory costs were assumed to increase hospitalization costs by 50%. Caregiver time costs were based on the minimum wage for Indonesia to account for the high rate of unemployment and relatively low wage for work outside the home of those who normally assume the caregiver role (Table 2).22,23

Costs of long-term disability were based on four additional outpatient services each year and one caregiver assigning a full workday to caring for the disabled child. Purchases of medications were also factored into the cost based on the amount calculated for acute illness. Costs of special education were not included because of the assumed low availability and ability to pay for families with disabled children. Total costs were calculated over the average life expectancy of 66 years discounted at 3% per annum.

**Table 2 Costs of disease**

<table>
<thead>
<tr>
<th>Cost component</th>
<th>Basis of costs</th>
<th>Estimate (2005 US$)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Meningitis (acute)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td>3 ICU days, 10 ward days</td>
<td>488.00</td>
<td>WHO20, Suwandono,21 primary data</td>
</tr>
<tr>
<td>Drugs/Lab tests</td>
<td>50% of hospitalization costs</td>
<td>244.00</td>
<td>WHO20</td>
</tr>
<tr>
<td>Caregiver time</td>
<td>1 month at minimum wage</td>
<td>35.00</td>
<td>Asian Economic News23</td>
</tr>
<tr>
<td>Transportation</td>
<td>Eight trips on local transportation</td>
<td>8.00</td>
<td>Eliot24</td>
</tr>
<tr>
<td>Lodging</td>
<td>15 days accommodation</td>
<td>84.00</td>
<td>Eliot24</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>859.00</td>
<td></td>
</tr>
<tr>
<td><strong>Meningitis (permanent disability)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient visits</td>
<td>Two additional per year</td>
<td>31.60</td>
<td>WHO20</td>
</tr>
<tr>
<td>Caregiver time</td>
<td>25% of time</td>
<td>420.00</td>
<td>Asian Economic News23</td>
</tr>
<tr>
<td>Medications</td>
<td>50% of out-patients cost</td>
<td>120.00</td>
<td>WHO20</td>
</tr>
<tr>
<td>Transportation</td>
<td>Eight trips on local transportation</td>
<td>8.00</td>
<td>Eliot24</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td>579.60</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>Discount rate of 3%</td>
<td>4178.13</td>
<td></td>
</tr>
<tr>
<td><strong>Pneumonia (non-severe)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient clinic visits</td>
<td>Three to primary care physician</td>
<td>23.70</td>
<td>WHO20</td>
</tr>
<tr>
<td>Drugs/Lab tests</td>
<td>25% of out-patient costs</td>
<td>5.93</td>
<td>WHO20</td>
</tr>
<tr>
<td>Caregiver time</td>
<td>3 days at minimum wage</td>
<td>2.90</td>
<td>Asian Economic News23</td>
</tr>
<tr>
<td>Transportation</td>
<td>Three trips on local transportation</td>
<td>3.00</td>
<td>Eliot24</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>40.63</td>
<td></td>
</tr>
<tr>
<td><strong>Pneumonia (severe)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td>1 ICU day, 6 ward days</td>
<td>255.00</td>
<td>WHO20, Suwandono et al.,21 primary data</td>
</tr>
<tr>
<td>Outpatient visits</td>
<td>3</td>
<td>23.70</td>
<td>WHO20</td>
</tr>
<tr>
<td>Caregiver time</td>
<td>21 days at minimum wage</td>
<td>24.50</td>
<td>Asian Economic News23</td>
</tr>
<tr>
<td>Medications lab tests</td>
<td>50% of out-patients cost</td>
<td>127.50</td>
<td>WHO20</td>
</tr>
<tr>
<td>Transportation</td>
<td>15 trips on local transportation</td>
<td>15.00</td>
<td>Eliot24</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>445.70</td>
<td></td>
</tr>
<tr>
<td><strong>Fatal Hib Cases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td>1 day hospital stay</td>
<td>18.10</td>
<td>WHO19</td>
</tr>
<tr>
<td>Outpatient visits</td>
<td>One primary care</td>
<td>7.90</td>
<td>WHO20</td>
</tr>
<tr>
<td>Transportation</td>
<td>One local trip</td>
<td>1.00</td>
<td>Eliot24</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>27.00</td>
<td></td>
</tr>
</tbody>
</table>
Among fatal cases of Hib that receive treatment, costs were assigned for one visit to an outpatient facility and 1 day of hospitalization as well as caregiver time. For fatal case in which no treatment was given, no costs were assigned (Table 2).

**DALYs**

Age-weighted DALYs were calculated for all relevant outcomes. Disability weights were apportioned according to the Global Burden of Disease. A 3% annual discount was applied for all DALY calculations. Life expectancy data reported by the WHO were used. DALYs for both treated and untreated disease were used in the model.

**Results**

**Cost-effectiveness**

If no Hib vaccine program is available to Indonesian infants, 84,100 infants were expected to develop invasive Hib infection in 1 year. The burden of disease and its sequelae would be 300,000 DALYs. Assuming herd immunity confers significant protection among those either not immune or not receiving at least one dose of vaccine, the number of cases of invasive disease would decrease to 7460 cases with a burden of 26,600 DALYs with a universally available vaccine. A total of 76,700 cases would therefore be averted with a decreased burden of 273,000 DALYs with implementing the vaccination program. An estimate of the monetary costs with no vaccine, assuming a low proportion of those with Hib receive clinical treatment, is US $9.06 million. The cost of implementing the vaccination program as an addition to the existing DTP–Hep B vaccine program is US $27.7 million. The incremental cost-effectiveness ratio (ICER) is US $67 per DALY averted. The number of deaths averted with the vaccine program is approximately 7150.

**Sensitivity analysis**

This paper conducted one- and two-way sensitivity analyses on variables associated with the greatest degree of uncertainty including the probability of developing immunity (including or excluding herd immunity), the incidence of invasive infection, vaccines price and costs of long-term disability.

The overall result of cost-effectiveness was not sensitive to changes in any variables in one-way sensitivity analyses. The incidence of severe pneumonia had the greatest effect on ICER estimates producing variation between US $32 and US $157 through the possible range of incidence. Fig. 2 shows the relative influence of all variables considered in one-way analysis.

All two-way combinations of uncertain variables were also modeled to assess simultaneous effects on the ICER. When the willingness-to-pay level was set at Indonesia’s GNI per capita of US $1280, the ICER continued to favor the pentavalent vaccine over the current strategy. The threshold of vaccine price for cost-effectiveness is US $30 per dose.

To determine the effect of uncertainty in multiple variables, this paper used Monte Carlo simulations to create a confidence interval based on 10,000 samples of triangle distributions of case fatality rates, disease incidences and probabilities of immunity and treatment. Using the standard error obtained, 95% confidence interval for the ICER of US $56.1/DALY–US $77.1/DALY was calculated.

This paper also modeled a ‘worst-case scenario’ of all possible extreme values that do not favor cost-effectiveness of the vaccine. These values included a vaccine cost 20% greater than the present value, a probability of immunization at 80% and disease incidences at the lowest point in the distribution. The result at UNICEF vaccine pricing was an increase in the ICER to US $1150 which is less than Indonesia’s per capita GNI.

**Discussion**

**Main findings**

Hib vaccination in Indonesia, when administered as a pentavalent formulation with DTP and hepatitis B through the existing program, is a cost-effective intervention compared to the status quo of DTP–Hep B vaccination only, assuming a willingness-to-pay of US $1280. At an ICER of US $67 per DALY averted at the UNICEF price and significant cost savings at Gavi pricing, the result highly favors program implementation. This finding is comparable to
cost-effectiveness reported by Miller and McCann for low-to-middle-income countries in Asia in a study from the societal perspective which showed an ICER range from US $79 to US $365 per life years saved in 1998.25

If the Indonesian government paid 90% of the vaccine cost as it does under the present childhood vaccination program, Hib vaccination would represent 0.28% of the total government health expenditure of about US $9.4 billion.26,27 While this is a small percentage, it would represent a much larger proportion of the current Expanded Program for Immunization budget. Affordability may be an impediment to implementation of Hib vaccination, if there is no increase in the vaccination line item of the health budget. The government also lacks incentive to act because it must pay for implementation while most costs of Hib disease are borne by the families of affected children. Rather than rolling out Hib vaccination nationwide, Indonesia may benefit from experience gained in implementing the program on a limited basis initially. Ongoing work in Lombok suggests that this island would be a good candidate for that purpose.1,28,29

Economic evaluations for other childhood vaccines such as pneumococcal, pediatric dengue and rotavirus are available for the region but not specifically for Indonesia.26,30,31 This makes comparison of cost-effectiveness between Hib and other vaccines difficult. Country-specific evaluations with standardized methodologies are necessary to firmly establish the relative economic merits of these programs to allow decision-makers to formulate policy based on valid comparisons of interventions.

Limitations
Few studies have determined the incidence of long-term disability from Hib infection and none specifically in Indonesia. Estimates used in this study were extrapolated from studies in other settings. Accounting for imprecision due to a lack of country-specific data by applying large ranges of uncertainty around the point estimates for sensitivity analysis did not make substantive changes in the finding of cost-effectiveness.

Costs of care for those with long-term disability were based on minimal costs for caregiver time. This paper used conservative estimates to minimize the possibility of bias in favor of the vaccine program and also did not include loss of productivity of the caregiver or those with long-term disability because of insufficient data. If the median or average salary was used instead of the minimum salary and if productivity losses were added, the result would have been even more strongly in favor of the vaccination program.

A wide margin for sensitivity around the vaccine cost reflects the different scenarios for vaccine purchase. Indonesia presently qualifies for support from the GAVI Alliance for their Hib program, so implementation costs would be limited during the initial stage. The estimate for vaccine price used in the model reflects a three-dose regimen given at the price offered by UNICEF. However, previous projections of pricing for Hib vaccine have been inaccurate. Using both GAVI and UNICEF pricing gave results of cost-effectiveness and were well below the threshold of US $30 per dose.

While sensitivity analysis on variables with the greatest uncertainty did not change the overall finding of cost-effectiveness in absolute terms, developing greater precision with the estimate of cost-effectiveness is desirable to place Hib vaccination in the correct order with other health interventions competing for limited resources. Future economic analyses should make use of epidemiological data of Hib disease and its consequences specific to Indonesia as they become available.

Conclusion
Estimates from this economic analysis provide a foundation from which policy decision-makers in Indonesia can make
informed choices about which childhood vaccination program to implement. This is particularly important in the context of application for GAVI Alliance support for rollout of new immunization programs.

Under conservative assumptions about costs of treatment of invasive Hib infection and low estimates of Hib disease incidence, introduction of the vaccination program appears to be a very good investment in the health of Indonesia’s children. At an incremental cost of ~US $67 per DALY averted at UNICEF pricing or a US $3.7 million saving with GAVI pricing, vaccination would prevent more than 76,600 cases of invasive infection and 7150 deaths due to Hib disease. The result of cost-effectiveness is not sensitive to the uncertainty surrounding estimates of disease incidence and costs of care for those with long-term disability.

While this result strongly supports implementation, greater investment by the government is required on an ongoing basis to ensure long-term sustainability of the program independent of multilateral donor aid. Future evaluations should focus on obtaining a more precise estimate of cost-effectiveness as more specific epidemiological data become available so that the Hib vaccine program can be placed accurately among competing health priorities.

Acknowledgment

I am grateful to Dr Damian Walker of the Johns Hopkins School of Public Health for valuable guidance in manuscript preparation.

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