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Cost-Effectiveness of *Haemophilus inuenzae* Type b Conjugate 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 *Haemophilus influenzae* type b (Hib) conjugate vaccine in low-and middle-income countries and identify the model variables, 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 4 country groups: countries eligible for funding by the GAVI Alliance in Africa and Asia, lower middle-income countries, and upper middle-income countries. 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 conjugate vaccine cost saving is 34%–53% in Global Alliance for Vaccines and Immunization eligible African and Asian countries, respectively. In middle-income countries, costs per discounted disability adjusted life year 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 cause the largest part of the uncertainty in the result.

Conclusions—Hib conjugate 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 conjugate vaccine prices and new data revealing the high costs of lost productivity associated with meningitis sequelae.

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 < 5 years of age. Hib conjugate vaccines became available during the early 1990s, and high-income countries quickly introduced the vaccine into routine vaccination programs, resulting

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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 conjugate 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. Although 181 of the world's 196 countries (92%) had adopted the vaccine by 2012, 52% of these had only done so during the past 8 years.[3]

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

Methods

A deterministic, aggregate-level, static decision tree model was developed. The model framework is seen in Figure 1. Hib disease was divided into 3 different groups: (1) meningitis; (2) pneumonia; and (3) 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 1 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 to be attributable to Hib. Cases of Hib meningitis and Hib NPNM were calculated directly from etiology-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 conjugate vaccine was estimated as the difference between scenarios with and without vaccination. In the Hib conjugate 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 modeling 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 epidemiologic group. Uncertain parameter values were assigned an uncertainty range and a statistical distribution, and 1000 random sample Monte Carlo simulations were run using Crystal Ball software (Oracle, Redwood Shores, California). This generated 95% CIs around the ICERs. The importance of individual parameters to uncertainty in the result was assessed by ANCOVA, which summarizes the proportion of the variance explained by variation in different input variables.[6] The simulation data were analyzed in Stata v. 11.0 (StataCorp, College Station, Texas). All variables are seen in Table I. The statistical distributions fitted to the variables are included in the Appendix (available at www.jpeds.com).

Study Populations

The model was run for cohorts of 1 million children in 4 different settings: (1) GAVI-eligible African countries; (2) GAVI-eligible Asian countries; (3) lower middle-income countries; and (4) upper middle-income countries. In 2012, GAVI offered support to countries with 2011 Gross National Income (GNI) per capita below US$1520.[7] Lower middle-income countries were classified as those with per capita GNI between the GAVI threshold and US $4035, and upper middle-income countries were those with GNI per capita between US $4036 and US$12 475.[8] The countries included in the 4 groups are listed in the Appendix. Several model input parameters were estimated as averages across the country groups. Since the results of the analysis is targeted country Governments, these averages were not weighted according to population size.

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 4 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 Appendix.

The most uncertain disease burden estimate is for Hib pneumonia. In 2008, pneumonia deaths in children aged 1–59 months caused approximately 14% of global deaths in children <5 years of age, and Hib conjugate 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 attributable to Hib cannot be differentiated from cases caused by other microorganisms.[15] The incidence of clinical pneumonia for the 4 country groups were taken

from recently completed estimates for the 2010 GBD study.[16] Details on these are given in the Appendix. Hib conjugate 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 2 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]

DALYs

DALYs were calculated as the sum of 3 components: years of life lost due to premature mortality, years of life with disability from acute disease, and years of life with disability due to meningitis sequelae. Average life expectancies across the 4 country groups were used for the years of life lost 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 with pneumonia than to meningitis (Appendix).

To estimate DALYs attributable 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 (Appendix).

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 World Health Organization treatment recommendations, all Hib disease, except nonsevere pneumonia, requires hospitalization.[25] Hence, if all children had access to appropriate health care, each case of meningitis, NPNM, and severe pneumonia would lead to at least 1 hospitalization and most likely also at least 1 outpatient visit, as hospitalizations 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 1. For those with access to care, it was assumed that: (1) each meningitis episode would lead to 1 hospital admission and 3 outpatient visits; (2) each severe pneumonia or NPNM episode would lead to 1 hospital admission and 1 outpatient visit; and (3) each nonsevere pneumonia episode would lead to 1 outpatient visit only. Based on evidence from the Indonesia Hib conjugate vaccine trial, 17% of clinical cases of Hib pneumonia 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 2000.[26]

Treatment Costs

Hospital treatment—Data were extracted from country-specific studies reporting on the costs of pneumonia and meningitis treatment (Appendix). 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: (1) costs of meningitis treatment in tertiary hospital = US$774 + 0.2645 (GNI); and (2) costs of pneumonia treatment in tertiary hospital = US$54 + 0.1255 (GNI). CIs around the regression coefficients were used for the uncertainty ranges.

Treatment costs of NPNM were assumed similar to pneumonia. Based on evidence from 3 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 (Appendix). In upper middle-income countries, it was assumed that 30% of cases of meningitis and severe pneumonia were admitted to tertiary hospitals and the remaining to secondary hospitals. For the remaining 3 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 World Health Organization Choosing Interventions that are Cost Effective on the costs per outpatient visit were averaged across the 4 country groups.[28] These estimates; however, do 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 <5 years of age were estimated as US$1.28 per case.[29] This amount was added to the visits costs in all 4 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 conjugate 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; however, can 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 nondiscounted lifetime sequelae costs were estimated at 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 4 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 Conjugate Vaccine Delivery

Incremental vaccine delivery costs were estimated as the difference between a routine vaccination schedule with and without Hib conjugate vaccine. Use of Hib combination vaccines was assumed. For GAVI-eligible countries the difference in 2011 United Nations Children's Fund prices of the 10 dose diphtheria-tetanus-pertussis (DTP)-hepatitis B-Hib conjugate vaccine and the 10 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 conjugate 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 conjugate vaccine dose was assumed. A 3-dose schedule was used in low- and lower middle-income countries and a 4-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 10-dose vials, with vaccine wastage of 25% (range 20%–30%) for 10 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 summarized in Table II. Per 1 million birth cohort, the vaccine is predicted to avert 4589 deaths in GAVI-eligible African countries, 3505 in GAVI-eligible Asian countries, 4048 in lower middle-income countries, and 1446 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 mortality rate of children <5 years of age per 100 000 ranges from 15 in Ukraine to 128 in Congo Brazzaville. This result, therefore, should be considered the most uncertain and the heterogeneity explains the relatively high proportion of mortality averted in children <5 years of age by Hib conjugate vaccine, which is 10% in the lower middle-income group, but only between 4% and 5% in the other 3 groups. The Hib GBD study estimated that Hib disease caused 4% of mortality in children <5 years of age in 2000.[4] When using an <5

years of age mortality of 100 instead of 37 in the lower middle-income group, the vaccine is predicted to avert 4% of mortalities in children <5 years of age.

In the base case, Hib conjugate 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 conjugate vaccine delivery (Table III). Incremental costs also are considerably less in GAVI-eligible Asia than in the 2 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 III).

Contribution of Uncertain Model Parameters

The distribution of 1000 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 variables were attached an uncertainty range and a statistical distribution, but only a few influenced variability in the ICERs to a substantial extent (Figure 3). From the government perspective, pneumonia incidence is the most important variable, 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 variable 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 variables influencing the result, albeit considerably less than the pneumonia and meningitis incidence rates, are Hib conjugate vaccine wastage, CFRs, and vaccine efficacy. Vaccine wastage is important because this affects vaccine costs. Because no uncertainty range was assumed for vaccine prices, the wastage rates were the only variables that influenced vaccine delivery costs. Even with a relatively narrow uncertainty range, this variable proved to be more important than many of the others, such as treatment costs and health care utilization.

Discussion

This study shows that Hib conjugate 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 conjugate vaccine prices and new data revealing the high costs of lost productivity associated with meningitis sequelae.

The cost-effectiveness of Hib conjugate vaccine is more favorable in GAVI-eligible than middle-income countries. The most important reason for the difference is the lower vaccine price obtained by GAVI compared with 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 conjugate

vaccine can be considered highly cost-effective in all the analyzed country groups. The average GNI per capita of the upper middle-income group is US$7259, 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 variables. 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 etiologic-specific pneumonia is intrinsically difficult to determine, and this remains the most important ambiguity when making conclusions about the value of Hib conjugate vaccine.[15,37] Because the reliability of the data for Hib meningitis are considerably better than for Hib pneumonia, the uncertainty range is less. However, because of the high costs of lost productivity attributable to meningitis sequelae, Hib meningitis incidence was the most important determinant of cost-effectiveness from the societal perspective. The present study shows 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 variables available for use in our model. In particular, herd effects (modeled by increasing the direct effect by a simple percentage), 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 variable reflect the extreme range of available country-level estimates in a given region/income strata. The variable distributions therefore reflect regional variation, which may be wider than the degree of variation expected at country level. 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 (ie, that no correlation exists between them). For example, in reality, countries with high meningitis CFRs also are likely to have high pneumonia CFRs, but this link is not reflected.

Our analysis is a global economic evaluation of Hib conjugate vaccine. Several country-specific studies have been published, but only a few of these are from low-and middle-income countries.[30] Our multicountry study provides broad conclusions about the cost-effectiveness of Hib conjugate vaccine, which is currently valuable. During the first 10 years of GAVI support, Hib conjugate vaccine prices remained substantially higher than prices of the traditional vaccines, contributing to slow uptake. However, additional vaccine suppliers entered the market during 2011, and the price has since decreased. The 10-dose pentavalent vaccine from Serum Institute of India (Chennai, 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 conjugate 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 vaccines have used comparable methods to the present study and similar conclusions have been made for these vaccines.[38–42] It is important to note 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 because 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 conjugate vaccination and populate the model with data that is credible at country level. In addition to Hib conjugate vaccine, our model can be used 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.

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Glossary

CFR	Case fatality ratio
DALY	Disability adjusted life year
DTP	Diphtheria-tetanus-pertussis
GBD	Global Burden of Disease
GNI	Gross National Income
Hib	*Haemophilus influenzae* type b
ICER	Incremental cost-effectiveness ratio
NPNM	Non-pneumonia-non-meningitis

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Appendix

Country Groups

Countries included in the 4 country groups analyzed are listed in Table I.

NPNM Disease Incidence Rates

The most common Hib diseases are meningitis and pneumonia. Other severe forms of Hib disease are epiglottitis and septicemia. Epiglottitis is a swelling and inflammation of the epiglottis and surrounding structures. The disease is considered a medical emergency because of the risk of sudden death from acute airway obstruction.[1] Septicemia occurs when an organism such as Hib enters the blood stream. It may cause no symptoms and resolve without treatment, but it also can be a serious, life-threatening infection. If left untreated, Hib septicemia develops to meningitis in approximately 25% of cases.[1] Rarer forms of invasive Hib diseases are cellulitis, osteomyelitis, septic arthritis, and pericarditis, which are infections of the skin, bones, joints, and lining of the heart, respectively. However, these are predominantly caused by other microbial agents than Hib. Since other Hib infections than meningitis and pneumonia are relatively rare, these were grouped into 1 syndrome as NPNM Hib disease.

Table I

Country groups

GAVI-eligible Africa	GAVI-eligible Asia	Lower middle-income	Upper middle-income
Benin	Afghanistan	Albania	Algeria
Burkina Faso	Bangladesh	Armenia *	Angola *
Burundi	Cambodia	Belize	Argentina
Cameroon	North Korea	Bhutan *	Azerbaijan *
Central African Rep.	India	Bolivia *	Belarus
Chad	Myanmar	Cape Verde	Bosnia and Herzegovina
Comoros	Nepal	Congo-Brazzaville *	Botswana
Côte d'Ivoire	Pakistan	Egypt	Brazil
Dem Rep of Congo	Papua New Guinea	El Salvador	Bulgaria
Djibouti	Solomon Islands	Fiji	Chile
Ethiopia	Timor-Leste	Georgia *	China
Gambia	Uzbekistan	Guatemala	Colombia
Ghana		Guyana	Costa Rica
Guinea		Honduras *	Dominican Republic
Guinea-Bissau		Indonesia *	Ecuador
Kenya		Iraq	Gabon
Lesotho		Moldova *	Grenada
Liberia		Mongolia *	Iran
Madagascar		Morocco	Jamaica
Malawi		Paraguay	Jordan
Mali		Philippines	Kazakhstan
Mauritania		Samoa	Latvia
Mozambique		Sri Lanka *	Lebanon
Niger		Swaziland	Lithuania
Nigeria		Tonga	Macedonia

GAVI-eligible Africa	GAVI-eligible Asia	Lower middle-income	Upper middle-income
Rwanda		Ukraine *	Malaysia
Sao Tome and Principe		Vanuatu	Mauritius
Senegal			Mexico
Sierra Leone			Montenegro
Somalia			Namibia
Sudan			Panama
Togo			Peru
Uganda			Romania
Tanzania			Russia
Yemen			Saint Lucia
Zambia			St Vincent
Zimbabwe			Serbia
			South Africa
			Thailand
			Tunisia
			Turkey
			Turkmenistan
			Uruguay
			Venezuela

* GAVI graduating country.

To determine the disease incidence relationship between Hib meningitis and Hib NPNM, surveillance studies reporting on all types of Hib diseases identified for the Hib GBD Study were reviewed.[2] The 22 ascertained studies are summarized in Table II. Although epiglottitis was the most common type of NPNM in the European and Australian studies, this disease was not detected in the studies from Bulgaria, The Gambia, India, Israel, South Africa, and Thailand. Low rates of epiglottitis also have been observed in indigenous populations in developed countries, such as in Australian Aboriginals.[3,4] The reason for this geographic- and population-specific difference is unclear but may relate to age exposure.[5] Epiglottitis is most often seen in children >2 years of age, so in places where Hib disease mainly occurs in children <2 years, the incidence of epiglottitis is likely to be low.

The estimates from the 2 Gambian studies were used for low-income Africa, the Indian study for low-income Asia, the South African study for lower middle-income countries, and the mean of the studies from Argentina, Bulgaria, Czech Republic, Guatemala, Jamaica, and Thailand were used for upper middle-income countries. The rates between cases of NPNM and meningitis were 0.06 in low-income Africa, 0.18 in low-income Asia, 0.12 in lower middle-income, and 0.35 in upper middle-income countries. When using these proportions in relation to the Hib meningitis disease incidence rates, NPNM incidence per 100 000 children aged <5 years were 3 (1, 6) in low-income Africa, 6 (1, 13) in low-income Asia, 4 (1, 13) in lower middle-income countries, and 8 (1, 34) in upper middle-income countries.

Clinical Pneumonia Incidence Rates

Although a large proportion of cases of pneumonia are relatively mild and can be treated without hospitalization, pneumonia also can develop into a severe and critical form. Very severe pneumonia is characterized by acute respiratory distress where the child is not able to drink, severe pneumonia is distinguished by chest indrawing, and nonsevere pneumonia is diagnosed by measuring fast breathing.[28] However, estimation of childhood pneumonia incidence rates is problematic because there is no single definition that is sensitive, specific, and can be widely implemented.[29] Second, many common conditions, including malaria, bacterial sepsis, and severe anemia, produce a spectrum of clinical symptoms and signs that overlaps with pneumonia, and it is difficult to differentiate between these conditions. Third, because disease severity varies widely, it is difficult to capture all cases in routine surveillance and in population-based studies.

Table II

Number of cases of different types of Hib disease detected in Hib sentinel surveillance studies that included NPNM syndromes

				NPNM Hib diseases										
Author	**Country**	**Meningitis**	**Pneumonia**	**Epiglottitis**	**Sepsis**	**Cellulitis**	**Arthritis**	**Pericarditis**	**Endocarditis**	**Osteomyelitis**	**Peritonitis**	**Cholangitis**	**Sinusitis**	**Total**
Torres[6]	Argentina	19	3	1	4	11	4	3			1			46
Asturias[7]	Guatemala	71	24	2	3	6	1							107
Forbes[8]	Jamaica	65	11	1	2		7							86
Takala[9]	Finland	152	11	97	23	21	27							331
Peltola[10]	Finland	492	17	187	25	19	21							761
Booy[11]	UK	289	8	48	15	28	21							409
Williams[12]	UK	142	6	23	5	12	12							200
Reinert[13]	France	177	17	20	15	11	16							256
Martin[14]	Spain	37	4	6		5	6							58
Muhleman[15]	Switzerland	1270		1392	62	69	64							2857
Kojouharova[16]	Bulgaria	21	2		1	1								25
Lebedova[17]	Czech Rep.	49	7	31	5		2							94
Dagan[18]	Israel	182	72	1	34	45	2	2	1	2		1	1	344
Madhi[19]	South Africa	26	13		1	2								42
O'Dempsey[20]	Gambia	10	18		1									29
Adegbola[21]	Gambia	141	31		3	1	4							180
Thomas[22]	India	78	20		6	3	5							112
Ishiwada[23]	Japan	39	0	3	2		3							47
Likitnukul[24]	Thailand	44	20		12	2	1							79
Anglaret[25]	N. Caledonia	22	3	1	1	1	3		1					32
Gilbert[26]	Australia	84	20	94	14	16	6							234
McIntyre[27]	Australia	143	12	91	5	18	13	1						283
Total		3553	319	1998	239	271	218	6	2	2	1	1	1	6612
Percent of total		54%	5%	30%	4%	4%	3%	0.09%	0.03%	0.03%	0.02%	0.02%	0.02%	

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Table III

2010 GBD incidence estimates for lower respiratory infections*

Region	Annual number of cases per 100 000 children aged <5 y
North America, High Income	9555
Latin America, Southern	10 750
Europe, Western	8500
Australasia	5995
Asia Pacific, High Income	5580
Europe, Eastern	10 245
Europe, Central	9755
Asia, Central	6440
Sub-Saharan Africa, West	19 675
Sub-Saharan Africa, Southern	15 855
Sub-Saharan Africa, East	26 125
Sub-Saharan Africa, Central	26 975
North Africa/Middle East	21 035
Asia, South	31 695
Asia, Southeast	15 865
Asia, East	12 215
Oceania	20 705
Latin America, Tropical	21 880
Latin America, Central	30 980
Latin America, Andean	26 585
Caribbean	33 310
Global	21 590

Source: Lozano et al.[32]

*Mean value between male and female estimates.

Global childhood pneumonia disease burden estimates were first prepared by Rudan et al in 2004 and updated in 2008.[30,31] New estimates have recently been completed for the 2010 GBD study. The GBD authors used 3 data sources for estimating the incidence of respiratory infections[32]: (1) a comprehensive literature review conducted by an expert group; (2) individual-level data from Demographic and Health Surveys and World Health Surveys; and (3) hospital discharge data from the US, Brazil, and 20 European countries.

Table IV

Annual clinical pneumonia incidence per 100 000 children aged <5 years used for the four country groups

Country group	GBD regional estimates used	Mean	Low	High
Low-income Africa	West Africa	24 258	19 675	26 975
	East Africa			

Country group	GBD regional estimates used	Mean	Low	High
	Central Africa			
Low-income Asia	South East Asia	23 780	15 865	31 695
	South Asia			
Lower middle-income	Central Latin America	21 300	12 215	30 980
	East Asia			
	Oceania			
Upper middle-income	Europe Eastern	14 733	9755	21 880
	Europe Central			
	Latin America Southern			
	North Africa			
	Tropical Latin America			

Upper respiratory infections were defined as children in surveys with cough and fever but no difficulty breathing and lower respiratory infections as children with cough, fever, and difficulty breathing. The GBD lower respiratory incidence estimates are summarized in Table III. There is marked variation across regions, ranging from 5580 in Asia Pacific to 33 310 per 100 000 children aged <5 years in the Caribbean. Estimates for the 4 country groups were calculated as averages of the regional GBD numbers as seen in Table IV.

Meningitis Sequelae DALY Disability Weight

In a systematic literature review by Edmond et al, sequelae types were divided into minor and major forms and a multiple impairment category was developed for children suffering from more than 1 disability type.[33] The case definitions are summarized in Table V. Four of the major sequelae case definitions were taken directly from the 1996 GBD study: cognitive deficit, seizures, hearing loss, and motor deficit. However, these were the only types of meningitis sequelae included in the original GBD study, with the associated disability weights found under the “meningococcemia without meningitis” category in the disability weight list as “mental retardation,” “seizure disorder,” “deafness,” and “motor deficit.”[34] Since there were no associated meningitis sequelae disability weights for the minor conditions, it was decided to exclude these in the analysis. For vision problems, the “low vision” disability weight with a value of 0.223 from the corneal scar, onchocerciasis, and trachoma categories was used. As the majority of children in the clinical impairment category had hydrocephalus (a build-up of fluid inside the skull, leading to brain swelling), the GBD disability weight for long-term intracranial injury of 0.359 was used for clinical impairments. For multiple sequelae, a weight of 0.627 was assumed, which is the highest value in the GBD disability weight list, similar to dementia.[34]

Table V

Sequelae case definitions and disability weights

	Minor sequelae	Major sequelae	
Type	**Case definition**	**Case definition**	**Disability weight**
Cognitive deficit	Learning difficulties or deficits with IQ >70 or speech/language impairment	Mental retardation with IQ <70	0.469
Seizures	-	Seizures of any type	0.099
Hearing loss	Unilateral sensorineural hearing loss with audiometric hearing threshold level (averaged over 0.5, 1, 2, 4 kHz) of >26 dBHL	Bilateral sensorineural hearing loss with audiometric hearing threshold level (averaged over 0.5, 1, 2, 4 kHz in the better ear) of >26 dBHL	0.223
Motor deficit	Isolated hypotonia, motor delay, ataxia, gait or coordination difficulties	Impairment, spasticity, or paresis of one or more limbs	0.388
Vision problems	Unilateral visual disturbance, diplopia, nystagmus, or cranial nerve dysfunction	Presenting visual acuity in the best eye of less than 6/12 or corresponding visual field loss	0.223
Clinical impairments	Any behavioral disorder attributed to the meningitis episode	Distinct pathologic entity with any impairment to activities of daily living	0.359
Multiple impairments	Distinct pathologic entity with no impairment to activities of daily living: Mild cerebral dilatation	≥1 of above domains	0.627

Sources: Edmond (2010)[33] for definitions and Mathers (2006) for disability weights.[34]

Table VI

Weighted average disability weights attributable to bacterial meningitis sequelae

Type of sequelae	Disability weight	Percent of cases	Percent distribution	Weighted average disability weight
Hib				
Cognitive difficulties	0.469	1.0%	10%	0.049
Seizure disorder	0.099	1.5%	16%	0.015
Hearing loss	0.223	3.2%	33%	0.074
Motor deficit	0.388	1.2%	13%	0.049
Visual disturbance	0.223	0.1%	1%	0.002
Clinical impairments	0.359	0.7%	7%	0.026
Multiple impairments	0.627	1.9%	20%	0.124
Total		9.6%	100.0%	0.340
Pneumococcal				
Cognitive difficulties	0.469	3.1%	13%	0.059
Seizure disorder	0.099	2.5%	10%	0.010
Hearing loss	0.223	6.7%	27%	0.061
Motor deficit	0.388	3.3%	13%	0.052
Visual disturbance	0.223	1.1%	4%	0.010
Clinical impairments	0.359	3.4%	14%	0.050
Multiple impairments	0.627	4.5%	18%	0.115

Type of sequelae	Disability weight	Percent of cases	Percent distribution	Weighted average disability weight
Total		24.7%	100%	0.356
Meningococcal				
Cognitive difficulties	0.469	0.4%	6%	0.026
Seizure disorder	0.099	0.5%	7%	0.007
Hearing loss	0.223	2.1%	30%	0.066
Motor deficit	0.388	0.8%	11%	0.044
Visual disturbance	0.223	2.1%	30%	0.066
Clinical impairments	0.359	0.2%	3%	0.050
Multiple impairments	0.627	1.0%	14%	0.088
Total		7.2%	100%	0.307

Source: Edmonds (2010).[33]

Weighted average disability weights for Hib, pneumococcal, and meningococcal meningitis sequelae were calculated from the disability weights in Table V, and the percentage breakdowns found in the literature review by Edmond et al (Table VI). The weighted disability weights were 0.340 for Hib, 0.356 for pneumococcal, and 0.307 for meningococcal meningitis sequelae. The 2 other types of meningitis serve as useful comparators to Hib meningitis sequelae.

Table VII

Overview of studies estimating the costs of pneumonia and meningitis treatment in children <5 years in low- and middle-income countries

First author	Country	Year	Types of diseases included	Facilities included	No. of inpatient records reviewed*	Number of patient interviews for household costs*
Krishnan[59]	India	2001	Pneumonia, meningitis and diarrhea <5 y	2 primary, 4 secondary, and 2 tertiary hospitals	372	355
Guzman[62]	Columbia	2005	Pneumonia in children <2 y	3 tertiary hospitals	128	Not included
Hussain[58]	Pakistan	2006	Pneumonia and meningitis in children <5 y	2 primary, 2 secondary, and 1 tertiary hospital	589	Not included
Constenla[61]	Brazil, Chile and Uruguay	2007	Pneumonia and meningitis in children <5 y	33 hospitals and 10 outpatient centers	753	Not included
Hussain[56]	Pakistan	2008	Pneumonia, severe pneumonia and very severe febrile disease in children <5 y	15 hospitals and clinics	NA	112
Chola[57]	Zambia	2009	Pneumonia and diarrhea in children <5 y	1 primary hospital	829	Not included
Ayieko[56]	Kenya	2009	Pneumonia, malaria, and	3 primary, 3 secondary, and 1 tertiary hospital	307	205

First author	Country	Year	Types of diseases included	Facilities included	No. of inpatient records reviewed*	Number of patient interviews for household costs*
			meningitis in children <5 y			
Madsen[55]	India	2009	Severe pneumonia in children <3 y	1 secondary and 1 tertiary hospital	56	56
Anh[54]	Vietnam	2010	Pneumonia, meningitis, and sepsis in children <5 y	1 tertiary hospital	980	Not included
Temple[53]	Fiji	2011	Outpatient pneumonia in children <5 y	2 tertiary hospital outpatient departments	400	400
Sinha[60]	South Africa	2012	Pneumonia in children <5 y	1 tertiary hospital	745	325

NA, nonapplicable.

*Count only for patients with pneumonia and meningitis. If other diseases were included in the study, these patients were excluded from the count.

Table VIII

Mean treatment costs of bacterial meningitis in tertiary hospitals (2010 US$)

Country	Mean costs (SD)	Reference
High-income:		
Australia	16 650	38
Israel	13 043	36
US	12 881	43
France	11 570	41
Sweden	10 490	39
Australia	9886	37
Slovenia	8366	42
Republic of Korea	3509	44
Middle-income		
Chile	5855	61
Russia	5616	46
Uruguay	4203	61
Columbia	1800	48
South Africa	1702	45
Brazil	1474	61
Low-income		
Pakistan	2758	58
India	750	59
Kenya	434 (365)	64
Indonesia	292	50
Vietnam	211 (172)	54

Country	Mean costs (SD)	Reference
Papua New Guinea	51	[51]

Hib Disease Treatment Costs

The costs of treating pneumonia and meningitis were estimated from regression analyses of country-specific data with GNI per capita as the independent variable. In a systematic literature review of economic evaluations of Hib vaccine, 15 studies reported on the costs of treating meningitis.[35] These studies were from Australia, Colombia, France, Indonesia, Israel, Kenya, Papua New Guinea, Russia, Slovenia, South Africa, South Korea, and Sweden.[36–52]

Specific pneumonia and meningitis treatment cost studies from low- and middle-income countries were identified from authors' files and PubMed. Eleven treatment cost studies, which were not part of Hib vaccine economic evaluations, were identified (Table VII). Six low-income countries (Fiji, India, Kenya, Pakistan, Vietnam, and Zambia[53–59]) and 5 middle-income countries (Columbia, Chile, Brazil, South Africa, and Uruguay[60–62]) were represented. Sample sizes for estimating patient-specific costs ranged from 56 patients in 1 of the 2 Indian studies to 980 patients in the study from Vietnam. Patient-specific resource utilization items, such as drugs, supplies, and diagnostic tests, were determined either by retrospectively reviewing patient records or by collecting data prospectively. Seven of the studies used microcosting methods of varying intensity for calculating the costs per hospital bed-day, which included annual costs of capital costs, staff, maintenance, electricity, consumables, etc. In 6 of the studies, caregivers were interviewed about their out-of-pocket costs, such as user fees and transport costs. A government health sector perspective was taken in the remaining 5 studies, with no household cost data collected.

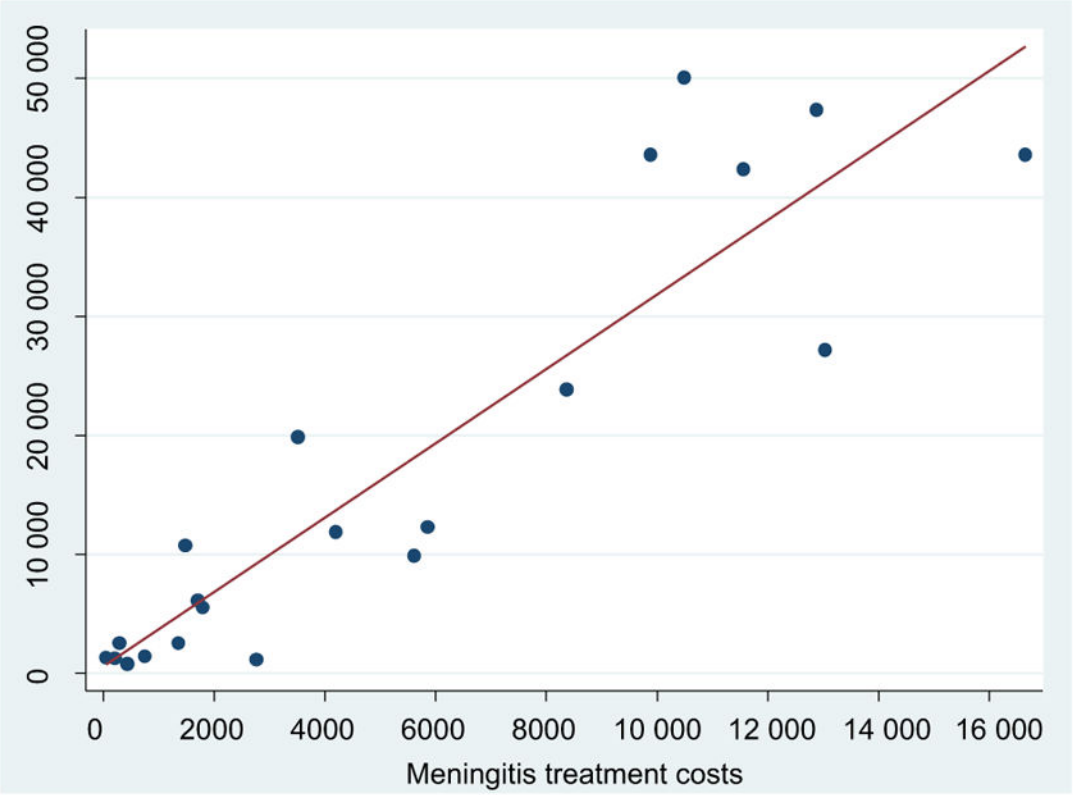

Figure 1.
Correlation between GNI per capita and costs of treating meningitis (2010 US$).

Table IX

Mean inpatient pneumonia treatment costs per case (2010 US$)

Country	Type of pneumonia	Type of hospital	Mean costs (SD or 95% CI)	Reference
Vietnam	Non-severe	Tertiary	36 (33)	[54]
Vietnam	Severe	Tertiary	42 (47)	[54]
Uruguay	All-cause	Tertiary	80	[61]
Vietnam	Very severe	Tertiary	89 (85)	[54]
India	All-cause	Secondary	93 (72–114)	[55]
India	All-cause	Secondary	94	[59]
Kenya	All-cause	Secondary	95	[64]
Pakistan	Non-severe	Secondary	96	[58]
Brazil	All-cause	Tertiary	127	[61]
Zambia	All-cause	Primary	252	[57]
India	All-cause	Tertiary	162 (133–191)	[55]
Kenya	All-cause	Tertiary	270 (316)	[64]
Chile	All-cause	Tertiary	284	[61]
Pakistan	Severe	Secondary	317	[58]
India	All-cause	Tertiary	319	[59]

Country	Type of pneumonia	Type of hospital	Mean costs (SD or 95% CI)	Reference
Brazil	Pneumococcal	Tertiary	628	[61]
South Africa	Severe	Primary	651 (607–694)	[60]
South Africa	Severe	Secondary	849 (793–906)	[60]
Columbia	Bacterial	Tertiary	1063 (914–1211)	[62]
South Africa	Severe	Tertiary	1160 (1083–1237)	[60]
Uruguay	Pneumococcal	Tertiary	2052	[61]
Chile	Pneumococcal	Tertiary	4502	[61]

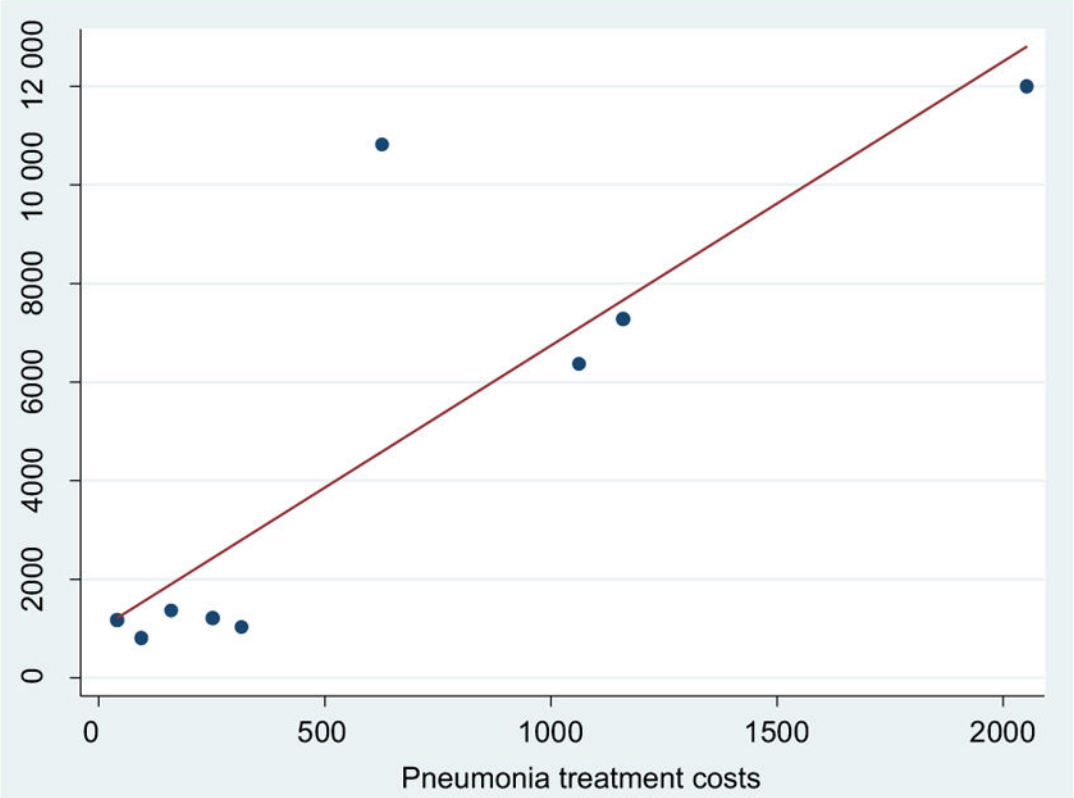

Figure 2.
Correlation between GNI per capita and costs of treating severe pneumonia (2010 US$).

Table X

Linear regression of the relationship between treatment costs and GNI per capita

	n	Constant	Predictor	F-test	R^2
Meningitis	21	774.27	0.2645	0.0001	0.8279
Pneumonia	9	54.49	0.1255	0.0037	0.7233

Estimates from all the 26 studies were converted to 2010 US$ values using local consumer price indices and average annual exchange rates.[63] Mean treatment costs per case are

summarized in and Tables VIII and IV for meningitis and pneumonia, respectively. The costs per meningitis case ranged from US$51 in Papua New Guinea to US$16 650 in Australia, and the costs per case of severe pneumonia ranged from US$36 in Vietnam to US $4502 in Chile. Although some of the variation between settings can be explained by methodological study differences, it is apparent that there is correlation between treatment costs and country income group.

Table XI

Statistical distributions and parameter values (minimum, maximum) used in the Monte Carlo simulation

Parameter	Statistical distribution	GAVI-eligible Africa	GAVI-eligible Asia	Lower middle-income	Upper middle-income
Hib disease burden					
Incidence rates per 100 000 children aged <5 y					
Hib pneumonia	Gamma	970 (243, 1698)	1,665 (238, 951)	852 (213, 1491)	589 (147, 1031)
Hib meningitis	Gamma	48 (14, 99)	31 (3, 71)	31 (4, 109)	22 (4, 96)
Hib NPNM	Gamma	3 (1, 6)	6 (1, 13)	4 (1, 13)	8 (1, 34)
% CFRs in ages 1–59 mo (%):					
Hib pneumonia	Beta	13 (8, 17)	10 (7, 12)	12 (8, 17)	6 (5, 14)
Hib meningitis	Beta	57 (37, 74)	44 (33, 55)	53 (38, 72)	29 (25, 60)
Hib NPNM	Beta	35 (14, 26)	18 (12, 25)	23 (15, 34)	10 (8, 27)
Hib meningitis survivors with major sequelae (%)	Beta	25 (19, 32)	22 (13, 32)	11% (8, 15)	9% (7, 12)
Hib vaccination coverage (%)					
Coverage of 1st dose	Beta	41 (86, 99)	90 (81, 99)	95 (79, 99)	94 (74, 99)
Coverage of 2nd dose	Beta	80 (30, 99)	87 (78, 96)	92 (70, 99)	92 (60, 99)
Coverage of 3rd dose	Beta	76 (24, 99)	85 (77, 94)	91 (66, 99)	91 (46, 99)
Vaccine efficacy (%)					
1 dose	Lognormal	63.4 (0.0, 88.7)	63.4 (0.0, 88.7)	63.4 (0.0, 88.7)	63.4 (0.0, 88.7)
2 doses	Lognormal	98.9 (0.0, 100.0)	98.9 (0.0, 100.0)	98.9 (0.0, 100.0)	98.9 (0.0, 100.0)
3 doses	Lognormal	0.0 (93.0, 97.0)	0.0 (93.0, 97.0)	0.0 (93.0, 97.0)	0.0 (93.0, 97.0)
Vaccine wastage (%)	Beta	25 (20, 30)	25 (20, 30)	25 (20, 30)	5 (2, 7)
Health care utilization					
Number of outpatient visits per case:					
Hib pneumonia/NPNM	Gamma	0.52 (0.31, 0.76)	0.54 (0.67, 0.81)	0.57 (0.34, 0.75)	0.86 (0.48, 0.90)
Hib meningitis	Gamma	1.55 (0.93, 2.27)	2.02 (1.62, 2.44)	1.71 (1.02, 2.25)	2.58 (1.44, 2.70)
Number of inpatient admissions per case:					
Hib pneumonia/NPNM	Gamma	0.05 (0.09, 0.13)	0.11 (0.09, 0.14)	0.10 (0.06, 0.13)	0.15 (0.08, 0.16)
Hib meningitis	Gamma	0.52 (0.31, 0.76)	0.67 (0.54, 0.81)	0.57 (0.34, 0.75)	0.86 (0.48, 0.90)
Treatment costs (2010 US$)					
Household cost per outpatient clinic visit	Gamma	1.35 (1.01, 1.68)	1.52 (1.14, 1.90)	2.41 (1.81, 3.01)	2.77 (2.08, 3.46)
Government cost per outpatient clinic visit	Gamma	1.67 (1.25, 2.08)	1.48 (1.11, 1.85)	4.17 (3.13, 5.22)	8.90 (6.68, 11.13)
Household costs per inpatient admission:					

Parameter	Statistical distribution	GAVI-eligible Africa	GAVI-eligible Asia	Lower middle-income	Upper middle-income
Hib pneumonia and NPNM:					
Secondary hospital	Gamma	22 (15, 29)	23 (15, 31)	112 (58, 166)	614 (518, 710)
Tertiary hospital	Gamma	62 (41, 83)	79 (50, 107)	153 (79, 226)	839 (708, 970)
Hib meningitis:					
Secondary hospital	Gamma	150 (144, 156)	147 (140, 154)	614 (518, 710)	614 (518, 710)
Tertiary hospital	Gamma	426 (409, 444)	499 (475, 522)	564 (502, 625)	839 (708, 970)
Government cost per inpatient admission:					
Hib pneumonia and NPNM:					
Secondary hospital	Gamma	27 (18, 36)	23 (15, 31)	193 (101, 286)	1358 (1146, 1570)
Tertiary hospital	Gamma	77 (51, 103)	77 (49, 104)	264 (137, 391)	1566 (1856, 2146)
Hib meningitis:					
Secondary hospital	Gamma	185 (178, 193)	144 (137, 151)	714 (636, 791)	1358 (1146, 1570)
Tertiary hospital	Gamma	527 (505, 549)	488 (465, 511)	975 (869, 1081)	1856 (1566, 2146)

Linear regressions between mean treatment costs and GNI per capita were done using Stata v. 11.2. The regression lines are seen in Figures 1 and 2. In the pneumonia analysis, the result from Chile was excluded because this was a considerable outlier, and it was not possible to understand the underlying reasons for this in the original study.[61] The correlations were highly significant for both diseases, with R^2 of 83% for meningitis and 72% for pneumonia (Table X).

The regression equations are as follows.

$$\text{Meningitis treatment costs} = 774.27 + 0.2645\ (\text{GNI})$$
$$\text{Pneumonia treatment costs} = 54.49 + 0.1255\ (\text{GNI})$$

The studies from India, Kenya, and South Africa presented estimates for different levels of facilities, so that the costs in tertiary hospitals can be compared with costs at lower levels facilities. The ratios between costs at tertiary and secondary facilities were US$1.72 in India, US$2.84 in Kenya, and US$1.37 in South Africa. These rates were used for GAVI-eligible Asia, GAVI-eligible Africa, and the 2 middle-income groups, respectively.

Statistical Distributions of Parameters

Probabilistic uncertainty analysis was undertaken to simultaneously assess the uncertainty around all parameter values, generate 95% CIs around the ICERs and determine which parameters are most important for variation in the result.

Statistical distributions were fitted to all uncertain parameters that were not methodological or structural. Parameters with fixed values that were not considered uncertain, such as vaccine and syringe prices and the 2010 birth cohort, were not varied either. All distributions used are summarized in Table XI.

Distributions were fitted to parameters according to recommendations by Briggs et al.[65] The beta distribution was used for probability parameters with values between 0 and 1, such as case fatality rates and the risk of meningitis sequelae. The lognormal distribution is frequently used to fit relative risks and this was used for the vaccine efficacy parameters. Treatment costs are often highly skewed to the right and the gamma distribution was used to fit these data, including health care utilization parameters. The SD was assumed similar to the mean value of all cost estimates, reflecting the findings of most of the treatment cost studies reviewed. The gamma distribution was used to fit the disease incidence parameters because the mean values are likely to be conservative estimates due to the great difficulties in detecting Hib disease.

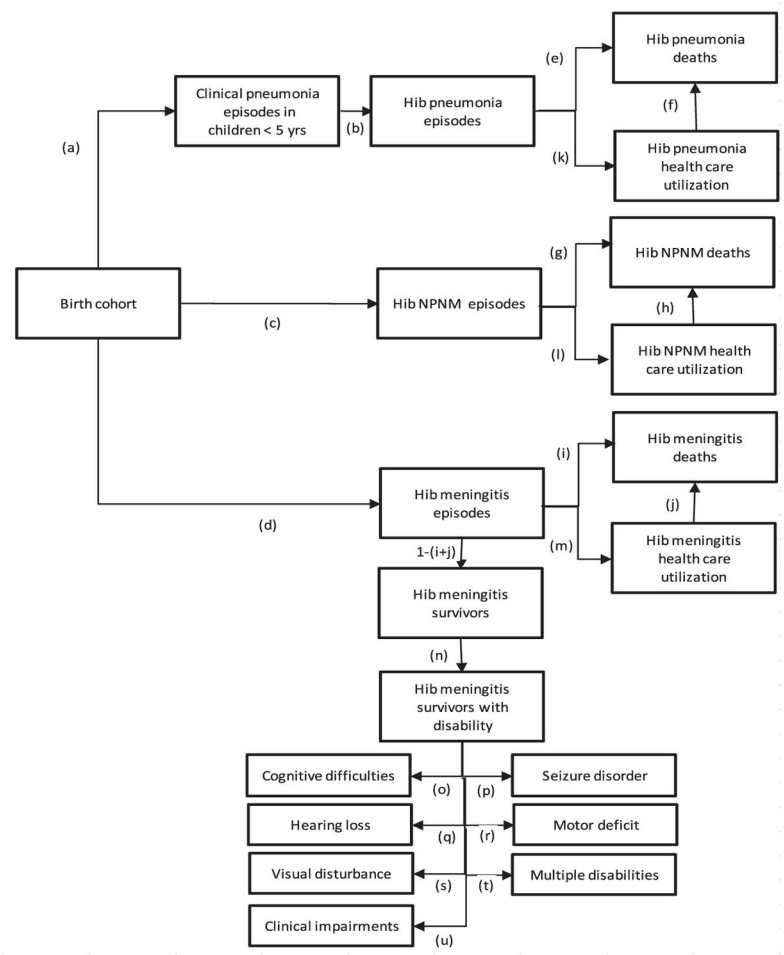

Figure 1.

Model framework. a, Clinical pneumonia incidence in children aged <5 years. b, Percent of clinical pneumonia caused by Hib. c, Hib NPNM incidence in children aged <5 years. d, Hib meningitis incidence in children aged <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 cases of Hib NPNM seeking care. m, Proportion of cases of Hib meningitis 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 multiple disabilities. u, Proportion with clinical impairments only.

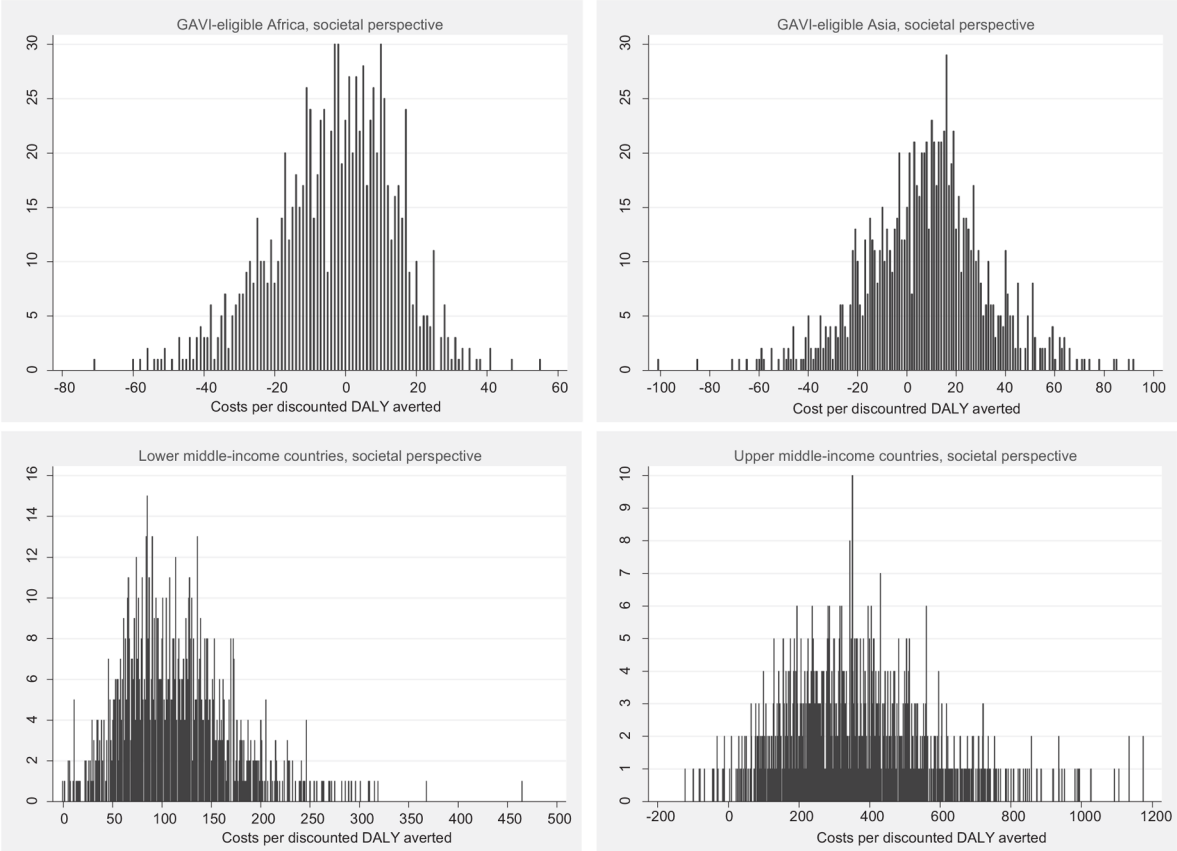

Figure 2.
Histogram of Monte Carlo simulations for costs per discounted DALY averted.

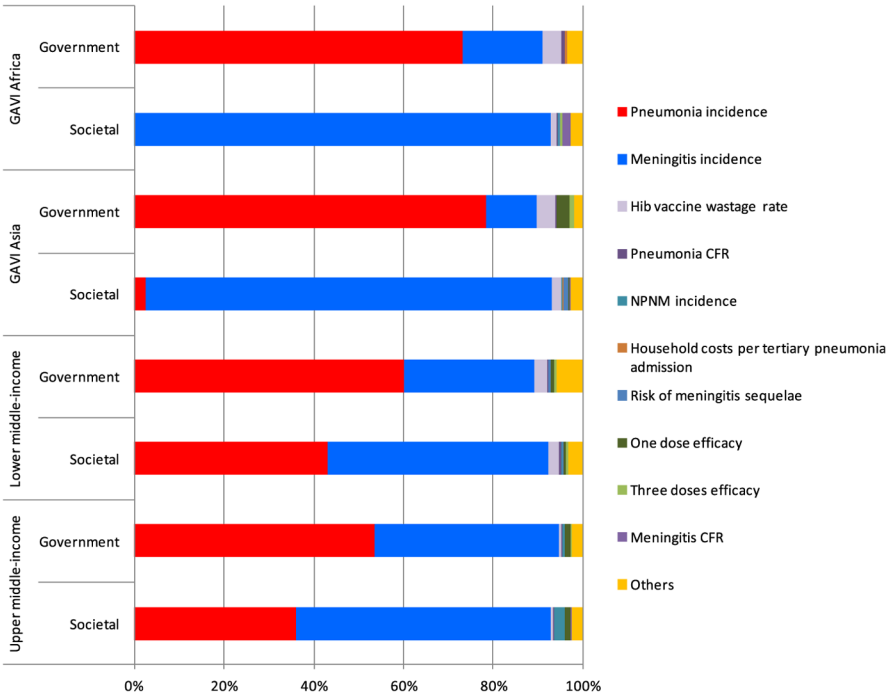

Figure 3.
Contribution to variance of uncertain variables.

Table I

Base case variables assumptions (low, high)

Variable	GAVI-eligible Africa	GAVI-eligible Asia	Lower middle-income	Upper middle-income	Source
Number of countries in group	38	13	27	42	[7,8]
Life expectancy from birth (y)	55	64	70	71	[44]
Infant mortality per 1000 live births	80	56	29	21	[44]
<5 years of age 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 y (%)	52 (31, 76)	67 (54, 81)	57 (34, 75)	86 (48, 90)	[26]
Hib disease burden					
Incidence rates per 100 000 children <5 y:					
Clinical pneumonia	24 258 (19 675, 26 975)	23 780 (15 865, 31 695)	21 300 (12 215, 30 980)	14 733 (9755, 21 880)	[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 Appendix
% of clinical pneumonia attributable to Hib	4 (1, 7)	4 (1, 7)	4 (1, 7)	4 (1, 7)	[17]
Case fatality rates with access to care:					
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]
Health care utilization					
Number of outpatient visits per case:					
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]
Number of inpatient admissions per case:					
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]
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]
Distribution of inpatient admissions:					
Hib pneumonia and NPNM:					

Variable	GAVI-eligible Africa	GAVI-eligible Asia	Lower middle-income	Upper middle-income	Source
Primary/secondary hospital	90%	90%	90%	80%	Assumption
Tertiary hospital	10%	10%	10%	20%	Assumption
Hib meningitis:					
Primary/secondary hospital	80%	80%	80%	70%	Assumption
Tertiary hospital	20%	20%	20%	30%	Assumption
Treatment costs (2010 US$):					
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]
Hib pneumonia and NPNM admission:					
Primary/secondary hospital	49 (33, 66)	46 (29, 62)	305 (159, 452)	707 (338, 1076)	See Appendix
Tertiary hospital	139 (92, 186)	155 (100, 211)	417 (217, 618)	966 (462, 1470)	See Appendix
Hib meningitis admission:					
Primary/secondary hospital	335 (322, 349)	291 (277, 304)	1226 (1003, 1248)	1972 (1664, 2280)	See Appendix
Tertiary hospital	953 (914, 992)	987 (940, 1033)	1538 (1371, 1706)	2695 (2274, 3115)	See Appendix
Annual sequelae costs	719	632	911	1560	[33]

Table II

Base case results of introducing Hib vaccine per 1 million birth cohort (societal perspective)

	GAVI-eligible Africa	GAVI-eligible Asia	Lower middle-income	Upper middle-income
Acute cases averted:	30 357	31 512	30 033	21 059
Hib pneumonia	28 835	30 322	28 863	20 039
Hib meningitis	1436	999	1049	748
Hib NPNM	86	191	121	272
Meningitis sequelae	155	123	54	48
Premature deaths averted:	4589	3505	4048	1446
Hib pneumonia	3749	3032	3464	1202
Hib meningitis	818	439	556	217
Hib NPNM	22	34	28	27
Percent of children aged <5 years mortality averted	3.59%	4.55%	10.94%	5.17%
Discounted DALYs averted	124	101	119	43
Outpatient visit costs averted (US$):				
Hib pneumonia	45 198	60 942	108 322	201 167
Hib meningitis	6707	6051	11 815	22 529
Hib NPNM	135	384	454	8192
Inpatient admission costs averted (US$):				
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	1194	3832	495 220
Meningitis sequelae costs averted (US$)	3 040 950	2 262 331	1 480 874	2 243 964
Total costs averted (US$)	3 586 785	2 807 797	3 338 104	6 660 240
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 III

Incremental costs per discounted DALY averted (2010 US$)

	GAVI-eligible Africa	GAVI-eligible Asia	Lower middle-income	Upper middle-income
GNI per capita *	676	803	2888	7259
Government perspective				
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
Societal perspective				
Base case	Cost saving	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]