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

## Web annex

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# 1 Country groups

Countries included in the four country groups analysed are listed in Table 1.

**Table 1: 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 Herze. |
| 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 | | Mongolia* | Grenada |
| Liberia | | Morocco | Iran |
| Madagascar | | Paraguay | Jamaica |
| Malawi | | Philippines | Jordan |
| Mali | | Republic of Moldova* | Kazakhstan |
| Mauritania | | Samoa | Latvia |
| Mozambique | | Sri Lanka* | Lebanon |
| Niger | | Swaziland | Lithuania |
| Nigeria | | Tonga | Malaysia |
| Rwanda | | Ukraine* | Mauritius |
| Sao Tome and Principe | | Vanuatu | Mexico |
| Senegal | | | Montenegro |
| Sierra Leone | | | Namibia |
| Somalia | | | Panama |
| Sudan | | | Peru |
| Togo | | | Romania |
| Uganda | | | Russian Federation |
| Tanzania | | | Saint Lucia |
| Yemen | | | St Vincent |
| Zambia | | | Serbia |
| Zimbabwe | | | South Africa |
| | | | TFYR Macedonia |
| | | | Thailand |
| | | | Tunisia |
| | | | Turkey |
| | | | Turkmenistan |
| | | | Uruguay |
| | | | Venezuela |

*GAVI graduating country

# 2 Non-pneumonia-non-meningitis 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 airways 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 can also be a serious, life-threatening infection. If left untreated, Hib septicemia develop 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 one syndrome as "non-pneumonia-non-meningitis" (NPNM) Hib disease.

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 Global Burden of Disease (GBD) study were reviewed [2]. The 22 ascertained studies are summarized in Table 2. While epiglottitis was the most common type of NPNM in the European and Australian studies, this disease was not detected in the studies from Bulgaria, Gambia, India, Israel, South Africa and Thailand. Low rates of epiglottitis have also 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]. Epilottitis is most often seen in children above two years of age, so in places where Hib disease mainly occurs in children younger than two years, the incidence of epiglottitis is likely to be low.

The estimates from the two Gambian studies were used for low-income Africa, the Indian study for low-income Asia, the South African study in 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 NPNM and meningitis cases 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 less than 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.

**Table 2: Number of cases of different types of Hib disease detected in Hib sentinel surveillance studies that included NPNM syndromes**

| | | | | Non-pneumonia-non-meningitis (NPNM) Hib diseases | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Author [ref.]** | **Country** | **Menin-gitis** | **Pneu-monia** | **Epiglot-titis** | **Sepsis** | **Cellulitis** | **Arthritis** | **Pericar-ditis** | **Endocar-ditis** | **Osteo-myelitis** | **Peritoni-tis** | **Cholan-gitis** | **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 | 1,270 | | 1,392 | 62 | 69 | 64 | | | | | | | 2 ,857 |
| 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*** | | ***3,553*** | ***319*** | ***1,998*** | ***239*** | ***271*** | ***218*** | ***6*** | ***2*** | ***2*** | ***1*** | ***1*** | ***1*** | ***6,612*** |
| ***Percent of total*** | | ***54%*** | ***5%*** | ***30%*** | ***4%*** | ***4%*** | ***3%*** | ***0.09%*** | ***0.03%*** | ***0.03%*** | ***0.02%*** | ***0.02%*** | ***0.02%*** | |

## 3 Clinical pneumonia incidence rates

While a large proportion of pneumonia cases are relatively mild and can be treated without hospitalization, pneumonia can also 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 non-severe 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]. Secondly, 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 thus difficult to differentiate between these conditions. Thirdly, since disease severity varies widely, it is difficult to capture all cases in routine surveillance and in population based studies.

Global childhood pneumonia disease burden estimates were first prepared by Rudan and colleagues in 2004 and updated in 2008 [30-31]. New estimates have recently been completed for the 2010 GBD study. The GBD authors used three 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
3. Hospital discharge data from the United States, Brazil, and 20 European countries

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 incidence estimates are summarised in Table 3. There is marked variation across regions, ranging from 5,580 in Asia Pacific to 33,310 per 100,000 children less than five years in the Caribbean. Estimates for the four country groups were calculated as averages of the regional GBD numbers as seen in Table 4.

**Table 3: 2010 Global Burden of Disease incidence estimates for lower respiratory infections***

| Region | Annual number of cases per 100,000 children < 5 years |
|---|---|
| North America, High Income | 9,555 |
| Latin America, Southern | 10,750 |
| Europe, Western | 8,500 |
| Australasia | 5,995 |
| Asia Pacific, High Income | 5,580 |
| Europe, Eastern | 10,245 |
| Europe, Central | 9,755 |
| Asia, Central | 6,440 |
| 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* |

*Mean value between male and female estimates

Source: Lozano et al. [32]

**Table 4: Annual clinical pneumonia incidence per 100,000 children < 5 years used for the four country groups**

| Country group | GBD regional estimates used | Mean | Low | High |
|---|---|---|---|---|
| Low-income Africa | West Africa<br>East Africa<br>Central Africa | 24,258 | 19,675 | 26,975 |
| Low-income Asia | South East Asia<br>South Asia | 23,780 | 15,865 | 31,695 |
| Lower middle-income | Central Latin America<br>East Asia<br>Oceania | 21,300 | 12,215 | 30,980 |
| Upper middle-income | Europe Eastern<br>Europe Central<br>Latin America Southern<br>North Africa<br>Tropical Latin America | 14,733 | 9,755 | 21,880 |

## 4 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 one disability type [33]. The case definitions are summarised in Table 5. 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 "Meningococcaemia 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].

Weighted average disability weights for Hib, pneumococcal and meningococcal meningitis sequelae were calculated from the disability weights in Table 5 and the percentage breakdowns found in the literature review by Edmond *et al*. (Table 6). The weighted disability weights were 0.340 for Hib,

0.356 for pneumococcal and 0.307 for meningococcal meningitis sequelae. The two other types of meningitis serve as useful comparators to Hib meningitis sequelae.

**Table 5: 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, 4kHz) of >26dBHL | Bilateral sensorineural hearing loss with audiometric hearing threshold level (averaged over 0.5, 1, 2, 4kHz in the better ear) of >26dBHL | 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 behavioural 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 |

IQ: Intelligence quotient

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

**Table 6: Weighted average disability weights due 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 |
| *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*** |

## 5 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 from Pubmed. Eleven treatment cost studies, which were not part of Hib vaccine economic evaluations, were identified (Table 7). Six low-income countries (Fiji, India, Kenya, Pakistan, Vietnam and Zambia [53-59]) and five 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 one of the two 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 micro-costing 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 six 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 five studies, with no household cost data collected.

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 summarised in Tables 7 and 8 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 severe pneumonia case ranged from US$ 36 in Vietnam to US$ 4,502 in Chile. While 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.

Linear regressions between mean treatment costs and GNI per capita were done using STATA version 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 10).

The regression equations are:
Meningitis treatment costs = 774.27 + 0.2645 (GNI)
Pneumonia treatment costs = 54.49 + 0.1255 (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 two middle-income groups, respectively.

**Table 7: Overview of studies estimating the costs of pneumonia and meningitis treatment in children < 5 years in low- and middle-income countries**

| First author [ref] | 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 diarrhoea < 5 years | 2 primary, 4 secondary and 2 tertiary hospitals | 372 | 355 |
| Guzman [62] | Columbia | 2005 | Pneumonia in children < 2 years | 3 tertiary hospitals | 128 | Not included |
| Hussain [58] | Pakistan | 2006 | Pneumonia and meningitis in children < 5 years | 2 primary, 2 secondary and 1 tertiary hospital | 589 | Not included |
| Constenla [61] | Brazil, Chile and Uruguay | 2007 | Pneumonia and meningitis in children < 5 years | 33 hospitals and 10 outpatient centres | 753 | Not included |
| Hussain [56] | Pakistan | 2008 | Pneumonia, severe pneumonia and very severe febrile disease in children < 5 years | 15 hospitals and clinics | NA | 112 |
| Chola [57] | Zambia | 2009 | Pneumonia and diarrhoea in children < 5 years | 1 primary hospital | 829 | Not included |
| Ayieko [56] | Kenya | 2009 | Pneumonia, malaria and meningitis in children < 5 years | 3 primary, 3 secondary and 1 tertiary hospital | 307 | 205 |
| Madsen [55] | India | 2009 | Severe pneumonia in children < 3 years | 1 secondary and 1 tertiary hospital | 56 | 56 |

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

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

NA: Non-applicable.

**Table 8: Mean treatment costs of bacterial meningitis in tertiary hospitals (2010 US$)**

| Country | Mean costs (standard deviation) | Ref. |
|---|---|---|
| **High-income:** | | |
| Australia | 16,650 | [38] |
| Israel | 13,043 | [36] |
| USA | 12,881 | [43] |
| France | 11,570 | [41] |
| Sweden | 10,490 | [39] |
| Australia | 9,886 | [37] |
| Slovenia | 8,366 | [42] |
| Republic of Korea | 3,509 | [44] |
| **Middle-income** | | |
| Chile | 5,855 | [61] |
| Russia | 5,616 | [46] |
| Uruguay | 4,203 | [61] |
| Columbia | 1,800 | [48] |
| South Africa | 1,702 | [45] |
| Brazil | 1,474 | [61] |
| **Low-income** | | |
| Pakistan | 2,758 | [58] |
| India | 750 | [59] |
| Kenya | 434 (365) | [64] |
| Indonesia | 292 | [50] |
| Vietnam | 211 (172) | [54] |
| Papua New Guinea | 51 | [51] |

**Table 9: Mean inpatient pneumonia treatment costs per case (2010 US$)**

| Country | Type of pneumonia | Type of hospital | Mean costs (SD or 95% CI) | Ref. |
|---|---|---|---|---|
| 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] |
| Brazil | Pneumococcal | Tertiary | 628 | [61] |
| South Africa | Severe | Primary | 651 (607-694) | [60] |
| South Africa | Severe | Secondary | 849 (793-906) | [60] |
| Columbia | Bacterial | Tertiary | 1,063 (914-1,211) | [62] |
| South Africa | Severe | Tertiary | 1,160 (1,083-1,237) | [60] |
| Uruguay | Pneumococcal | Tertiary | 2,052 | [61] |
| Chile | Pneumococcal | Tertiary | 4,502 | [61] |

**Table 10: 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 |

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

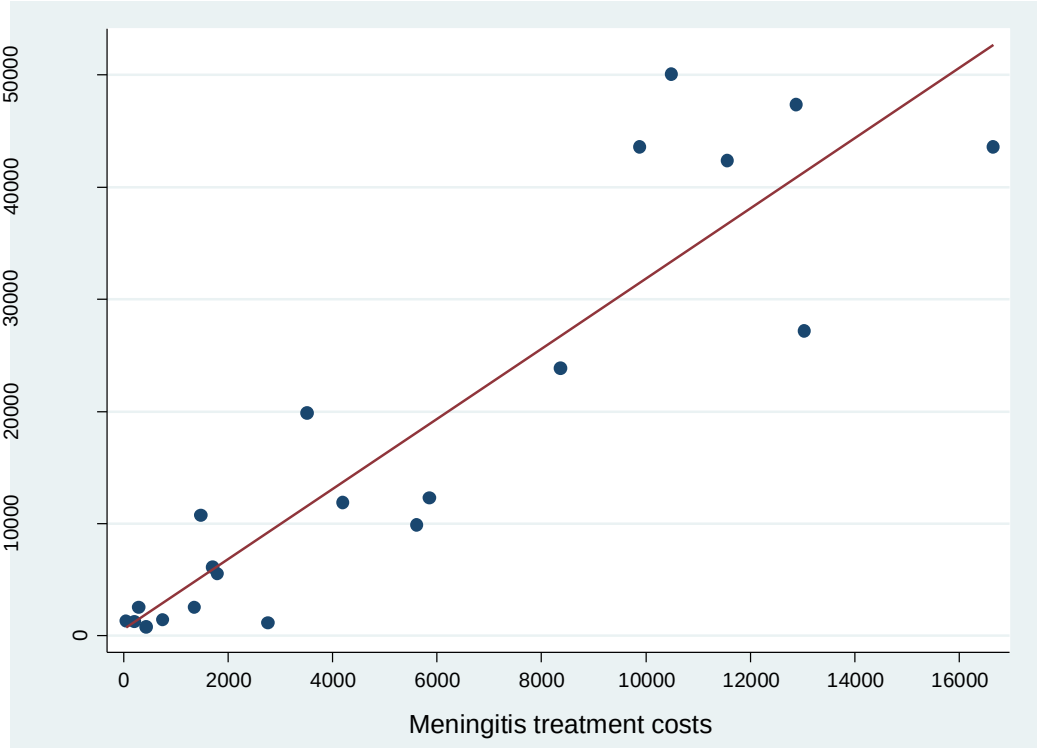
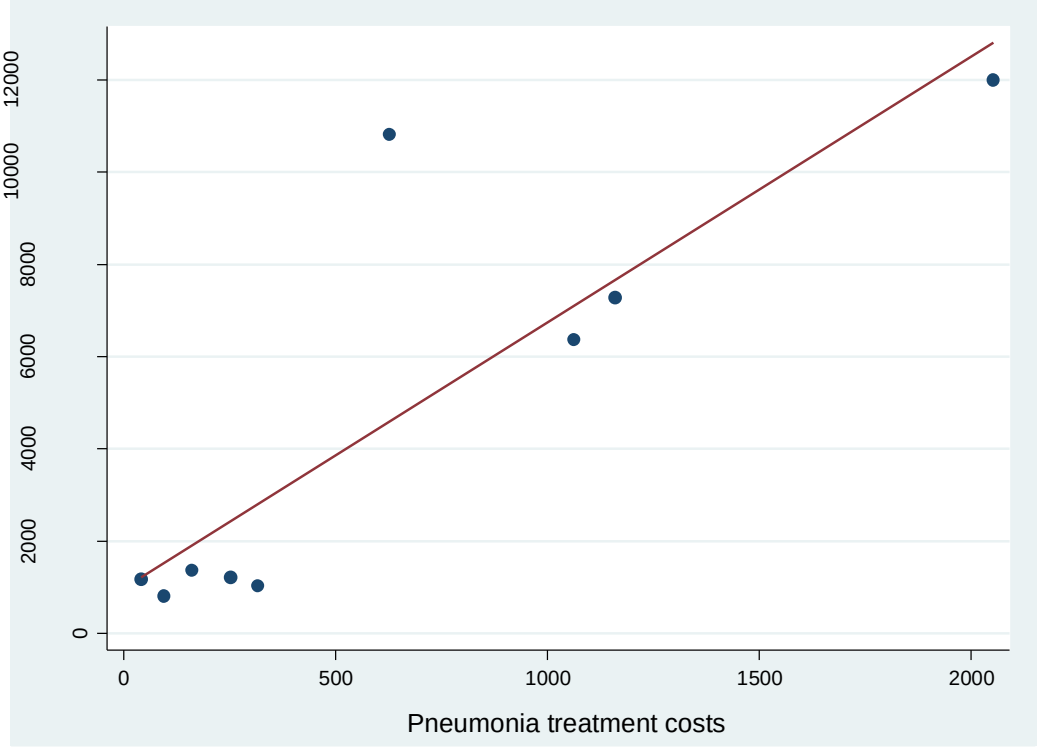



**Figure 2: Correlation between GNI per capita and costs of treating severe pneumonia (2010 US$)**



## 6 Statistical distributions of parameters

Probabilistic uncertainty analysis was undertaken to simultaneously assess the uncertainty around all parameter values, generate 95% confidence intervals around the incremental cost-effectiveness ratios 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 summarised in Table 11.

Distributions were fitted to parameters according to recommendations by Briggs and colleagues [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 utilisation parameters. The standard deviation 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.

**Table 10: Statistical distributions and parameter values (min, max) 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 < 5 years* | | | | | |
| Hib pneumonia | Gamma | 970 (243, 1,698) | 1,665 (238, 951) | 852 (213, 1,491) | 589 (147, 1,031) |
| 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) |
| *% case fatality ratios in ages 1-59m (%):* | | | | | |
| 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) |

| Parameter | Statistical distribution | GAVI eligible Africa | GAVI eligible Asia | Lower middle-income | Upper middle-income |
|---|---|---|---|---|---|
| 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: | | | | | |
| *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) | 1,358 (1,146, 1,570) |
| Tertiary hospital | Gamma | 77 (51, 103) | 77 (49, 104) | 264 (137, 391) | 1,566 (1,856, 2,146) |
| *Hib meningitis:* | | | | | |
| Secondary hospital | Gamma | 185 (178, 193) | 144 (137, 151) | 714 (636, 791) | 1,358 (1,146, 1,570) |
| Tertiary hospital | Gamma | 527 (505, 549) | 488 (465, 511) | 975 (869, 1,081) | 1,856 (1,566, 2,146) |

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