Burden of disease caused by *Streptococcus pneumoniae* in children younger than 5 years: global estimates

Katherine L O'Brien, Lara J Wolfson, James P Watt, Emily Henkle, Maria Deloria-Knoll, Natalie McCall, Ellen Lee, Kim Mulholland, Orin S Levine, Thomas Cherian, for the Hib and Pneumococcal Global Burden of Disease Study Team*

Summary

Background *Streptococcus pneumoniae* is a leading cause of bacterial pneumonia, meningitis, and sepsis in children worldwide. However, many countries lack national estimates of disease burden. Effective interventions are available, including pneumococcal conjugate vaccine and case management. To support local and global policy decisions on pneumococcal disease prevention and treatment, we estimated country-specific incidence of serious cases and deaths in children younger than 5 years.

Methods We measured the burden of pneumococcal pneumonia by applying the proportion of pneumonia cases caused by *S pneumoniae* derived from efficacy estimates from vaccine trials to WHO country-specific estimates of all-cause pneumonia cases and deaths. We also estimated burden of meningitis and non-pneumonia, non-meningitis invasive disease using disease incidence and case-fatality data from a systematic literature review. When high-quality data were available from a country, these were used for national estimates. Otherwise, estimates were based on data from neighbouring countries with similar child mortality. Estimates were adjusted for HIV prevalence and access to care and, when applicable, use of vaccine against *Haemophilus influenzae* type b.

Findings In 2000, about 14·5 million episodes of serious pneumococcal disease (uncertainty range 11·1–18·0 million) were estimated to occur. Pneumococcal disease caused about 826 000 deaths (582 000–926 000) in children aged 1–59 months, of which 91 000 (63 000–102 000) were in HIV-positive and 735 000 (519 000–825 000) in HIV-negative children. Of the deaths in HIV-negative children, over 61% (449 000 [316 000–501 000]) occurred in ten African and Asian countries.

Interpretation *S pneumoniae* causes around 11% (8–12%) of all deaths in children aged 1–59 months (excluding pneumococcal deaths in HIV-positive children). Achievement of the UN Millennium Development Goal 4 for child mortality reduction can be accelerated by prevention and treatment of pneumococcal disease, especially in regions of the world with the greatest burden.

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GAVI's PneumoADIP, Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA (K L O'Brien MD, E Henkle MPH, M Deloria-Knoll PhD, N McCall MD, E Lee MD, O S Levine PhD)**; World Health Organization, Geneva, Switzerland** (L J Wolfson PhD, T Cherian MD)**; Hib Initiative, Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA** (J P Watt MD)**; and London School of Hygiene and Tropical Medicine, London, UK** (Prof K Mulholland MD)

Correspondence to:
Dr Katherine L O'Brien, Johns Hopkins Center for American Indian Health, 621 N Washington Street, Baltimore, MD 21205, USA
klobrien@jhsph.edu

Introduction

Streptococcus pneumoniae is a leading cause of bacterial pneumonia, meningitis, and sepsis in children. Recent estimates of child deaths caused by *S pneumoniae* range from 700 000 to 1 million every year worldwide.[1–3]

Since resources for child survival are increasing, estimates of pneumococcal disease burden based on comprehensive, clear, and rigorous methods are needed. Although global estimates are valuable for international institutions and global initiatives, they have limited use for national policy makers. Progress in pneumonia case and death prevention will be facilitated by cause-specific estimates that help local and regional policy makers to prioritise interventions, such as vaccines or antibiotic treatments, specific for particular pneumonia causes.

We estimated the burden of serious pneumococcal cases and deaths in children younger than 5 years for the year 2000 at global, regional, sub-regional, and country levels by systematic, transparent methods (webappendix), including a comprehensive literature review.[4]

Methods

We used distinct methods to estimate pneumococcal disease burden from three serious clinical syndromes: meningitis, pneumonia, and non-pneumonia, non-meningitis invasive disease (defined as isolation of *S pneumoniae* from a normally sterile body fluid). Methods are described in detail in the webappendix pp 3–9; however, here we provide a concise description of the main components.

To obtain data for the models of meningitis and non-pneumonia, non-meningitis invasive disease, we did a comprehensive literature review of published papers from 1980 to 2005 from five global databases (Medline, Embase, CAB Health, Cochrane, 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 reported data. Data were included in the analysis only when these criteria were met. A full description of the literature

See **Online** for webappendix

review search terms and article review procedures is published elsewhere.[4] An Independent Expert Panel reviewed and advised on methods and results. To comply with WHO guidelines for release of country-specific disease burden measures,[5] we submitted to every country their specific pneumococcal disease burden estimates. A final analysis, with updated input variables, included a few reports published in 2006–07, which were identified through the country consultation process or the expert review panel. These studies contributed data obtained before the end of 2005; met all inclusion, exclusion, and quality criteria; and came from areas of the world that otherwise had few or no country-specific data.

Meningitis

We used HIV-adjusted, country-specific pneumococcal incidence rates combined with numbers of children younger than 5 years to estimate the number of pneumococcal meningitis cases. We applied to these estimates the country-specific pneumococcal meningitis case-fatality ratios, also derived from the literature review, to estimate the number of pneumococcal meningitis deaths.

If there were estimates from several studies for a particular country, they were summarised by a random-effects meta-analysis.[6] Because data are not available for each variable in every country, we extrapolated known information to settings where information was unavailable. Meningitis incidence rates are correlated with child mortality and vary geographically. To ensure that the data used for each country were as epidemiologically representative and local as possible, narrow geographic and child-mortality strata were defined, and, in a step-wise fashion, those strata were hierarchically expanded when data were not available within a given stratum. We defined mortality strata of children younger than 5 years as low (<30 deaths per 1000 livebirths), medium (30–<75), high (75–<150), or very high (≥150) mortality. We grouped countries according to these strata and geographic regions (based on 21 geographic subregions using UN definitions[7]), plus a stratification for the African meningitis belt. Random-effects meta-analyses of all available studies within a given group (defined as the most local combination of mortality strata and geographic region with available data) were used to impute an estimate for countries in the group for which no country-specific data were available.

Disease rates are underestimated when children do not reach facilities for case ascertainment. Some studies estimated the proportion of cases missed and provided adjusted incidence rates or data allowing quantitative adjustment of reported rates; adjusted rates were used whenever reported.

Similarly, case-fatality rates are expected to be greater in children without access to care than in those receiving treatment. We adjusted meningitis case-fatality rates for access to care, applying a 90% case-fatality rate for the proportion of cases not reaching care. We used the proportion of children younger than 5 years with suspected pneumonia in the previous 2 weeks who were taken to a health-care provider from the Multiple Indicator Cluster Surveys (MICS) as a proxy for access to care.[8] For countries without MICS data, we applied the regional estimates from MICS data, if available, or the third dose of diphtheria toxoid, tetanus toxoid, and pertussis vaccine (DTP3) coverage in the absence of such data.[9] For countries in Latin America where no other data were available, and for developed countries, 100% access to care was assumed.

Children with HIV infection have a substantially higher risk of invasive pneumococcal disease, including meningitis, than those not infected.[10] We adjusted the country-specific pneumococcal meningitis incidence rates for the difference in HIV-infection rate when applying meningitis data to another country.

Non-pneumonia, non-meningitis disease

Estimates of burden of non-pneumonia, non-meningitis disease were based on meningitis incidence and case-fatality rate extrapolations. Few data were available on the incidence of pneumococcal non-pneumonia, non-meningitis disease but many studies report the relative proportion of meningitis and non-pneumonia, non-meningitis pneumococcal cases. We established the ratio of non-pneumonia, non-meningitis to meningitis cases from previous studies, separately for very high and high, and for medium and low child mortality settings, and combined them through a random-effects meta-analysis. We multiplied the country-specific pneumococcal meningitis case estimates by the summary ratio of non-pneumonia, non-meningitis to meningitis cases for the relevant mortality strata to estimate non-pneumonia, non-meningitis cases. Pneumococcal non-pneumonia, non-meningitis cases, derived from the literature review, were classed as severe (ie, admitted to hospital) and non-severe (ie, outpatient bacteraemia). The latter cases were assumed to have a case-fatality rate of 0. Deaths caused by non-pneumonia, non-meningitis disease were estimated by multiplying the country-specific severe cases by a country-specific case-fatality rate, the latter derived by estimating a mortality strata-specific ratio of case-fatality rate for pneumococcal non-pneumonia, non-meningitis disease and for meningitis from the published literature, and applying that to the country-specific pneumococcal meningitis case-fatality rates.

Pneumonia

To estimate the number of pneumococcal pneumonia cases, we applied to estimated all-cause pneumonia cases in children younger than 5 years[11] the proportion attributable to *S pneumoniae*. We adjusted for higher pneumococcal incidence rates in HIV-positive children and reductions in pneumonia cases from the use of vaccine against *Haemophilus influenzae* type b in 2000. The number of pneumococcal pneumonia deaths was

similarly estimated by applying the proportion of all-cause pneumonia deaths attributable to *S pneumoniae* to country-specific estimates of pneumonia deaths in children aged 1–59 months.[12] To determine the proportions of pneumonia cases or deaths attributable to *S pneumoniae*, we relied on four efficacy trials of pneumococcal conjugate vaccine. For each trial, the efficacy of the vaccine against a relevant definition of pneumonia was adjusted to account for vaccine serotype coverage and efficacy against pneumococcal pneumonia. Results of all trials were combined in a random-effects meta-analysis. We used the conjugate vaccine efficacy against WHO-defined clinical pneumonia as a measure of the proportion of pneumonia cases attributable to *S pneumoniae*. Efficacy against WHO-defined chest-radiography-positive pneumonia was used as a measure for the proportion of pneumonia deaths attributable to *S pneumoniae*. This approach assumes that the proportion of radiographic pneumonia cases caused by *S pneumoniae* was similar to the proportion of pneumonia deaths caused by *S pneumoniae* (webappendix pp 4,5). The case-fatality rate for pneumococcal pneumonia is inferred by combination of the independent estimates of deaths and cases.

WHO estimates of all-cause pneumonia deaths do not include those in HIV-positive children. We determined pneumococcal deaths in HIV-positive children by applying the derived pneumococcal pneumonia case-fatality rate in HIV-negative children to the cases estimated to have occurred in HIV-positive children. Pneumococcal deaths in HIV-positive children from the pneumonia, meningitis, and non-pneumonia, non-meningitis models are reported separately.

Uncertainty ranges

We report results of pneumococcal disease burden with uncertainty ranges (UR), grouping countries by WHO regions. Uncertainty ranges for meningitis and non-pneumonia, non-meningitis disease indicate the uncertainty associated with choice of the model approach, inclusion of data, and statistical uncertainty (webappendix pp 6,7). We did a jackknife analysis in which the base model is repeatedly rerun, removing one study at a time from the dataset. We report uncertainty of the country-specific estimates according to the algorithm shown in the webappendix p 14. For the pneumonia model, the analysis, removing one conjugate-vaccine trial at a time, provides the uncertainty range.

Reporting

Global and regional results are the sum of country results. Global and regional totals 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; differences in the aggregated results from the sum of country results are thus due to rounding.

Role of the funding source

Results

The comprehensive literature review[4] yielded 156 studies with data for the meningitis or the non-pneumonia, non-meningitis disease models after application of the inclusion, exclusion, and quality criteria (webappendix pp 30–37). All regions, except southeast Asia, had at least some data for pneumococcal meningitis incidence. All regions, except eastern Mediterranean, had data for pneumococcal meningitis case-fatality ratio (table 1). Overall, 15% of countries had pneumococcal meningitis incidence data. Europe had the highest proportion (23%) of countries with pneumococcal meningitis incidence data, whereas southeast Asia and eastern Mediterranean had the lowest proportions (0% and 5%, respectively).

Four randomised trials tested efficacy of pneumococcal conjugate vaccines against either clinical pneumonia or radiography-confirmed pneumonia.[13–17] They all used a WHO standard definition of chest-radiography-confirmed pneumonia,[18] and included both inpatients and outpatients. One trial with pneumonia efficacy data did not meet meta-analysis inclusion criteria because it used community allocation and included only inpatient pneumonia cases (O'Brien K, Johns Hopkins Bloomberg School of Public Health, MD, USA, personal communication). Figure 1 shows the efficacy of pneumococcal conjugate vaccines against clinical and chest-radiography-confirmed pneumonia, and the meta-analysis estimate of the proportion of pneumococcal pneumonia from the adjusted trial endpoints (webappendix pp 4,5 and 11,12). Each trial result is adjusted for three factors: proportion of pneumococcal disease caused by vaccine serotypes (based on serotypes causing invasive disease in the trial population); vaccine efficacy against vaccine-serotype

	AFR	AMR	EMR	EUR	SEAR	WPR	Total
Meningitis incidence	7 (5)	13 (6)	1 (1)	20 (12)	0 (0)	10 (6)	51 (30)
Meningitis CFR	4 (3)	11 (7)	0 (0)	4 (3)	1 (1)	3 (3)	23 (17)
NPNM disease distribution	4 (3)	15 (9)	0 (0)	12 (7)	3 (2)	4 (1)	38 (22)
NPNM disease and meningitis CFR	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	2 (2)

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 *Streptococcus pneumoniae* disease burden data that populated the meningitis and non-pneumonia, non-meningitis disease models*, by WHO region**
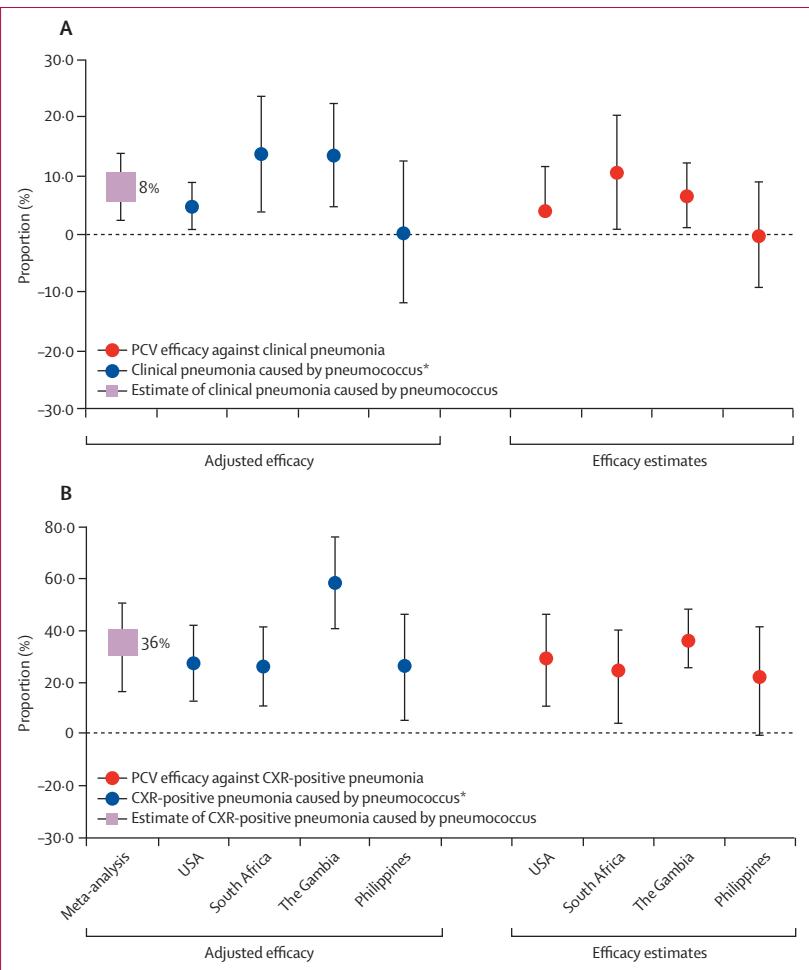
Figure 1: Efficacy of pneumococcal conjugate vaccines
(A) Against clinical pneumonia. (B) Against chest-radiography-positive pneumonia. Error bars indicate 95% CI on the efficacy estimates and the adjusted efficacy estimates. PCV=pneumococcal conjugate vaccine. CXR=chest radiography. *Efficacy adjusted for serotype distribution, efficacy against vaccine type IPD (a proxy for efficacy against vaccine type pneumococcal pneumonia), and Hib vaccine use.

pneumococcal disease; and the concurrent use of vaccine against *H influenzae* type b (figure 1). The unadjusted estimates of efficacy of pneumococcal conjugate vaccine from disparate geographic and epidemiological settings did not differ substantially, although after adjustment a difference between the Gambian[16] and the other trials[14,15,17] was seen. In a sensitivity analysis (webappendix p 12), the estimate of the proportion of deaths caused by *S pneumoniae* declined from 35·8% (16·0–50·9%) to 26·2% (19·0–32·8%) when the Gambian trial was excluded from the radiographic pneumonia outcome, whereas exclusion of any of the other trials had little effect.

In 2000, an estimated 826 000 pneumococcal deaths occurred in children aged 1–59 months, of whom 91 300 were HIV-positive (table 2). Country-specific figures are provided on the WHO website. Africa had both the highest rate of pneumococcal mortality and the largest

number of total deaths from pneumococcal disease because of both high incidence rate and the highest overall case-fatality ratio.

Figure 2 shows pneumococcal mortality rate (HIV-negative only) by country. The highest mortality rates and case-fatality ratios (data not shown) were in sub-Saharan Africa and south Asia. Ten countries, all in Africa and Asia, account for 61% (43–79%) of all pneumococcal deaths (pneumococcal deaths in HIV-negative children only). These ten countries include those with high mortality rates but small populations and those with moderate mortality rates but large populations (figure 3). Of the pneumococcal deaths (HIV-positive and HIV-negative), 90% were caused by pneumonia, 7% by meningitis, and 3% by serious non-pneumococcal, non-meningitis clinical syndromes.

We estimated that the total number of pneumococcal cases (irrespective of HIV status) was 14·5 million (table 2); this estimate includes pneumococcal clinical pneumonia (not just severe pneumonia cases) and bacteraemia cases treated as outpatients, but excludes upper-respiratory disease such as otitis media and sinusitis. The annual pneumococcal disease incidence varied greatly by country, from 188 (131–284) to 6387 (4937–7909) per 100 000 children younger than 5 years. Africa had the highest incidence rate, but the greatest number of cases was in southeast Asia because of the larger population.

The ten countries with the highest numbers and proportions of pneumococcal cases were all in Asia and Africa; they account for 66% (44–88%) of pneumococcal cases worldwide (India 27%, China 12%, Nigeria 5%, Pakistan 5%, Bangladesh 4%, Indonesia 3%, Ethiopia 3%, Congo 3%, Kenya 2%, and the Philippines 2%). Of the 14·5 million pneumococcal cases, 95·6% were cases of pneumonia, 3·7% non-pneumonia, non-meningitis invasive pneumococcal syndromes, and 0·7% meningitis.

The global incidence of pneumococcal meningitis in children, irrespective of HIV status, was 17 cases per 100 000, with an estimated 103 000 pneumococcal meningitis cases in 2000. The incidence of meningitis was lowest in Europe and highest in Africa (table 2). Whichever region was assessed, the case-fatality ratio for pneumococcal meningitis was high. The global pneumococcal meningitis case-fatality ratio was 59%, ranging from 29% in the western Pacific to 73% in Africa.

The global incidence of pneumococcal pneumonia was 13·8 million cases in children younger than 5 years in 2000. This total includes severe and non-severe cases, accounting for 8·6% of all clinical pneumonia cases (160 million) in children younger than 5 years in 2000.[9] Of these cases, southeast Asia had the highest number, whereas Africa had the highest incidence (table 2). Pneumococcal pneumonia deaths in HIV-negative children account for 36% (27–40%) of the estimated 1·8 million HIV-negative all-cause pneumonia deaths in 2000. The greatest number of deaths and highest

	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‡	2331 (1785–2904)	3627 (2708–4518)	920 (711–1154)	2358 (1826–2932)	504 (395–632)	2991 (2329–3717)	1842 (1401–2307)
Cases	14 500 000 (11 100 000–18 000 000)	4 060 000 (3 030 000–5 060 000)	713 000 (551 000–95 000)	1 510 000 (1 170 000–1 880 000)	260 000 (204 000–326 000)	5 480 000 (4 270 000–6 810 000)	2 430 000 (1 850 000–3 040 000)
Death rate‡	133 (94–149)	399 (275–441)	43 (30–51)	156 (113–173)	29 (22–34)	102 (75–113)	33 (22–43)
Total deaths	826 000 (582 000–926 000)	447 000 (308 000–494 000)	33 100 (23 600–39 500)	100 100 (72 400–110 700)	15 100 (11 300–17 500)	187 000 (13 000–207 000)	43 700 (29 100–57 100)
Total deaths in HIV-positive	91 300 (63 100–101 500)	88 300 (60 900–98 100)	500 (400–600)	800 (600–900)	100 (100–100)	1400 (1100–1600)	200 (100–200)
Total deaths in HIV-negative	735 000 (519 000–825 000)	359 000 (247 000–396 000)	32 600 (23 200–38 900)	99 300 (71 800–109 800)	15 000 (11 200–17 300)	186 000 (137 000–206 000)	43 600 (29 000–56 900)
Pneumonia							
Incidence rate‡	2228 (1733–2772)	3397 (2643–4227)	836 (651–1040)	2264 (1762–2817)	462 (359–574)	2911 (2265–3622)	1775 (1381–2208)
Cases	13 800 000 (10 800 000–17 200 000)	3 810 000 (2 960 000–4 740 000)	648 000 (505 000–807 000)	1 450 000 (1 130 000–1 810 000)	238 00 (185 000–296 000)	5 330 000 (4 150 000–6 640 000)	2 340 000 (1 820 000–2 910 000)
CFR	5% (4–9%)	11% (7–18%)	4% (3–6%)	6% (4–11%)	5% (4–9%)	3% (2–5%)	2% (1–3%)
Death rate‡	119 (87–130)	362 (265–394)	31 (23–34)	144 (105–156)	25 (18–28)	92 (68–100)	28 (20–30)
Deaths	741 000 (542 000–805 000)	406 000 (297 000–441 000)	24 300 (17 800–26 000)	92 100 (67 500–100 200)	13 000 (9500–14 200)	169 000 (124 000–184 000)	36 500 (26 800–39 700)
Deaths in HIV-positive	82 700 (60 600–89 900)	80 000 (58 600–87 000)	400 (300–500)	700 (500–800)	<100 (NA)	1300 (1000–1400)	200 (100–200)
Deaths in HIV-negative	658 000 (482 000–716 000)	326 000 (239 000–354 000)	23 900 (17 500–26 000)	91 400 (66 900–99 400)	12 900 (9500–14 100)	168 000 (123 000–182 000)	36 400 (26 600–39 600)
Meningitis							
Incidence rate‡	17 (8–21)	38 (11–48)	12 (9–17)	15 (10–18)	6 (5–9)	13 (11–16)	10 (3–14)
Cases	103 000 (51 500–131 000)	43 100 (11 900–54 300)	9500 (6800–13 000)	9700 (6600–11 700)	3300 (2800–4500)	24 200 (19 500–28 500)	13 100 (3900–19 000)
CFR	59% (27–80%)	73% (18–94%)	48% (31–70%)	57% (35–74%)	38% (32–58%)	57% (44–71%)	29% (10–68%)
Death rate‡	10 (4–13)	28 (7–36)	6 (4–9)	9 (5–11)	3 (2–4)	7 (6–9)	3 (1–7)
Deaths	60 500 (27 300–82 200)	31 700 (7900–40 500)	4500 (2900–6700)	5500 (3300–7100)	1300 (1100–1900)	13 700 (10 700–17 100)	3700 (1300–8900)
Deaths in HIV-positive	6500 (1900–8700)	6300 (1800–8300)	<100 (NA)	<100 (NA)	<100 (NA)	<100 (NA)	<100 (NA)
Deaths in HIV-negative	53 900 (25 400–73 500)	25 400 (6200–32 100)	4473 (2900–6600)	5500 (3300–7000)	1200 (1100–1900)	13 600 (10 700–17 000)	3700 (1300–8900)
NPNM							
Incidence rate‡	87 (44–111)	192 (54–243)	71 (51–97)	79 (54–96)	36 (31–49)	67 (53–79)	58 (17–84)
Severe	11 (5–14)	15 (5–20)	15 (11–21)	10 (7–12)	7 (6–9)	6 (5–8)	12 (3–18)
Non-severe	76 (38–97)	177 (49–222)	56 (40–77)	69 (47–84)	30 (25–40)	61 (49–71)	45 (14–66)
Cases (severe/ non-severe)	538 000 (271 000–690 000)	215 000 (60 200–272 000)	55 400 (39 800–75 400)	50 500 (34 500–61 600)	18 600 (15 800–25 300)	122 000 (97 800–145 000)	76 100 (22 400–111 000)
Severe	65 200 (34 000–88 100)	16 900 (5300–22 400)	11 700 (8600–15 900)	6100 (4400–7700)	3400 (2900–4700)	11 100 (8400–13 800)	16 100 (4500–23 500)
Non-severe	473 000 (237 000–601 000)	198 000 (54 900–249 000)	43 700 (31 300–59 500)	44 400 (30 200–54 000)	15 200 (13 000–20 500)	111 000 (89 500–131 000)	60 000 (17 900–87 200)
CFR (severe only)§	45% (21–62%)	58% (14–74%)	37% (24–55%)	44% (27–57%)	29% (25–45%)	44% (34–56%)	22% (8–53%)
Death rate‡	4 (2–6)	8 (2–11)	6 (4–8)	4 (2–5)	2 (1–3)	3 (2–3)	3 (1–6)
Deaths	25 200 (12 300–38 800)	9500 (2600–12 700)	4300 (2800–6300)	2500 (1600–3400)	800 (700–1400)	4700 (3500–6400)	3500 (1100–8500)
Deaths in HIV-positive	2000 (700–2900)	1900 (600–2800)	<100 (NA)	<100 (NA)	<100 (NA)	<100 (NA)	<100 (NA)
Deaths in HIV-negative	23 200 (11 700–35 900)	7600 (2000–9900)	4200 (2800–6300)	2500 (1600–3400)	800 (700–1400)	4700 (3500–6400)	3500 (1100–8500)

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 19. †Data from reference 7. ‡Per 100 000. §Data from the model that we are reporting.

Table 2: Pneumococcal cases and deaths, with uncertainty estimates, by syndrome and WHO region
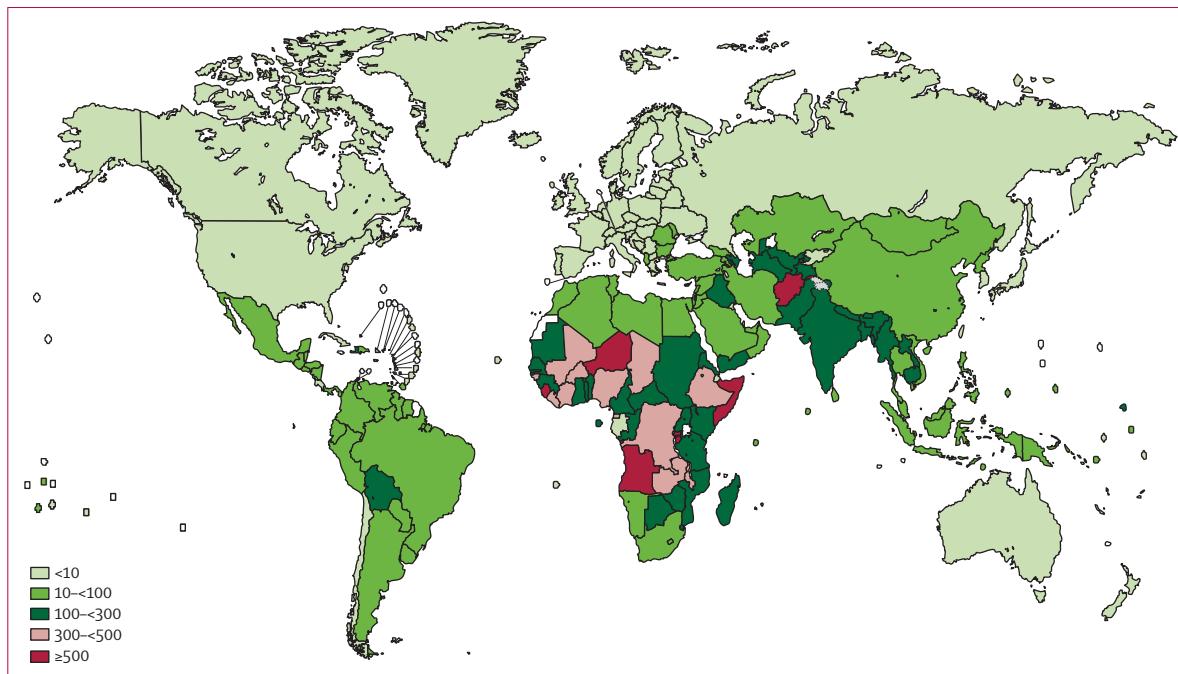
Figure 2: Pneumococcal mortality rate
Pneumococcal deaths in children aged 1–59 months per 100 000 children younger than 5 years (HIV-negative pneumococcal deaths only). The boundaries shown and the designations used on this map do not imply the expression of any opinion by WHO concerning the legal status 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.
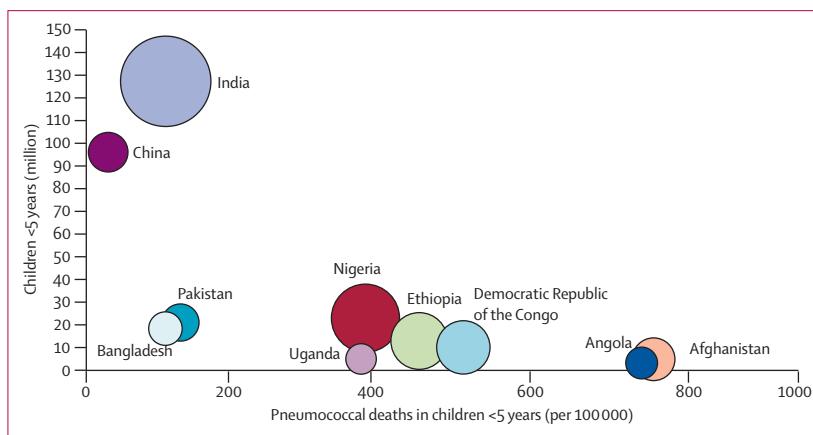
Figure 3: Ten countries with the greatest number of pneumococcal deaths in children aged 1–59 months*
Bubble size indicates the number of pneumococcal deaths. *Country (number of deaths): India (142 000), Nigeria (86 000), Ethiopia (57 000), Democratic Republic of the Congo (51 000), Afghanistan (31 000), China (30 000), Pakistan (27 000), Bangladesh (21 000), Angola (20 000), and Uganda (19 000).

pneumococcal meningitis cases varied from –5·7% to 5·9%. Regionally, the variation was more pronounced, ranging from 18% (in southeast Asia) to –19% (in America). For the ten countries with the greatest number of pneumococcal meningitis cases, the greatest estimate variability changes from the jackknife analysis were in Mexico and Brazil (reduction of 61% and 39%, respectively) and in India, Nigeria, Pakistan, Bangladesh, Ethiopia, and Congo, where the biggest changes in case estimates were increases of 17–20%.

The plausibility of the estimates was assessed for cases in Bangladesh and for deaths in The Gambia. In Bangladesh, the model predicts a pneumococcal disease incidence of 3351 cases per 100 000 children younger than 5 years. A population-based, active-surveillance, active-case detection study measured an invasive pneumococcal disease rate of 447 cases per 100 000 children younger than 5 years.[20] We used the trial in The Gambia[16] to establish an adjustment factor for lack of blood-culture sensitivity to detect *S pneumoniae* (ie, the conjugate vaccine prevented 13 cases per 1000 child-years with a radiographic pneumonia definition compared with 1·9 cases per 1000 child-years for culture-confirmed invasive pneumococcal disease, for an adjustment factor of 6·84). Use of this factor gave an estimated incidence of pneumococcal disease in Bangladesh of 3058 cases per 100 000 children (ie, 447 cases per 100 000×6·84), which is within 10% of the incidence rate estimated by our model.

pneumococcal pneumonia mortality rate were in Africa. The inferred case-fatality ratio for pneumococcal clinical pneumonia ranged from 2% in western Pacific to 11% in Africa (table 2).

Globally, cases of invasive pneumococcal non-pneu-monia, non-meningitis disease were 538 000, of which only 65 000 were categorised as severe (table 2).

We did a jackknife analysis to determine the sensitivity of the results to specific studies included in the analysis dataset (webappendix pp 5,6). The global estimate of

We also compared pneumococcal mortality results of our model for The Gambia to those established by a randomised, controlled conjugate-vaccine trial in 2000–04.[16] The trial showed a 16% reduction in all-cause mortality (95% CI 3% to 29%) in children aged 3–29 months receiving a nine-valent conjugate vaccine.[16] It also reported a 50% reduction in culture-confirmed all-serotype invasive pneumococcal disease (implying 32% of deaths in children aged 3–29 months in the control group were estimated to be caused by *S pneumoniae*). By disaggregating our estimated pneumococcal and all-cause deaths in The Gambia in children aged 3–29 months, the model predicted that less than 32% of deaths were caused by *S pneumoniae*; estimates fell within the confidence limits of the efficacy trial (data not shown). This observation suggests that our model might underestimate the contribution of pneumococcal disease in high-mortality areas, such as The Gambia, because the model is limited by all-cause pneumonia mortality data. The generalisation of mortality patterns in the trial population to the entire population of The Gambia might also affect this comparison.

Discussion

735 000 pneumococcal deaths (519 000–825 000) in HIV-negative children account for 11% (8–12%) of 6·6 million total deaths in children aged 1–59 months[19,21] and for 7% (5–8%) of 10·6 million deaths in children younger than 5 years including neonatal deaths.[19] Although these numbers represent the most rigorous estimate of child deaths caused by *S pneumoniae*, they are probably an underestimate. Surveillance in high-mortality developing countries usually under-detects bacterial meningitis and sepsis incidence owing to the low sensitivity of diagnostic tests and limited access to care. Pneumococcal estimates are highly sensitive to the all-cause pneumonia death estimate to which the pneumococcal proportion is applied. Our model assumed that 1·8 million pneumonia deaths occurred in children aged 1–59 months in 2000. Other WHO estimates in 2000 range from 1·9 to 2·0 million.[22,23] These estimates do not include neonatal pneumococcal deaths. An estimated 1 million neonatal deaths are caused by pneumonia, sepsis, and meningitis.[21,24] *S pneumoniae* is an important cause of serious infections in the neonatal age group.[25]

Other efforts have been made to estimate global or regional pneumococcal disease burden in young children.[2,3,26,27] The pneumococcal disease burden project of the Sabin Vaccine Institute and the Pan American Health Organization for Latin America and the Caribbean[27] calculated 18 000 pneumococcal deaths in children younger than 5 years, whereas we estimated 33 000 (23 000–39 000) for the same region. The Sabin Vaccine Institute and the Pan American Health Organization found 327 000 cases of pneumonia and 3900 of meningitis, whereas we estimated 595 000 (463 000–741 000) cases of pneumonia and

8400 (6000–11 500) of meningitis. These differences probably result from different literature review and modelling strategies; for example, the model developed by the Sabin Vaccine Institute and the Pan American Health Organization did not adjust for HIV prevalence or access to care, therefore lowering incidence and fatality rates.

Interpretation of estimates is especially challenging for large countries such as China, Indonesia, India, and Nigeria because pneumonia incidence, access to care, and childhood mortality vary substantially within the country. Pneumococcal disease risk will simultaneously be overestimated in some subpopulations and under-estimated in others. Disaggregation to state and provincial levels was possible only for India. Aggregated pneumococcal case and death estimates for the states both were within 0·2% of the country-level estimates (data not shown).

Some limitations of disease burden estimates are inherent to the unique epidemiological profile and reports on pneumococcal disease. Pneumococcal meningitis estimates are based on incidence reports from surveillance studies in 30 countries and case-fatality rates from 20 countries. Surveillance studies underestimate disease because of failure to obtain cultures, specimen transport and culturing limitations, and previous antibiotic treatment.[28,29] Even with the best possible surveillance and laboratory methods, surveillance alone cannot estimate the total pneumococcal disease burden because most cases of pneumococcal pneumonia are not bacteraemic and will not be identified by cultures of sterile site body fluids. Clinical trials have consistently shown that pneumococcal conjugate vaccines prevent more pneumonia cases than those detected by blood cultures or lung aspirates. Until new diagnostic methods become available, models using the vaccine probe approach are the most accurate method of estimating cause-specific pneumonia disease burden.

Outside the USA, Canada, and Australia, few studies systematically obtained blood cultures from febrile infants and children to identify pneumococcal bacteraemia. The threshold for obtaining a blood culture determines the number of cases identified, so most studies underestimate the burden of non-pneumonia, non-meningitis diseases. Where systematic blood culture of febrile infants has been implemented, a substantial burden of pneumococcal disease is seen—including severe disease or death even in children initially managed as outpatients.[30]

Our pneumonia estimates have different limitations. Unlike *H influenzae* type b, all pneumococcal conjugate vaccine trials on pneumonia outcome used the WHO radiology reading method,[18] so trial data from North America, Africa, and Asia could be compared. Nevertheless, because only four trials have been done, only one meta-analysis estimate of the proportion of

pneumonia caused by *S pneumoniae* was applied globally rather than regionally.

Our approach to measure disease burden allows the assessment of the effect that new studies or surveillance could have on disease burden estimates. By calculating the uncertainty range, we have tried to account for the potential variability in key assumptions balanced against the usefulness of the estimates. We acknowledge that not all possible uncertainties have been accounted for and that ranges might be larger than we have calculated. The syndrome accounting for the greatest number of pneumococcal deaths and cases is pneumonia. Pneumonia estimates strongly depend on estimates of all-cause pneumonia cases and deaths and on the proportion attributable to *S pneumoniae*. Vital registration to ascribe cause of death to pneumonia is unlikely to become available in most developing countries soon, so the current approach for determining pneumonia mortality[12,19,22,23,31–33] is likely to be used for the foreseeable future. Estimates of all-cause pneumonia cases[11] have been based on a few studies that used active-case ascertainment methods (periodic home visits) and case definitions that sometimes differed from those in pneumococcal conjugate vaccine trials. Chest radiography was not done routinely and interpretation was not standardised. Furthermore, the all-cause pneumonia case estimates do not explicitly include or exclude neonates. Because neither the pneumonia surveillance studies in that model nor the pneumococcal meningitis incidence studies used here systematically included neonates, our pneumococcal case estimates are likely to underestimate neonatal pneumococcal cases.

Disaggregation of all-cause pneumonia case and death estimates into pneumococcal-specific episodes is based on trials that measured the effect of pneumococcal conjugate vaccines on clinical and radiographic cases, respectively. The assumption that the proportion of radiographic pneumonia cases caused by *S pneumoniae* is similar to that of pneumonia deaths caused by *S pneumoniae* is a potential source of error, but generally accepted as valid by the Independent Expert Review Panel. Without sensitive and specific diagnostic assays, the vaccine probe approach will continue to be the most accurate method for allocating the aetiological fractions. Uncertainty bounds for the pneumococcal pneumonia death estimates indicate the sensitivity of the analysis to the results in the pneumococcal conjugate vaccine trials. One additional trial with a pneumonia outcome is under way, but its findings will be difficult to incorporate into the model because the vaccine used might also have an effect on non-typeable *H influenzae*, a known cause of pneumonia. Therefore, substantial changes to the pneumococcal pneumonia model inputs are unlikely in the foreseeable future. Appropriately designed studies of the effect of pneumococcal conjugate vaccines in developing countries might improve our understanding of pneumococcal disease burden. In Asia, decisions about prevention approaches of pneumococcal disease will need to be made on the basis of limited regional data, extrapolation from other regions, or from pneumonia vaccine impact studies.

Pneumococcal meningitis is very severe but much less common than pneumonia. We identified only eight studies of pneumococcal meningitis incidence from three regions with the most pneumococcal deaths. Because of the consistency of pneumococcal meningitis disease incidence and case-fatality ratio from studies in Africa, further assessments are unlikely to change estimates for that region substantially. In Asia, pneumococcal meningitis estimates for medium-mortality and high-mortality countries are based on an incidence study from Mongolia,[34] whereas case-fatality ratio is based (depending on the country and its mortality rate in children younger than 5 years) on studies from Bangladesh (Saha SK, ICDDR,B personal communication), Burkina Faso,[35,36] Cameroon,[37] and Kenya.[30] Additional data are unlikely to change greatly pneumococcal mortality estimates globally or for most regions because of the small contribution of meningitis to the overall pneumococcal mortality. Also, data from countries in southeast Asia for all-cause meningitis incidence and the proportion caused by *S pneumoniae* can be used to infer pneumococcal meningitis incidence, giving rates similar to those used for our model (data not shown). National decision makers might need more locally representative data, but they require time and resources; a wait for additional data is unlikely to change disease burden estimates substantially but could delay decision making. Thus, efforts and resources might be invested in decision making and implementation of prevention strategies. Where additional disease burden data will be obtained, efforts to incorporate non-culture-based diagnostic tests should be encouraged because of the increased detection with their use.[28,29]

Some countries with many children younger than 5 years have little or no information about pneumococcal disease burden. Of the ten countries with the greatest number of pneumococcal deaths, only Bangladesh had high-quality data for the models of meningitis or non-pneumonia, non-meningitis disease, whereas the other nine derived their estimates from data of countries within or outside their region. We did not systematically search publications in Chinese, but other studies have not identified reports that would have met our inclusion criteria.

Prevention of pneumococcal disease and death is achievable only if efforts to deliver and implement prevention in regions with the greatest burden of disease are successful. By August, 2008, 24 high-income and two middle-income countries[38] had initiated routine pneumococcal conjugate vaccination, but none in Africa or Asia, which have the highest numbers of pneumococcal deaths and cases. These 26 countries accounted for less than 0·2% of global childhood pneumococcal deaths in

2000, and the risk of childhood pneumococcal death was much lower than in countries not yet using the vaccine (median 1·5 [UR 1–2] deaths per 100 000 *vs* 58 [44–68] deaths per 100 000). Through the GAVI Alliance, low-income countries can access existing and future pneumococcal vaccines with a small self-financed contribution (US$0·15 to $0·30 per dose) for the next 7 years. By February, 2009, 11 countries had received GAVI Alliance approval for support to vaccine introduction, eight in Africa and Asia. Rwanda is the first GAVI-eligible country to have introduced the vaccine in April, 2009. More than 30 GAVI-eligible countries have expressed interest in applying for pneumococcal vaccine support.

Improved outcomes for pneumonia are possible through implementation of existing WHO and UNICEF policies for community-based treatment. Meningitis mortality can be reduced by improvement of access to, and quality of, care in hospitals, and the use of more effective antibiotics. Penicillin and chloramphenicol are still commonly used despite widespread resistance. Both vaccination and improved treatment are urgently needed in Africa and Asia, which together account for 95% of all pneumococcal deaths. Our results indicate that large benefits would be achieved by focusing on countries with large populations and moderate incidence, and on selected countries with high incidence and mortality. Pneumococcal deaths in HIV-negative children account for 11% of all mortality in children younger than 5 years. Prevention of pneumococcal disease will greatly accelerate progress towards Millennium Development Goal 4,[39,40] which aims to reduce mortality in children younger than 5 years by two-thirds between 1990 and 2015.

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