Burden of disease caused by *Haemophilus influenzae* type b in children younger than 5 years: global estimates

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Summary

Background ***Haemophilus influenzae*** **type b (Hib) is a leading cause of childhood bacterial meningitis, pneumonia, and other serious infections. Hib disease can be almost completely eliminated through routine vaccination. We assessed the global burden of disease to help national policy makers and international donors set priorities.**

Methods We did a comprehensive literature search of studies of Hib disease incidence, case-fatality ratios, age distribution, syndrome distribution, and effect of Hib vaccine. We used vaccine trial data to estimate the proportion of pneumonia cases and pneumonia deaths caused by Hib. We applied these proportions to WHO country-specific estimates of pneumonia cases and deaths to estimate Hib pneumonia burden. We used data from surveillance studies to develop estimates of incidence and mortality of Hib meningitis and serious non-pneumonia, non-meningitis disease. If available, high-quality data were used for national estimates of Hib meningitis and non-pneumonia, non-meningitis disease burden. Otherwise, estimates were based on data from other countries matched as closely as possible for geographic region and child mortality. Estimates were adjusted for HIV prevalence and access to care. Disease burden was estimated for the year 2000 in children younger than 5 years.

Findings We calculated that Hib caused about 8·13 million serious illnesses worldwide in 2000 (uncertainty range 7·33–13·2 million). We estimated that Hib caused 371 000 deaths (247 000–527 000) in children aged 1–59 months, of which 8100 (5600–10 000) were in HIV-positive and 363 000 (242 000–517 000) in HIV-negative children.

Interpretation Global burden of Hib disease is substantial and almost entirely vaccine preventable. Expanded use of Hib vaccine could reduce childhood pneumonia and meningitis, and decrease child mortality.

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Introduction

Haemophilus influenzae type b (Hib) is a common cause of serious diseases in children worldwide. Its most frequent manifestations are pneumonia and meningitis, but it can also cause infections of the epiglottis, soft tissues, bones, joints, and other sites.

Highly effective and safe protein–polysaccharide conjugate Hib vaccines have been available for almost 20 years. They have almost completely eliminated Hib disease in both developed and developing countries in which they are routinely used.[1–7] These vaccines also reduce asymptomatic nasopharyngeal carriage and substantially protect unvaccinated people even at moderate vaccine coverage (40–50%).[8–11] After licensure, Hib vaccines have been quickly introduced in North America and western Europe, but slowly in developing countries[12] because of high cost, concerns about programme sustainability, limited vaccine supply, and uncertainty about Hib disease burden.[13–15]

Hib pneumonia is difficult to identify, and surveillance studies underestimate the burden of other diseases caused by Hib.[15–18] WHO has developed a rapid Hib disease assessment method that accounts for limitations of meningitis surveillance. The method also estimates the burden of Hib pneumonia on the basis of two clinical trials of Hib vaccine, which suggest that, for every case of Hib meningitis, there are five cases of radiographic Hib pneumonia.[19–22] Vaccine trials to measure non-laboratory-confirmed Hib disease burden have provided important insights into the limitations of conventional surveillance studies and the burden of Hib disease.

WHO estimated that Hib causes about 3 million cases of serious disease and 386 000 child deaths every year.[23] The Bellagio Child Survival Study Group suggested that Hib vaccine could prevent 403 000 childhood deaths every year.[24] We undertook this new analysis of the global burden of Hib disease for two reasons. The completion of two additional vaccine trials[25,26] has helped to clarify the burden of Hib disease in Asian countries (where conventional methods showed low incidence of Hib meningitis) and provided data for the proportion of pneumonia preventable by Hib vaccines in Asia.[15] We developed methods for country-specific and regional estimates of Hib disease burden that are systematic and well documented. Our effort was done together with a project to estimate the global burden of *Streptococcus pneumoniae* disease in children.[27]

Methods

Methods are described in detail in the accompanying webappendix pp 3–9, but a concise description is provided here. We did a literature review and developed methods for

See **Online** for webappendix

estimating Hib disease burden from three serious clinical syndromes: meningitis, pneumonia, and non-pneumonia, non-meningitis invasive disease (disease in which Hib was isolated from a normally sterile body fluid).

We did a literature review of studies published between 1980 and 2005. We used broad search criteria to identify relevant studies from six global databases (Medline, Embase, CAB Health, Cochrane, Pascal, and Biosis) and four regional databases (African Index Medicus, Index Medicus for the WHO eastern Mediterranean region, Latin American and Caribbean Health Sciences Information, and Health Literature, Library and Information Services). Inclusion and exclusion criteria and quality assessments were applied to the studies identified. Literature review procedures are described elsewhere[28] and in the webappendix pp 3,4.

According to WHO guidelines for release of country-specific disease burden estimates, we undertook a country consultation process in 2007.[29] An Independent Expert Panel reviewed twice, and advised on, the project methods. In response to these consultations, a small number of reports published in 2006–07 were included in the final analysis. These reports provided high-quality data based on the same quality assessment used for studies identified in the literature review from regions with scarce information.

Meningitis

We based our estimates of Hib meningitis incidence and case-fatality ratios on data from the literature review. Where country-specific data were available, we used them to develop estimates for that country. If there were several estimates from a country, we generated a summary value using a random-effects meta-analysis. When country-specific data were not available, we developed estimates using data from epidemiologically similar countries. We hypothesised that reported Hib meningitis incidence and case-fatality ratios would correlate with child mortality and vary geographically. We defined mortality strata of children younger than 5 years as low (<30 deaths in 1000 livebirths), medium (30–<75), high (75–<150), or very high (≥150). For countries without data, we used data from countries in the same child-mortality category. Geographic regions were defined as the 21 UN subregions[30] plus an African meningitis belt stratification. Estimates for countries without data were sought from other countries within the same subregion and mortality stratum. If no such data were available, the geographic area was hierarchically expanded until data were available. If many studies were available within a given grouping, random-effects meta-analysis was used to determine a summary estimate for countries in that grouping without data.

Most reported estimates of Hib meningitis incidence come from hospital-based surveillance studies. Some studies adjusted the incidence rates for case-ascertainment limitations or provided data from which adjustments could be made. Adjusted rates were used whenever available. Most estimates of Hib meningitis case-fatality ratios are from hospitalised case series. Because untreated Hib meningitis is fatal in most cases, case-fatality ratios for children without access to health care are likely to exceed those from studies in which treatment was provided. We adjusted the meningitis case-fatality ratios to account for access to health care. For the proportion of meningitis cases not reaching care, we assumed a 90% case-fatality ratio. We used the proportion of children younger than 5 years with suspected pneumonia in the past 2 weeks who were taken for care from the Multiple Indicator Cluster Surveys (MICS) as a proxy for the proportion of meningitis cases with access to care.[31] For countries without MICS data, we applied regional MICS estimates. When those were unavailable, we used the third dose of diphtheria toxoid, tetanus toxoid, and pertussis vaccine (DTP3) coverage reported by WHO.[32] For countries in Latin America where no other data were available, and for developed countries, we assumed 100% access to care.

We identified studies that quantified the relative risk for serious Hib disease associated with HIV infection and developed a summary risk ratio. We adjusted Hib meningitis incidence rates to account for differences in HIV prevalence when data from other countries were used to develop estimates. We combined the estimated country-specific Hib meningitis incidence and the number of children younger than 5 years to determine the number of Hib meningitis cases. We applied the country-specific case-fatality ratio to calculate the number of Hib meningitis deaths.

Non-pneumonia, non-meningitis disease

We based our estimates for non-pneumonia, non-meningitis disease burden on published series of confirmed, invasive Hib-disease cases that reported the anatomic site of disease. For each report, we calculated the ratio of non-pneumonia, non-meningitis disease to meningitis cases, and derived a mortality strata-specific summary estimate of the ratio by combining relevant studies in a random-effects meta-analysis. This ratio was applied to the country-specific meningitis cases to estimate cases with non-pneumonia, non-meningitis disease. We used a similar approach to assess the case-fatality ratio of non-pneumonia, non-meningitis disease. The relation between mortality from Hib non-pneumonia, non-meningitis disease and from Hib meningitis was determined from published studies, and a summary estimate was generated from random-effects meta-analysis. This estimate was applied to the country-specific Hib meningitis case-fatality ratio to measure the case-fatality ratio for non-pneumonia, non-meningitis disease, which was then applied to the estimated non-pneumonia, non-meningitis disease cases to measure country-specific Hib non-pneumonia, non-meningitis disease deaths. Adjustments for access to care and HIV prevalence were incorporated, as appropriate.

Pneumonia

Because no sensitive and specific tests for the diagnosis of Hib pneumonia are available, conventional surveillance studies for Hib pneumonia are insufficient and Hib pneumonia case-fatality ratios cannot be directly measured. Hib vaccine trials provide data, unrestricted by diagnostic test availability, for the proportion of pneumonia disease and deaths prevented by Hib vaccine.[21] We identified studies that used a random or systematic allocation of Hib conjugate vaccine to measure a reduction in overall pneumonia incidence in vaccinated compared with unvaccinated children. This reduction in disease incidence is a function of both the proportion of disease caused by Hib and the efficacy of the vaccine against Hib pneumonia. We have used vaccine efficacy against invasive Hib disease to approximate the vaccine efficacy against Hib pneumonia and to estimate the proportion of pneumonia caused by Hib for each study. Using random-effects meta-analysis, we developed a summary estimate of the proportion of all-cause pneumonia cases caused by Hib. Owing to the small number of studies, a summary estimate was used for all countries and applied to country-specific estimates of all-cause pneumonia cases.[33] Adjustments for the increased risk of disease in HIV-positive children were incorporated.

A similar approach was taken to estimate deaths caused by Hib pneumonia. Although a reduction in pneumonia mortality is difficult to measure experimentally, several studies have evaluated the difference in incidence of pneumonia with radiographic consolidation between vaccinated and unvaccinated children. We assumed this difference would be similar to the proportion reduction in all-cause pneumonia mortality associated with Hib vaccine use, and therefore the proportion of pneumonia deaths caused by Hib. Using a random-effects meta-analysis, we combined estimates of the proportion reduction in pneumonia with radiographic consolidation from studies that used a random or systematic allocation of Hib-conjugate vaccine. We applied this proportion to WHO country-specific estimates of all-cause pneumonia deaths in children aged 1–23 months to calculate the number of Hib-specific pneumonia deaths by country.[34] Because clinical trials mainly included children younger than 2 years, we have no data for Hib pneumonia deaths in older children. Most serious Hib disease occurs before 2 years of age; therefore, we assumed no Hib pneumonia deaths after the second year of life. WHO estimates of all-cause pneumonia deaths do not include HIV-infected children. To estimate Hib pneumonia deaths in those children, we applied the derived country-specific Hib pneumonia case-fatality ratio of HIV-negative children to the estimated number of cases of Hib pneumonia in HIV-positive children. All Hib disease burden estimates in HIV-infected children are reported separately.

Uncertainty ranges

We report our estimates together with uncertainty ranges (UR; webappendix pp 5–7). The uncertainty bounds indicate the range of results generated by modifying the model structure or the literature estimates of disease incidence, and the statistical uncertainty.

Hib vaccine use

We estimated incidence rates in the absence of Hib vaccine. We then calculated cases and deaths for the year 2000, accounting for direct and indirect protection from Hib vaccine and coverage for countries where vaccine was widely used. The number of serious Hib illnesses and deaths presented here, therefore, takes into account Hib-vaccine use in 2000. We also measured the number of serious illnesses and deaths prevented by Hib vaccine in children born in 2000, some of which would have occurred in subsequent years.

Reporting

Global and regional results are the sum of country-level results. Total values have been rounded and reported with three significant digits, and never more specific than hundreds of cases or deaths. Country-specific results are reported without rounding.

For more on **country-specific results** see http://www.who.int/immunization_monitoring/burden/en/

Role of the funding source

The sponsor had no role in the design, data collection, analysis, interpretation, or writing of the report. This work was done in collaboration with WHO, the PneumoADIP, and the Hib Initiative. The PneumoADIP and the Hib Initiative are funded by the GAVI Alliance and the Vaccine Fund. All authors had full access to the data and had final responsibility for the decision to submit for publication.

Results

We identified 15 099 studies by our literature search.[35] 205 studies contributed data to Hib primary endpoints. For Hib meningitis, 110 studies provided incidence data, of which 59 met quality criteria; 116 provided age distribution data, and 50 reported data for case-fatality ratio. Data availability substantially varied in different regions (table 1). Of the 59 Hib meningitis incidence

	AFR	AMR	EMR	EUR	SEAR	WPR	Total
Meningitis incidence	10 (5)	12 (6)	5 (5)	16 (8)	3 (3)	13 (8)	59 (35)
Meningitis CFR	10 (8)	14 (8)	2 (2)	10 (6)	2 (2)	12 (7)	50 (33)
NPNM syndrome distribution	4 (2)	7 (6)	1 (1)	9 (7)	2 (2)	4 (3)	27 (21)
NPNM disease and meningitis CFR	0 (0)	1 (1)	0 (0)	2 (1)	0 (0)	2 (1)	5 (3)

Data are numbers of studies (countries). AFR=Africa. AMR=the Americas. EMR=eastern Mediterranean. EUR=Europe. SEAR=southeast Asia. WPR=western Pacific. CFR=case-fatality ratio. NPNM=non-pneumonia, non-meningitis. *Models grouped countries by UN subregions; therefore, this table does not fully reflect the number of countries, the model estimates of which were drawn from data within their region.

Table 1: **Number of studies with *Haemophilus influenzae* type b disease burden data that populated the meningitis and non-pneumonia, non-meningitis models*, by WHO region**

studies meeting quality criteria, only five were from the WHO eastern Mediterranean and three from southeast Asia region. By contrast, 16 were from Europe, 12 from the Americas, 13 from the western Pacific, and ten from Africa. Substantially fewer data were available for non-pneumonia, non-meningitis disease.[35]

We identified six studies that used Hib vaccine to measure the burden of Hib pneumonia; four met our inclusion criterion of having randomised or systematic vaccine distribution.[21,22,25,26,36] We excluded two case-control studies[37,38] done after routine Hib-vaccine introduction because access to vaccination might be independently associated with risk of Hib disease. Two studies from The Gambia[21,36] and Indonesia[25] provided data for the proportion of clinical pneumonia prevented by Hib vaccine, whereas all four studies showed data for the proportion of pneumonia with radiographic consolidation prevented by the vaccine. Figure 1 shows the efficacy of Hib vaccine against different pneumonia endpoints for each study, the estimated proportion of each endpoint attributable to Hib, and the meta-analysis of the proportion of disease attributable to Hib.

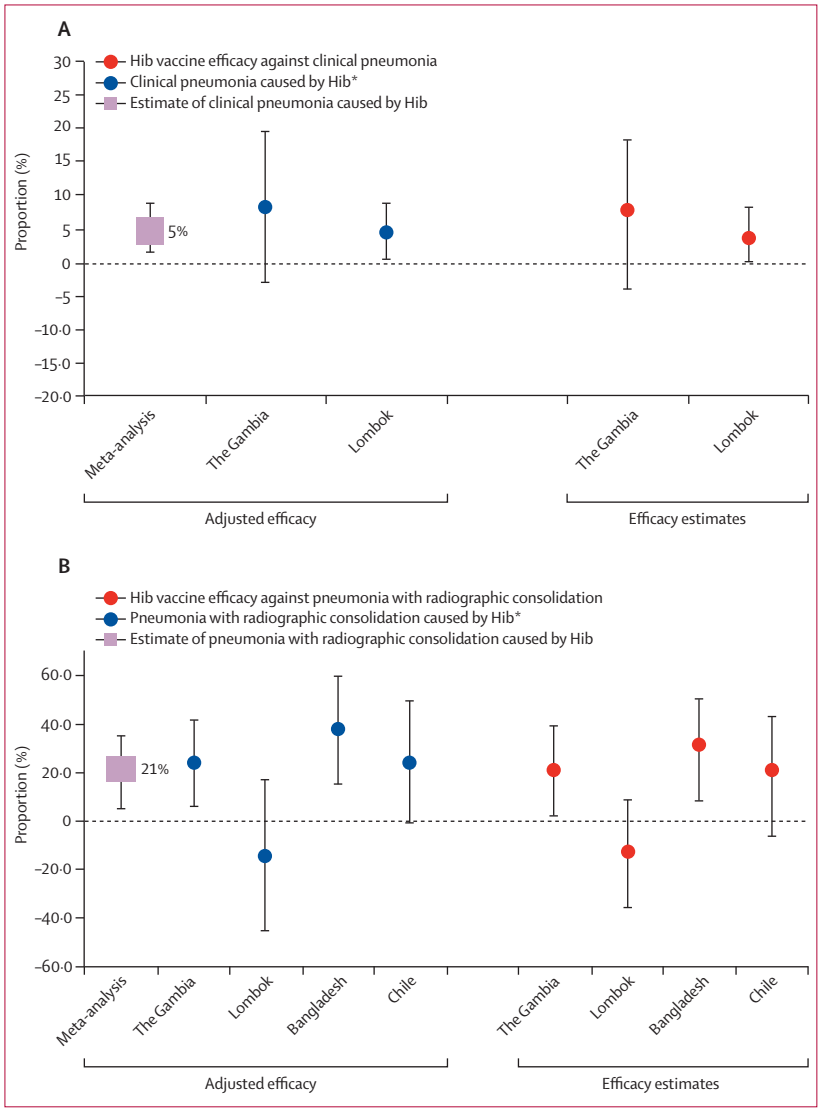

Figure 1: **Hib vaccine efficacy**
(A) Against clinical pneumonia. (B) Against pneumonia with radiographic consolidation. Error bars indicate 95% CI on the efficacy estimates and the adjusted efficacy estimates. *Adjusted for Hib vaccine efficacy against invasive disease (a proxy for vaccine efficacy against Hib pneumonia).

We calculated that in 2000, Hib caused 8·13 million cases of pneumonia, meningitis, and invasive non-pneumonia, non-meningitis disease in children younger than 5 years of age (uncertainty range [UR] 7·3–13·2 million). These cases resulted in an estimated 371000 deaths in children 1–59 months of age, which includes 8100 deaths in HIV-positive children (table 2).

Southeast Asia had the largest numbers of cases and deaths, followed by Africa, the western Pacific, and the eastern Mediterranean. Widespread Hib vaccine use had a substantial effect on the burden of Hib disease in the Americas and Europe. We estimated that, for children born in 2000, about 338000 future Hib cases (304000–542000) and 12500 future Hib deaths (8300–20000) were averted by vaccination.

The estimated global incidence of Hib meningitis, in the absence of vaccination, was 31 cases per 100000 children younger than 5 years. Estimated incidence varied by region (table 2). Uncertainty ranges substantially overlapped across regions. Direct comparison between regions is complicated by differences in methods and health-care services in the studies contributing to the estimates. In all regions, Hib meningitis was a severe disease with reported case-fatality ratios ranging from 22% to 67%.[35]

The estimated global incidence of Hib pneumonia, in the absence of vaccination, was 1304 per 100000 children younger than 5 years (table 2). Because we developed a single global estimate for the proportion of Hib pneumonia cases, the main sources of regional variability in estimated Hib pneumonia incidence were the variability in all-cause pneumonia incidence and the prevalence of childhood HIV infection.

We identified only two studies with data for the proportion of clinical pneumonia prevented by Hib vaccine. One suggested that Hib vaccine prevented 7·7% of clinical pneumonia cases (95% CI –4·1% to 18·2%) in The Gambia, whereas the other estimated that Hib vaccine prevented 3·8% of such cases (–0·2% to 7·7%) in Indonesia.[25,36] This proportion has a large effect on our estimates. We identified four studies[21,22,25,26,36] with data for the proportion of pneumonia with radiographic consolidation prevented by Hib vaccine. Estimates from these studies varied substantially (figure 1). The study from Indonesia[25] found no reduction of pneumonia with radiographic consolidation in vaccinated children. Without this study, the overall model estimate of the proportion of pneumonia with radiographic consolidation caused by Hib increases from 21% to 28%. By contrast, the case-control study from Bangladesh[26] found

that Hib vaccine prevented 32% of pneumonia with radiographic consolidation (95% CI 8–50%). Omission of this study results in a decrease in the overall model estimate from 21% to 15%. Thus, our uncertainty ranges for the contribution of Hib to pneumonia cases and deaths are wide.

To evaluate the stability of the meningitis disease burden estimate, we omitted each study individually

	Global	Africa	Americas	Eastern Mediterranean	Europe	Southeast Asia	Western Pacific
Total							
Deaths of children <5 years*	10 600 000						
Children <5 years†	620 422 370	112 039 778	77 548 765	64 100 843	51 511 782	183 259 338	131 961 864
Incidence rate‡	1342 (1210–2180)	1778 (1610–2877)	544 (488–875)	1417 (1284–2310)	304 (274–491)	1822 (1647–2969)	1142 (1017–1853)
Cases	8 130 000 (7 330 000–13 200 000)	1 970 000 (1 780 000–3 190 000)	286 000 (257 000–463 000)	899 000 (815 000–1 470 000)	129 000 (116 000–209 000)	3 340 000 (3 020 000–5 440 000)	1 500 000 (1 340 000–2 440 000)
Death rate‡	60 (40–85)	162 (112–224)	11 (7–15)	76 (52–110)	17 (11–24)	53 (33–77)	21 (12–31)
Total deaths	371 000 (247 000–527 000)	181 000 (126 000–251 000)	8400 (5200–11 700)	48 500 (33 300–70 400)	8600 (5900–12 600)	97 200 (61 300–141 000)	27 200 (16 100–40 600)
Total deaths in HIV-positive	8100 (5600–10 000)	7800 (5400–9700)	<100 (NA)	<100 (NA)	<100 (NA)	<100 (NA)	<100 (NA)
Total deaths in HIV-negative	363 000 (242 000–517 000)	173 000 (120 000–242 000)	8400 (5200–11 600)	48 400 (33 300–70 300)	8600 (5900–12 600)	97 100 (61 200–140 000)	27 200 (16 100–40 600)
Pneumonia							
Incidence rate‡	1304 (1191–2131)	1724 (1574–2817)	510 (466–834)	1387 (1267–2267)	283 (259–463)	1790 (1635–2925)	1097 (1001–1792)
Cases	7 910 000 (7 230 000–12 900 000)	1 910 000 (1 740 000–3 120 000)	275 000 (251 000–450 000)	880 000 (804 000–1 440 000)	122 000 (112 000–200 000)	3 280 000 (3 000 000–5 360 000)	1 450 000 (1 320 000–2 360 000)
CFR	4% (2–7%)	8% (5–14%)	1% (1–3%)	5% (3–9%)	5% (3–9%)	2% (1–4%)	1% (1–2%)
Death rate‡	47 (33–69)	130 (92–189)	6 (4–9)	65 (46–95)	13 (9–18)	41 (29–60)	13 (9–19)
Deaths	292 000 (206 000–425 000)	146 000 (103 000–212 000)	4900 (3400–7100)	41 600 (29 300–60 700)	6500 (4600–9500)	75 300 (53 000–109 900)	17 600 (12 400–25 600)
Deaths in HIV-positive	6400 (4500–8000)	6200 (4400–7800)	<100 (NA)	<100 (NA)	<100 (NA)	100 (80–130)	<100 (NA)
Deaths in HIV-negative	286 000 (201 000–417 000)	140 000 (99 000–205 000)	4900 (3400–7100)	41 500 (29 200–60 600)	6500 (4600–9500)	75 200 (52 900–109 700)	17 600 (12 400–25 600)
Meningitis							
Incidence rate‡	31 (16–39)	46 (31–52)	25 (16–30)	24 (14–35)	16 (12–22)	27 (11–38)	34 (11–46)
Cases	173 000 (85 300–226 000)	51 300 (33 900–57 300)	8000 (4600–10 200)	15 400 (9100–22 300)	5200 (3300–7300)	49 700 (19 600–68 800)	43 800 (14 800–59 700)
CFR	43% (23–55%)	67% (44–75%)	28% (15–36%)	44% (26–62%)	27% (17–41%)	44% (17–62%)	22% (8–34%)
Death rate‡	13 (7–16)	31 (20–35)	5 (2–6)	11 (6–15)	4 (3–6)	12 (5–17)	7 (3–11)
Deaths	78 300 (41 600–101 600)	34 600 (22 500–38 800)	3500 (1800–4600)	6800 (4000–9700)	2000 (1300–3100)	21 800 (8300–30 600)	9500 (3700–14 800)
Deaths in HIV-positive	1600 (1000–2000)	1600 (1000–1900)	<100 (NA)	<100 (NA)	<100 (NA)	<100 (NA)	<100 (NA)
Deaths in HIV-negative	76 600 (40 600–99 600)	33 000 (21 500–36 900)	3500 (1800–4500)	6800 (4000–9600)	2000 (1300–3100)	21 800 (8300–30 600)	9500 (3700–14 800)
NPNM							
Incidence rate‡	7 (4–10)	8 (5–9)	9 (6–10)	5 (3–8)	5 (4–7)	5 (2–7)	11 (4–16)
Cases	39 600 (18 800–52 500)	8300 (5500–9300)	2600 (1600–3300)	320 (1800–4900)	1400 (1000–2100)	9100 (3900–12 500)	15 000 (5000–20 400)
CFR	1% (0–1%)	2% (1–2%)	1% (0–1%)	1% (1–1%)	1% (0–1%)	1% (0–1%)	1% (0–1%)
Death rate‡	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
Deaths	400 (200–500)	100 (80–140)	<100 (NA)	<100 (NA)	<100 (NA)	<100 (NA)	<100 (NA)
Deaths in HIV-positive	<100 (NA)	<100 (NA)	<100 (NA)	<100 (NA)	<100 (NA)	<100 (NA)	<100 (NA)
Deaths in HIV-negative	400 (200–500)	100 (80–140)	<100 (NA)	<100 (NA)	<100 (NA)	<100 (NA)	<100 (NA)

Data are estimates (uncertainty range). CFR=case-fatality rate. NPNM=non-pneumonia, non-meningitis disease. NA=not applicable. Uncertainty ranges not listed for fewer than 100 cases or deaths. *Data from reference 28. †Data are from reference 30. ‡Per 100 000.

***Table 2: Haemophilus influenzae* type b cases and deaths, with uncertainty estimates, by syndrome and WHO region**

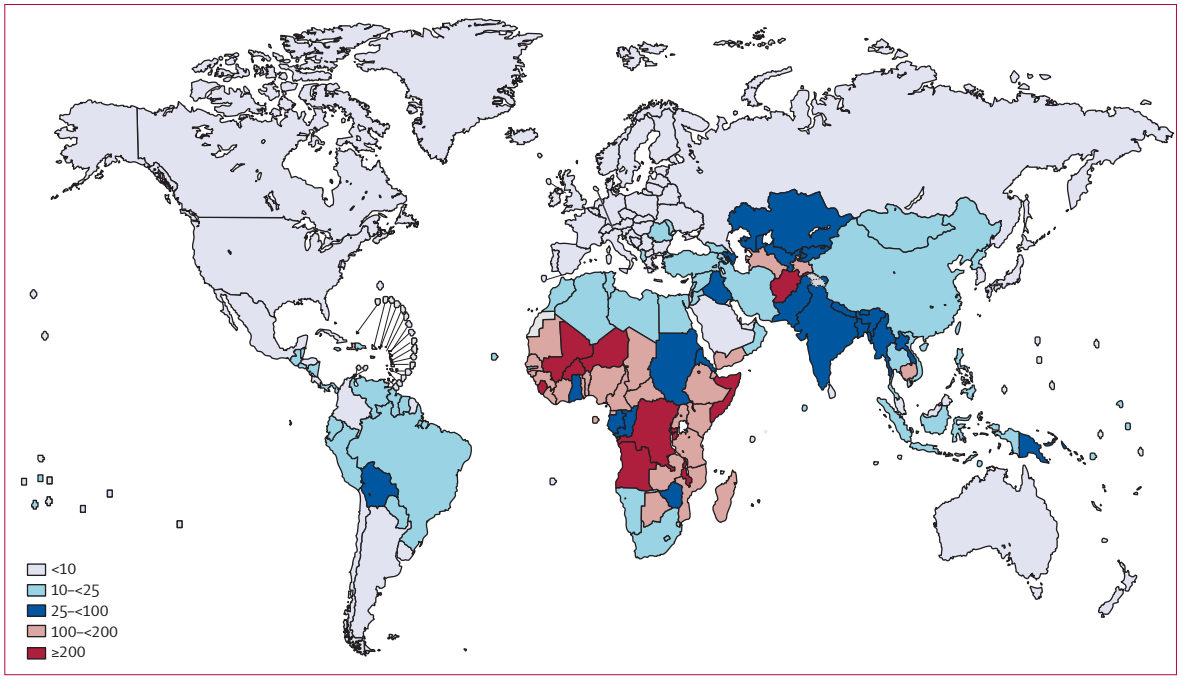

Figure 2: **Hib mortality rate**
Hib deaths in children aged 1–59 months per 100 000 children (HIV-negative Hib deaths only). The boundaries shown and the designations used on this map do not imply the expression of any opinion by WHO concerning the legal status of any country, territory, city, or area, or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

from the model to determine the individual contribution to the overall estimate. The estimated number of cases changed by more than 2% for only three studies, from Mongolia (18·9% decrease when omitted), Kenya (4·1% increase), and Indonesia (26·2% increase).[5,25,39] Exclusion of data from Indonesia left no Asian studies in high-mortality strata, which necessitated the use of data from African high-mortality populations. The use of these data for Asian high-mortality settings resulted in increased estimated Hib meningitis incidence. The decrease in cases when the Mongolia study was omitted resulted from a higher reported incidence from Mongolia than from other Asian medium-mortality populations.

Discussion

For more on **Hib vaccination** see http://www.who.int/nuvi/Hib/slides/VaccUtilisation06.pdf

We estimate that, in 2000, Hib caused 8·13 million serious illnesses (UR 7·33–13·2 million) and 371 000 deaths (247 000–527 000) in children younger than 5 years. Of the deaths, 8100 (5600–10 000) occurred in HIV-infected children. Hib disease accounted for 5·6% (3·9–7·7%) of the estimated 6·6 million post-neonatal child deaths and 16% of the estimated 1·8 million pneumonia deaths in HIV-negative children.[28,40] These Hib-attributable deaths in children are almost entirely vaccine preventable. Our estimate of childhood mortality caused by Hib is consistent with previous estimates.[23,24] Because most deaths occurred in developing countries in Africa and Asia, Hib disease contributed to the disparity in child mortality between developed and developing countries (figure 2). Just ten countries, all in Asia or Africa, account for an estimated 61% of childhood Hib deaths (figure 3). These countries include those with high-mortality rates but small populations and those with moderate-mortality rates but large populations.

In 2000, the only regions with widespread use of Hib vaccine were Europe and the Americas. By 2006, however, 108 countries—representing more than 55% of the world's children—had implemented routine Hib vaccination.[12] WHO and the GAVI Alliance, through their support for the Hib Initiative, have been working to expand supplies of Hib vaccine, reduce vaccine cost, and assist countries with vaccine introduction.[12] Our data suggest that expanded use of Hib vaccines could considerably reduce child mortality worldwide.

Hib is also a major cause of child morbidity. We estimated that, in the absence of vaccination, 1·3% of children younger than 5 years (1·2–2·1%) would have an episode of Hib pneumonia each year—about 5·0% of cases of clinical pneumonia in 2000.[33] Our estimate of Hib morbidity is substantially higher than previous estimates, mainly because we included Hib clinical pneumonia.

Our estimate of Hib meningitis disease burden is likely to be too low. Most Hib meningitis incidence studies we identified were surveillance studies, which systematically underestimate the burden of Hib disease. Trials to assess the effect of Hib vaccine on clinical meningitis or culture-negative meningitis have shown that use of laboratory-confirmed disease alone substantially underestimates the burden of Hib

meningitis, even with optimum laboratory facilities.[25,26,41] Hib non-pneumonia, non-meningitis disease burden is also likely to be underestimated because it is based on the meningitis disease burden estimates. Furthermore, most studies of invasive Hib disease we identified focused on meningitis. Data of the proportion of Hib non-pneumonia, non-meningitis diseases are scarce, and the proportion identified is likely to be underestimated by studies mainly focused on meningitis.

The paucity and variability of available data is reflected in our wide uncertainty ranges. These ranges are the results generated by modifying model structure, literature estimates of disease incidence, and statistical uncertainty of meningitis estimates. Our assumptions, if not valid, could increase the estimated uncertainty in unquantifiable ways. We tried to assess the quality of study data and to include those studies with the most reliable results in our model. Only 29 of 110 studies (26%) of Hib meningitis incidence met our a-priori criteria for reliable results and almost all were done in developed countries.[35] To encompass data from a wider range of countries, we included those studies judged to have reliable results by one of the two reviewers, resulting in a total of 59 studies for the meningitis incidence model. Almost half of the identified studies were excluded because both reviewers identified data-quality limitations. The large number of Hib meningitis incidence studies with unreliable results has contributed to uncertainty about Hib disease burden in many countries. Better standardisation and reporting of methods and limitations for surveillance studies are needed.[17]

We considered different approaches to estimate the burden of Hib pneumonia (webappendix pp 4,5). Because no sensitive and specific diagnostic tests for Hib pneumonia exist, few data for Hib pneumonia burden are available. Our use of results from Hib vaccine probe studies to determine the incidence of vaccine-preventable pneumonia has drawbacks. The incidence of vaccine-preventable disease is a function of total incidence and vaccine efficacy. The efficacy of Hib vaccine against Hib pneumonia is not known. We have used the efficacy of Hib vaccine against invasive Hib disease as a proxy, but it is likely that this efficacy against Hib pneumonia is lower, leading to a bias towards underestimating Hib pneumonia incidence and disease burden. Only two studies of Hib vaccine effect on clinical pneumonia met our inclusion criteria.[21,25,36] The proportion of clinical pneumonia caused by Hib is crucial for our estimate of Hib cases. The small number of studies and substantial variability between them led to wide uncertainty bounds around these estimates. Additionally, the case-detection method for clinical pneumonia cases differed between vaccine trials and all-cause pneumonia incidence studies. If the contribution of Hib to clinical pneumonia cases identified in the incidence studies is less than in vaccine trials, we might have overestimated Hib pneumonia cases. This would not affect the Hib pneumonia mortality estimates.

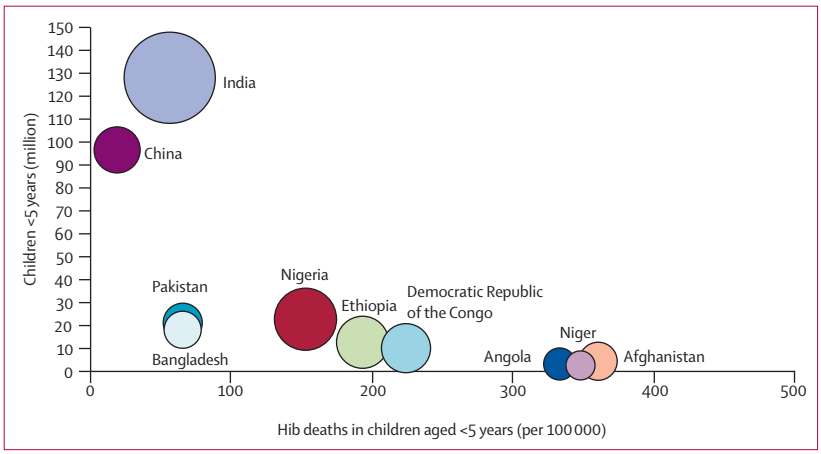

Figure 3: **Ten countries with the greatest number of Hib deaths***
HIV infected and uninfected. Bubble size indicates the number of Hib deaths. *Country (number of deaths): India (72 000), Nigeria (34 000), Ethiopia (24 000), Democratic Republic of the Congo (22 000), China (19 000), Afghanistan (14 000), Pakistan (13 000), Bangladesh (12 000), Angola (9000), and Niger (8000).

Similarly, only four vaccine probe studies[21,22,25,26,36] had data for pneumonia with radiographic consolidation, which we used in our Hib pneumonia death model. The study methods and definition for radiographic consolidation were not standardised across these studies: two were randomised clinical trials with a-priori pneumonia endpoints;[25,36] one was a case-control trial with systematic vaccine allocation;[26] and one was a post-hoc analysis of a Hib-vaccine trial.[22] Differences in methods and results in these studies make comparisons difficult and lead to uncertainty in our estimates of Hib pneumonia mortality. Estimates of Hib pneumonia deaths are highly sensitive to the estimate of all-cause pneumonia deaths. Uncertainty in this estimate contributes to uncertainty in our results (webappendix p 5).[42,43] A single estimate of the proportion of pneumonia with radiographic consolidation due to Hib was applied globally. The contribution of Hib might, however, vary by region. The Hib pneumonia case-fatality ratio is likely to be lower in settings with ready access to health care than where access is limited. Our model assumes that the Hib pneumonia case-fatality ratio is the same as for all other pneumonia causes, so we might have overestimated the burden of Hib pneumonia deaths in settings with ready access to care and underestimated it in settings with limited access. Because most Hib pneumonia deaths are in settings with limited access to health care, our model probably underestimates the global burden of Hib pneumonia deaths.

Vaccine studies on which our Hib pneumonia estimates are based focused on children younger than 2 years, and the number of Hib pneumonia cases and deaths in children older than 2 years is not known. For Hib meningitis, we found that the proportion of cases in children aged 2–4 years was 4–18%, depending on

childhood mortality (data not shown). Thus, some Hib pneumonia cases and deaths probably also occur in children older than 2 years. However, in the absence of vaccine trial data for Hib pneumonia in children older than 2 years, we assumed that there were no Hib pneumonia deaths in this age group, and consequently we might have underestimated Hib pneumonia deaths. Because data are available, our estimates of Hib meningitis and non-pneumonia, non-meningitis diseases deaths include children aged 2–4 years. Furthermore, our estimates are subject to general methodological limitations (webappendix pp 3–9).

Our methods for estimating the burden of Hib pneumonia and Hib meningitis differed substantially. The overall ratio of Hib pneumonia to meningitis cases based on these two different approaches was 46:1, substantially higher than the 5:1 ratio estimated by previous studies.[21,22] There are several possible explanations for this finding. The 5:1 ratio was based on pneumonia with radiographic consolidation, whereas our estimates are of Hib-attributable clinical pneumonia. Studies upon which the 5:1 ratio is based might have underestimated the pneumonia incidence because of incomplete case ascertainment, resulting in an underestimation of the pneumonia-to-meningitis ratio.[21] Also, we might have underestimated Hib meningitis burden or overestimated the burden of Hib clinical pneumonia, as described above.

Our study identified several important limitations in data availability. Additional high-quality Hib-disease-burden studies could narrow the uncertainty ranges and result in disease estimates that are higher or lower than those provided here. However, such studies, especially vaccine probe studies, are expensive, time consuming, and ethically questionable since WHO has recommended inclusion of Hib vaccines in all routine immunisation programmes without waiting for local disease-burden data.[23] Furthermore, Hib vaccines are increasingly available, prices are declining, and vaccine financing through the GAVI Alliance is available for low-income countries.[12] Doubts might remain about the true burden of Hib disease, especially in parts of Asia, but their importance decreases as vaccine availability increases and prices fall. Studies in developing countries that have introduced Hib vaccine with GAVI support should help resolve many issues regarding disease burden and vaccine effect.

Widespread implementation of safe and effective Hib vaccines could reduce mortality of children younger than 5 years. We hope that these estimates will assist national and international policy makers in their assessments of the value of prevention of Hib disease.

Contributors

KLO'B, LJW, JPW, EH, MD-K, and TC participated in the design, data collection, analysis, and report writing. NMC participated in data collection, analysis, and report writing. KM and OSL participated in the design, analysis, and report writing. RH participated in the analysis and report writing. EL participated in data collection.

Hib and Pneumococcal Global Disease Burden Working Group

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Conflicts of interest

We declare that we have no conflicts of interest.

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