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*Original article*

**Cost-effectiveness of *Haemophilus influenzae* type b vaccine in low- and middle-income countries: Regional analysis and assessment of major determinants**

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## **Abstract**

### **Objectives**

To estimate the cost-effectiveness of Hib vaccine in low- and middle-income countries and identify the model parameters which are most important for the result.

### **Study design**

A static decision tree model was developed to predict incremental costs and health impacts. Estimates were generated for four country groups: Countries eligible for funding by the GAVI Alliance in Africa and Asia, lower middle-income countries and upper middle-income countries. Parameter values, including disease incidence, case fatality rates and treatment costs, were based on international country estimates and the scientific literature.

### **Results**

From the societal perspective, it is estimated that the probability of Hib vaccine being cost saving is 53% and 34% in GAVI eligible African and Asian countries, respectively. In middle-income countries, costs per discounted DALY averted are between US\$ 37 and US\$ 733. Variation in vaccine prices and risks of meningitis sequelae and mortality explain most of the difference in results. For all country groups disease incidence parameters cause the largest part of the uncertainty in the result.

### **Conclusion**

Hib vaccine is cost saving or highly cost-effective in low- and middle-income settings. This conclusion is especially influenced by the recent decline in Hib vaccine prices and new data revealing the high costs of lost productivity associated with meningitis sequelae.

## **Introduction**

Prior to the introduction of vaccines, *Haemophilus influenzae* type b (Hib) was the most common cause of bacterial meningitis and an important cause of pneumonia in children less than five years of age. Hib conjugate vaccines became available during the early 1990s and high-income countries quickly introduced the vaccine into routine vaccination programmes, resulting in a near disappearance of Hib disease [1]. However, relatively high vaccine prices and uncertainties about Hib disease burden led to slow uptake in low- and middle-income countries. Even though the GAVI Alliance began to offer Hib vaccine to the poorest countries of the world in 2001, it took almost a decade until the majority of these had introduced the vaccine [2]. Similar late introductions were seen in middle-income countries. While 181 of the world's 196 countries (92%) have adopted the vaccine in 2012, 52% of these had only done so during the past eight years [3].

To better understand the relative contribution of costs, health systems aspects and disease parameters for assessment of the value of vaccines, this study was conducted to determine and compare the cost-effectiveness of Hib vaccine between countries in various income and epidemiological categories.

## **Methods**

### ***Decision-analytic model***

A deterministic, aggregate-level, static decision tree model was developed. The model framework is seen in Figure 1. Hib disease was divided into three different groups; (i) meningitis, (ii) pneumonia and (iii) less common non-pneumonia-non-meningitis (NPNM), following methods used in the Hib Global Burden of Disease (GBD) study [4]. Projected numbers of person-years lived between one and 59 months were multiplied by age-specific disease incidence rates to estimate Hib cases in each cohort. The time horizon was until everyone in the cohort had died.

An all-cause pneumonia incidence rate was used to calculate total pneumonia cases and a proportion of these were assumed due to Hib. Hib meningitis and Hib NPNM cases were calculated directly from aetiology specific incidence rates. Numbers of deaths were estimated from case fatality ratios (CFRs). A risk of sequelae was applied to all survivors of Hib meningitis and classified according to type of

complication. A proportion of cases were assumed to seek health care and treatment costs varied according to outpatient visits and hospital admissions. The analysis was undertaken from both a government health sector and a societal perspective; the difference being that household out-of-pocket treatment costs and meningitis sequelae productivity costs were only included in the societal perspective.

The impact of Hib vaccine was estimated as the difference between scenarios with and without vaccination. In the Hib vaccine scenario, cases were reduced by age-specific vaccination coverage rates and dose-specific vaccine efficacy. Incremental cost-effectiveness ratios (ICERs) were calculated by subtracting annual treatment costs from annual vaccine delivery costs and dividing by incremental health effects, expressed as Disability Adjusted Life Years (DALYs) averted. Future costs and health effects were discounted by 3% per year [5].

### ***Monte Carlo simulation***

Most parameter values in decision-analytic modelling are surrounded by uncertainty [6]. In the present study this is important because a number of international sources and global assumptions were used, which have not been reviewed at country level. Thus, the aim was not to generate results for a single country, but to determine a plausible range of cost-effectiveness for a given country income and epidemiological group. Uncertain parameter values were assigned an uncertainty range and a statistical distribution, and 1,000 random sample Monte Carlo simulations were run using Oracle Crystal Ball<sup>®</sup> software. This generated 95% confidence intervals around the ICERs. The importance of individual parameters to uncertainty in the result was assessed by analysis of covariance (ANCOVA), which summarises the proportion of the variance explained by variation in different input parameters [6]. The simulation data were analysed in STATA version 11.0. All parameter values are seen in Table 1 with explanations given in the sections below. The statistical distributions fitted to the parameters are included in the web annex.

### ***Study populations***

The model was run for cohorts of one million children in four different settings: (i) GAVI eligible African countries, (ii) GAVI eligible Asian countries, (iii) lower middle-income countries and (iv) upper middle-income countries. In 2012 GAVI offered support to countries with 2011 Gross National Income (GNI) per capita below US\$ 1,520 [7]. Lower middle-income countries were classified as those with per capita GNI between the GAVI threshold and US\$ 4,035, and upper middle-income countries were those with GNI per capita between US\$ 4,036 and US\$ 12,475 [8]. The countries included in the four groups are listed in the web annex.

### ***Hib disease incidence rates***

Country specific studies have shown great variation in Hib disease incidence rates and this has been the subject of much research and some controversy [9]. One of the most debated topics is the disease incidence in Asia where some studies have shown rates one tenth of those observed in North America and Europe [10-11]. There is still not enough knowledge to conclude whether these results reflect a true low disease burden or whether they are due to problems in detection, such as widespread use of antibiotics before hospitalization and/or suboptimal microbiologic capacity for identifying Hib in clinical specimens [12].

Hib meningitis incidence rates for the four groups were calculated as averages of the Hib GBD study country-specific estimates for the year 2000. The GBD study authors conducted a systematic literature review and extrapolated published estimates to countries without data [4, 13]. The uncertainty range was assumed as the lowest and highest country-specific values of the respective group. NPNM incidence was estimated as a proportion of the meningitis incidence rates, as explained in the web annex.

The most uncertain disease burden estimate is for Hib pneumonia. In 2008, pneumonia deaths in children aged one to 59 months caused approximately 14% of global under-five deaths and Hib vaccines are seen as an important tool to reduce this mortality [14]. However, the true incidence of Hib pneumonia is largely unknown because the signs and symptoms due to Hib cannot be

differentiated from cases caused by other microorganisms [15]. The incidence of clinical pneumonia for the four country groups were taken from recently completed estimates for the 2010 GBD study [16]. Details on these are given in the web annex. Hib vaccine trials in Indonesia and Gambia have demonstrated efficacy against all cause clinical pneumonia with a pooled estimate of 4% (95% CI 1% - 7%) and no heterogeneity between the two studies [17-19] and this was assumed as the vaccine preventable proportion.

### ***Case fatality rates and risk of meningitis sequelae***

The risk of mortality from Hib disease increases substantially if access to antibiotics and appropriate treatment are not available. Without access to health care, case fatality rates were assumed to be 100% for meningitis, 50% for NPNM, and 24% for pneumonia [20-21]. Hospital case fatality rates were based on studies from the respective regions and a global review [9].

The risk of meningitis sequelae increases with delay in treatment as untreated patients are likely to experience coma, seizures and prolonged fever [22]. Estimates were taken from a meta-analysis of the risk of sequelae according to pathogen, region and country income group [23].

### ***Disability adjusted life years***

DALYs were calculated as the sum of three components: Years of life lost (YLL) due to premature mortality, years of life with disability (YLD) from acute disease and YLD due to meningitis sequelae. Average life expectancies across the four country groups were used for the YLL estimates. Disability weights were 0.279 and 0.616 for pneumonia and meningitis, respectively [24]. In the original GBD study there were no disability weights for any of the NPNM diseases, probably because these are all relatively rare syndromes. In such instances, it is common practice to use a disability weight for a comparable disease. For middle-income countries, the meningitis disability weight was used because epiglottitis has comparable severity to meningitis. For the low-income groups, the pneumonia disability weight was used, as there is currently no evidence of epiglottitis in these countries and the remaining NPNM diseases have more comparable severity to pneumonia than to meningitis (see web annex for more details).

To estimate DALYs due to meningitis sequelae, the proportional distributions of sequelae complications were determined from the literature review by Edmond *et al.* [23] and appropriate disability weights were assigned. The weighted average disability weight for meningitis sequelae was 0.340 (see web annex).

### ***Access to health care***

Assumptions about access to care were expressed in terms of number of outpatient visits and hospital admissions per case. According to WHO treatment recommendations, all Hib disease except non-severe pneumonia requires hospitalisation [25]. Hence, if all children had access to appropriate health care, each case of meningitis, NPNM and severe pneumonia would lead to at least one hospitalisation and most likely also at least one outpatient visit, as hospitalisations are generally referred during an outpatient consultation. The number of outpatient visits per case would exceed one in places with high access to care as clinical follow-up is commonly recommended after hospital discharge, especially for meningitis. If access to health care is limited, the number would be less than one. For those with access to care, it was assumed that each meningitis episode would lead to one hospital admission and three outpatient visits, severe pneumonia and NPNM to one hospital admission and one outpatient visit, and non-severe pneumonia to one outpatient visit only. Based on evidence from the Indonesia Hib vaccine trial, 17% of clinical Hib pneumonia cases were presumed severe [18]. Assumptions about access to care were based on the percentage of children with acute respiratory symptoms taken to a health facility reported in Demographic and Health surveys from the respective regions since year 2000 [26].

### ***Treatment costs***

#### Hospital treatment

Data were extracted from country specific studies reporting on the costs of pneumonia and meningitis treatment (see web annex for details). Nine studies with pneumonia data and 21 studies with meningitis data were identified. For both syndromes there were strong correlations between mean costs per case and GNI per capita and the following regressions were generated:

- Costs of meningitis treatment in tertiary hospital = US\$ 774 + 0.2645(GNI)



- Costs of pneumonia treatment in tertiary hospital = US\$ 54 + 0.1255(GNI)

Confidence intervals around the regression coefficients were used for the uncertainty ranges.

Treatment costs of NPNM were assumed similar to pneumonia. Based on evidence from three studies that provided estimates from different levels of facilities, mean treatment costs in secondary facilities were 65%, 71% and 27% less than in tertiary facilities, for low-income African countries, low-income Asian and middle-income countries, respectively (see web annex). In upper middle-income countries it was assumed that 30% of meningitis and severe pneumonia cases were admitted to tertiary hospitals and the remaining to secondary hospitals. For the remaining three regions, 20% of cases were supposed admitted to tertiary hospitals and 80% to secondary.

The proportion of treatment costs paid by household as out-of-pocket payments was calculated as averages of country-specific data from National Health Accounts [27]. These were 45% in low-income African countries, 51% in low-income Asian countries, 37% in lower middle-income countries and 31% for upper middle-income countries.

#### Outpatient treatment

Country-specific estimates from WHO CHOICE on the costs per outpatient visit were averaged across the four country groups [28]. These estimates do however not include the costs of drugs and diagnostics. In a study from Fiji, mean costs of drugs and medical supplies for pneumonia outpatient treatment of 387 children less than five years were estimated as US\$ 1.28 per case [29]. This amount was added to the visits costs in all four country groups. For the uncertainty intervals, the mean estimates were varied by 25% in each direction.

#### Meningitis sequelae

The costs of meningitis sequelae have rarely been included in Hib vaccine economic evaluations from low- and middle-income countries [30]. This is in contrast to high-income country studies where sequelae costs have been one of the most important determinants of cost-effectiveness and a key supporting argument for the vaccine [31-32]. In these countries, cost estimates were based on data from education agencies, disability services and medical insurance companies. These assumptions can

however not easily be made for low- and middle-income countries with limited access to health care and hardly any disability rehabilitation services. In a recent study from Senegal, data were collected from 49 families with children suffering from meningitis sequelae. Mean non-discounted lifetime sequelae costs were estimated as US\$ 53,165 (95% CI US\$ 68 -148,067 ) per child, with treatment costs comprising 1%, childcare costs 9% and productivity costs of caregivers 90% [33]. The costs of meningitis sequelae were approximately 26 times higher than the mean costs of treatment of the acute meningitis episode, and this result was used in the present analysis for the four country groups. As the costs of sequelae are primarily borne by households in low- and middle-income countries, these costs were only included in the societal perspective.

### ***Costs of Hib vaccine delivery***

Incremental vaccine delivery costs were estimated as the difference between a routine vaccination schedule with and without Hib vaccine. Use of Hib combination vaccines was assumed. For GAVI eligible countries the difference in 2011 UNICEF prices of the ten dose diphteria-tetanus-pertussis (DTP)-hepatitis B-Hib vaccine and the ten dose DTP-hepatitis B vaccine amounted to US\$ 1.13 per dose (US\$ 1.75 – US\$ 0.62) [34]. For upper middle-income countries, Belarus prices of US\$ 5.30 per dose of DTP-Hib vaccine and US\$ 0.15 per dose of DTP were used [21]. Hence, the incremental costs per dose were US\$ 4.95. In the lower middle-income group several graduating GAVI countries are included and the price that these countries will obtain after GAVI support ends is still uncertain [35]. An incremental price of US\$ 3 per Hib vaccine dose was assumed. A three dose schedule was used in low- and lower middle-income countries and a four dose schedule in upper middle-income countries, reflecting common practices [36]. It was assumed that upper middle-income countries used single dose vials and the remaining countries ten-dose vials, with vaccine wastage 25% (range 20% - 30%) for ten dose and 5% (range 2% - 7%) for single dose vials [7].

## Results

### Health impact, net costs and costs per discounted DALY averted

Base case health impacts and incremental costs from a societal perspective are summarised in Table 2. Per one million birth cohort, the vaccine is predicted to avert 4,589 deaths in GAVI eligible African countries, 3,505 in GAVI eligible Asian countries, 4,048 in lower middle-income countries and 1,446 in upper middle-income countries. Pneumonia comprises between 82% and 87% of all premature deaths averted. The lower middle-income group is the most heterogeneous as health indicators vary considerably between the countries; the under- five mortality rate per 100,000 children ranges from 15 in Ukraine to 128 in Congo Brazzaville. This result should therefore be considered the most uncertain and the heterogeneity explains the relatively high proportion of under-five mortality averted by Hib vaccine, which is 10% in the lower middle-income group, but only between 4-5% in the other three groups. The Hib GBD study estimated that Hib disease caused 4% of under- five mortality in 2000 [4]. When using an under-five mortality of 100 instead of 37 in the lower middle-income group, the vaccine is predicted to avert 4% of under-five mortality.

In the base case, Hib vaccine is cost saving from a societal perspective in GAVI eligible African countries, which means that health care costs avoided exceed the costs of Hib vaccine delivery (Table 2). Incremental costs are also considerably less in GAVI eligible Asia than in the two middle-income country groups. This difference is particularly due to the lower vaccine price, but also explained by the greater risk of meningitis sequelae, which leads to higher averted sequelae costs. From a government perspective, incremental costs per discounted DALY averted range from US\$ 35 (95% CI 19, 57) in GAVI eligible African countries to US\$ 453 (95% CI 202, 796) in upper middle-income countries (Table 3).

### Contribution of uncertain model parameters

The distribution of 1,000 Monte Carlo simulations generated from the societal perspective is seen in Figure 2. The simulations predict that the probabilities of the vaccine being cost-saving are 53%, 34%, 0.1% and 1.6% in GAVI eligible African, Asian, lower middle-income and upper middle-

income countries, respectively. A total of 40 parameters were attached an uncertainty range and a statistical distribution, but as seen in Figure 3, only a few influenced variability in the ICERs to a substantial extent. From the Government perspective, pneumonia incidence is the most important parameter, contributing to 53% of the variance in upper middle-income countries and 78% in GAVI eligible Asia. However, from a societal perspective the meningitis incidence is the most important because sequelae costs are included. This parameter is especially important in the GAVI eligible countries because of the higher risk of sequelae in settings with limited access to health care services.

Other parameters influencing the result, albeit considerably less than the pneumonia and meningitis incidence rates, are Hib vaccine wastage, CFRs and vaccine efficacy. Vaccine wastage is important because this affects vaccine costs. Since no uncertainty range was assumed for vaccine prices, the wastage rates were the only parameters that influenced vaccine delivery costs. Even with a relatively narrow uncertainty range, this parameter proved to be more important than many of the others, such as treatment costs and health care utilisation.

## **Discussion**

This study shows that Hib vaccine is cost saving in GAVI eligible Africa and highly cost-effective in low- and middle-income settings. These findings are especially influenced by the recent decline in Hib vaccine prices and new data revealing the high costs of lost productivity associated with meningitis sequelae.

The cost-effectiveness of Hib vaccine is more favourable in GAVI eligible than middle-income countries. The most important reason for the difference is the lower vaccine price obtained by the GAVI Alliance compared to when countries procure independently. Another critical explanation is that the baseline Hib mortality burden, expressed as case fatality rates, is higher, leading to more deaths averted per child vaccinated. However, Hib vaccine can be considered highly cost-effective in all the analysed country groups. The average GNI per capita of the upper middle-income group is US\$ 7,259, which is 10 - 93 times more than the societal cost-effectiveness range of US\$ 78 – US\$ 733.

The Monte Carlo simulation incorporated parameter uncertainty into the analysis and it was shown that variations in cost-effectiveness are explained by only a few parameters. As might have been expected, Hib pneumonia and meningitis incidences were the most important drivers of the result. Hib pneumonia was important both because this is the most frequent type of Hib disease and because of the relatively wide uncertainty range. The burden of clinical as well as aetiological specific pneumonia is intrinsically difficult to determine and this remains the most important ambiguity when making conclusions about the value of Hib vaccine [15, 37]. Since the reliability of Hib meningitis data are considerably better than for Hib pneumonia, the uncertainty range is less. However, due to the high costs of lost productivity due to meningitis sequelae, Hib meningitis incidence was the most important determinant of cost-effectiveness from the societal perspective. The present study is the first to have shown the importance of incorporating sequelae costs in low-income settings. A recent study from Senegal showed that the costs to families of caring for a disabled child are substantial [33]. When these costs were included, the cost-effectiveness range includes negative values, meaning that there is probability of the vaccine being cost saving. Similar conclusions were made in high-income country studies twenty years ago [30].

There are some important limitations to this analysis. First, this evaluation did not include all parameters available in our model. In particular, herd effects (modelled by increasing the direct effect by a simple %), clustering of deaths in the unvaccinated group, and reductions in the baseline trend of Hib disease mortality in the absence of vaccination. Each of these has proven to be influential in simpler univariate analysis. Second, the ranges chosen for each parameter reflect the extreme range of available country-level estimates in a given region/income strata. The parameter distributions therefore reflect regional variation, which may be wider than the degree of variation expected at country level and cost-effectiveness may thus appear particularly sensitive to parameters with large variation, which may to some extent be explained by fairly extreme outliers. Third, this analysis has assumed independence between parameters in each 'run' of the Monte Carlo simulation, i.e. that no correlation exists between them. For example, in reality countries with high meningitis CFRs are also likely to have high pneumonia CFRs, but this link is not reflected.

Our analysis is the first global economic evaluation of Hib vaccine. Several country specific studies have been published, but only few of these are from low- and middle-income countries [30]. Our multi-country study provides broad conclusions about the cost-effectiveness of Hib vaccine, which is valuable at the present moment in time. During the first ten years of GAVI Alliance support, Hib vaccine prices remained substantially higher than prices of the traditional vaccines, contributing to slow uptake of the vaccine. However, additional vaccine suppliers entered the market during 2011 and the price has since decreased. The ten dose pentavalent vaccine from Serum Institute of India is procured for approximately 50% less than previous price levels [34]. Our comparison between GAVI eligible and middle-income countries clearly showed the importance of the lower vaccine price for cost-effectiveness of the vaccine. Middle-income countries have not yet benefited from price decreases and 17 of these have not yet introduced the vaccine [3]. However, our analysis showed that Hib vaccine is highly cost-effective across all current price levels. This result is important for countries that are graduating from GAVI support in the near future [35].

Global economic evaluations of pneumococcal, rotavirus and human papillomavirus (HPV) vaccines have used comparable methods to the present study and similar conclusions have been made for these vaccines [38-42]. It is important to bear in mind that the unique purpose of these global analyses is not to provide accurate cost-effectiveness estimates for a given country, but to give an indication of what the plausible range of cost-effectiveness is likely to be for countries in a particular region/income strata, and to identify the most important determinants of cost-effectiveness for those countries. An alternative approach could have been to run the analysis for all countries separately, as in the studies by Kim *et al.* and Goldie *et al.* [39, 42]. However, this level of disaggregation could be misleading since a number of country-specific estimates are generated without any primary data collection. If cost-effectiveness estimates are to have any real influence on decision-making at country-level, countries need to have ownership over the data, assumptions and results of the model. To facilitate this, the model used in this study has a user friendly interface and automated features for sensitivity and scenario analysis [43]. The model is available for use by Ministries of Health who wish to assess the cost-effectiveness of Hib vaccination and populate the model with data that is credible at country

level. In addition to Hib vaccine, our model can be relevant for other vaccines that contribute to prevention of pneumonia and meningitis, as it takes into account various factors associated with pneumonia assumptions, as well as the costs related to meningitis long term sequelae.

**Table 1: Base case parameter assumptions (low, high)**

| <b>Parameter</b>  | <b>GAVI eligible Africa</b> | <b>GAVI eligible Asia</b> | <b>Lower middle-income</b> | <b>Upper middle-income</b> | <b>Source</b> |
|---|-----------------------------|---------------------------|----------------------------|----------------------------|---------------|
| Number of countries in group                              | 38                          | 13                        | 27                         | 42                         | [7-8]         |
| Life expectancy from birth (years)                        | 55                          | 64                        | 70                         | 71                         | [44]          |
| Infant mortality per 1000 live births                     | 80                          | 56                        | 29                         | 21                         | [44]          |
| Under five mortality per 1000 live births                 | 128                         | 77                        | 37                         | 28                         | [44]          |
| Hib dose 1 vaccination coverage (%)                       | 86                          | 90                        | 95                         | 94                         | [45]          |
| Hib dose 3 vaccination coverage (%)                       | 76                          | 85                        | 91                         | 91                         | [45]          |
| Access to health care for children < 5 years (%)          | 52 (31, 76)                 | 67 (54, 81)               | 57 (34, 75)                | 86 (48, 90)                | [26]          |
| <b>Hib disease burden</b>                                 |                             |                           |                            |                            |               |
| <i>Incidence rates per 100,000 children &lt; 5 years:</i> |                             |                           |                            |                            |               |
| Clinical pneumonia  | 24258<br>(19675, 26975)     | 23780<br>(15865, 31695)   | 21300<br>(12215, 30980)    | 14733<br>(9755, 21880)     | [16]          |
| Hib meningitis  | 48 (14,99)                  | 31 (12,71)                | 31 (4, 109)                | 22 (4,96)                  | [4]           |
| Hib NPNM  | 3 (1, 6)                    | 6 (1,13)                  | 4 (1,13)                   | 8 (1,34)                   | See annex     |
| Percent of clinical pneumonia due to Hib                  | 4 (1, 7)                    | 4 (1, 7)                  | 4 (1, 7)                   | 4 (1, 7)                   | [17]          |
| <i>Case fatality rates with access to care:</i>           |                             |                           |                            |                            |               |
| Hib pneumonia   | 3% (2, 4)                   | 3% (2, 4)                 | 2% (1, 3)                  | 1% (0.5, 2)                | [46]          |
| Hib meningitis  | 25% (18, 38)                | 17% (13, 20)              | 12% (3, 17)                | 4% (3, 5)                  | [9, 46-48]    |
| Hib NPNM  | 3% (2, 4)                   | 3% (2, 4)                 | 2% (1, 3)                  | 4% (3, 5)                  | Assumption    |
| Risk of major meningitis sequelae                         | 25% (19, 32)                | 22% (13, 32)              | 11% (8, 15)                | 9% (7, 12)                 | [23]          |
| <b>Health care utilization</b>                            |                             |                           |                            |                            |               |
| <i>Number of outpatient visits per case:</i>              |                             |                           |                            |                            |               |
| Hib pneumonia/NPNM  | 0.52 (0.31, 0.76)           | 0.67 (0.54, 0.81)         | 0.57 (0.34, 0.75)          | 0.86 (0.48, 0.90)          | [26]          |
| Hib meningitis  | 1.55 (0.93, 2.27)           | 2.02 (1.62, 2.44)         | 1.71 (1.02, 2.25)          | 2.58 (1.44,2.70)           | [26]          |
| <i>Number of inpatient admissions per case:</i>           |                             |                           |                            |                            |               |
| Hib pneumonia/NPNM  | 0.09 (0.05, 0.13)           | 0.11 (0.09, 0.14)         | 0.10 (0.06, 0.13)          | 0.15 (0.08, 0.16)          | [26]          |



| <b>Parameter</b>                             | <b>GAVI eligible Africa</b> | <b>GAVI eligible Asia</b> | <b>Lower middle-income</b> | <b>Upper middle-income</b> | <b>Source</b> |
|--|-----------------------------|---------------------------|----------------------------|----------------------------|---------------|
| Hib meningitis                               | 0.52 (0.31, 0.76)           | 0.67 (0.54, 0.81)         | 0.57 (0.34, 0.75)          | 0.86 (0.48, 0.90)          | [26]          |
| <b>Distribution of inpatient admissions:</b> |                             |                           |                            |                            |               |
| <i>Hib pneumonia and NPNM:</i>               |                             |                           |                            |                            |               |
| Primary/secondary hospital                   | 90%                         | 90%                       | 90%                        | 80%                        | Assumption    |
| Tertiary hospital                            | 10%                         | 10%                       | 10%                        | 20%                        | Assumption    |
| <i>Hib meningitis:</i>                       |                             |                           |                            |                            |               |
| Primary/secondary hospital                   | 80%                         | 80%                       | 80%                        | 70%                        | Assumption    |
| Tertiary hospital                            | 20%                         | 20%                       | 20%                        | 30%                        | Assumption    |
| <b>Treatment costs (2010 US\$):</b>          |                             |                           |                            |                            |               |
| Outpatient visit                             | 3.01 (2.26, 2.77)           | 3.00 (2.25, 3.75)         | 6.58 (4.94, 8.23)          | 12.93 (9.69, 16.16)        | [49]          |
| <i>Hib pneumonia and NPNM admission:</i>     |                             |                           |                            |                            |               |
| Primary/secondary hospital                   | 49 (33, 66)                 | 46 (29, 62)               | 305 (159, 452)             | 707 (338, 1076)            | See annex     |
| Tertiary hospital                            | 139 (92, 186)               | 155 (100,211)             | 417 (217,618)              | 966 (462,1470)             | See annex     |
| <i>Hib meningitis admission:</i>             |                             |                           |                            |                            |               |
| Primary/secondary hospital                   | 335 (322, 349)              | 291 (277, 304)            | 1226 (1003, 1248)          | 1972 (1664, 2280)          | See annex     |
| Tertiary hospital                            | 953 (914,992)               | 987 (940,1033)            | 1538 (1371,1706)           | 2695 (2274, 3115)          | See annex     |
| Annual sequelae costs                        | 719                         | 632                       | 911                        | 1560                       | [33]          |

**Table 2: Base case results of introducing Hib vaccine per one million birth cohort (societal perspective)**

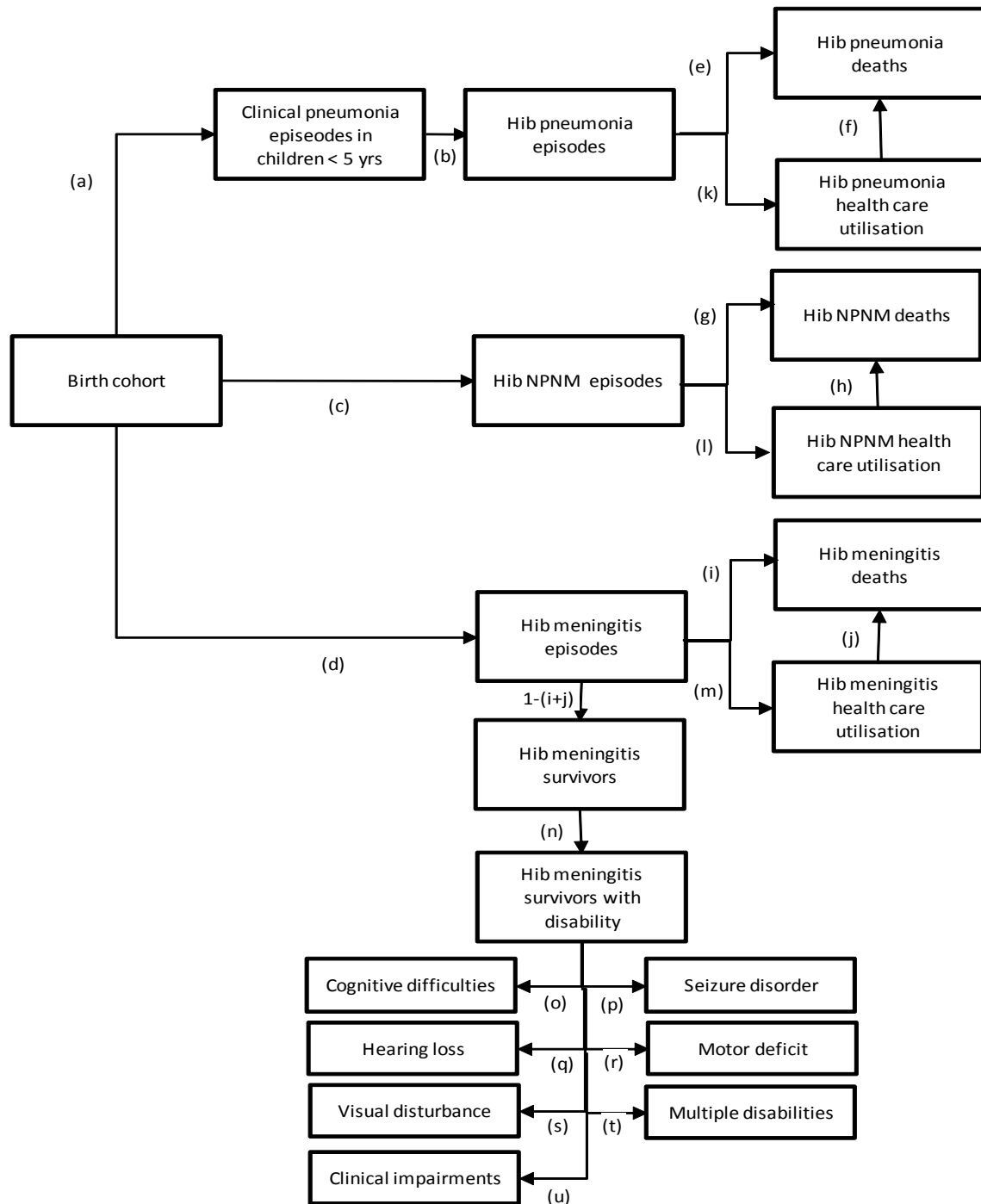
|  | <b>GAVI<br/>eligible Africa</b> | <b>GAVI<br/>eligible Asia</b> | <b>Lower middle-<br/>income</b> | <b>Upper middle-<br/>income</b> |
|--|---------------------------------|-------------------------------|---------------------------------|---------------------------------|
| <i>Acute cases averted:</i>                      | 30,357                          | 31,512                        | 30,033                          | 21,059                          |
| Hib pneumonia                                    | 28,835                          | 30,322                        | 28,863                          | 20,039                          |
| Hib meningitis                                   | 1,436                           | 999                           | 1,049                           | 748                             |
| Hib NPNM   | 86                              | 191                           | 121                             | 272                             |
| Meningitis sequelae                              | 155                             | 123                           | 54                              | 48                              |
| <i>Premature deaths averted:</i>                 | 4,589                           | 3,505                         | 4,048                           | 1,446                           |
| Hib pneumonia                                    | 3,749                           | 3,032                         | 3,464                           | 1,202                           |
| Hib meningitis                                   | 818                             | 439                           | 556                             | 217                             |
| Hib NPNM   | 22                              | 34                            | 28                              | 27                              |
| <i>Percent of under five mortality averted</i>   | 3.59%                           | 4.55%                         | 10.94%                          | 5.17%                           |
| <i>Discounted DALYs averted</i>                  | 124                             | 101                           | 119                             | 43                              |
| <i>Outpatient visit costs averted (US\$):</i>    |                                 |                               |                                 |                                 |
| Hib pneumonia                                    | 45,198                          | 60,942                        | 108,322                         | 201,167                         |
| Hib meningitis                                   | 6,707                           | 6,051                         | 11,815                          | 22,529                          |
| Hib NPNM   | 135                             | 384                           | 454                             | 8,192                           |
| <i>Inpatient admission costs averted (US\$):</i> |                                 |                               |                                 |                                 |
| Hib pneumonia                                    | 150,751                         | 189,215                       | 913,521                         | 2,280,831                       |
| Hib meningitis                                   | 342,594                         | 287,680                       | 819,286                         | 1,408,337                       |
| Hib NPNM   | 450                             | 1,194                         | 3,832                           | 495,220                         |
| <i>Meningitis sequelae costs averted (US\$)</i>  | 3,040,950                       | 2,262,331                     | 1,480,874                       | 2,243,964                       |
| <b>Total costs averted (US\$)</b>                | <b>3,586,785</b>                | <b>2,807,797</b>              | <b>3,338,104</b>                | <b>6,660,240</b>                |
| Incremental vaccination costs (US\$)             | 3,421,479                       | 3,778,486                     | 14,179,079                      | 22,470,704                      |
| Total incremental costs (US\$)                   | -165,308                        | 970,688                       | 10,840,973                      | 15,810,462                      |

**Table 3: Incremental costs per discounted DALY averted (2010 US\$)**

|   | <b>GAVI eligible<br/>Africa</b> | <b>GAVI eligible<br/>Asia</b> | <b>Lower middle-<br/>income</b> | <b>Upper middle-<br/>income</b> |
|---|---------------------------------|-------------------------------|---------------------------------|---------------------------------|
| GNI per capita*                           | 676                             | 803                           | 2888                            | 7259                            |
| <b><i>Government perspective:</i></b>     |                                 |                               |                                 |                                 |
| Base case                                 | 25                              | 35                            | 110                             | 453                             |
| Mean (95% CI) from Monte Carlo simulation | 35 (19, 57)                     | 47 (26, 79)                   | 138 (69, 234)                   | 453 (202, 796)                  |
| Median from Monte Carlo simulation        | 33                              | 44                            | 128                             | 422                             |
| <b><i>Societal perspective:</i></b>       |                                 |                               |                                 |                                 |
| Base case                                 | -1                              | 10                            | 91                              | 369                             |
| Mean (95% CI) from Monte Carlo simulation | -2 (-34, 22)                    | 8 (-33, 48)                   | 115 (37, 215)                   | 368 (78, 733)                   |
| Median from Monte Carlo simulation        | -3                              | 9                             | 108                             | 348                             |

\*Source: World Bank [8]

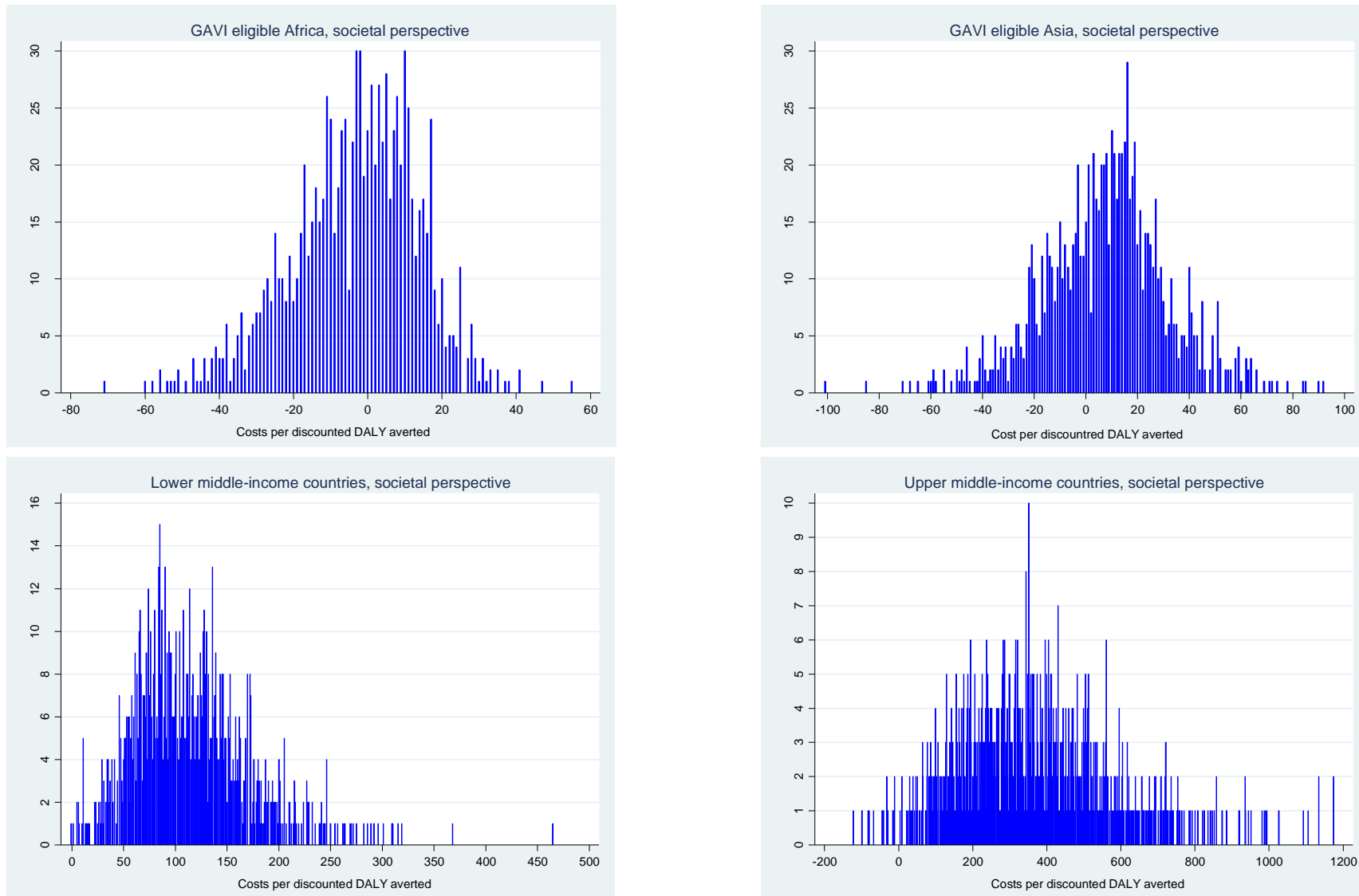
**Figure 1: Model framework**



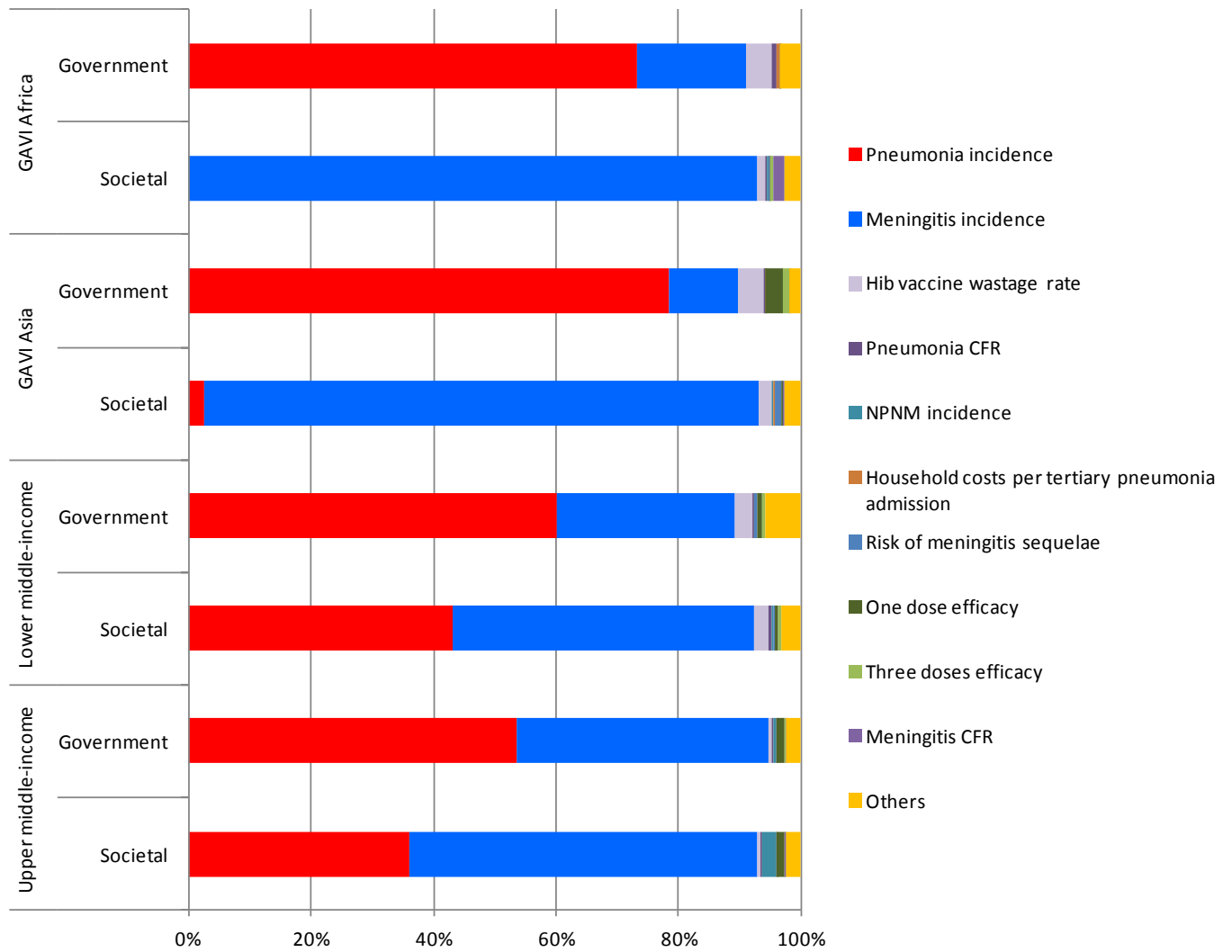
- (a) Clinical pneumonia incidence in children < 5 yrs
- (b) Percent of clinical pneumonia caused by Hib
- (c) Hib NPNM incidence in children < 5 years
- (d) Hib meningitis incidence in children < 5 years
- (e) Pneumonia CFR without access to care
- (f) Pneumonia CFR with access to care
- (g) Hib NPNM CFR without access to care
- (h) Hib NPNM CFR with access to care
- (i) Hib meningitis CFR without access to care
- (j) Hib meningitis CFR with access to care
- (k) Proportion of Hib pneumonia cases seeking care

- (l) Proportion of Hib NPNM cases seeking care
- (m) Proportion of Hib meningitis cases seeking care
- (n) Proportion of Hib meningitis survivors with disability
- (o) Proportion with cognitive difficulties only
- (p) Proportion with seizure disorders only
- (q) Proportion with hearing loss only
- (r) Proportion with motor deficit only
- (s) Proportion with visual disturbance only
- (t) Proportion with clinical impairments only
- (u) Proportion with multiple disabilities

**Figure 2: Histogram of Monto carlo simulations for costs per discounted DALY averted**



**Figure 3: Contribution to variance of uncertain parameters**



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