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Impact and Cost-Effectiveness of *Haemophilus influenzae* Type b Conjugate Vaccination in India

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Abstract

Objective—To estimate the potential health impact and cost-effectiveness of nationwide *Haemophilus influenzae* type b (Hib) vaccination in India.

Study design—A decision support model was used, bringing together estimates of demography, epidemiology, Hib vaccine effectiveness, Hib vaccine costs, and health care costs. Scenarios favorable and unfavorable to the vaccine were evaluated. State-level analyses indicate where the vaccine might have the greatest impact and value.

Results—Between 2012 and 2031, Hib conjugate vaccination is estimated to prevent over 200 000 child deaths (~1% of deaths in children <5 years of age) in India at an incremental cost of US $127 million per year. From a government perspective, state-level cost-effectiveness ranged from US$192 to US$1033 per discounted disability adjusted life years averted. With the inclusion of household health care costs, cost-effectiveness ranged from US$155-US$939 per discounted disability adjusted life year averted. These values are below the World Health Organization thresholds for cost effectiveness of public health interventions.

Conclusions—Hib conjugate vaccination is a cost-effective intervention in all States of India. This conclusion does not alter with plausible changes in key parameters. Although investment in Hib conjugate vaccination would significantly increase the cost of the Universal Immunization Program, about 15% of the incremental cost would be offset by health care cost savings. Efforts should be made to expedite the nationwide introduction of Hib conjugate vaccination in India.

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During the last decade 1 in every 10 children born in India died before reaching their fifth birthday, representing around 20% of child deaths globally.[1] A nationally representative mortality survey conducted in India between 2001 and 2003 (the “Million Death Study”) estimated that 16% of deaths of children <5 years of age were caused by pneumonia and ~4% by invasive bacterial diseases such as meningitis.[2] *Haemophilus influenzae* type b (Hib), a bacterium transmitted from person to person by the respiratory route, is a leading cause of bacterial pneumonia in countries where the vaccine is not used. Safe and effective national Hib conjugate vaccination programs are now implemented in most countries worldwide, but introduction has been delayed considerably in India compared with other countries. In June 2008, the Indian National Technical Advisory Group on Immunization recommended nationwide introduction of Hib conjugate vaccination.[3,4] It subsequently took 3.5 years to initiate phased introduction, starting in December 2011 with Tamil Nadu and Kerala, 2 states covering less than 5% of the national child mortality burden. To date, the vaccine is yet to be introduced in any of the high mortality states.

Several challenges have contributed to the delayed introduction. In particular, there has been a lack of technical consensus on the public health need and cost-effectiveness of including the vaccine in the national immunization program. In July 2005, a pilot Hib disease surveillance study was initiated to lay the groundwork for a large vaccine probe study to document the burden of Hib disease in India and the impact of vaccination.[5] The probe study was, however, never conducted, as it was judged unethical following a World Health Organization (WHO) position that “conjugate Hib conjugate vaccines should be included in all routine infant immunization programs.”[6] Also, at this time, Hib conjugate vaccines became widely available in the private sector in India and several Indian manufacturers were producing the vaccine. The only randomized controlled trial in Asia (Lombok Island, Indonesia; 1998–2002) reported a preventable incidence of both clinical pneumonia (1561 per 100 000 aged <2 years) and meningitis (16 per 100 000 aged <2 years). Confusingly, however, the same study reported no preventable burden of radiologic pneumonia.[7] A case control study (Dhaka city, Bangladesh; 2000–2003) reported a 32% protective effect against radiologic pneumonia. However, results from this study varied considerably depending on who read the chest radiographs and whether the controls were hospital- or community-based (16%–44%).[8] The mixed evidence from the region and the lack of strong evidence from India have made it difficult for country officials to make a decision about Hib conjugate vaccination, and some local groups have argued against its inclusion in the routine program.[9] Where uncertainties exist and are likely to continue to exist, decision support models can help decision makers consider the potential impact and cost-effectiveness of the vaccine under a range of plausible favorable, and more importantly, unfavorable, assumptions.

In this analysis, a decision support model was used to bring together the best available evidence and calculate, for a broad range of scenarios, the impact and value (cost-effectiveness) of Hib conjugate vaccination in India. We estimated this for individual states and aggregated to the national level over the period 2012–2031. With an annual birth cohort of ~26 million, the Ministry of Health and Family Welfare has to consider very carefully the economic implications of universal Hib conjugate vaccination. The aim of cost-effectiveness analysis is to help decision-makers make investments in health interventions, which provide good value for money when compared with recognized benchmarks or competing health

priorities. This study estimate, the potential cost-effectiveness of nationwide Hib conjugate vaccination in India.

Methods

The decision-support model has been described in detail elsewhere.[10] In short, the model tracks the experience of 20 successive birth cohorts. Cost-effectiveness is based on the aggregated costs and benefits over this sustained period of routine vaccination (2012–2031) allowing key parameters to vary over time. Vaccination program costs are assumed to occur in the first year of each cohort. Disease cases, deaths, and treatment costs are estimated for the first 5 years of age, but lost life-years, disability adjusted life years (DALYs), and sequelae costs are estimated over expected lifetimes. State-level estimates of numbers of births, infant mortality, mortality of children <5 years of age, and life-expectancy were based on the 2001 census projections.[11] State-level estimates of numbers of births were scaled to be consistent with the national United National Population projections (2008 Revision) for India.[1] Estimates of neonatal mortality for each state were based on the 2005–2006 Indian National Family Health Survey (NFHS).[12] Hib disease is divided into 3 categories defined by the Hib global burden of disease project[13]: pneumonia, meningitis, and “non-pneumonia-non-meningitis” (NPNM) invasive diseases. NPNM diseases, such as cellulitis and epiglottitis, were grouped for simplicity because they are less common than meningitis and pneumonia. The model structure is shown in Figure 1. Outputs are compared with a scenario with no Hib conjugate vaccination. The analysis was undertaken from a societal perspective, including costs incurred by the Indian Government, the GAVI Alliance, and Indian households. Future program costs, treatment costs averted, and health benefits were discounted by 3% per year.[14] We did not assume age weighting on DALYs (ie, no greater preference was assigned to life-years gained in the working age range). Costs were estimated in 2010 US$ using an exchange rate of 45.7 Indian rupees for one US$.[15]

Cases of Hib Meningitis, Deaths, and Sequelae

Between 1997 and 1999, a prospective hospital surveillance study in Vellore reported Hib to be the cause of 44% (8 of 18) of confirmed cases of bacterial meningitis, with ~7 confirmed cases per 100 000 children aged less than 5 years.[16] Recent multicenter surveillance estimates from Vellore, Chennai, Lucknow, and New Delhi suggest that 70% of bacterial meningitis may be caused by Hib.[17] We used the lower and more conservative estimate of 44%, but made adjustments to account for cases of Hib that were not detected in the laboratory and cases that did not have access to care. Because 57% (24 of 42) of the purulent (probable) cases had no confirmed pathogen in the Vellore study, we assumed the percent of unconfirmed cases attributable to Hib to be the same as the percent of confirmed cases attributable to Hib (44%), based on WHO guidelines [18] and following methods used in other bacterial meningitis etiology studies.[19] In addition, we assumed that 23% of the cases would not have had access to formal medical care during this study based on the proportion of children living in Vellore who, according to the NFHS, did not seek care for acute lower respiratory infection (ALRI) in 2006.[12] Hence, the final adjusted Hib meningitis incidence was 22 per 100 000 children <5 years [7.12/(1–57%)]/(1–23%). We assumed this incidence estimate for all states.

State-level Hib meningitis case fatality ratios (CFRs) were calculated by adjusting the 11% CFR reported in multicenter bacterial surveillance sites in Chennai, Vellore, Lucknow, and New Delhi[17] by the state-level proportion of children without access to medical care. For children with no access to care, a 100% CFR was assumed.[10] State-level estimates of access to care were based on the NFHS 2006 survey with care seeking for ALRI considered to be a proxy for meningitis. The median state-level estimate of access to a medical provider was 71% and ranged from 44%–89% across the states.[12] After adjusting for access to care, the median meningitis CFR was 36% and ranged from 21%–61% across states.

A proportion of survivors of Hib meningitis suffer lifelong disabilities. Studies reporting the risk of sequelae following bacterial meningitis have been conducted in Chandigargh,[20] Kerala,[21] Varanasi,[22] Hyderabad,[23] and Pune.[24] Hib-specific data were presented in 3 of the studies,[20,23,24] but the study in Hyderabad only assessed hearing deficit and, therefore, was excluded. The pooled risk of major sequelae following Hib meningitis from the 2 remaining studies in Pune (5 of 13) and Chandigarh (4 of 13) was 35%.[20,24] These proportions are similar to the proportion of children who suffered sequelae in the US and other countries prior to the use of Hib conjugate vaccines.

Cases of Hib Pneumonia and Deaths

Various studies of clinical pneumonia incidence have been conducted among children aged less than 5 years at the community-level in India. In these studies, the incidence per child per year was reported to be 0.54 (Haryana),[25] 0.29 (Pune),[26] 0.86 (Rajasthan),[27] 0.31 (Delhi),[28] 0.07 (Maharastra),[29] 0.10 (Lucknow),[30] 0.4 (Tripura),[31] 0.67 (Delhi),[32] and 0.53 (Karnataka).[33] These studies vary in terms of geographical location, study design, period of reporting, and definition of ALRI. We assumed the IQR from all reported estimates to give a plausible national range (ie, 0.29–0.54 episodes per child per year). This is broadly consistent with previous estimates for India.[34]

We assumed that the fraction of ALRI caused by Hib would be equal to the fraction of ALRI prevented by Hib conjugate vaccination (3.8%) in the only randomized controlled trial conducted in Asia (Lombok Island, Indonesia).[7] The IQR of Hib pneumonia incidence was therefore 1102 (3.8% × 29 000) to 2052 (3.8% × 54 000) per 100 000 children <5 years of age. The state-level distribution of Hib pneumonia incidence was assumed to be the same as the state-level distribution for the prevalence of underweight children,[12] a consistently reported risk factor for pneumonia in India.[35,36] Underweight children have weight-for-age that is 2 or more SDs lower than the median weight-for-age of an international reference population, which includes healthy children from Brazil, Ghana, India, Norway, Oman, and the US.[37]

Regional estimates of the proportion of mortality of children <5 years of age caused by pneumonia in children aged 1–59 months were reported in the Million Death Study: West (13%); South (8%); East (18%); North (15%); Northeast (16%); and, Central (17%).[2] These were multiplied by total deaths in children <5 years of age in each state to estimate pneumonia deaths in this age group.

The fraction of pneumonia deaths in children aged 1–59 months caused by Hib is a contentious parameter and an important driver of cost-effectiveness results.[10] We derived this fraction by combining: (1) state-level estimates of Hib pneumonia incidence described above; (2) recent multisite estimates of hospitalised pneumonia incidence and CFRs, extrapolated to parent regions[5]; and (3) state-level estimates of access to medical care from the 2005–2006 NFHS survey.[12] We further assumed a 23.6% CFR for all severe untreated pneumonia based on a community-based trial among children 0–4 years in Gadchiroli, central India.[38] Using this approach (Figure 2), we estimated 7% of pneumonia deaths in children aged 1–59 months to be caused by Hib nationally, ranging from 1%–11% across states. The 7% estimate is broadly consistent with the pooled 5% reduction in radiologic pneumonia found when combining the results from the only 2 Hib conjugate vaccine studies conducted in Asia. Using inverse variance meta-analysis, 64% weight was assigned to the randomized controlled trial in Indonesia (vaccine effectiveness –10%; 95% CI −33%, 9%) and 36% weight to the case control study in Bangladesh (vaccine effectiveness 32%; 95% CI −2%, 54%).[39] This pooled estimate is, however, subject to large heterogeneity (I-squared 82%) and is far lower than previously reported global estimates. We, therefore, evaluated a separate scenario assuming Hib to be the cause of 20% of pneumonia deaths 1–59 months across all states. The Hib global burden of disease project estimated 21% globally in children aged 1–23 months based on a global meta-analysis using studies from Bangladesh, Indonesia, Chile, and The Gambia.[13] This is similar to the fraction reported by a hospital etiology study conducted in New Delhi around 20 years ago. In this study, Hib was estimated to be the cause of 19% (21 of 110) of hospitalized pneumonia in children <5 years,[40] although the study did not define whether the positive results of latex agglutination were found in urine (lower validity) or serum (higher validity). Two other studies from New Delhi and Chandigarh, estimated *Haemophilus influenzae* to be the cause in 16% (20 of 122)[41] and 13% (6 of 46)[42] of hospitalized pneumonia cases respectively, but did not distinguish type b from nontypeable or other *Haemophilus influenzae* types.

Cases of Hib NPNM and Deaths

In the multicenter Invasive Bacterial Infections Surveillance Project (Chennai, Lucknow, Nagpur, New Delhi, Thiruvananthapuram, Vellore) one case of invasive NPNM Hib disease was confirmed for every 5.5 cases of Hib meningitis.[43] We applied this ratio to the meningitis incidence rate to derive an NPNM incidence rate of 4 per 100 000 children <5 years of age. We assumed 4.3% CFR for those with access to medical care based on the CFR reported by the Invasive Bacterial Infections Surveillance Project for Hib-positive cases without associated meningitis. We doubled the CFR for children without access to medical care (8.6%), but this conservative assumption is likely to underestimate the true mortality burden for invasive NPNM diseases. The adjusted state-level CFRs ranged from 5%–7%.

Please see Table I for a full summary of the disease burden parameters used for each state.

Health Care Utilization

For cases of Hib meningitis and Hib NPNM, we assumed that children with access to medical care would be admitted to hospital and also have 1 outpatient consultation, either as a referral or follow-up visit. For all cases of pneumonia, we assumed 1 outpatient visit per

case for those with access to medical care and that a fraction of these would also be admitted to hospital. Severe clinical hospitalized pneumonia per 100 000 per year in children aged <2 years was recently reported in Chandigarh (2717), Vellore (3075), and Kolkata (7890). To avoid over-estimation of incidence, we converted incidence at age <2 years into incidence at age <5 years using national age distribution assumptions. We then used state-level estimates of clinical pneumonia incidence at age <5 years and access to medical care to calculate the fraction of cases with access to medical care who were hospitalized. We estimated that 3%, 6%, and 13% were hospitalized in each of the 3 sites. On this basis, we assumed 3% for all North and North Eastern States, 6% for the South and Western States, and 13% for the Central and Eastern States. We further assumed that these all-cause pneumonia fractions would apply to Hib pneumonia, to give median state-level incidence of admissions of 55 per 100 000 per year among children aged <5 years, ranging from 22–185 across states.

Health Service Costs

Costs for outpatient care differed according to whether the child was taken to a public or private facility, a traditional healer, or whether only drugs were purchased at a pharmacy. Costs for inpatient admissions varied with the level and type of hospital. The NFHS was used to estimate the proportion of children accessing each type of provider according to State (Table II).[12] The NFHS only includes a primary and a secondary/tertiary hospital level category for the public sector. To account for differences in costs between secondary and tertiary levels, we crudely assumed that tertiary-level care accounted for 5% of the reported visits/admissions in the combined secondary/tertiary category.

Treatment cost estimates are summarized in Table III. Two published sources were used. Household expenses were collected from the 60th round of the Government of India National Sample Survey Organization socioeconomic survey, conducted in 2004.[44] Questions on morbidity and health care were incorporated in the survey, including detailed questions about medical expenditures according to type of disease. Information was collected for every inpatient admission and outpatient visit for each member of the sample household during the 365 and 15 days preceding the survey, respectively. Household expenditures were categorized according to medicines, user fees, lodging, transport, etc. Results of the survey on respiratory ailments in children <5 years old were used for approximating household costs of pneumonia treatment. For this disease category, the nationwide sample sizes were 644 outpatient episodes and 238 inpatient admissions. The cost of a traditional healer consultation was assumed to be one-half the cost of a public sector clinic visit.

To estimate household costs of meningitis treatment, the pneumonia costs were adjusted upwards in accordance with the additional lengths of stay in hospital as reported in multicenter surveillance in Lucknow, Chennai, Vellore, and New Delhi in preparation for the Hib probe study.[5] This was 6 days for pneumonia/NPNM and 10 days for meningitis. Opportunity costs, in terms of time spent while looking after a sick child, were included in the sensitivity analysis by assuming the minimal wage rate of US$3.4 per day,[45] multiplied by the average length of stay in hospital. There is no empirical evidence from India on the costs of treating a case of sequelae or the life-time earnings lost because of caring for a child

with permanent disability, so we did not include sequelae costs in the base case. However, in a scenario analysis based on a recent sequelae costing study from Senegal, we assumed undiscounted lifetime costs of US$53 165 per child with sequel.[46] To allow discounting of future costs, these costs were converted into annual costs spread over the entire life expectancy of each state.

Government costs of meningitis and pneumonia treatment were derived from a micro-costing study by Krishnan et al undertaken in the State of Haryana in children aged <5 years.[47,48] Data were collected from 2 primary health centers, 6 secondary hospitals, and 2 tertiary hospitals; 6 of these were government facilities and 2 were private. Another study on costs of severe pneumonia from 2 non-government organization hospitals in Vellore was used as a comparator.[49]

Age Distributions and DALY Estimates

The age distribution of Hib disease also was derived from the multicenter surveillance study. Among children <2 years of age with confirmed Hib disease, 24% were aged <3 months, 20% 3–5 months, 21% 6–8 months, 11% 9–11 months, and 23% 12–23 months old.[5] We assumed that 6% of children <5 years of age would occur between 24 and 59 months,[50] so proportions for <24 months were adjusted accordingly.

The original DALY formula and disability weights of 0.279 for pneumonia and 0.616 for meningitis were used.[51] Because there are no standard disability weights available for any of the NPNM diseases, the pneumonia weight was used. The weighted average disability weight for meningitis sequelae was 0.34 based on the reported global distribution of sequelae syndromes[52] and their respective disability weights.[51] The most common types of single sequela from Hib meningitis are hearing loss and seizures, comprising 33% and 16% of sequelae cases, respectively. Multiple sequelae are seen in approximately 20% of sequelae cases.[52]

Vaccine Coverage and Efficacy

To account for gradual or phased Hib conjugate vaccine introduction, we assumed 50% and 75% of diphtheria-tetanus-pertussis (DTP) coverage levels in the first 2 years and full DTP coverage thereafter. Coverage of the first 3 doses of DTP were based on the 2009 State-Level Coverage Evaluation Survey.[53] In the base case, we assumed no improvement in coverage over time, but this assumption was varied in scenario analysis to allow for annual improvements (reductions in the unvaccinated) over the period 2012–2030. Many children do not receive their vaccines according to the recommended 6-, 10-, and 14-week schedule. We, therefore, estimated the timeliness of vaccination (age-specific coverage) for each state using previously described methods.[54]

Simple multiplication of vaccine efficacy and vaccine coverage is likely to overestimate the impact of vaccination because children who receive the vaccine may not be at the highest risk of mortality. To account for this relative coverage effect, we estimated DTP2 coverage of underweight children relative to the total DTP2 coverage reported for the cohort,[12] the implication being that underweight children are likely to be at higher risk of death, and that DTP2 would broadly represent the relative coverage for all three doses. Relative coverage

multipliers (coverage in underweight children divided by coverage in the cohort) were calculated for each State (Figure 3).

To estimate the percent reduction in disease, the base case estimates accounted for state-level timeliness of vaccination, dose-specific coverage, and relative coverage. Vaccine efficacy was determined from a recent meta-analysis of controlled clinical Hib conjugate vaccine trials. In this analysis, efficacy against all forms of invasive Hib disease was 93% (95% CI 83%, 97%) following 3 doses, 92% (95% CI, 69%, 98%) following 2 doses, and 59% (95% CI 0%, 86%) following 1 dose.[55]

Herd immunity and waning dose protection were not considered in the base case, but were included in scenarios. We assumed that vaccine protection could wane at a fixed rate of up to 5% per year, and that herd immunity could increase overall impact by up to 20%.[56]

Hib Conjugate Vaccine Cost Assumptions

Four Indian companies produce and market Hib conjugate vaccine: Serum Institute of India (Pune), Panacea Biotec (New Delhi), Bharat Biotech (Hyderabad), and Biological E (Hyderabad). The presentations are monovalent Hib conjugate vaccine and Hib combined with DTP and hepatitis B vaccines ("pentavalent vaccine"). Although Indian vaccine procurement is normally processed between the government and the manufacturers directly, Global Alliance for Vaccines and Immunization Alliance funded vaccines are purchased through United Nations Children's Fund, which only accepts WHO prequalified vaccines. The vaccine used in Tamil Nadu and Kerala is the 10-dose vial pentavalent vaccine produced by Serum Institute of India procured at a United Nations Children's Fund price of US$1.75 per dose.[57] For the base case we assumed a cost of $1.82 per dose (including 4% tax) and no decline in dose price over time. A declining price trend was evaluated in scenario analysis.

When estimating the incremental costs of Hib conjugate vaccine, we calculated the cost difference between a schedule with pentavalent vaccine and with DTP and hepatitis B vaccines. Phased introduction of monovalent hepatitis B vaccine in a 10-dose vial started in 2002 with nationwide uptake in 2011. The 2010 prices per dose of DTP and hepatitis B vaccines were US$0.04 and US$0.11, respectively.[58] Because a 10-dose pentavalent vaccine vial is used, there is no need to allow for cold chain expansion.

Uncertainty Analysis

First, we varied each parameter in turn by ±10% to establish the parameters with the greatest influence on the cost-effectiveness results (univariate 1-way sensitivity analysis). Second, we ran 19 alternative scenarios (10 favorable and nine unfavorable) to evaluate how sensitive the results were when we changed combinations of influential parameters (multivariate scenario analysis) (eg, given the uncertainty around the incidence of Hib disease in India), the most unfavorable scenario assumed a dramatically reduced incidence rate for both Hib pneumonia (50% of the base value) and Hib meningitis (32% of the base value) combined with several other unfavorable assumptions.

Results

Hib Conjugate Vaccine Impact

Between 2012 and 2031, Hib conjugate vaccination is estimated to prevent 207 859 undiscounted child deaths (<1% of deaths in children <5 years of age) assuming no benefit from herd immunity. Undiscounted lives saved were 127 869 for Hib pneumonia, 77 840 for Hib meningitis, and 2150 for Hib NPNM. The median reduction in total deaths of children <5 years of age was 0.9% and ranged from 0.3%–2.0% across states (Table IV and Figure 4).

Hib Conjugate Vaccine Program Costs

The incremental costs of introducing Hib conjugate vaccination would be approximately US $127 million per year based on current vaccine prices (Table V). Without Hib conjugate vaccination, the cost of a fully vaccinated child (including monovalent hepatitis B) is US $2.19. Introduction of Hib conjugate vaccine increased annual costs four-fold, leading to costs per fully vaccinated child of US$8.81. The estimated total incremental cost for 2012–2031 was US$2006 million after discounting at 3% per year.

Health Care Costs Avoided by Hib Conjugate Vaccination

Around 15% of the vaccine costs would be offset by health care cost savings due to reduced cases of Hib disease. This percentage varied considerably by state; in the Central region around a one-quarter of the vaccine costs were offset by health care costs (Table IV). Total costs avoided over the 2012–2031 period would be US$310 million after discounting at 3% per year. Around 77% (US$240 million) would be avoided by households, with the remaining US$70 million by the government.

Hib Conjugate Vaccine Cost-Effectiveness

From a government perspective, state-level cost-effectiveness ranged from US$192-US $1033 per DALY averted after discounting costs and benefits at 3% per year. With the inclusion of household health care costs, cost-effectiveness ranged from US$155-US$939 per discounted DALY averted. The vaccine would be most cost-effective in the Central and Eastern States (Figure 4). States with the highest percentage reductions in under-5 deaths were as diverse as Madhya Pradesh, Jharkhand, West Bengal, and Kerala.

Uncertainty and Scenario Analyses

For a 10% change in each parameter, in all states the parameter with the largest percent impact on the discounted cost per DALY averted was relative coverage (12%–17% effect across states), a parameter rarely included in cost-effectiveness studies of vaccines. In all states, the parameter with the second largest influence was vaccine dose price (11%–16% effect). The influence and rank of other parameters varied by state, but the incidence of Hib pneumonia deaths and the efficacy of the vaccine against Hib pneumonia had important effects (7%–14%) in all states.

A variety of assumptions, favorable and unfavorable to Hib conjugate vaccine introduction, were considered in scenario analysis (Figure 5). Costs per DALY averted ranged from a cost

saving scenario, in which health care cost savings are greater than the cost of the vaccine program itself, to an unfavorable scenario costing US$1830 per discounted DALY averted. Figure 5 shows the cost per DALY averted of the base case scenario (US$331) and the cumulative effect of introducing favorable and unfavorable assumptions in sequence. Hence, the most unfavorable scenario (US$1830) combines all unfavorable assumptions listed above the base case scenario, and the cost saving scenario combines all favorable assumptions listed below the base case scenario.

Discussion

Models of this kind cannot and do not seek to estimate the precise epidemiologic "truth" about the impact of a vaccine. Instead, they provide a framework for exploring the implications of a range of plausible scenarios or "futures," recognizing that, even with a large body of accumulated (and forthcoming) clinical evidence, there will be inherent and unavoidable uncertainties in a population as large and diverse as India's.

A large body of local epidemiologic evidence is available from India for many of the parameters considered in this model. Where information is lacking or uncertain, we have had to make assumptions. For example, "all-cause pneumonia" was used as a proxy when identifying risk-factors for "Hib pneumonia" and estimating access to care. Several assumptions also were required to generate plausible estimates of state-level variation. However, where significant uncertainties exist, we have varied them in scenario analysis to test the extent to which they have an important bearing on the results. Our scenario analysis explored the cumulative effect of adding a series of favourable and unfavorable assumptions in sequence. In our most unfavorable scenario, we assumed 50% of the base case incidence for Hib pneumonia, and the unadjusted incidence of 7 per 100 000 <5 years for Hib meningitis (less than one-third of the base case estimate). We also applied a 5% discount rate, 10% fewer outpatient visits and hospitalizations, 10% lower health care costs, lower vaccine efficacy (83% for 1 dose, 69% for 2 doses, 0% for 1 dose), no herd effect, delayed timing of vaccination, clustering of deaths in the unvaccinated population (relative coverage), 5% waning dose protection per year, and exclusion of all household health care cost savings. In spite of this extreme combination of unfavorable assumptions, the cost per DALY averted remained between 1 and 3 × gross domestic product (GDP) per capita, and would still be considered cost-effective according to WHO benchmarks.[59] Nearly all other scenarios, including the base case scenario, are considered highly cost-effective with costs/DALY below US$1410, which was the per capita GDP in India in 2010.[60] The WHO thresholds have been widely debated,[61] but the fact that all scenarios, even those with unfavorable combinations of assumptions, are within 3 times the GDP per capita, suggest that the vaccine would be good value for the Indian Government.

A state-level cost-effectiveness analysis of Hib conjugate vaccination was conducted in the State of Haryana using an earlier version of our model. With different estimates and assumptions for their base case scenario,[62] the authors report a discounted cost per DALY averted from a government perspective of US$819, which is similar to our estimate for Haryana State (US$903).

Investment in Hib conjugate vaccination would increase annual vaccine costs from US$42 million to US$170 million. However, current government spending on vaccines is very low (around 2% of the national health budget)[63] and US$8.81 per vaccinated child is still far less than other countries with similar economies spend on vaccines.[64,65] In addition, we estimate that about 15% of the additional vaccine program costs would potentially be offset by health care cost savings. Because the Indian health system is dominated by a large private sector, health care costs are largely in the form of out-of-pocket costs, which often result in substantial financial burdens to households. It is estimated that more than 40% of Indian households have to borrow money or sell assets to cover hospital expenses.[66] In our analysis, the costs avoided by households accounted for 77% of the total health care costs avoided.

Our evaluation supports nationwide introduction of Hib conjugate vaccination. It is encouraging that Hib conjugate vaccines have already been introduced in Tamil Nadu and Kerala, but we estimate that these states represent as little as 4% of the potential lives that could be saved each year in India. Hib conjugate vaccination would be most cost-effective in the Central and Eastern regions where there the vaccine has the greatest potential to reduce absolute numbers of deaths. Efforts should therefore be made to expedite nationwide introduction. The impact of Hib conjugate vaccination in India has already been demonstrated in a limited setting in India.[67] Nonetheless, it will be important to continue adequate surveillance to monitor the impact of this vaccine as introduction scales up.

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Glossary

ALRI	Acute lower respiratory infection
CFR	Case fatality ratio
DALY	Disability adjusted life year
DTP	Diphtheria-tetanus-pertussis
GDP	Gross domestic product
Hib	*Haemophilus influenzae* type b
NFHS	National Family Health Survey (also known as the Demographic and Health Survey or DHS)
NPNM	Non-pneumonia-non-meningitis
WHO	World Health Organization

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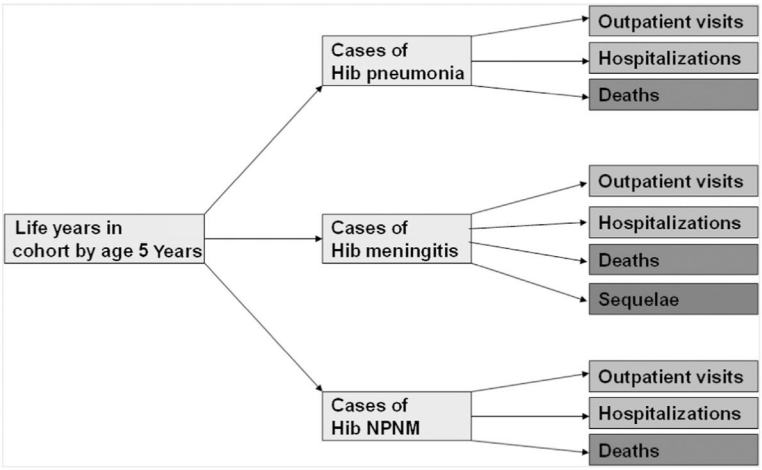

Figure 1.
Simplified structure of the Hib disease burden model.

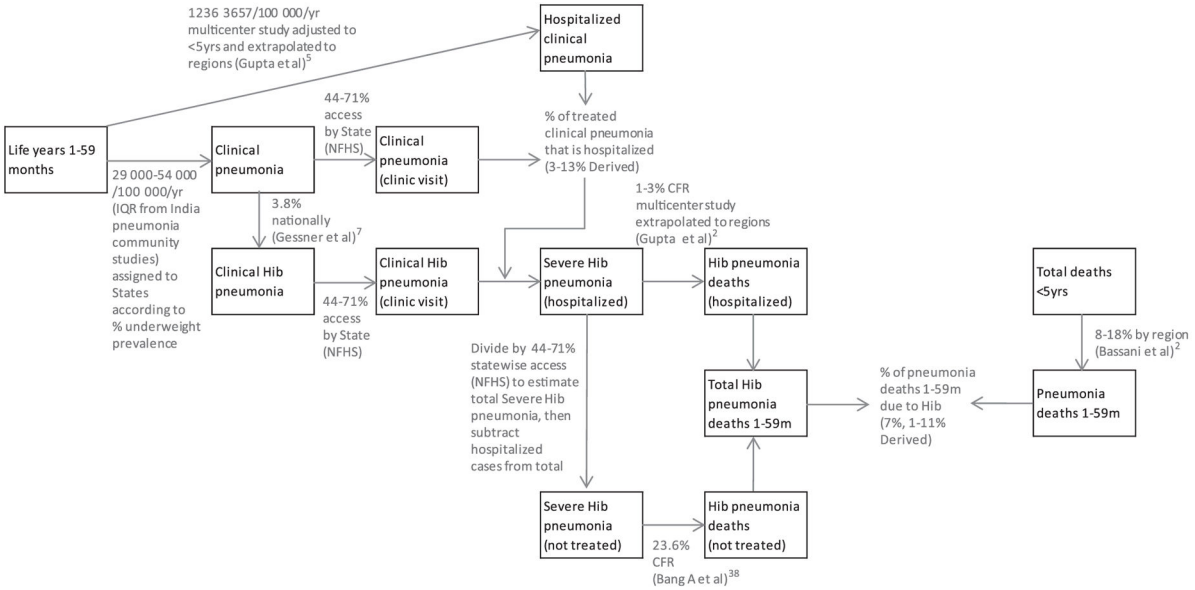

Figure 2.

Method for estimating state-level Hib pneumonia cases and deaths at ages 1–59 months.

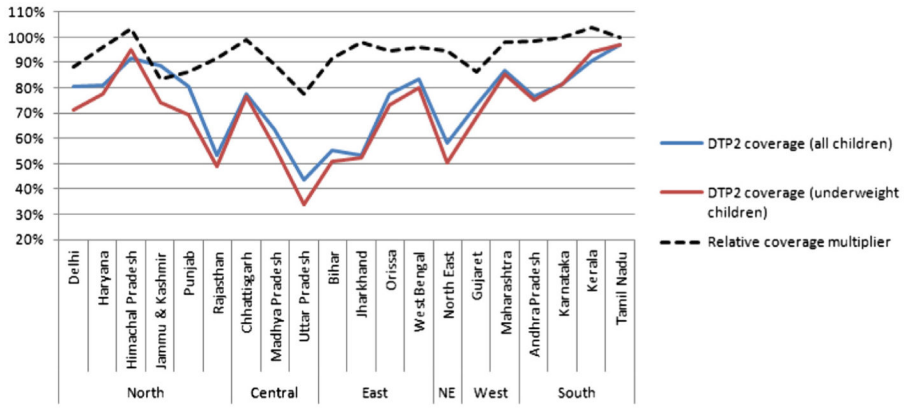

Figure 3.

State-level coverage of DTP2 vaccination: underweight infants relative to all infants. DTP2 coverage data from NFHS 2006.

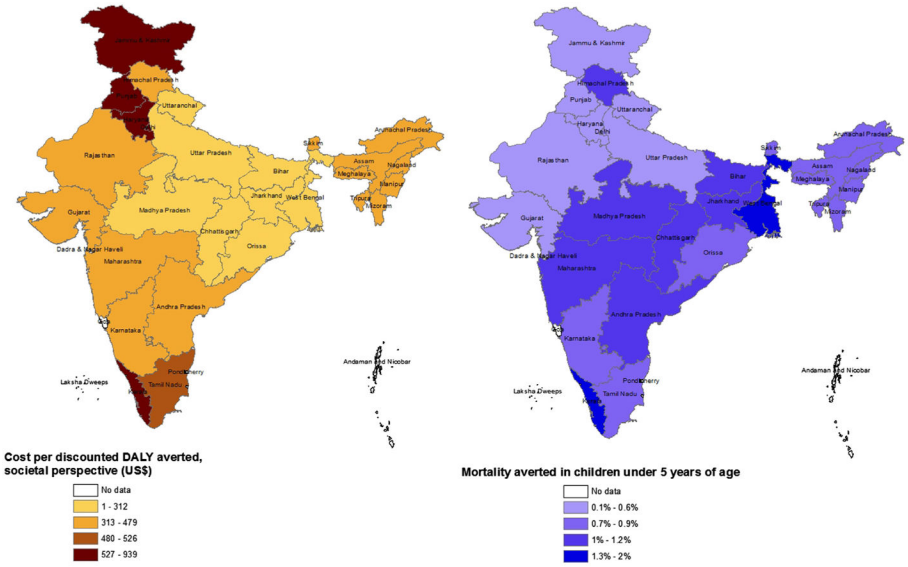

Figure 4.
Impact and cost-effectiveness of Hib vaccination by State of India.

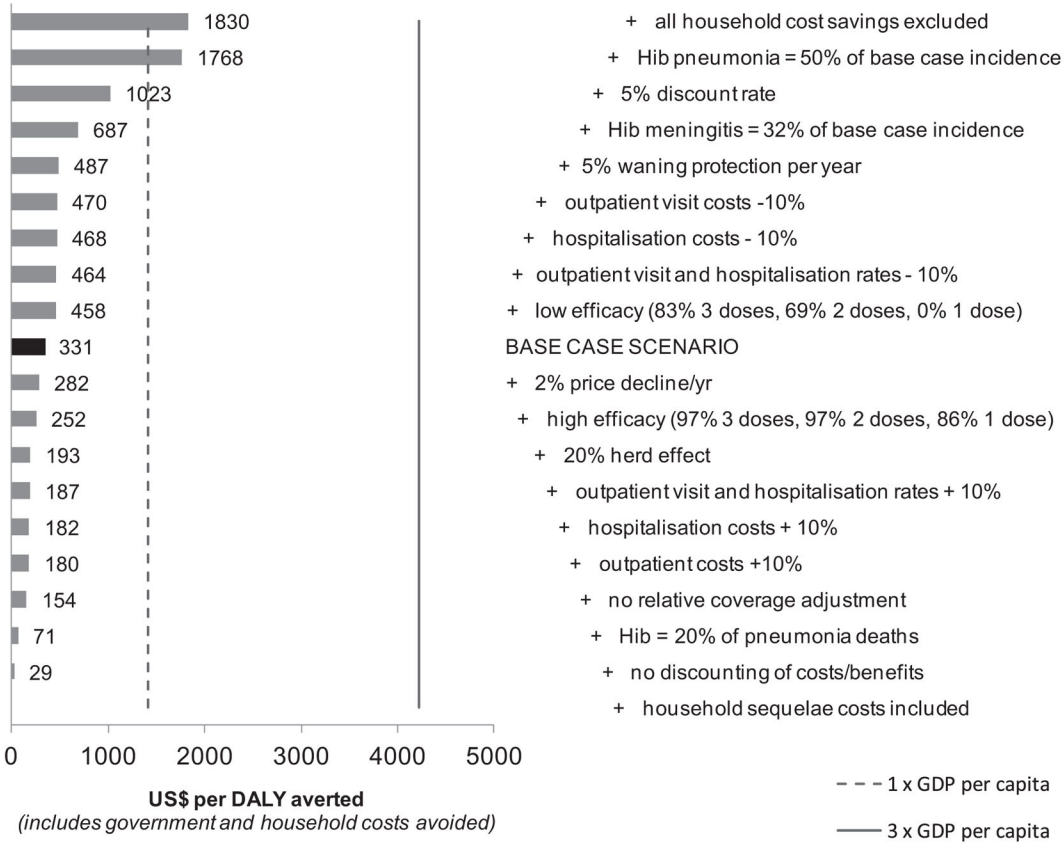

Figure 5.

Scenario analysis showing the cost per DALY averted for the base case scenario and the cumulative effect of introducing favourable and unfavorable assumptions in sequence. The *plus symbol* (+) indicates the sequential and cumulative addition of assumptions to the base case. These are either favorable to the vaccine (*bottom* half of chart) or unfavorable to the vaccine (*top* half of chart).

Table I

Burden-of-disease parameters by state

State	Region	Births per 1000	Mortality children <5 yrs per 1000	Life expectancy	Percent underweight*	Access to care	Incidence per 100 000, 1–59 mo			CFRs 1–59 mo		
							Hib pneumonia	Hib. meningitis	Hib NPNM	Hib pneumonia	Hib. meningitis	Hib NPNM
Delhi	North	351	25	74	26%	89%	1184	22	4	0.1%	21%	5%
Haryana	North	547	64	70	40%	88%	1530	22	4	0.1%	22%	5%
Himachal Pradesh	North	125	42	73	37%	69%	1450	22	4	0.3%	39%	6%
Jammu and Kashmir	North	267	76	68	26%	73%	1171	22	4	0.3%	35%	5%
Punjab	North	519	52	71	25%	87%	1153	22	4	0.1%	22%	5%
Rajasthan	North	1735	79	69	40%	66%	1537	22	4	0.3%	41%	6%
Chhattisgarh	Central	629	93	64	47%	67%	1722	22	4	1.3%	41%	6%
Madhya Pradesh	Central	1981	94	65	60%	53%	2052	22	4	1.7%	53%	6%
Uttar Pradesh	Central	6216	85	66	42%	76%	1601	22	4	1.1%	32%	5%
Bihar	East	2487	65	69	56%	72%	1947	22	4	1.2%	36%	6%
Jharkhand	East	780	72	67	57%	71%	1962	22	4	1.2%	37%	6%
Orissa	East	837	83	66	41%	76%	1558	22	4	1.1%	32%	5%
West Bengal	East	1675	46	71	39%	70%	1507	22	4	1.2%	38%	6%
North East†	North East	281	46	71	36%	44%	1430	22	4	0.5%	61%	7%
Gujaret	West	1203	58	71	25%	64%	1156	22	4	0.5%	43%	6%
Maharashtra	West	2258	39	70	37%	74%	1463	22	4	0.4%	34%	5%
Andhra Pradesh	South	1619	55	69	33%	60%	1348	22	4	0.6%	46%	6%
Karnataka	South	1165	53	70	38%	71%	1478	22	4	0.4%	37%	6%
Kerala	South	578	12	75	23%	89%	1102	22	4	0.2%	21%	5%
Tamil Nadu	South	1159	43	70	30%	77%	1279	22	4	0.3%	31%	5%

*Weight for age < –2SD from WHO reference population.

†The North East region includes Sikkim, Arunachal Pradesh, Nagaland, Manipur, Mizoram, Tripura, Meghalaya, and Assam.

Table II

Distribution of inpatient admissions and outpatient visits by type of provider by state

		Inpatient distribution				Outpatient distribution							
State	**Region**	**Priv hosp All**	**Gov hosp 1ary**	**Gov hosp 2ary**	**Gov hosp 3ary**	**Priv trad***	**Priv pharm**	**Priv clinic**	**Priv hosp All**	**Gov clinic**	**Gov hosp 1ary**	**Gov hosp 2ary**	**Gov hosp 3ary**
Delhi	North	61%	0%	37%	2%	0%	1%	67%	13%	12%	0%	8%	0%
Haryana	North	83%	0%	16%	1%	3%	3%	75%	15%	0%	0%	3%	0%
Himachal Pradesh‡	North	39%	38%	21%	1%	2%	6%	51%	14%	5%	14%	8%	0%
Jammu and Kashmir	North	18%	62%	19%	1%	1%	19%	31%	8%	3%	28%	9%	0%
Punjab	North	72%	0%	26%	1%	0%	5%	73%	16%	0%	0%	6%	0%
Rajasthan	North	32%	49%	18%	1%	2%	7%	41%	14%	6%	22%	8%	0%
Chhattisgarh	Central	43%	16%	39%	2%	0%	6%	66%	7%	12%	2%	6%	0%
Madhya Pradesh	Central	46%	23%	29%	2%	12%	4%	55%	12%	4%	6%	8%	0%
Uttar Pradesh	Central	23%	64%	12%	1%	2%	7%	80%	2%	1%	6%	1%	0%
Bihar	East	86%	7%	6%	0%	6%	18%	61%	11%	3%	1%	1%	0%
Jharkhand	East	62%	0%	36%	2%	3%	11%	74%	6%	3%	0%	4%	0%
Orissa	East	18%	59%	22%	1%	12%	6%	31%	8%	4%	27%	10%	1%
West Bengal	East	22%	31%	44%	2%	16%	6%	62%	3%	3%	4%	6%	0%
North East†,‡	North East	14%	61%	24%	1%	19%	19%	29%	3%	10%	14%	6%	0%
Gujaret	West	67%	9%	23%	1%	0%	4%	51%	28%	4%	4%	9%	0%
Maharashtra	West	56%	9%	32%	2%	4%	3%	62%	17%	0%	3%	10%	1%
Andhra Pradesh	South	67%	0%	32%	2%	0%	0%	40%	40%	0%	0%	19%	1%
Karnataka	South	70%	18%	12%	1%	4%	0%	38%	38%	3%	10%	6%	0%
Kerala	South	63%	0%	35%	2%	11%	0%	4%	50%	7%	0%	27%	1%
Tamil Nadu	South	41%	17%	40%	2%	4%	1%	25%	28%	0%	12%	28%	1%

1ary, primary; *2ary*, secondary; *3ary*, tertiary; *gov*, government; *hosp*, hospital; *pharm*, pharmacy; *priv*, private; *trad*, traditional.

*Priv Trad refers to private nonmedical healthcare provider (eg, traditional healer).

†The North East region includes Sikkim, Arunachal Pradesh, Nagaland, Manipur, Mizoram, Tripura, Meghalaya, and Assam. The following smaller areas were excluded from the evaluation: Andoman and Nicobar Islands, Chandigarh, Dadra and Nagar Haveli, Daman and Diu, Goa, Lakshadweep, Pondicherry, and Uttaranchal.

‡Regional distribution was used because estimates for this state were based on a low sample of children (weighted number of children <25).

Table III

Average Hib disease treatment costs per inpatient admission and outpatient visit (2010 US$)

		Cost per inpatient admission				Cost per outpatient visit			
Type of Hib disease	**Region**	**Priv hosp All**	**Gov hosp 1ary**	**Gov hosp 2ary**	**Gov hosp 3ary**	**Priv trad**	**Priv pharm**	**Priv clinic or hosp**	**Gov clinic or hosp**
Meningitis	North	204	336 (51%)	343 (50%)	551 (31%)	6	1	11	15 (81%)
	Central	345	505 (67%)	513 (66%)	721 (47%)	1	1	9	6 (49%)
	East	229	217 (24%)	225 (23%)	433 (12%)	5	1	5	13 (77%)
	Northeast	468	206 (20%)	213 (19%)	422 (10%)	3	1	5	10 (70%)
	West	483	232 (29%)	240 (28%)	448 (15%)	0	1	6	4 (18%)
	South	193	201 (18%)	208 (17%)	417 (9%)	1	1	7	5 (37%)
Pneumonia/NPNM	North	126	202 (52%)	207 (51%)	329 (32%)	6	1	11	15 (81%)
	Central	213	307 (69%)	312 (68%)	434 (48%)	1	1	9	6 (49%)
	East	141	129 (25%)	134 (24%)	256 (13%)	5	1	5	13 (77%)
	Northeast	289	122 (21%)	127 (20%)	249 (10%)	3	1	5	10 (70%)
	West	298	139 (30%)	143 (29%)	266 (16%)	0	1	6	4 (18%)
	South	119	119 (19%)	124 (18%)	246 (9%)	1	1	7	5 (37%)

Parentheses show the percentage of total costs by households at government providers.

Table IV

Hib vaccine impact and cost-effectiveness by state: aggregate estimates over the period 2012–2031

		Vaccine impact, undiscounted					Cost-effectiveness, discounted at 3%					
State	Region	Pneumonia lives saved	Meningitis lives saved	NPNM lives saved	Total lives saved	Percent of U5MR averted	Vaccine costs (millions)	Gov cost savings (millions)	Family cost savings (millions)	Total DALYs averted	US$ per DALY averted (government perspective)	US$ per DALY averted (societal perspective)
Delhi	North	278	807	34	1119	0.6%	$36	$0.6	$3.2	34 470	1033	939
Haryana	North	472	1038	42	1552	0.3%	$43	$0.3	$4.9	47 096	903	800
Himachal Pradesh	North	253	506	13	773	1.0%	$10	$0.3	$1.0	20 314	500	453
Jammu and Kashmir	North	262	662	19	943	0.3%	$20	$0.5	$1.2	25 620	777	728
Punjab	North	364	1048	41	1453	0.4%	$45	$0.4	$3.7	44 145	1017	934
Rajasthan	North	2942	5492	140	8575	0.4%	$118	$3.0	$9.9	220 070	524	479
Chhattisgarh	Central	6050	2315	59	8424	1.0%	$51	$2.8	$11.3	197 709	245	188
Madhya Pradesh	Central	21 415	7010	152	28 578	1.1%	$133	$5.6	$24.4	661 798	192	155
Uttar Pradesh	Central	30 054	12 112	364	42 531	0.5%	$432	$24.6	$82.6	1 040 354	392	312
Bihar	East	19 200	6431	179	25 810	1.0%	$169	$2.4	$24.4	617 964	269	229
Jharkhand	East	7482	2493	68	10 043	1.2%	$62	$2.5	$7.8	237 934	252	219
Orissa	East	4820	1995	60	6876	0.7%	$58	$4.7	$4.9	169 599	315	286
West Bengal	East	12 577	5468	147	18 191	1.5%	$130	$8.3	$8.9	439 363	276	256
North East *	North East	614	1170	23	1807	0.9%	$19	$0.3	$0.4	43 599	420	411
Gujaret	West	2419	3793	94	6305	0.6%	$83	$1.1	$7.0	161 467	506	463
Maharashtra	West	6073	7993	233	14 299	1.0%	$204	$4.6	$22.2	374 003	533	474
Andhra Pradesh	South	6019	7979	188	14 186	1.0%	$147	$2.2	$7.7	351 765	411	389
Karnataka	South	3645	4636	127	8408	0.9%	$104	$1.7	$7.1	216 132	474	441
Kerala	South	662	1403	58	2123	2.0%	$51	$1.3	$3.2	64 781	775	725
Tamil Nadu	South	2266	3490	107	5863	0.8%	$90	$3.1	$4.4	156 945	555	526
India		127 869	77 840	2150	207 859		$2006	$70	$240	5 125 128	378	331

* The North East region includes Sikkim, Arunachal Pradesh, Nagaland, Manipur, Mizoram, Tripura, Meghalaya, and Assam.

Table V

Vaccine and syringe costs of the schedule* with and without Hib conjugate vaccine (2010 US$)

	Doses in schedule	Costs per dose†	Vaccine costs	Injection supply costs	Total
Bacille Calmette Guerin	1	0.04	2 565 849	2 137 351	4 703 199
DTP	3	0.04	2 977 936	3 594 400	6 572 336
Hepatitis B	3	0.11	9 854 186	3 594 400	13 448 586
Measles	1	0.20	7 603 174	1 467 332	9 070 505
Polio	4	0.08	8 272 044	-	8 272 044
Total without Hib vaccine			31 273 189	10 793 483	42 066 671
Costs per child without Hib vaccine			1.63	0.56	2.19
DTP-hepatitis B-Hib vaccine	3	1.82	143 600 101	3 594 400	147 194 502
Total with Hib vaccine			162 041 168	7 199 083	169 240 250
Costs per child with Hib vaccine			8.44	0.37	8.81
Annual incremental cost			130 767 979	−3 594 400	127 173 579

Price per injection syringe was US$0.06. Price per safety box with capacity of 100 used syringes was US$1.50. Vaccine wastage rates were 61% for Bacille Calmette Guerin, 27% for DTP and pentavalent vaccine, 33% for hepatitis B vaccine, 35% for measles and 47% for polio.[58]

* The routine schedule includes booster doses for DTP, polio, and measles at the age of 16–24 mo, but these costs are not included.

† 4% tax is added to the price per dose.