Cost-effectiveness of *Haemophilus influenzae* type b (Hib) vaccine introduction in the universal immunization schedule in Haryana State, India

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**Objective** In India, *Haemophilus influenzae* type b (Hib) vaccine introduction in the universal immunization programme requires evidence of its potential health impact and cost-effectiveness, as it is a costly vaccine. Since childhood mortality, vaccination coverage and health service utilization vary across states, the cost-effectiveness of introducing Hib vaccine was studied in Haryana state.

**Methodology** A mathematical model was used to compare scenarios with and without Hib vaccination to estimate the cost-effectiveness of Hib vaccine in Haryana from 2010 to 2024. Demographic and National Family Health Surveys were used to estimate vaccination coverage and mortality rates among children under 5. Hib pneumonia, Hib meningitis and invasive Hib disease incidence were based on Indian studies. Vaccine and syringe prices of the UNICEF supply division were used. Cost-effectiveness from government and societal perspectives was calculated as the net incremental cost per unit of health benefit gained [disability-adjusted life years (DALYs) averted, life years saved, Hib cases averted, Hib deaths averted]. Sensitivity analysis was done using variation in parameter estimates among different states of India.

**Findings** The incremental cost of Hib vaccine introduction from a government and a societal perspective was estimated to be US$81.4 and US$27.5 million, respectively, from 2010 to 2024. Vaccination of 73.3, 71.6 and 67.4 million children with first, second and third dose of pentavalent vaccine, respectively, would avert 7,067,817 cases, 31,331 deaths and 994,564 DALYs. Incremental cost per DALY averted from a government (US$819) and a societal perspective (US$277) was found to be less than the per capita gross national income of India in 2009. In sensitivity analysis, Hib vaccine introduction remained cost-effective for India.

**Conclusion** Hib vaccine introduction is a cost-effective strategy in India.

**Keywords** Cost-effectiveness, Hib, vaccine, India, model, incremental cost
KEY MESSAGES

- Hib vaccine introduction in the universal immunization schedule was found to be cost-effective, from both societal and government perspectives, in Haryana State, India.
- The incremental cost-effectiveness ratio per DALY averted from a government (US$819) and a societal (US$277) perspective was less than the per capita gross national income of India in 2009.
- Policy makers should therefore introduce the Hib vaccine into the universal immunization programme.

Introduction

Infections due to the bacterium *Haemophilus influenzae* type b (Hib) represent a serious cause of vaccine-preventable morbidity and mortality among children worldwide (Levine et al. 1998). Peltola (1999) found that Hib is responsible for 30–50% of confirmed bacterial meningitis and is the second leading cause of bacterial pneumonia among children under 5 years of age in Asia. In India, the Invasive Bacterial Infections Surveillance Group (IBIS Group 1998) has shown that Hib meningitis is severe (case fatality ratio of 25%), occurs primarily in infants (76% cases) and that 40–50% of isolates are resistant to first-line antibiotics. Minz et al. (2008) found that the annual incidence of Hib meningitis was at least 32 per 100,000 in infants aged 0–11 months and 19 per 100,000 among children aged 12–23 months in a south Indian community of Vellore.

The safety and immunogenicity of Hib vaccine has been demonstrated worldwide (Adams et al. 1993). Evidence from two randomized controlled trials by Mulholland et al. (1997) and Levine et al. (1999) reveals that 20–25% of radiologically confirmed pneumonia cases with consolidation can be prevented with use of Hib conjugate vaccine. Moreover, it has been observed by Adegbola et al. (2005) and Lewis et al. (2008) that with relatively high vaccination coverage rates, near elimination of Hib disease had been achieved after introduction of Hib vaccine in the Gambia and Uganda. Although vaccination has been recognized as one of the most cost-effective health interventions to improve child survival, financial and programmatic constraints are often cited as important operational bottlenecks for the introduction of newer vaccines into the routine immunization schedule (Darmstadt et al. 2005). This is particularly relevant to Hib vaccine given its relatively high retail cost. In Kenya, Akumu et al. (2007) has shown that Hib vaccine is highly cost-effective and would be cost saving if the vaccine price was less than half of the present level. Despite the existence of Hib disease in India and documented evidence of preventable burden after the introduction of Hib vaccine in other developing countries, policy makers need reassurance that this vaccine represents a cost-effective health intervention.

Considering the marked variability in childhood mortality rates, vaccination coverage and treatment-seeking behaviour of the population in various states of India, cost-effectiveness analysis should ideally be considered at the state level. This study estimated the cost-effectiveness of introducing Hib vaccine in the north Indian state of Haryana. This is one of the wealthiest states of India, having the third highest per capita income in the country, and also one of the most economically developed regions in South Asia because of sustained growth of its agricultural and manufacturing industry (Byres et al. 1999; Government of Haryana 2010a).

Methods

A mathematical model, developed at the London School of Hygiene and Tropical Medicine (LSHTM), was used to track costs and health benefits for children born in the state of Haryana from 2010 to 2024, as shown in Figure 1 (Hib Initiative 2009). The model was prepared using MS-Excel spreadsheet software. We followed a birth cohort in the year 2010, for a period of 15 years, with the addition of children born in subsequent years and removing those who die as a result of Hib diseases or all-cause mortality at different age groups. Two scenarios were compared, i.e. (1) using a pentavalent (DPT-HBV-Hib) vaccine, and (2) the current strategy in Haryana, where children are immunized with DPT (diphtheria-pertussis-tetanus) and HBV (hepatitis B virus) vaccine. Children in both arms were then followed to study the outcomes in terms of Hib diseases, i.e. Hib meningitis, clinical pneumonia due to Hib and invasive Hib disease (non-pneumonia and non-meningitis). Clinical pneumonia was further stratified into severe and non-severe. Health-seeking behaviour estimates from a Haryana study were used to estimate the number of children who report to a health facility to seek care (ICMR 2008). Further, the visits to a health facility were categorized into those at private (non-medical faith healer, pharmacy, clinic and hospital) and public (clinic, primary health care, secondary and tertiary hospital) facilities. Cost at each facility per child treated was used to estimate the cost of treatment (Hussain et al. 2006; Madsen et al. 2009). Both health system and out-of-pocket costs were considered.

Cost of immunization in each arm was estimated based on the vaccines delivered, i.e. pentavalent (DPT-HBV-Hib) vs DPT and HBV vaccine. Costs of delivering vaccination in terms of unit price of vaccine, cost of syringes, safety boxes, wastage factor, handling and freight charges were included. Overall, costs in terms of delivering the immunization programme and treating children with Hib diseases were compared in the two arms. Incremental benefits were computed as the difference in cumulative cases, deaths and disability-adjusted life years (DALYs), respectively, in the two comparator scenarios. Net incremental cost of Hib vaccination was calculated by subtracting the projected treatment cost savings from the total incremental vaccination cost. Cost-effectiveness was then calculated as the net incremental cost per unit of health benefit (DALYs gained, life years saved, Hib cases averted, Hib deaths averted). DALYs were age weighted and future costs and health benefits were discounted back to the year 2010 using a discount rate of 3% per year. Age weighting has been done as per the methodology described by Murray and Lopez (1996) in the methods for the Global Burden of Disease study. We have
used age weights and a normalization constant of 0.04 and 0.1658, respectively. We assumed a median age of onset of disability of 2.5 years and a life expectancy of 64 years. The 2010 average exchange rate of Indian Rupees (INR) 46.0 to US$1.0 was used in all calculations. Parameters and assumptions used in the mathematical model to estimate the incremental cost-effectiveness ratio (ICER) before and after the introduction of Hib vaccine from a government as well as a societal perspective are described below (Table 1).

Demography

Demographic parameters were based on census projections for Haryana state. According to the 2001 census, Haryana had a population of 21.14 million and a decadal growth rate of 28% (Registrar General of India 2001). The projected population for 2010 has been estimated as 25 million (Registrar General of India 2006). In 2008, the birth rate of Haryana was 23/1000 population (20.4/1000 urban, 24.2/1000 rural) and the infant mortality rate was 54/1000 live births (43/1000 urban, 58/1000 rural) (Registrar General of India 2009). Fifty-three per cent and 63.5% of infant mortality was among neonates in urban and rural areas, respectively. The urban to rural ratio of mortality among infants and among children aged 12–59 months was 0.8 and 0.4, respectively, according to the National Family Health Survey (NFHS-3) conducted in 2005–06 (IIPS 2007).

Vaccine coverage

Hib vaccine will be delivered along with DPT through the existing health system. The National Family Health Survey (NFHS) and District Level Household Survey (DLHS) estimates of DPT vaccine coverage were used to estimate historical vaccination coverage and as a basis for extrapolating the future trend from 2010 to 2024 (MOHFW 2006; IIPS 2007). Annual projections were made on the basis of the parameter ‘percentage increase in DPT1 coverage per year’. We assumed that coverage level should rise to cover all children, i.e. 99%. In order to achieve this we assumed that the incremental improvement in coverage will be gradual. This annual incremental change has been assumed to be 2% of the gap between current coverage level and desired peak (99%). With these assumptions, our DPT coverage levels for Haryana peak at about 88% in 2015 and go further to reach 92% if extrapolated till 2049. The base year for these reductions was 2000 and a benchmark check made against the reported NFHS-3 coverage figure for the year 2005 showed that the trend was plausible.

Coverage of DPT2 and DPT3 was calculated by multiplying the DPT1 coverage by the DPT1 to DPT2 and DPT1 to DPT3 dropout rate, respectively, as estimated in NFHS-3. It has been assumed, that due to greater focus brought by the introduction of a new vaccine, there will be a relative decline in the DPT1 to DPT3 drop-out rate of about 2%. With this assumption, the drop-out rate in our model for Haryana declines from 10% to 8% between 2010 and 2024. Based on these assumptions, our
results match UNICEF coverage evaluation survey results for 2010 (UNICEF 2010b). Rural to urban ratios of coverage rates of DPT 1, 2 and 3 were taken as 0.87, 0.91 and 0.84, respectively, as per the NFHS-3 survey (IIPS 2007). We assumed phased introduction of Hib vaccine in the national immunization schedule as a pentavalent vaccine, i.e. 6% in 2010, 8% in 2011, 60% in 2012, 80% in 2013 and 85% in 2014. The immunization coverage rates thus assumed were similar to rates from the NFHS-3 and those obtained by Prinja et al. (2010).}

**Hib disease incidence**

Invasive Hib disease manifests in three forms: (1) Hib pneumonia, (2) Hib meningitis and (3) non-pneumonia and non-meningitis invasive Hib disease (Hib NPNM). Incidence of Hib pneumonia among children under 5 years has been estimated from severe clinical pneumonia incidence in Haryana. A multicentre surveillance study, where one centre was Khizrabad block in Yamunanagar district in Haryana (Gupta et al. 2010), found incidence of severe clinical pneumonia was at least 2717/100,000 child years of observation among children under 2 years in Haryana. Incidence of acute lower respiratory tract infection (ALRI)/pneumonia was taken as 10 times the under 2 years in Haryana. Incidence of acute lower respiratory pneumonia, (2) Hib meningitis and (3) non-pneumonia and non-meningitis invasive Hib disease (Hib NPNM). Incidence of Hib pneumonia among children under 5 years has been estimated from severe clinical pneumonia incidence in Haryana. A multicentre surveillance study, where one centre was Khizrabad block in Yamunanagar district in Haryana (Gupta et al. 2010), found incidence of severe clinical pneumonia was at least 2717/100,000 child years of observation among children under 2 years in Haryana. Incidence of acute lower respiratory tract infection (ALRI)/pneumonia was taken as 10 times the incidence of severe clinical pneumonia based on studies by Datta et al. (1987) and Acharya et al. (2003). The urban to rural ratio of the burden of ALRI cases and deaths was found to be 0.2 (Registrar General of India 2009). Hib is responsible for between 13 and 19% of pneumonia and lower lung disease in Indian studies (Kumar and Ayyagari 1984; Bahl et al. 1995; Patwari et al. 1996). In our model, we used a base assumption of the proportion of Hib cases among total pneumonia and lower lung disease cases of 13%. The case fatality ratio (CFR) of Hib pneumonia was assumed to be 16% based on a study by the Invasive Bacterial Infections Surveillance Group (IBIS Group 2002). The fraction of under-5 deaths due to ALRI was taken as 19% as per the World Health Organization (WHO) ‘Mortality country fact sheet’ of 2006 and the Million Death Study (WHO 2006a; Million Death Study Collaborators 2010).

Severe pneumonia was defined as cough or difficult breathing or tachypnea and at least one of the following symptoms/signs: lower chest wall in-drawing, nasal flaring, grunting, central cyanosis, inability to feed, lethargy, unconsciousness or head nodding. Radiological pneumonia was defined as severe pneumonia with radiographic evidence of consolidation meeting the WHO clinical trialist group primary endpoint criteria (WHO 2001). The incidence of Hib meningitis in under-5s was estimated to be 7.1 [95% confidence interval (CI) 3.1 to 14] per 100,000 child years of observation based on a prospective surveillance study in Vellore, Tamil Nadu during 1997 and 1999 (Minz et al. 2008). The proportion of Hib meningitis to other forms of invasive Hib disease (or non-pneumonia, non-meningitis) was assumed to be 0.05 based on global estimates by Watt et al. (2009). Kabra et al. (1991) and Chinchankar et al. (2002) reported a CFR of 20–29% for Hib meningitis in India. A review by WHO (2006b) found a CFR of between 16% and 20% for invasive Hib disease (including meningitis) in the Western Pacific Region.

The age distribution of all invasive Hib disease cases was assumed to be 60% aged <12 months, 30% aged 12–23 months, 5% 24–35 months, 4% 36–47 months and 1% aged 48–59 months, based on the study by the Invasive Bacterial Infections Surveillance Group (IBIS Group 2002). Using evidence from a local study in Chandigarh, India, by Singh et al. (2007), we assumed that 40% of survivors of Hib meningitis would develop a permanent lifelong disability and 30% of those lifelong sequelae would be ‘major’. Major sequelae included persistent seizures, mental retardation and hearing loss. We assumed Global Burden of Disease disability weights (fraction of healthy time lost to disability) of 0.28 and 0.61 for pneumonia and meningitis/NPNM, respectively (Murray and Lopez 1996). For non-severe pneumonia we assumed a weight of 0.14, assuming half of the reported weight for pneumonia. For minor and major sequelae, we assumed weights of 0.20 and 0.46, respectively, as per the WHO Global Burden of Disease 2004 update (WHO 2004). The mean duration of illness for Hib non-severe pneumonia, Hib severe pneumonia, Hib meningitis, Hib NPNM

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base case value</th>
<th>Range used in uncertainty analysis</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth rate per 1000 mid-year population</td>
<td>23</td>
<td>14.3–29.1</td>
<td>Sample Registration System (Registrar General of India 2009)</td>
</tr>
<tr>
<td>Vaccine coverage of 1st dose of DPT (%)</td>
<td>84</td>
<td>55.7–98.1</td>
<td>National Family Health Survey 2005–06 (IIPS 2007)</td>
</tr>
<tr>
<td>Vaccine coverage of 3rd dose of DPT (%)</td>
<td>74</td>
<td>28.7–95.7</td>
<td>National Family Health Survey 2005–06 (IIPS 2007)</td>
</tr>
</tbody>
</table>

**Burden of Hib disease**

- Annual Hib meningitis incidence per 100,000 children <2yrs: 7 (3.1–14) (Minz et al. 2008)
- Annual severe clinical pneumonia per 100,000 children <2yrs: 2717 (2313–9000) (Gupta et al. 2010)

**Vaccine costs**

- DTP-HepB-Hib (liquid) per dose (US$): 1.5 (1.0–3.6) (UNICEF vaccine projections (UNICEF 2008))

**Vaccine efficacy**

- Hib vaccine (%): 95 (67–99) (Mulholland et al. 1997)
was assumed to be 7, 15, 20 and 30 days, respectively, based on a 2008 surveillance report of pneumonia and meningitis in Haryana (ICMR 2008).

Vaccine efficacy
Efficacy against Hib disease from one, two and three doses of Hib vaccine was assumed to be 47%, 75% and 95%, respectively (Eskola et al. 1990; Booy et al. 1994; Mulholland et al. 1997).

Incremental cost of introducing Hib vaccine
We estimated the cost-effectiveness of pentavalent Hib vaccine (DPT+HepB+Hib) introduction in Haryana. We used the 2009 vaccine and syringe prices of UNICEF supply division for a 10-dose vial (liquid) (UNICEF 2009). However, we assumed that the cost for this vaccine would be US$1.5 per dose in India (a decline in the vaccine price is expected due to the large number of children to be vaccinated in India). Vaccine delivery cost includes the price of vaccines, administering syringes, safety boxes, percentage waste factor, handling and freight charges. Based on discussions with the national EPI Manager, we assumed there would be no other major incremental vaccine delivery costs to the programme for introducing Hib vaccine into the national immunization programme. This assumes that training and communication costs would be minimal, and that there is currently enough space in the cold-chain to accommodate the pentavalent vaccine. Moreover, evidence from Akumu et al. (2007) from Kenya shows that such costs account for 0.13% of total incremental costs of vaccine delivery. We also estimated the variation in the ICER with a change in the cost of pentavalent vaccine (DPT+HepB+Hib).

Health service utilization and costs
Information on access to health services was obtained from a local surveillance report of pneumonia and meningitis in Haryana (ICMR 2008). Government facilities included only outpatient departments/clinics and indoor facilities at primary, secondary and tertiary level. Private facilities included pharmacies and outpatient departments with indoor facilities in urban and rural areas. The treatment-seeking behaviour for pneumonia and meningitis among children by type of facility is given in Table 2.

Cost of treatment in formal care was estimated for the following diseases: non-severe pneumonia, severe pneumonia, Hib meningitis and Hib NPNM cases, Hib minor sequelae and Hib major sequelae. Travel cost to the health facility and cost of treatment was obtained from the local surveillance report of pneumonia and meningitis in Khizrabad block, Haryana (ICMR 2008). The information on costs of treatment was supplemented with the results of the 61st round of the National Sample Survey (NSSO 2006), a study in south India (Madsen et al. 2009) and a study from a neighbouring country with similar socio-demographic characteristics and treatment-seeking practices (Hussain et al. 2006). The estimated costs of treatment in US dollars (US$) from a government and a societal perspective are given in Table 3.

Sensitivity analysis
We undertook a univariate sensitivity analysis to assess the impact of uncertainty in parameter values on cost-effectiveness estimates. Ranges of parameters used in uncertainty analysis are given in Table 1. The uncertainty range for parameter base values was derived using variation in parameter estimates among different states in India, so as to assess the generalizability of the Haryana study to other Indian states. Since there are significantly lower estimates of Hib disease burden reported from other settings such as Gambia and Indonesia, we varied our assumption of the fraction of Hib cases among total pneumonia cases from 5% to 15% (Watt et al. 2009), to assess the cost-effectiveness of Hib vaccine in conditions of lower disease burden.

Results
Hib disease incidence
According to model estimates, there would be about 1500 cases of Hib meningitis (incidence 9.8/10,000) among children under 5 years without Hib vaccination in Haryana, which would reduce to 67 cases (incidence 0.3/10,000) in the year 2024.
following Hib vaccine introduction in the national immunization programme. Similarly, incidence of severe Hib pneumonia would reduce from 831/10,000 cases to 52/10,000 cases among children under 5. There would be a 93% reduction in the number of deaths due to severe Hib pneumonia and a 95% reduction in deaths due to Hib meningitis. The number of life years saved would be about 0.1 million in the year 2024 (Table 4).

Cost-effectiveness

It was estimated that, by 2024, the incremental cost from government and societal perspectives would be US$81.4 million and US$27.5 million, respectively. Mortality and morbidity averted as a result of Hib vaccination would include 7,067,817 cases and 31,331 deaths (994,564 DALYs). This gives a ratio of about 31.7 DALYs per death averted. With the introduction of the Hib vaccine, the Government of Haryana would spend an additional US$165 to US$551 per DALY averted when the cost of Hib vaccine ranged from US$1 to US$3.5 per dose, respectively (Figures 2 and 3). Assuming high Hib burden and low vaccine cost, i.e. high ALRI incidence and low estimate for Hib vaccine cost, Hib vaccination is a cost-saving intervention and dominates the scenario with ‘no-vaccination’ from a societal perspective.

Sensitivity analysis

Incidence of acute lower respiratory infections (ALRI) and Hib vaccine cost were found to be the most important determinants of cost-effectiveness. However, even with the extremes of variation in cost of vaccine per dose and ALRI incidence, Hib vaccination was found to be cost-effective from both government and societal perspectives. Hib vaccination would cost the Government of Haryana an additional US$1336 per DALY averted, which is also within cost-effective bounds according to the WHO threshold (between 1 to 3 times per capita GDP).

Cost to government

<table>
<thead>
<tr>
<th>Health facility</th>
<th>Travel cost</th>
<th>Total drugs and diagnostics cost</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Non-severe pneumonia</td>
</tr>
<tr>
<td><strong>Government cost per patient per outpatient visit</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sub-centre</td>
<td>1.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Primary health care facility</td>
<td>1.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Secondary health care facility</td>
<td>1.4</td>
<td>3.0</td>
</tr>
<tr>
<td>Tertiary health care facility</td>
<td>2.1</td>
<td>17.0</td>
</tr>
<tr>
<td><strong>Government cost per inpatient bed day</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary health care facility</td>
<td>4.6</td>
<td>10.0</td>
</tr>
<tr>
<td>Secondary health care facility</td>
<td>6.1</td>
<td>25.0</td>
</tr>
<tr>
<td>Tertiary health care facility</td>
<td>8.3</td>
<td>71.0</td>
</tr>
<tr>
<td><strong>Cost to household</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Government health centre / private pharmacy</td>
<td>1.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Government primary hospital</td>
<td>2.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Government secondary hospital</td>
<td>3.0</td>
<td>95.0</td>
</tr>
<tr>
<td>Government tertiary hospital / private health facility</td>
<td>6.0</td>
<td>150.0</td>
</tr>
<tr>
<td><strong>Household cost per inpatient bed day</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Government primary hospital</td>
<td>2.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Government secondary hospital</td>
<td>3.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Government tertiary hospital / private health facility</td>
<td>6.0</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Sources: ICMR (2008), Madsen et al. (2009), Hussain et al. (2006), NSSO (2006).

Note: NPNM = non-pneumonia, non-meningitis.
effects on the estimate of cost-effectiveness. Although high levels of vaccine efficacy (95%) have been observed with three doses of pentavalent vaccine, a variation of between 67% and 99% efficacy has been documented in the literature (Mulholland et al. 1997). With this variation in vaccine efficacy, cost per DALY averted ranged from US$791 to US$370, respectively, from a health system perspective, and from US$373 to US$248, respectively, from a societal perspective.

Discussion

This study has demonstrated that the introduction of Hib vaccine in the universal immunization schedule is cost-effective in Haryana state of India. According to the World Country Classification System, which uses 2008 gross national income (GNI) per capita (in US$) calculated using the World Bank Atlas method, India is a lower-middle-income country with a GNI between US$996 and US$3945 (World Bank 2010). According to WHO vaccine introduction guidelines, any intervention is cost-effective if the cost-effectiveness ratio of that intervention is less than three times the per capita GNI of that nation (WHO 2005). This classification has been used by WHO in their review of Hib disease burden and Hib vaccine cost-effectiveness in the Western Pacific Region (WHO 2006b). The net cost per DALY gained is estimated as US$277 in the present study, which is less than the GNI of India and hence Hib vaccine introduction is a cost-effective intervention. The State government of Haryana has allocated US$2283 million for its annual budget plan 2010–11, of which about US$245 million (10.7%) will be spent on health (Government of Haryana 2010b). The incremental cost (US$6.6 million) of introducing pentavalent Hib vaccine appears to be affordable from a fiscal perspective. According to the Disease Control Priority Project’s cost-effectiveness estimation for adding pentavalent Hib vaccine, the incremental discounted cost per death averted is US$10 950 for South Asia (DCPP 2006). This cost was estimated to be higher (US$26 004) in Haryana. This could be due to relatively lower incidence of Hib disease in Haryana state (Gupta et al. 2010), which means vaccine introduction would be even more cost-effective in other parts of India which have higher incidence levels.

Further, our analysis has shown that introduction of Hib vaccine is more cost-effective from a societal perspective, as 80% of households pay out-of-pocket for treatment of pneumonia and meningitis. Hence the introduction of this vaccine will not only help in reducing the disease burden, but it will also prevent the regressive effects of high out-of-pocket payments for health care in India.

The current price of pentavalent vaccine in India is US$1.75 (UNICEF 2010a). GAVI has reported a decline of 14% in the price of pentavalent vaccine from 2009 to 2010 (GAVI 2009) and UNICEF has registered an annual decline of 20.4% during this period (UNICEF 2009; UNICEF 2010a). A vaccine price estimate of US$1.5 was used in this study because when India plans to introduce the vaccine into its national immunization schedule, the additional demand of nearly 75 million doses

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Without Hib vaccination</th>
<th>With Hib vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 2024</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccine coverage</td>
<td>0%</td>
<td>&gt;85%</td>
</tr>
<tr>
<td>Total acute cases</td>
<td>749 948</td>
<td>46 876</td>
</tr>
<tr>
<td>Hib non-severe pneumonia</td>
<td>598 695</td>
<td>37 444</td>
</tr>
<tr>
<td>Hib severe pneumonia</td>
<td>149 674</td>
<td>93 61</td>
</tr>
<tr>
<td>Hib meningitis</td>
<td>1504</td>
<td>67</td>
</tr>
<tr>
<td>Hib NPNM</td>
<td>75</td>
<td>3</td>
</tr>
<tr>
<td>Total deaths</td>
<td>3286</td>
<td>201</td>
</tr>
<tr>
<td>Hib non-severe pneumonia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hib severe pneumonia</td>
<td>2993</td>
<td>187</td>
</tr>
<tr>
<td>Hib meningitis</td>
<td>279</td>
<td>13</td>
</tr>
<tr>
<td>Hib NPNM</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Total sequelae</td>
<td>489</td>
<td>21</td>
</tr>
<tr>
<td>Minor</td>
<td>367</td>
<td>16</td>
</tr>
<tr>
<td>Major</td>
<td>122</td>
<td>5</td>
</tr>
<tr>
<td>Total disability-adjusted life years lost</td>
<td>104 181</td>
<td>6317</td>
</tr>
<tr>
<td>Acute disease</td>
<td>3386</td>
<td>211</td>
</tr>
<tr>
<td>Minor sequelae</td>
<td>2163</td>
<td>95</td>
</tr>
<tr>
<td>Major sequelae</td>
<td>1691</td>
<td>75</td>
</tr>
<tr>
<td>Premature death</td>
<td>96 940</td>
<td>5937</td>
</tr>
</tbody>
</table>

Note: NPNM = non-pneumonia, non-meningitis.
(based on birth cohort size) should lead to a higher rate of decline in vaccine prices. Moreover, sensitivity analysis revealed that even at a price of US$3.5 per dose, the introduction of Hib vaccine in the universal immunization schedule remains cost-effective.

Various studies elsewhere have also found the introduction of Hib vaccine into national immunization schedules to be cost-effective. In Kenya, Akumu et al. (2007) found that vaccination of children with Hib vaccine in one area was cost-effective in comparison to a control area without the vaccination. A ratio of about 30 DALYs per Kenyan child death averted was observed, similar to that in the present study. In Colombia, a Hib vaccination programme could prevent around 25,000 cases of invasive disease per year, 700 deaths per year and save 44,054 years of life per year, representing a cost saving of at least US$15 million annually (Alvis et al. 2006).

An assessment of the value of Hib conjugate vaccine in Asia using a model predicted that approximately 136,000 (87%) Hib deaths could be prevented annually with incorporation of Hib vaccine into the Expanded Program for Immunization based on current vaccination coverage rates for the individual countries considered (Miller 1998). For each of the countries, routine vaccination with Hib would cost between 0.1% and 3.0% of per capita gross national product per child under 5 years. According to the assessment, Hib vaccine was considered to be a cost-effective public health intervention, but was likely to be cost-prohibitive to implement in the lowest income countries without initial donor assistance.

In Santiago, Chile, Levine et al. (1993) compared the potential benefits to the Chilean Ministry of Health in terms of treatment costs averted by prevention of Haemophilus influenzae type b invasive disease, and the costs of adding Hib conjugate vaccine

Figure 2 Univariate sensitivity analysis of incremental cost-effectiveness ratio (US$ per DALY averted) with respect to DPT 1st and DPT 3rd dose coverage, incidence of acute lower respiratory infections (ALRI) and Hib meningitis, Hib vaccine cost and efficacy.

Figure 3 Incremental cost-effectiveness ratio per disability-adjusted life year (DALY) averted from a government perspective with respect to cost of pentavalent (DPT+HepB+Hib) vaccine per dose (US$).
to the DPT immunization routinely administered to infants. Assuming a cost of US$1 for a full three-dose regimen of vaccine, they find a benefit/cost ratio of 1.66, with a net discounted saving of over US$40 322, which shows Hib vaccine to be cost-beneficial.

In the model in the present study, assumptions about Hib disease in Haryana were based on minimal incidence of Hib meningitis in Tamil Nadu (Minz et al. 2008) and of pneumonia in Haryana (Gupta et al. 2010). However, the methodology used by Minz et al. to determine the minimal incidence of Hib meningitis in Tamil Nadu was less than ideal, i.e. hospital-based surveillance. With such methodology, many cases of disease can be missed due to poor health-seeking behaviour and barriers to access in poor developing country contexts. This is corroborated by findings from a study in Lombok (Gessner et al. 2005). Minz et al. also report that eight children in the study area, who did not use medical care in study hospitals, died with signs suggestive of central nervous system (CNS) infection. Moreover, due to a poor patient–physician ratio, some cases could not be subjected to lumber puncture, especially outside routine working hours. Hence, the base estimates for Hib disease incidence used in our model could be considered on the low side of what may be the true burden of disease, making the vaccine even more cost-effective.

The 15-year time horizon used in our study was based on the epidemiology of Hib. Risk of falling ill as a result of Hib disease peaks at mid-infancy or early childhood, and gradually wanes thereafter. Worldwide, most cases of *H. influenzae* occur between the ages of 2 months and 3 years; it is unusual beyond 5 years of age (Wenger 1998). According to the Invasive Bacterial Infections Surveillance Group study from India, 90% of *H. influenzae* cases (pneumonia, meningitis and invasive Hib disease) occurred among children under 15 years, of which more than 96% were under 5 (IBIS Group 2002). There is minimal risk of Hib disease beyond the age of 15. Hence, a 15-year time horizon gives a proxy for an analysis which provides life-time benefits.

In India, since Hib vaccination is not done routinely, a cost-effectiveness study can be useful for policy makers in deciding whether to introduce the vaccine in the universal immunization schedule. In its position paper on Hib conjugate vaccine, WHO has recommended inclusion of Hib vaccination in all countries (WHO 2006c), but since it is an expensive vaccine, governments are hesitant to introduce it at national level; they would like information on its cost-effectiveness. A literature review reveals that the Hib burden is best estimated using vaccine probe studies (Mulolland et al. 1997; Levine et al. 1999), but a vaccine probe study in which only one group will be given the vaccine will be ethically problematic in light of the WHO recommendation. Hence, cost-effectiveness analysis based on a model remains one way to inform policy makers in their decision-making on the introduction of Hib vaccine into routine immunization.

A limitation of this study is that the cost of additional training for implementing the vaccine as part of routine immunization was considered minimal. As vaccines will be delivered in the routine programme rather than through a social mobilization campaign, interpersonal communication by health workers during their routine duties was considered to be enough. Evidence from Kenya indicates that the cost of additional training and community sensitization was about US$100 000. Assuming this amount will last over a period of 15 years, and discounting for future costs at 5%, the annualized value (US$9634) is 0.13% of the total incremental cost of implementing pentavalent Hib vaccine in Kenya (Akumu et al. 2007).

Our base estimate results show Hib vaccine to be a cost-effective option for preventing childhood morbidity, disability and deaths in Haryana. We carried out a sensitivity analysis using the uncertainty range for different parameters, which was reflective of state-wise differences in the parameter estimates in India. Using uncertainty around all model parameters, our results from univariate sensitivity analysis show that Hib vaccine introduction in the national immunization schedule as a pentavalent vaccine is cost-effective in India. It is even more cost-effective in states which have a higher burden of acute lower respiratory infections. Hence, policy makers should consider introduction of Hib vaccine in the universal immunization schedule of India.

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**Conflict of interest**

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