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Contents

Abbreviations

AFR	African Region (WHO)
AMR	Region of the Americas (WHO)
CSF	cerebrospinal fluid
ELISA	enzyme-link immunosorbent assay
EMR	Eastern Mediterranean Region (WHO)
EUR	European Region (WHO)
Hib	*Haemophilus influenzae* type b
PAHO	Pan American Health Organization
SAGE	Strategic Advisory Group of Experts
SEAR	South-East Asia Region (WHO)
V&B	Department of Vaccines and Biologicals (WHO)
WHO	World Health Organization
WPR	Western Pacific Region (WHO)

Executive summary

Most of the morbidity and mortality due to *Haemophilus influenzae* type b (Hib) worldwide occurs in children < 5 years of age. The role of Hib in meningitis can be more readily and reliably established than its role in infections in other sites. Thus, the incidence of Hib meningitis in children < 5 years of age has been used as a standard measure for comparing Hib disease burden between and among countries. This review summarizes the findings of Hib meningitis studies in all regions of the world (Annex 1) in the pre-vaccine era.

A comprehensive literature search, carried out with the assistance of the WHO regional offices, identified some 229 studies with information about Hib meningitis in children < 5 years of age conducted before the widespread introduction of Hib vaccine. Annex 2 of this document consists of tables that systematically summarize information from these 229 studies, by WHO region. Annex 3 lists the references for Annex 2, by WHO region.

The text of this document contains scientific analyses of data abstracted from the 229 studies. The entire data set includes nearly 30 000 cases of Hib meningitis in children < 5 years of age and more than 2100 deaths. Studies were identified from all WHO regions, with 43 (19%) from Africa (AFR), 44 (19%) from the Americas (AMR), 23 (10%) from the Eastern Mediterranean (EMR), 72 (31%) from Europe (EUR), 12 (5%) from South-East Asia (SEAR), and 35 (15%) from the Western Pacific (WPR). Sixty-two percent of the 229 studies were conducted in developing countries.

Hib meningitis incidence. There were 132 population-based studies with incidence data and 97 hospital-based studies. Eleven of the 132 population-based studies concerned special-risk groups in industrialized countries [Aboriginals (Australia), Alaskan Eskimos (USA), Apache Indians (USA), Keewatin Natives (Canada), and Navajo Indians (USA)]. For the special-risk groups, the mean annual incidence of Hib meningitis in children < 5 years of age was 418.1/100 000, with a range of 34.5 to 530. For the remaining 121 population-based studies, the mean annual incidence of Hib meningitis in children < 5 years of age was 22.8/100 000, with a median of 18.0, and a range 0.9 to 94.6.

Many factors can affect the quality of population-based studies of Hib meningitis, including patient access to and utilization of medical services, pre-treatment of patients with antibiotics, and quality of laboratory methods. Studies in this review provided sufficient data to examine several of these factors. Data from 3 566 patients showed that when children received pre-admission treatment with antibiotics, the frequency of a positive bacterial culture of cerebrospinal fluid was only 52%, compared with 74% when children had not received prior antibiotic treatment ($p<0.0001$).

Data from 13 studies conducted in the pre-vaccine era — most from developing countries — permitted assessment of the efficiency of antigen tests for Hib, which were able to detect an organism in 32% of cerebrospinal fluid specimens that were negative on bacterial culture.

Age distribution of Hib meningitis cases. Overall, 22.6% of < 5 year Hib meningitis cases were in children 1-5 months of age, 35.6% in children 6–11 months of age, and 23.8% in children 12-23 months of age. Several previous authors have reported a younger median age at onset of Hib meningitis when there is a high incidence of Hib meningitis in children < 5 years of age. This paper explores this topic in considerable detail, using age distributions, graphing of cumulative age distributions, and logistic and linear regression. The greater the proportion of Hib meningitis cases in children 0–11 months old, the higher the overall incidence of Hib meningitis in children < 5 years of age. The percentage of studies with $\geq$ 60% of cases in children 0–11 months of age was 100% in SEAR (n=5), 92% in EMR (n=13), 90% in AFR (n=19), 53% in WPR (n=19), 50% in AMR (n=24), and 8% in EUR (n=38).

Hib meningitis case-fatality rates. A total of 127 studies had information on case-fatality rates. The mean case-fatality rate for children with Hib meningitis was 13.8%, with a median of 10%, and a range of 0% to 65%. The mean case-fatality rate was 17.3% for developing countries, compared with 3.2% for industrialized countries. By region, mean case-fatality rates ranged from a low of 4.1% in EUR to a high of 27.6% in AFR.

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The authors thank Barbara Aronson, WHO Library, for guidance in conducting the literature searches; staff from the WHO regional offices and country offices for help in acquiring local medical literature; and the members of the WHO/V&B Steering Committee on Epidemiology and Field Research for their scientific oversight of this project. We are grateful to Jay Wenger for reviewing evolving versions of Annex 2 and for helping identify studies conducted therein; David Kleinbaum and John Boring for reviewing the logistic regression analysis; and Frances Porcher for editorial assistance. Helpful comments were received from Abdulaziz Adish, Alenka Kraigher, Marc LaForce, Takashi Nakano, Heikki Peltola, Mary Ramsay, Sriluck Simasathein, Claudia Stein, Timo Vesikari, Jay Wenger, Lara Wolfson, and Peter Wright on earlier versions of this review.

1. Introduction

Haemophilus influenzae type b (Hib) causes serious diseases manifested by meningitis, pneumonia, septicaemia, epiglottitis, cellulitis, septic arthritis, and osteomyelitis. The vast majority of Hib morbidity and mortality occurs in children < 5 years of age *(WHO/GPV 1998*).

Since June 1997, the World Health Organization (WHO) has recommended including Hib vaccine, as appropriate to national capacities and priorities, in routine infant immunization programmes *(SAGE 1997)*. Safe and effective conjugated vaccines against Hib are available. Their use has led to dramatic declines in the incidence of Hib disease in countries such as Finland *(Peltola et al. 1992)*, Gambia *(Adegbola et al. 1999)*, Israel *(Dagan et al. 1998*), the United Kingdom *(Slack et al. 1998)*, Uruguay *(Ruocco et al. 1999)*, and the United States of America *(Adams et al. 1993)*. One deterrent to the introduction of Hib vaccines has been the lack of local information in many countries on the burden due to Hib disease *(Lau 1999, Wenger et al. 2000)*. A second deterrent to Hib vaccine introduction has been the cost of the vaccine. For most countries, the price of a 3-dose series of Hib vaccine far exceeds the price of all other vaccines in the routine infant immunization schedule *(Wenger et al. 2000)*; however, prices have been dropping. In 2001, prices of vaccines purchased by countries in Latin America and the Caribbean through the Pan American Health Organization (PAHO) Revolving Fund for Vaccine Procurement were US$ 2.50 to US$ 2.56 per dose of single-antigen Hib vaccine, and US$ 3.50 per dose of pentavalent diphtheria–tetanus–pertussis–hepatitis B–Hib vaccine *(PAHO 2000)*. Based on data reported to WHO as of July 2000, some 50 countries had implemented routine Hib immunization for infants *(WHO/V&B 2000)* and as of May 2002 this number had risen to 89 countries *(WHO/V&B 2002*).

Since the mid-1990s, there has been recognition that further work was needed to assess the disease burden due to Hib. The Steering Committee on Epidemiology and Field Research of the WHO Department of Vaccines and Biologicals has carried out three types of activities aimed at addressing this issue: (a) development of a standard population-based protocol for assessing the local Hib disease burden in children < 5 years of age, (b) sponsorship of a limited number of large-scale studies using the WHO protocol, and (c) organization of a global review of studies on Hib meningitis with the assistance of the WHO regional offices.

In 1995, WHO released the "Generic protocol for the assessment of disease burden due to *Haemophilus* meningitis in children younger than five years of age" *(Levine et al. 1995)*. Meningitis was the deliberate focus, since the role of Hib in meningitis can generally be established far more readily and reliably than in infections in other sites, such as pneumonia and epiglottitis. By 2001, more than 3000 copies of the WHO protocol had been distributed worldwide.

During 1997–1999, large-scale population-based Hib meningitis surveillance studies were initiated with funding from WHO in six countries: Bulgaria, Dominican Republic, Guatemala, India, Poland, and the Russian Federation. Each of these studies was based on the WHO generic protocol *(Levine et al. 1995)* and a WHO manual of laboratory procedures *(Popovic et al. 1997)*. The Steering Committee on Epidemiology and Field Research provided scientific oversight for these studies, which included peer review of the original study protocols, critical assessment of progress reports, site visits where indicated, and laboratory proficiency testing.

As part of the WHO response to the need for more in-depth information on the incidence of Hib meningitis worldwide, a review of the global literature was begun in 1999 under the sponsorship of the Steering Committee on Epidemiology and Field Research. This has focused on obtaining publications listed in standard biomedical literature indexing databases, those in regional medical literature indexing databases, and (with the assistance of the WHO regional offices) reports not included in the indexing databases. These efforts add to those of others who have conducted regional or global literature reviews on Hib meningitis *(Sow and Denis 1979, Wright 1989, Funkhauser et al. 1991, Bijlmer 1991, Claesson 1993, Peltola 1997–2001, Lau 1999, Lolekha et al. 2000)*.

2. Methods

2.1 Literature search

Studies of "meningitis", "bacterial meningitis", "*Haemophilus* meningitis", and "Hib meningitis" were identified by conducting online literature searches using Ovid software (*http://www.ovid.com*). There were no restrictions on language of publication or date of publication. We searched the following databases:

- Medline, the United States National Library of Medicine bibliographic database, which covers over 3800 international biomedical journals from 1966 on;
- African Index Medicus (AIM) database, produced by the Association for Health Information and Libraries in Africa with the technical support of WHO;
- CAB Health database (*http:/www.cabi.com*), which indexes articles from over 3300 serial resources related to communicable diseases, community and public health, human nutrition, and tropical diseases;
- Index Medicus for the WHO Eastern Mediterranean Region (IMEMR), a database managed by the WHO Eastern Mediterranean Regional Office;
- Latin American and Caribbean Health Science Information (LILACS) database, which incorporates citations from over 6000 health science journals published since 1982 in countries of the region. LILACS is produced by BIREME, the Latin American and Caribbean Center on Health Sciences Information, which receives support from the WHO Regional Office for the Americas.

At the WHO Library in Geneva, two of the authors hand-searched the following medical journals: *Annals of Saudi Medicine* (from 1985); *Bahrain Medical Journal* (from 1985); *Emirates Medical Journal* (from 1980); *Indian Pediatrics* (from 1975); *Malawi Medical Journal* (from 1985); *Medical Journal of Malaysia* (from 1975); *Medical Journal of Zambia* (from 1975); *Papua New Guinea Medical Journal* (from 1975); *Philippines Journal of Pediatrics* (from 1975).

We reviewed progress reports on studies of Hib meningitis receiving financial support from the WHO Department of Vaccines and Biologicals.

Requests were made to national ministries of health through the WHO regional and country offices for data on Hib meningitis from local medical journals, newsletters, university theses, and unpublished reports.

In addition to studies identified through these sources, lists of references in published papers were also reviewed and used to identify other relevant publications.

The database was closed on 31 October 2001.

2.2 Inclusion criteria

Unless otherwise qualified, in this paper the term "case" is used to signify a Hib meningitis patient, and the term "rate" to signify the number of cases per 100 000 population of children in the specified age group. The term "case-fatality rate" (ratio) is used to signify the percentage of children with Hib meningitis who died from this condition. The convention in this paper is for a hyphen between numbers to mean "through" (for example, 0–11 months means 0 months through 11 months, and 1992–1994 means 1992 through 1994).

Study results were included in our database if data could be extracted for time periods when the country was not using Hib vaccine on a national or widespread basis and contained age-specific information on cases of Hib meningitis or, except as noted below, age-specific incidence data for children < 5 years of age (that is, 0–59 months of age), hereafter referred to as < 5 years. We substituted the rate for children < 6 years (0–71 months) of age where it was the only rate reported (Annex 2, studies number 46 and 134). We substituted the rate for children < 4 years (0–47 months) of age where it was the only rate reported (Annex 2, studies number 100 and 116).

We accepted each author's definition of meningitis and their methods for identifying specific bacterial etiologies. *Haemophilus* strains were rarely typed, but when they were, almost all were type b. Antigen detection tests, used in some studies, are specific for type b; thus we counted all *Haemophilus* strains identified in cerebrospinal fluid or blood as type b by this method.

2.3 Classification of studies

Studies were classified as having incidence data or not. Studies with incidence data were classified as having prospective population-based data, retrospective population-based data, or national (passive) surveillance data. Studies without incidence data were classified as prospective hospital-based studies and retrospective hospital-based studies. Because there were already a large number of population-based studies available for industrialized countries of the WHO Region of the Americas and the WHO European Region, we did not include studies without incidence data from industrialized countries in these two regions.

2.4 Classification of countries

Countries were grouped according to the six WHO regions: the African Region (AFR), the Region of the Americas (AMR), the Eastern Mediterranean Region (EMR), the European Region (EUR), the South-East Asia Region (SEAR), and the Western Pacific Region (WPR) (Annex 1). Countries were classified based on their United Nations development status as either industrialized or developing, with the latter category including countries with economies in transition, developing, or least developed *(WHO/V&B 2000)*. Certain groups in industrialized countries with a known special risk for Hib meningitis were examined separately, specifically Aboriginals (Australia), Alaskan Eskimos (USA), Apache Indians (USA), Keewatin Natives (Canada), and Navajo Indians (USA). Names of these special-risk groups are those reported by study authors.

2.5 Information abstracted

Some references contained information on more than one study. The following information was systematically abstracted for each study: the country where the study was conducted, the study site, the year the study began, the study duration, and the ages of persons included. For industrialized countries, we noted whether the populations involved were previously known to be at special risk for Hib disease.

For children < 5 years, information was collected on the total number of bacterial meningitis cases, the number and percentage of such cases for which an etiology was established, and the proportion of all < 5 year bacterial meningitis with established etiologies attributed to Hib. When available, we also noted the number of Hib meningitis cases in children 5–16 years of age. The number of < 5 year cases of meningitis caused by *Streptococcus pneumoniae* (also known as pneumococcus) was tallied and used to calculate both a ratio of such cases to < 5 year Hib meningitis cases and a rate for < 5 year pneumococcal meningitis. We excluded meningitis caused by *Mycobacterium tuberculosis.* We also excluded data for years in which epidemics of *Neisseria meningitidis* (also known as meningococcus) occurred.

The case-fatality rate for Hib meningitis was collected or calculated for < 5 year cases. When the < 5 year Hib case-fatality rate was not available, the rate for all children was used.

We tallied the numbers and the proportion of children who received antibiotics before specimens were collected for diagnosis. When the information was available, we recorded the frequencies with which bacteria were cultured from clinical specimens from children with and without a history of receipt of prior antibiotics.

Few details on specific laboratory methods were reported for most studies. We recorded whether chocolate agar or chocolate agar supplemented with X and V factors was specifically stated to have been used in the initial cultures of clinical specimens. We also recorded information on antigen tests that were used and the results.

As available, the number of bacterial meningitis cases with established etiology and the number of Hib meningitis cases were tallied for each of the following age groups: < 1 month (neonates), < 6 months (that is, 0–5 months), < 12 months (that is, 0–11 months), < 24 months (that is, 0–23 months), and 24–59 months of age. Subsequent analysis permitted age-specific estimates of the proportion of < 5 year meningitis of known causes that were attributable to Hib, as well as the percentage of < 5 year Hib meningitis cases.

Special emphasis was placed on < 5 year Hib meningitis rates. For 75 studies, we used the rate as given in the paper itself. For 17 studies, the < 5 year Hib meningitis rate was obtained from the duration of the study and age-specific information on groups within those < 5 years for rates, populations, and cases, or by using three of these four pieces of information to derive the other. This information was then combined, as necessary, to obtain an overall < 5 year Hib meningitis rate (Annex 2, studies number 4, 5, 50, 55, 60, 61, 65, 91, 111, 112, 134, 136, 144, 153, 169, 172, and 176). For 14 studies the < 5 year Hib meningitis rate, although not provided in the paper itself, could be readily calculated from the duration and given

numbers for < 5 year cases and denominators (Annex 2, studies number 3, 44, 48, 89, 92, 115, 116, 117, 118, 119, 125, 132, 200, and 213). For 11 studies, the < 5 year Hib meningitis rate was obtained from a < 5 year Hib invasive disease rate and the proportion of < 5 year invasive cases that were meningitis (Annex 2, studies number 53, 69, 127, 149, 159, 161, 167, 168, 197, 211, and 214). For eight studies, the < 5 year Hib meningitis rate was calculated from age-specific rates within children < 5 years by assuming equal-sized yearly cohorts (Annex 2, studies number 65, 89, 119, 125, 136, 138, 152, and 164). For four studies, the < 5 year Hib meningitis rate was obtained from the United Nations population estimate *(United Nations Population Division 2001)* for the < 5 year denominator (Annex 2, studies number 49, 138, and 207) or obtained from another relevant source (Annex 2, study number 51). For three studies, rates were recalculated from data given in the paper (Annex 2, studies number 88, 127, and 212).

For five studies (Annex 2, studies number 119, 125, 136, 152, and 164) the age distribution of cases was determined by assuming equal sized yearly cohorts. The assumption of equal numbers of children in each yearly cohort makes it possible to determine the value for any one of the following three variables (< 5 year rate, proportion of <5 year cases in an age range, age-specific rate for the age range) when values for the other two variables are known. For example, given a <5 year rate of 40/100 000 and information that 70% of < 5 cases are 0–11 months of age, then the rate of Hib meningitis among children 0–11 months of age would be 40 * 70/20 = 140/100 000 since it is assumed that 20% of the < 5 year population is 0–11 months of age. The terms in this formula may be rearranged to determine a missing value for any of the three variables.

2.6 Data analysis

Data were entered in EpiInfo 6.0 and Excel spreadsheet files and analysed in EpiInfo *(Dean et al. 1994)*. Logistic regression was conducted with the program of Dallal *(Dallal 1989)*. For normally distributed data ANOVA tests were used to evaluate the statistical significance. Mann-Whitney U tests were used for nonparametric results.

SPSS version 9.0 *(SPSS Inc., Chicago, USA)* was used to conduct nonparametric analyses and prepare selected figures comparing regional data. This produced a box-and-whiskers presentation to show median, quartiles, and extreme values *(Platonov 2000, Tukey 1977)*. The box represents the interquartile range that contains 50% of values. A line across the box indicates the median. The whiskers are lines that extend from the box to the highest and lowest values, excluding outliers. Outliers are values more than 1.5 box lengths from the upper edge (75% quartile) or lower edge (25% quartile) of the box. Outliers were included in calculating the median and quartiles, but omitted from the figures to simplify the presentation.

We used the K-means variant of cluster analysis *(Hartigan 1975)*. This procedure attempts to identify relatively homogeneous groups of studies based on values of selected variables and to calculate iteratively the cluster centres. Distances between studies are computed using simple Euclidean distance. Hierarchical cluster analysis using the standardizing transformation of variables, a variety of distance or similarity measures, and classification algorithms leads to the same basic conclusions concerning the cluster membership of studies.

Regional characteristics were established in a data set that excluded special-risk groups, as these represent only a very small and nonrepresentative fraction of the overall < 5 year populations in AMR and WPR.

Studies with fewer than 15 total < 5 year Hib meningitis cases or fewer than 15 values for particular variables were excluded in some analyses, and this is noted in the results. This helped assure that studies with very small sample sizes were not given equal weight with larger studies in calculating averages. Additionally, this helped assure that distributions of < 5 year cases by age did not include studies where only a few cases represented a large proportion of all < 5 year cases.

3. Results

3.1 Overall findings

Our literature search identified a total of 390 studies. We excluded 161 studies, however, for the following reasons: 55 because the age groups of interest could not be ascertained; 51 because either they were review papers without original data or they concerned types of studies not relevant to our analysis (nasal carriage studies, vaccine serosurveys, etc.); 27 described results published previously (and already included in the database); 26 were carried out after widespread introduction of Hib vaccine; and 2 presented Hib meningitis incidence rates that we were unable to reconcile. Thus 229 studies met the inclusion criteria for our database. Annex 2 is a line listing of selected information from the 229 studies. Annex 3 contains the Hib meningitis references for these studies, by WHO region.

Studies in Annex 2 are grouped by WHO region; within each region, studies with incidence data are presented first. Studies with incidence data for special-risk groups in industrialized countries in AMR and WPR are listed separately at the end of the incidence data for these regions. Of the 229 studies, 43 (19%) were from AFR, 44 (19%) were from AMR, 23 (10%) were from EMR, 72 (31%) were from EUR, 12 (5%) were from SEAR, and 35 (15%) were from WPR. Of the 229 studies, 143 (62%) were conducted in developing countries.

The data set of 229 studies includes nearly 30 000 < 5 year Hib meningitis cases and more than 2100 deaths in that group from this infection.

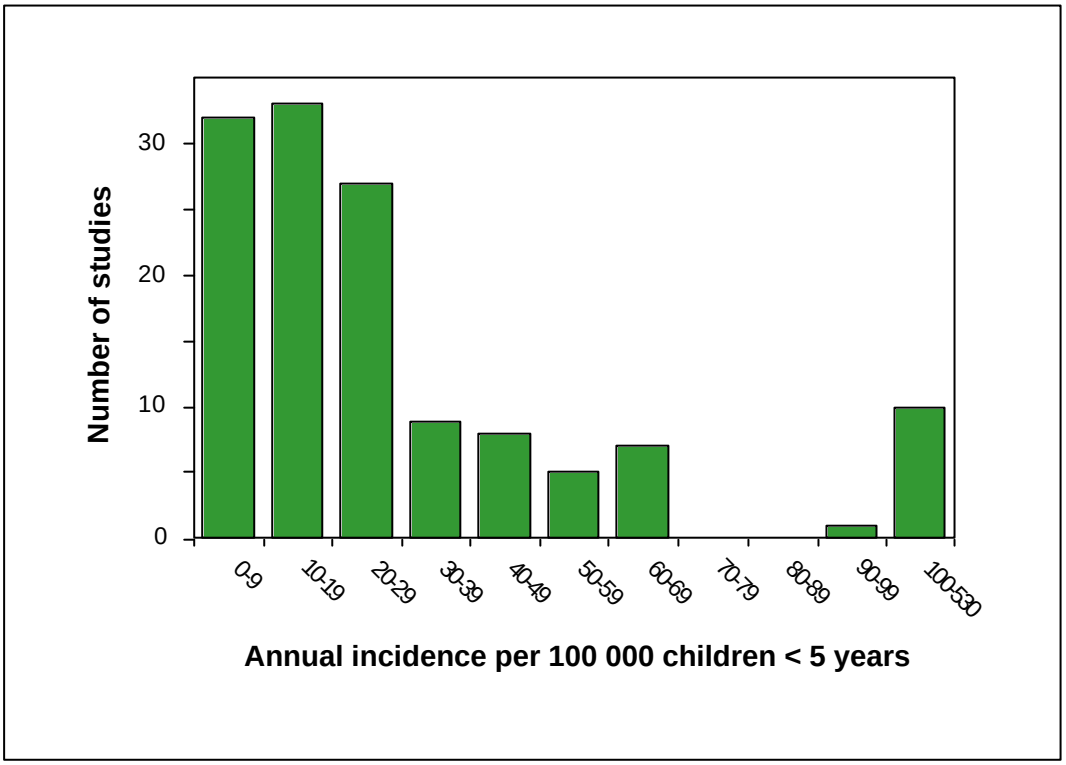
For the data set as a whole, there were 132 studies with incidence data (population-based studies) and 97 studies without incidence data (hospital-based studies). The median annual < 5 year Hib meningitis rate in 132 population-based studies in this data set with incidence data was 21 cases/100 000 population in that age group, with a mean of 44.1 and a range of 0.9 to 530. Figure 1 shows the distribution of studies by mean annual < 5 year Hib meningitis incidence rates. All rates above 100 occurred in special-risk groups; the mean annual < 5 year Hib meningitis incidence for special-risk groups was 418.1/100 000 with a range of 34.5 to 530. When the 11 studies of special-risk groups are excluded, the mean annual < 5 year Hib meningitis incidence for the remaining 121 studies was 22.8/100 000 with median of 18.0 and a range of 0.9 to 94.6.

For 74 studies in industrialized countries, the mean annual < 5 year Hib meningitis incidence was 23.9 cases/100 000, with a median of 22.0, and a range of 1.4 to 68.6. For 47 studies in developing countries, the mean annual < 5 year Hib meningitis incidence was 21.0, with a median of 15.2, and a range of 0.9 to 94.6. The < 5 year

Hib meningitis incidence was significantly higher ($p < 0.03$, Mann-Whitney) in industrialized countries than in developing countries, and this phenomenon remained after controlling for decade of study.

The < 5 year rates of Hib meningitis were closely comparable and not significantly different for 42 prospective studies (46.8) and 73 retrospective studies (49.2). Although the overall rate for the 17 surveillance studies was substantially lower (15.6), this observation is confounded by region, since 15 of the 17 surveillance studies came from EUR. Within EUR, < 5 year Hib meningitis rates were 14.5, 17.5, and 15.2 for prospective, retrospective, and surveillance studies, respectively.

Figure 1: Distribution of 132 studies by annual incidence of Hib meningitis per 100 000 children < 5 years of age

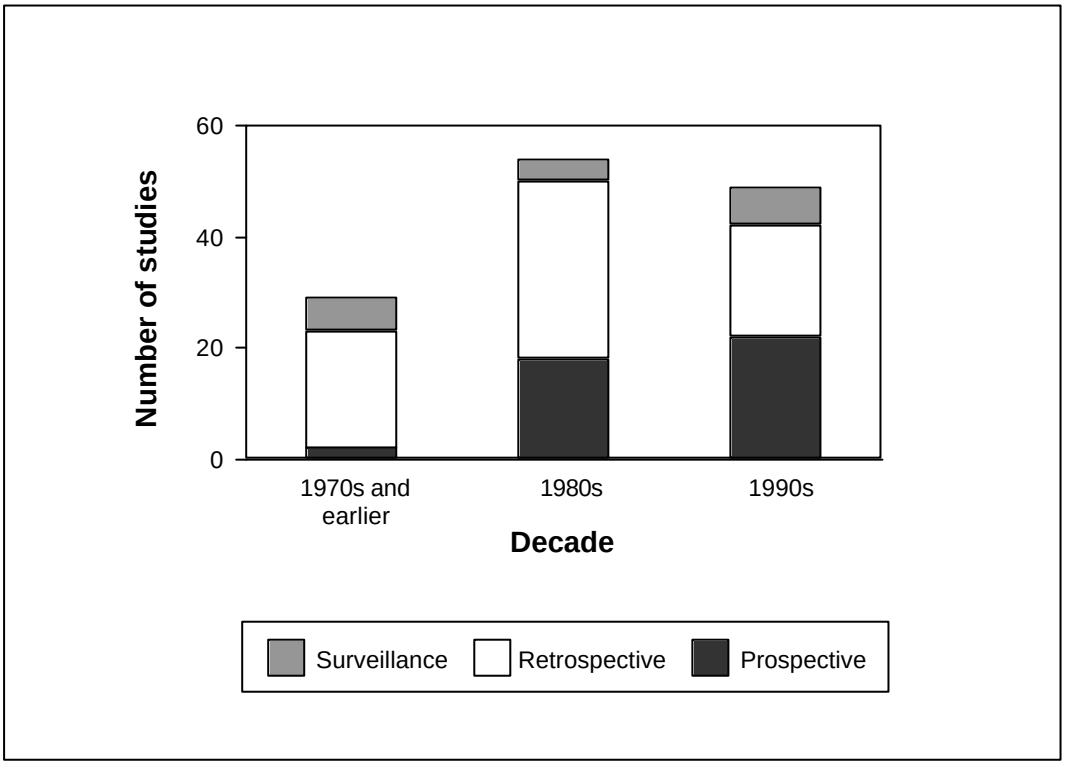


3.2 Time trends

Among the 229 studies, the number of studies beginning in each decade starting with the 1940s was 1, 3, 10, 43, 102, and 70, respectively. Among the 132 studies with Hib meningitis incidence data, the number of studies beginning in each decade starting with the 1940s was 1, 1, 5, 22, 54, and 49, respectively. The 11 incidence studies of special-risk groups were excluded, and for the remaining 121 incidence studies, mean annual incidence was calculated by decade. The mean annual incidence of < 5 year Hib meningitis in the 1990s was significantly lower than in the 1980s and earlier decades (data not shown). This decline is attributable to significant declines in the 1990s in EUR and AMR. Mean annual < 5 year Hib meningitis incidence rates by decade remained unchanged in AFR and WPR, but rose significantly in EMR ($p=0.05$). For SEAR, there was only one incidence study.

The mean duration of studies with < 5 year Hib meningitis incidence data was 4.8 years, with a range of 0.5 to 21.5 years, median of 3 years, and mode of 2 years. The mean duration declined significantly ($p<0.0001$) by decade from 8.6 to 4.9 to 2.5 years for incidence studies beginning in the 1970s and earlier, 1980s, and 1990s, respectively. Decreases in duration with time were noted for all types of incidence studies. These changes in study duration were accompanied by a major change in study type. Prospective studies accounted for only 6.9% of incidence studies instituted in the 1970s and earlier, but this increased to 33.3% in the 1980s and became the single most common form of incidence study, 44.9%, in the 1990s (Figure 2).

Figure 2: Distribution of 132 studies with data on Hib meningitis incidence in children < 5 years of age, by decade and type of study



3.3 Antibiotic pre-treatment

The proportion of children treated with antibiotic agents before specimens were collected for etiologic diagnosis was reported for 28 studies, with a mean of 37%, a median of 33%, and range of 7% to 100%. The impact of prior antibiotics on cultures of cerebrospinal fluid could be evaluated in 13 studies from 11 countries (Table 1). In all instances, positive cultures for bacterial agents were more frequent in those without prior treatment, being statistically significantly more frequent ($p \leq 0.05$) in nine studies. Overall, 74% of all cultures in those without prior treatment yielded bacterial agents, while such agents were found in only 51% of those who had prior antimicrobial treatment ($p < 0.0001$). Compared with those who had prior treatment, the yield by culture was thus about 50% higher in those without prior treatment. Closely comparable results were found when only those studies having at least 15 children who had received prior antibiotic treatment were selected ($n = 10$) and arithmetic means were used to assess outcomes. In this subanalysis, the average frequency of isolating a bacterial agent was 79% in those without prior treatment, and 52% in those who had received prior treatment ($p < 0.05$).

Table 1: Frequency of growth on cerebrospinal (CSF) fluid culture of any bacteria, based on whether the patient received antibiotic treatment prior to lumbar puncture

Country	Prior treatment			No prior treatment			p value	Reference
		CSF positive			CSF positive			
	No. tested	Number	Percent	No. tested	Number	Percent		
Bahrain	195	68	35%	248	160	65%	<0.001	Khan 1988
Barbados	12	6	50%	31	26	84%	0.047	St. John 1981
Brazil	898	530	59%	1 143	834	73%	<0.001	Bryan 1990
Colombia	30	18	60%	65	62	95%	<0.001	Otero 1988
Malawi	59	13	22%	208	162	78%	<0.001	Molyneux 1998
Philippines	50	13	26%	32	18	56%	0.006	Reyes 1979
Philippines	76	46	61%	68	53	78%	0.11	Santana 1992
Russian Federation	89	19	21%	130	92	71%	<0.001	Platonov 2001
Saudi Arabia	30	22	73%	94	81	86%	0.10	Babiker 1984
Saudi Arabia	22	15	68%	27	23	85%	0.19	Azubuike 1990
Singapore	8	0	0%	30	17	57%	0.005	Lee 2000
Swaziland	6	0	0%	79	51	65%	0.003	Ford 1994
USA	19	16	84%	20	20	100%	0.11	Gilsdorf 1977
Overall	**1 494**	**766**	**51%**	**2 175**	**1 599**	**74%**	**<0.0001**	

Only three studies specifically addressed the impact of prior treatment on isolation of Hib from cerebrospinal fluid. In each study, isolation was more common in cerebrospinal fluid from children without prior treatment, but this did not reach significance in one study (Table 2). The overall results showed a significant increase in isolation in the absence of antibiotics ($p = 0.001$).

Table 2: Frequency of Hib growth on CSF culture, based on antiobiotic treatment of patient prior to lumbar puncture

Country	Prior treatment			No prior treatment			p value	Reference
		CSF positive			CSF positive			
	No. tested	Number	Percent	No. tested	Number	Percent		
Guatemala	39	18	46%	34	26	77%	0.01	Asturias 2001
Philippines	50	3	6%	32	4	13%	0.42	Reyes 1979
Russian Federation	89	7	8%	130	30	23%	0.003	Platonov 2001
Overall	**178**	**28**	**16%**	**196**	**60**	**31%**	**0.0001**	

3.4 Antigen tests

A variety of different antigen tests for Hib were used, but the results of such tests were often not reported separately. Latex and counterimmunoelectrophoresis were by far the most common, with coagglutination and ELISA (enzyme-linked immunosorbent assay) used in a few studies. The separate contributions of antigen tests were reported in 35 studies conducted in the pre-vaccine era, and these increased the overall identification of Hib in cerebrospinal fluid by about 25%. However, for many of these studies it was not possible to determine whether the antigen tests had been obtained only on culture-negative cerebrospinal fluid specimens. Results of cultures and antigen tests on the same cerebrospinal fluid specimens were available for 13 studies, nearly all from developing countries (Table 3). Overall, more than twice as many Hib cases were identified by antigen testing alone (31%) than by culture (14%) alone ($p < 0.0001$). Of all specimens with Hib identified, 86% were positive by antigen tests, which was significantly higher than the 69% of all identified Hib that were found by culture ($p < 0.0001$). When analysis was restricted to the eight studies that had 15 or more Hib identifications, the mean percent positive by antigen test alone (27%) continued to be significantly higher than the percent positive by culture alone (8%), and 92% versus 73% of all Hib identifications were made by antigen tests and cultures, respectively ($p < 0.05$).

Most antigen tests were latex tests, and overall results were similar when studies were evaluated in which some or all of the antigen tests were known to be latex tests (Table 4). Of the 366 total Hib specimens identified from cerebrospinal fluid in such studies carried out in the pre-vaccine era, 31% were identified only by antigen tests, and 15% only by culture ($p < 0.0001$); 85% of all Hib identifications were obtained from antigen tests versus only 68% of the total from cultures ($p < 0.0001$).

Table 3: Comparison of Hib results when the same CSF specimen was tested by both antigen test and culture.

(Antigen tests include latex, counterimmunoelectrophoresis, coagglutination, and ELISA)

Country	Total number of specimens with Hib identified	Only antigen test* positive for Hib	Only culture positive for Hib	Both antigen test and culture positive for Hib	Percent of all Hib identifications that were antigen test positive	Reference
Brazil	26	12%	0%	88%	100%	Weiss 2001
Dominican Republic	84	10%	8%	82%	92%	SESPAS 2000
Greece	14	20%	7%	73%	93%	Syrogiannopoulos 1995
India	17	19%	0%	81%	100%	Kumar 1980
India	6	40%	0%	60%	100%	Steinhoff 2001
Indonesia	2	0%	0%	100%	100%	Pusponegoro 1998
Kenya	42	58%	13%	29%	87%	Nesbitt 1988
Nigeria	12	38%	0%	62%	100%	Emele 2000
Philippines	118	47%	35%	18%	65%	Limcangco 2000
Poland	17	41%	6%	53%	94%	Zielinski 2001
Poland	19	26%	0%	74%	100%	Tomaszunas 1999
Russian Federation	39	5%	5%	90%	95%	Platonov 2001
United Arab Emirates	13	69%	0%	31%	100%	Uduman 2000
Total	**409**	**126/409 (31%)**	**57/409 (14%)**	**226/409 (55%)**	**352/409 (86%)**	

Table 4: Comparison of results when some or all antigen tests were latex texts and results of culture available on the same CSF specimens

Country	Number of specimens with Hib identified	Only latex test* positive for Hib	Only culture positive for Hib	Both latex test and culture positive for Hib	Percent of all Hib identified by latex tests	Reference
Brazil	26	12%	0%	88%	100%	Weiss 2001
Dominican Republic	84	10%	8%	82%	92%	SESPAS 2000
India	6	40%	0%	60%	100%	Steinhoff 2001
Indonesia	2	0%	0%	100%	100%	Pusponegoro 1998
Kenya	42	58%	13%	29%	87%	Nesbitt 1988
Philippines	118	47%	35%	18%	65%	Limcangco 2000
Poland	17	41%	6%	53%	94%	Zielinski 2001
Poland	19	26%	0%	74%	100%	Tomaszunas 1999
Russian Federation	39	5%	5%	90%	95%	Platonov 2001
United Arab Emirates	13	69%	0%	31%	100%	Uduman 2000
Total	**366**	**115/366 (31%)**	**56/366 (15%)**	**195/366 (53%)**	**310/366 (85%)**	

3.5 Chocolate agar culture medium

Little information was available to assess the quality of the bacteriological procedures. Most commonly the text simply referred to "standard methods" of isolation and omitted details concerning culture media, X and V factor supplementation, incubation temperature, and CO_2 supplementation. The specific use of chocolate (heated blood) agar as the medium for primary cultures of clinical specimens was mentioned in 49 studies. Supplementation with X and V factors was noted in only 10 of the 49 studies. The specific species source of blood used in preparing chocolate agar was invariably omitted. It is likely that chocolate agar was used in many of the studies that did not specifically acknowledge its use.

3.6 Ratio of Hib meningitis to pneumococcal meningitis

The number of pneumococcal meningitis cases in children < 5 years was available in 115 studies for which such information was also available for Hib. Hib was more frequent in 92 of the 115 studies (Table 5). Hib increased significantly in predominance with time and was more common than pneumococcus as a cause of < 5 year meningitis in 94% of the studies that began in the 1990s. Little change was noted in time for either AMR or EUR, where Hib outnumbered pneumococcus in 36 of the 37 total studies from these two regions. When considered as a group, AFR, EMR, SEAR, and WPR showed consistent increases by decade in the proportion of studies where Hib predominated (data not shown).

Table 5: Hib versus pneumococcal meningitis in children < 5 years of age, by WHO region

WHO region	Number of studies with data on both organisms	Predominant organism			
		Hib		Pneumococcus	
		No.	Percent	No.	Percent
Africa	33	17	52% *	16	48%
Americas	18	18	100%	0	0%
Eastern Mediterranean	19	17	89%	2	11%
Europe	19	18	95%	1	5%
South-East Asia	7	5	71% **	2	29%
Western Pacific	19	17	89%	2	11%
Total	**115**	**92**	**80%**	**23**	**20%**

* Africa is significantly less than other WHO regions except South-East Asia ($p<=0.05$).
** South-East Asia is not significantly less than other WHO regions.

There were 42 instances in which the ratio of < 5 year Hib meningitis to < 5 year pneumococcal meningitis could be calculated and where the < 5 year bacterial meningitis incidence was also available. Thus, < 5 year pneumococcal meningitis rates could be obtained for these studies. By decade, there was a significant decline in preponderance of pneumococcus relative to Hib as a cause of bacterial meningitis. By decade, there was also a significant decline in rates of < 5 year pneumococcal meningitis (data not shown). The number of studies with such rates is too small to permit meaningful analysis of trends in < 5 year pneumococcal meningitis rates by region.

3.7 Bacterial meningitis

About two-thirds of all bacterial meningitis cases in children < 5 years of age had an etiologic agent identified. In 65 studies containing entries for both the number of < 5 year bacterial meningitis cases and the number of such cases where an etiology was established, there were a total of 18 463 meningitis cases with the etiology established for 12 630 of them. Thus, an etiologic agent was found in an overall frequency of 68.4%, which is closely comparable with the average percentage identified per study, 67.3%.

No significant change in average percent of < 5 year bacterial meningitis that had etiologies established was noted by the decade when studies began, and there was no significant relationship in linear regression between frequency of identifying agents and frequency of antibiotic use in the 22 studies with values for both variables.

Overall, Hib contributed an average of 42.4% to all < 5 year bacterial meningitis cases with known etiology, ranging from 9% of neonatal meningitis cases to 44.2% of meningitis cases in children < 2 years of age (Table 6). It should be noted that the majority of cases of *Haemophilus* meningitis in neonates are caused by non-capsulated strains of *H. influenzae (Wallace et al. 1983, Falla et al. 1993).*

Table 6: Bacterial meningitis in children < 5 years of age with known etiology: percentage due to Hib, by age group

Age group (months)	Number of studies	Mean percentage due to Hib (95% confidence interval)	
<1	23	9.0%	(0.3% - 17.7%)
0 - 5	26	32.7%	(25.8% - 39.6%)
0 - 11	65	39.1%	(34.2% - 44.0%)
0 - 23	52	44.2%	(39.8% - 48.6%)
24 - 59	48	35.3%	(28.9% - 41.7%)
0 - 59	121	42.4%	(39.2% - 45.6%)

3.8 Age distribution of Hib meningitis cases

The number of studies with information on particular age groups varied widely (Table 7). The cumulative distribution shows that nearly 60% of all cases in children < 5 years occurred before age 12 months. Cumulative mean and median values for 19 studies with values for all five age groups were similar to those shown in Table 7. It can be inferred from the cumulative information that 35.6% of all < 5 year Hib meningitis cases occurred in children 6–11 months of age, with roughly equivalent contributions of the age groups 1–5 months and 12–23 months (22.6% and 23.8%, respectively).

3.8.1 Neonates

Only 1.6% of < 5 year cases occurred in neonates (Table 7). Nevertheless, the vast majority (81%) of all studies, 186 of 229, included neonatal meningitis cases. The mean annual rate of < 5 year Hib meningitis cases was 45/100 000 children in the < 5 year group for the 118 incidence studies that included neonates, compared with 37/100 000 for the 14 studies that excluded neonates, and these rates were not significantly different. This reflects the small proportion of < 5 year cases that occur in neonates. Too few studies had specific information on neonates for a reliable assessment of age-specific incidence (three studies, mean age-specific incidence of 22.4).

Table 7: Distribution of cases of Hib meningitis in children < 5 years, by age group

Age group (months)	Number of studies	Cumulative percentage of cases
<1	36	1.6%
0 - 5	84	24.2%
0 - 11	151	59.8%
12 - 23	138	83.6%
24 - 59	134	100.0%

3.8.2 Children < 5 years of age

Table 8 presents mean incidence rates for those < 5 year age groups where rates were available. Rates for children 0–5 months and 0–11 months of age are similar and higher than rates for children 0–23 months of age. The rate for children 24–59 months of age is substantially lower than all other rates.

Table 8: Number of cases of Hib meningitis per 100 000 population per year, by age group and number of studies (excludes studies of special-risk groups)

Age group (months)	Number of studies	Mean (95% confidence interval) age-specific annual incidence of Hib meningitis per 100 000	
0 - 5	17	73.7	(4.5 - 142.9)
0 - 11	47	77.8	(53.3 - 102.3)
0 - 23	35	49.0	(25.3 - 72.7)
24 - 59	34	9.1	(4.9 - 13.3)

To assess the suitability of the assumption of equal-sized yearly cohorts among children <5 years of age as a basis for estimating age-specific rates, the actual and estimated age-specific incidence rates were calculated for a subset of qualifying studies. Studies that qualified had (1) actual incidence rates for the different age groups, (2) the proportion of < 5 year cases in each age group, and (3) the < 5 year Hib meningitis incidence rate. Age groups examined were 0–5 months, 0–11 months, 0–23 months, and 24–59 months. Studies of special-risk groups and studies with <15 total Hib meningitis patients < 5 years of age were excluded. The mean and median differences between actual and estimated rates are very small, as is the range of differences in the 25% and 75% quartiles (Table 9). Correlation coefficients from 0.78 (for children 24–59 months of age) to 0.99 (for children 0–11 months of age) confirm this strong relationship ($p < 0.0001$) for all.

Table 9: Comparisons of actual and estimated age-specific rates of Hib meningitis per 100 000 population per year*

Age group (months)	Number of qualifying studies**	Differences between pairs of actual and estimated values***		Range of middle quartiles	Correlation coefficient
		Mean	Median		
0 - 5	13	4.30%	-0.80%	-2.2% to 3.1%	0.90
0 - 11	41	-1.40%	-0.10%	-4.2% to 2.4%	0.99
0 - 23	27	3.20%	0.00%	-0.7% to 2.5%	0.81
24 - 59	26	6.30%	0.00%	-5.6% to 3.8%	0.78

* Excludes studies of special-risk groups and studies with < 15 Hib meningitis cases in < 5 years.

** Studies having actual incidence rate for the age group, known proportion of < 5 year cases in the age group, and < 5 year rate.

*** Estimated rate for individual studies is proportion of < 5 year cases in age group/proportion of < 5 year population in age group (assumed) times < 5 year rate.

Therefore, we estimated age-specific annual incidence rates for mutually exclusive age groups for which actual rates were not available. Studies in special-risk populations and those with < 15 Hib meningitis cases in children < 5 years old were excluded. The estimated Hib meningitis incidence of 67.1 cases/100 000 population in the age group 6–11 months was highest, but similar to the rate for children 1–5 months old (Table 10). The estimated rate of 31.9 cases/100 000 for children aged 12–23 months was substantially lower.

Table 10: Age-specific incidence of Hib meningitis per 100 000 population as predicted from age distributions of cases, by age group

Age group (months)	Number of studies*	Mean incidence (95% confidence interval) per 100 000 population	
1 - 5	8	57.9	(0 - 115.9)
6 - 11	38	67.1	(48.5 - 85.7)
12 - 23	58	31.9	(26.3 - 37.5)

* Excludes studies in special-risk groups and those with < 15 Hib meningitis cases < 5 years; includes only studies where the proportion of cases in the specified age group could be determined and < 5 year Hib meningitis incidence was known.

A higher percentage of < 5 year Hib meningitis cases in children aged 0–11 months was associated with a higher rate of < 5 year Hib meningitis. Table 11 depicts this relationship for 75 studies with at least 15 Hib meningitis patients < 5 years of age. The incidence of < 5 year Hib meningitis systematically and significantly increased with increasing proportions of < 5 year cases that were in children 0–11 months of age.

Table 11: Relationship between percentage of Hib meningitis cases in children 0–11 months of age and incidence of Hib meningitis per 100 000 children < 5 years of age

Percentage of cases in children 0 - 11 months	Number of studies*	Incidence per 100 000 children < 5 years
0% - 19%	2	5.3
20% - 39%	23	19.7
40% - 59%	23	23.2
60% - 79%	15	39.7
80% - 100%	12	151.4 p=0.001

* Excludes studies with < 15 Hib meningitis cases in < 5 years.

Figure 3 shows the frequency distribution for proportions of < 5 year Hib meningitis cases aged 0–11 months in 118 studies, after excluding studies with < 15 patients. A bimodal distribution is apparent, with peaks at both 0.40 to 0.44 and at 0.80 to 0.84, and separation of the two populations at 0.60, which is also exactly the median value. The average < 5 year incidence rate for 27 studies at or above 0.60 was 89.7 and 19.2 for 48 studies below 0.60 (p = 0.001 Mann-Whitney). All eight studies of special-risk groups with age information available had values above 0.60. Bimodality was also apparent but less strikingly so for proportions of < 5 year cases in children 0–5 months, 0–23 months, and 24–59 months.

Figure 3: Distribution of 118 studies with at least 15 cases by percentage of Hib meningitis in children < 5 years of age occurring in children 0–11 months of age

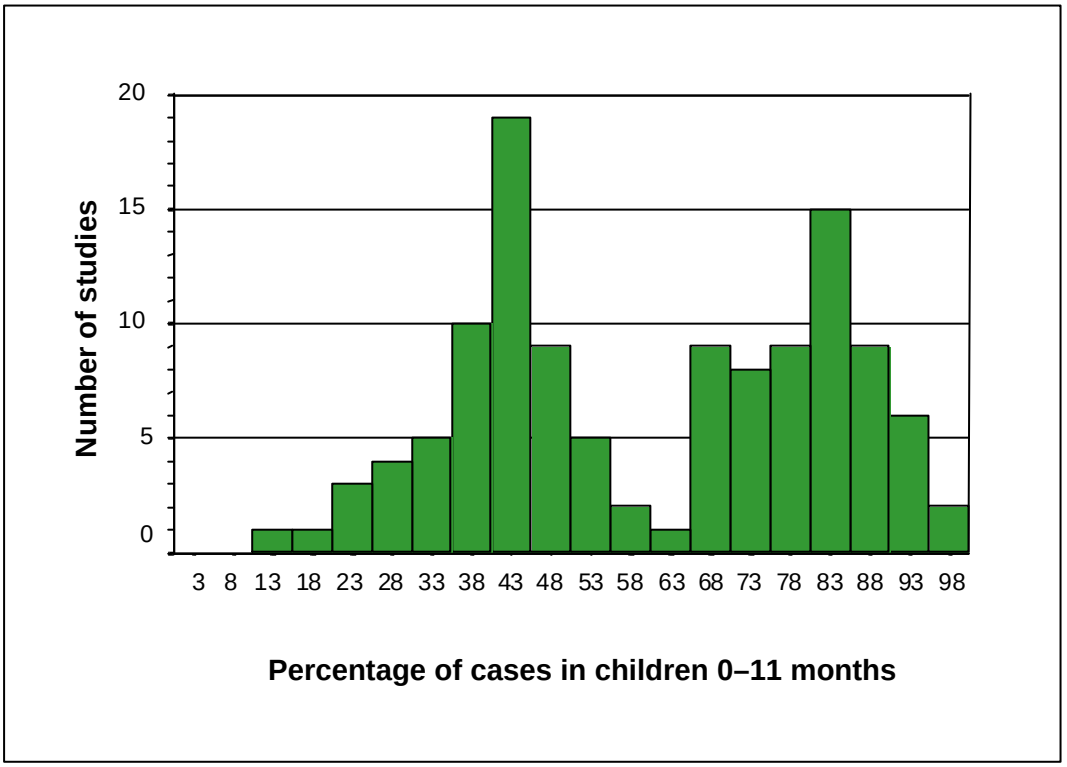
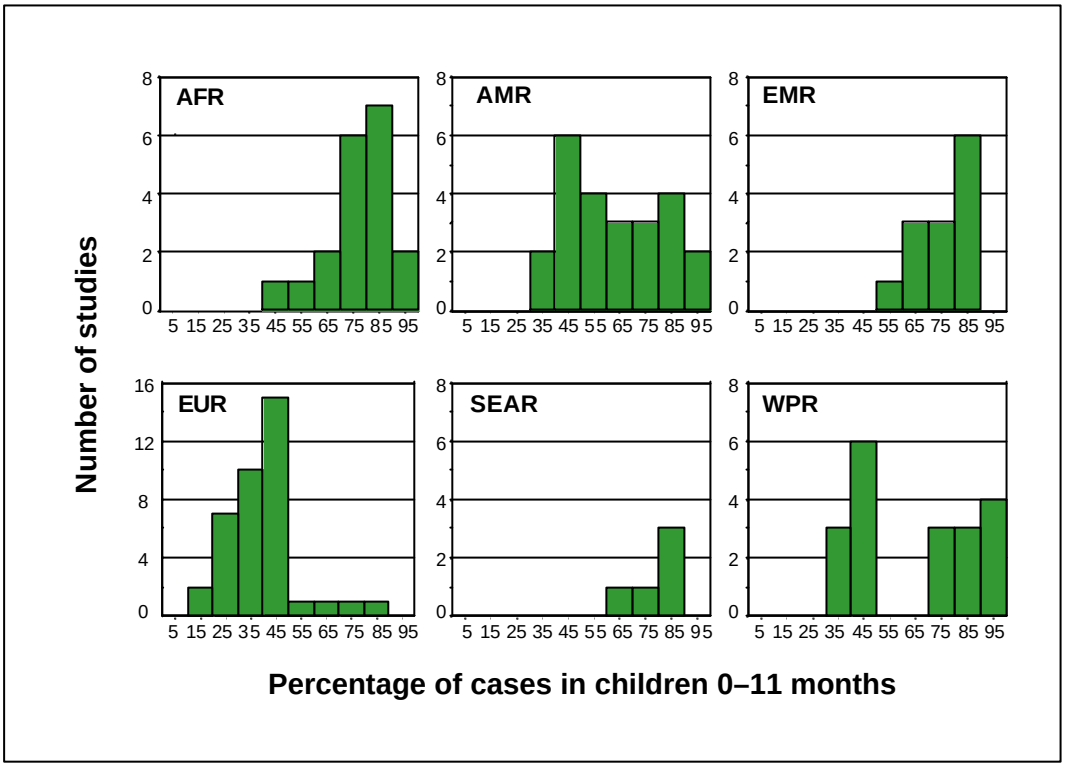


Figure 4 shows the distribution by region for proportions of < 5 year Hib meningitis cases in infants 0–11 months old. While there is bimodality in WPR, this is not apparent for any other region. The percentage of studies with $\geq$ 60% of cases in children 0–11 months of age was 100% in SEAR (n=5), 92% in EMR (n=13), 90% in AFR (n=19), 53% in WPR (n=19), 50% in AMR (n=24), and 8% in EUR (n=38).

Figure 4: Distribution of 118 studies with at least 15 cases by percentage of Hib meningitis in children < 5 years of age occurring in children 0–11 months of age, by WHO region



3.8.3 Older children (5–16 years)

There were 98 studies with both the number of Hib cases in children 5–16 years of age and the number of < 5 year cases. A total of 242 cases occurred in children 5–16 years old and 6268 in children < 5 years. This suggests the total childhood burden of Hib meningitis is about 4% greater than reflected in the < 5 year group alone.

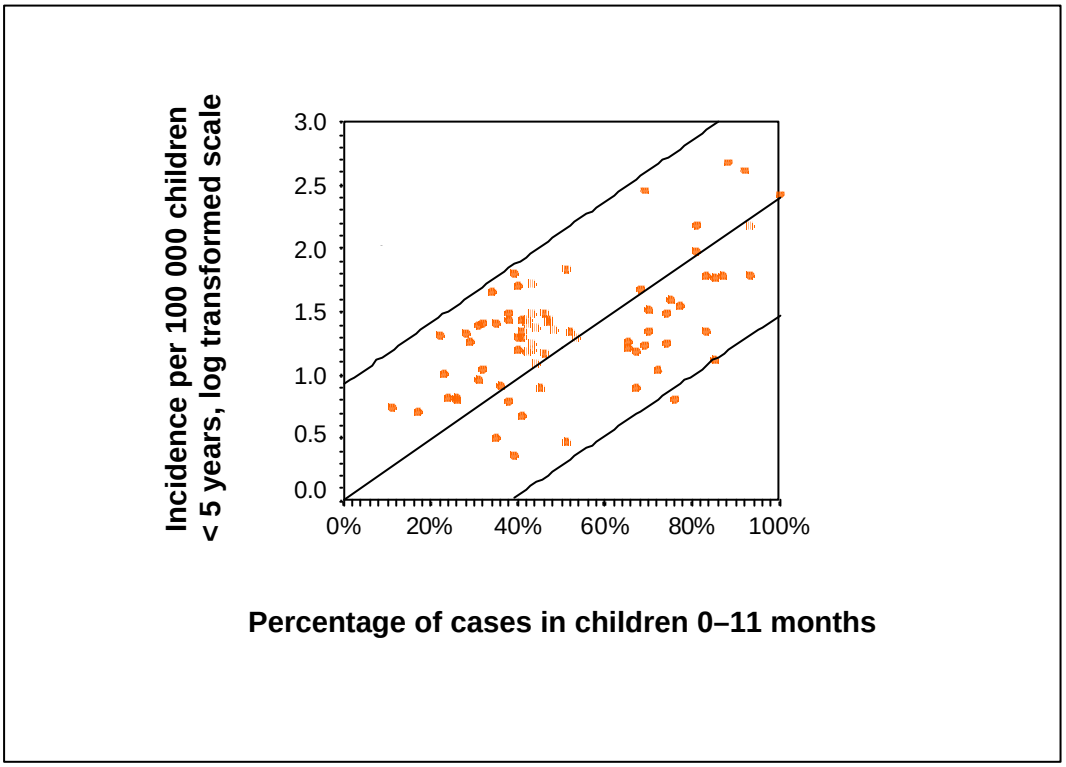
3.9 Age and incidence analysis

3.9.1 Correlation and cluster analysis

The percentage of < 5 year Hib cases in children 0–11 months of age (X) and the < 5 year Hib meningitis incidence (Y) tended to relate positively (the greater is X, the greater is Y). Better proportionality was achieved after logarithmic transformation of Y ($\log_{10}$ Y = k * X) for 75 studies, including studies of special-risk groups, having $\geq$ 15 Hib meningitis cases and values for both X and Y (Figure 5). The Spearman correlation coefficient (r) of X and Y was equal to 0.50 ($p < 0.001$) and the regression coefficient was $k \approx 0.025$.

Figure 5: Relationship between percentage of < 5 year Hib meningitis cases occurring in children 0–11 months of age and incidence of Hib meningitis in children < 5 years

(Central line shows a trend (linear regression) and border lines show 95% confidence interval)

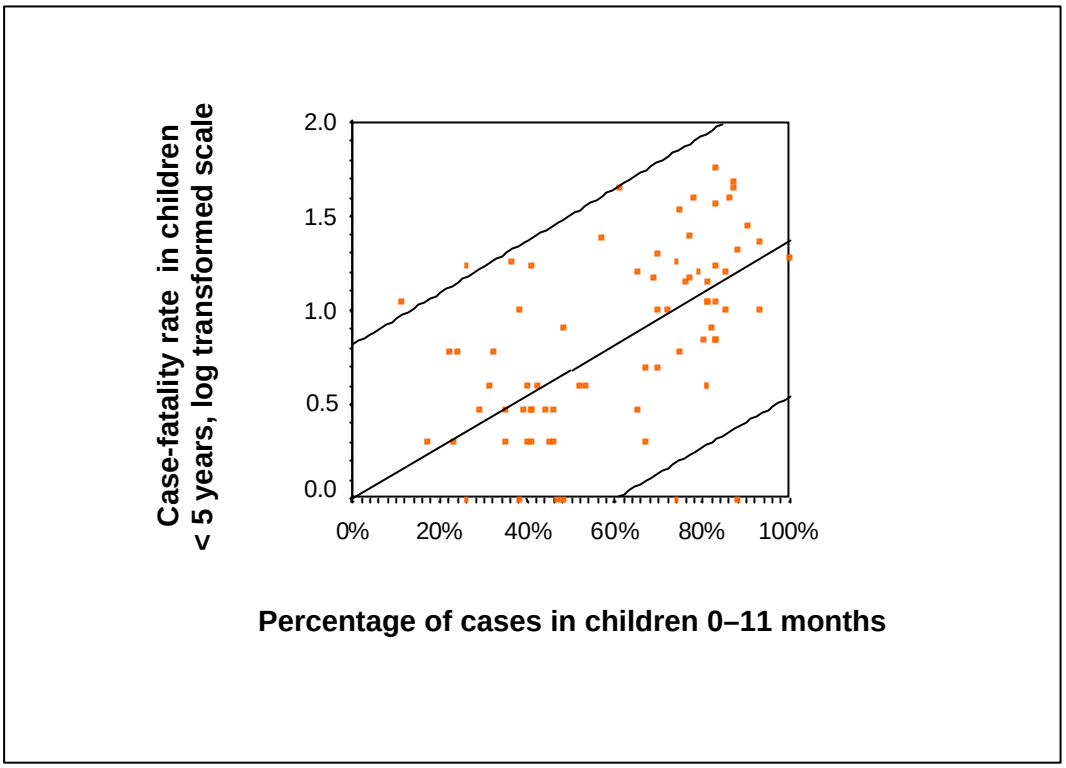


Similarly, both the percentage of < 5 year Hib meningitis cases in children 0–5 months of age and 0–23 months of age were positively correlated with $\log_{10}$ transformed rates ($r = 0.47$, $p = 0.06$ and $r = 0.51$, $p < 0.001$, respectively).

The relationship between the proportion of < 5 year Hib meningitis cases in children 0–11 months of age (X) and the < 5 year Hib case-fatality rate (Z) also became more evident after logarithmic transformation of the case-fatality rate ($\log_{10}$ Z = m * X) (Figure 6). The Spearman correlation coefficient was 0.61($p < 0.001$) and the regression coefficient $m \approx 0.015$. This implies that the case-fatality rate increases when the proportion of cases 0–11 months is higher.

Figure 6: Relationship between percentage of < 5 year Hib meningitis cases occurring in children 0–11 months of age and the < 5 year Hib meningitis case-fatality rate

(Central line shows a trend (linear regression) and border lines show 95% confidence interval)

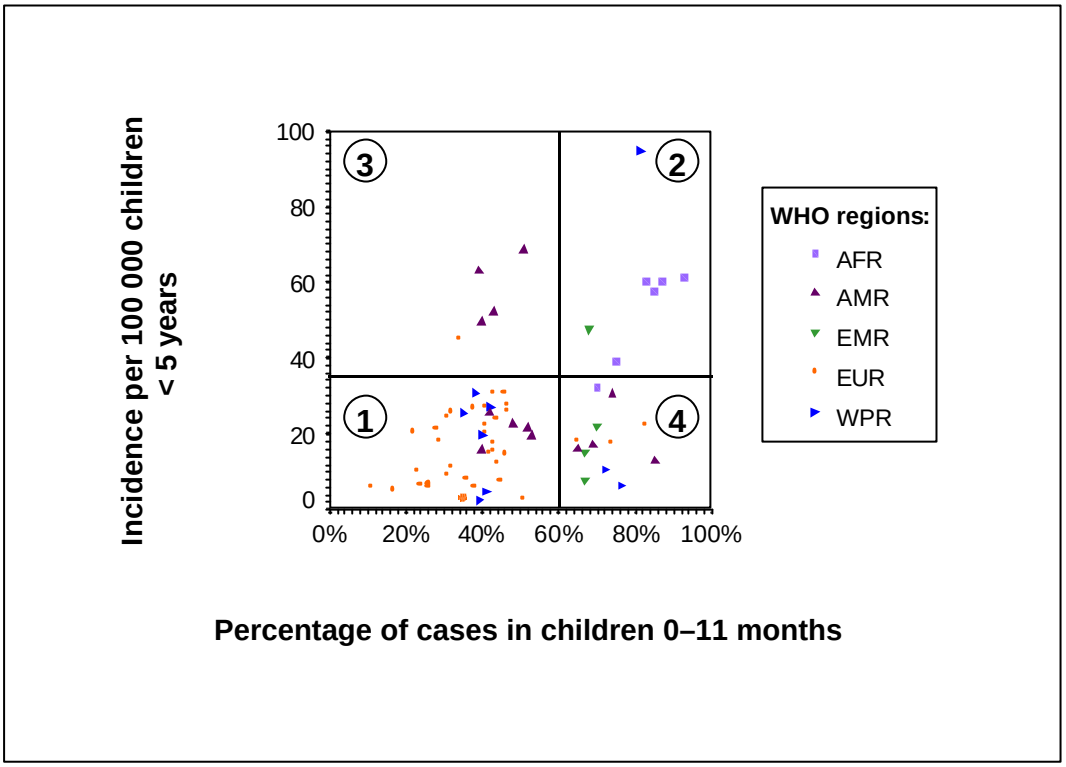


Studies with high < 5 year Hib meningitis incidence rates and low proportions of cases occurring in children 0–11 months of age (or vice versa) may be considered to contain "outlying" data. Although such studies might make the "ideal regression" worse, they might also contain information of value in understanding relationships. To analyse this possibility, we graphed the < 5 year Hib meningitis incidence rate and the proportion of cases occurring in children 0–11 months of age as a scatter plot, after excluding studies of special-risk groups and those with <15 Hib meningitis cases < 5 years (Figure 7). The data set can be seen to be divided into four distinct clusters. The K-means cluster analysis confirms the presence of four clusters which have their centres at the following approximate coordinates: for cluster No. 1 X=38, Y=17; for cluster No. 2 X=83, Y=64; for cluster No. 3 X=41, Y=56; for cluster No. 4 X=71, Y=19. Thus cluster No. 1 represents "low/low" epidemiologic features (that is, low proportion of cases in children 0–11 months/low < 5 year Hib meningitis incidence). Cluster No. 2 represents "high/high" features. Cluster No. 3 represents "low/high" features. Cluster No. 4 represents "high/low" features. The threshold values of X= 60% and Y=35 cases per 100 000 children divide the entire data set into four quarters, each corresponding to one of the clusters. There are 43, 7, 5, and 13 studies in clusters No. 1, No. 2, No. 3, and No. 4, respectively.

Studies of special-risk groups formed a separate fifth cluster, but these have been omitted from Figure 7. The special-risk groups formed a cluster with "high/very high" features, with coordinates of X=86, Y=252. There were seven studies in cluster No. 5.

Figure 7: Relationship between percentage of < 5 year Hib meningitis cases occurring in children 0–11 months of age and the incidence of Hib meningitis in children < 5 years

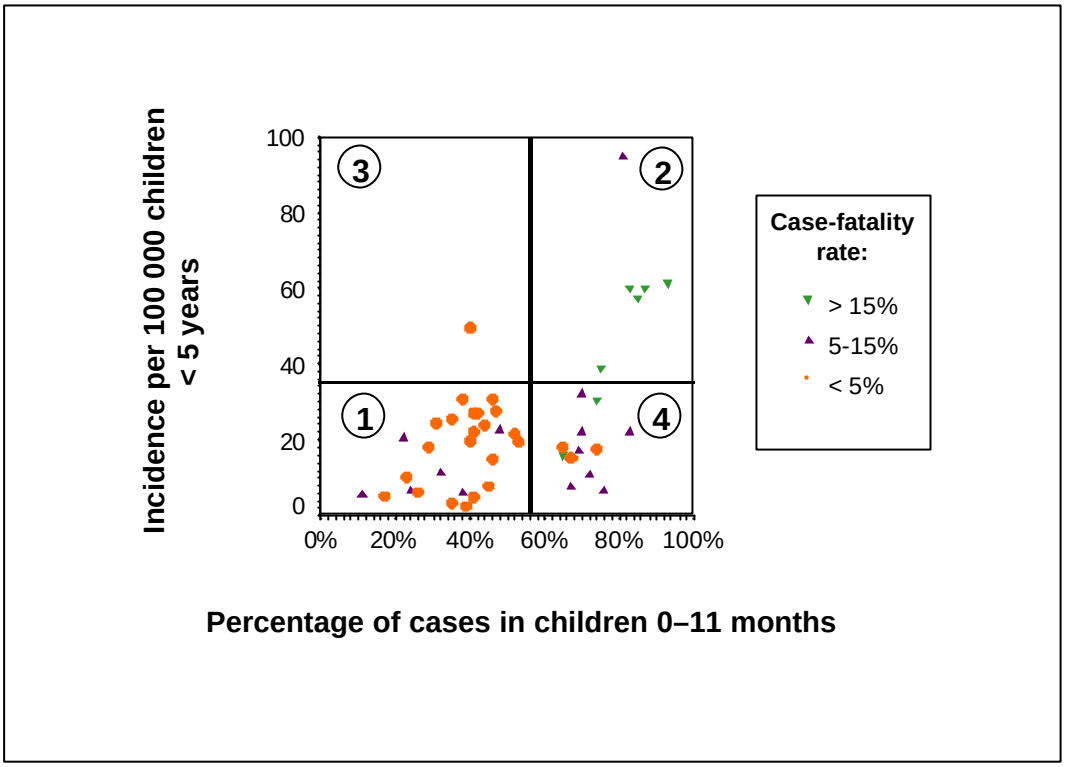
(Vertical and horizontal lines indicate borders of four clusters; cluster numbers are circled)



The inclusion of a third variable, the case-fatality rate (Z), into the cluster analysis supports the presence of the same clusters (Figure 8). For cluster No. 1, case-fatality rates ranged from 0% to 17%, with a mean of 4%. For cluster No. 2, most studies had case-fatality rates of > 15%, with a mean of 28%. For cluster No. 3 there was only one study, with a case-fatality rate of 2%. For cluster No. 4, case-fatality rates ranged from 2% to 37%, with a mean value of 9%. For cluster No. 5 (special-risk groups), the mean case-fatality rate was 6%.

Figure 8: Relationship between percentage of < 5 year Hib meningitis cases occurring in children 0–11 months of age, the incidence of Hib meningitis in children < 5 years, and the < 5 year Hib meningitis case-fatality rate

(Vertical and horizontal lines indicate borders of four clusters; cluster numbers are circled)



Annex 4 shows the relationship between the cluster assignment and the country of study. Cluster No. 1 (low/low) includes 32 studies from EUR and 11 additional studies from Australia, Canada, Cuba, Japan, and the USA. Cluster No. 2 (high/high) includes five of six studies from AFR, as well as studies from the Philippines and Saudi Arabia. Cluster No. 3 (low/high) consists of four studies from the USA and one from Iceland. Cluster No. 4 (high/low) is more heterogeneous, with studies from developing countries in AFR (South Africa), AMR (Argentina, Brazil, Chile, Dominican Republic), EMR (Kuwait, United Arab Emirates), EUR (Israel), and WPR (China, Malaysia).

These observations may help explain why the relationship between the proportion of < 5 year Hib meningitis cases occurring in children aged 0–11 months and the < 5 year incidence of Hib meningitis are not so evident *within* any geographic region. Low Hib meningitis incidence, low proportion of < 5 year cases in infancy, and low case-fatality rate was the pattern typical for European countries, as well as for other industrialized countries in temperate climate zones. High Hib meningitis incidence, high proportion of < 5 year cases occurring in infancy, and high case-fatality rate was the typical pattern for studies from Africa and a few other developing countries. The USA appears to have had its own type of Hib epidemiology in the pre-vaccine era. Cluster No. 4 includes a heterogeneous group of developing countries from four regions. No incidence data from SEAR met inclusion criteria for the cluster analysis; therefore, this region had no studies attributed to any cluster.

3.9.2 Logistic regression analysis

The 132 studies with < 5 year Hib meningitis incidence rates were divided into two groups based on incidence rates above or below 35 (see section 3.9.1 on cluster analysis). A rate at or above 35 (that is, a high rate) was selected as the dependent variable. The independent variable of principal interest was the proportion of < 5 year Hib cases occurring during infancy. In univariate unconditional regressions, the following variables were positively associated with a high rate: the proportion of < 5 year Hib cases occurring in infancy ($p < 0.001$); the proportion of < 5 year cases that had an established etiology ($p = 0.064$); and the proportion of all < 5 year meningitis with a defined etiology of Hib ($p = 0.07$). The latter two variables both increase significantly as < 5 year Hib incidence increases; they are largely the consequences of Hib incidence, rather than its determinants. Using studies that began before 1980 as a reference, studies undertaken in the 1980s and 1990s had reduced odds ratios, with p values of 0.12 and < 0.001, respectively.

Subsequent analysis showed the age distributions of < 5 year Hib meningitis cases to be similar in AFR, EMR, and SEAR; therefore, studies from these three regions were grouped together to evaluate regional influences. With EUR as a reference (that is, an odds ratio of 1.0) odds ratios for WPR, AMR, and AFR–EMR–SEAR were 8.5, 25.9, and 18.3, respectively, with all p values ≤ 0.005.

None of the following variables were significantly associated with the dependent variable: stated use of chocolate agar for primary culture, inclusion or exclusion of neonates from studies, known use of latex antigen detection tests, proportion of children getting antibiotics before microbiologic evaluations, and the development status of the country where the study was conducted.

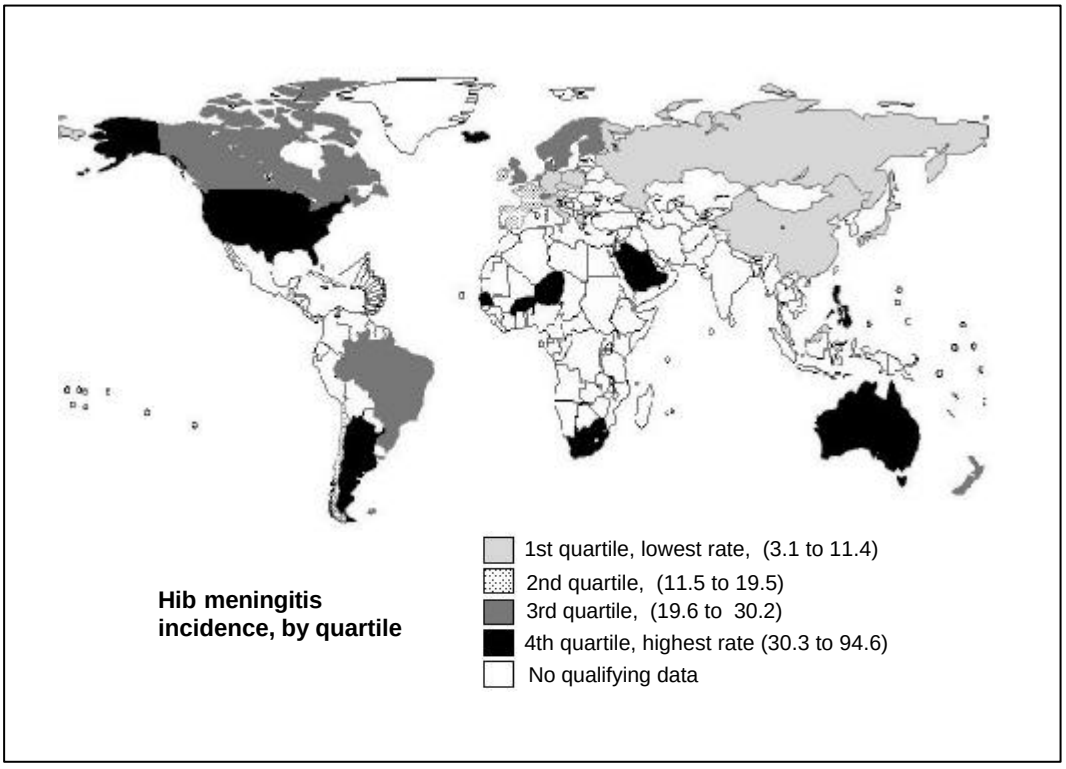
After controlling for decade when studies were undertaken and region, the proportion of < 5 year Hib cases occurring in children 0–11 months of age remained significant ($p = 0.006$, by likelihood ratio statistic). Its odds ratio increased 1.7 times (1.1 to 2.5) for every increase of 10% in the proportion of cases in children 0–11 months of age. This variable was collinear with the proportion of < 5 year cases of bacterial meningitis with established etiologies as well as the proportion of all < 5 year bacterial meningitis cases caused by Hib. Adding either of the latter variables to this model resulted in instability.

3.10 Risk of Hib meningitis, by country

Available data from each country were averaged to obtain mean < 5 year Hib meningitis incidence, and mean proportion of < 5 year cases in children 0–11 months of age. These averages excluded studies of high-risk groups and those with < 15 cases of < 5 year Hib meningitis.

The mean Hib incidence rate for children < 5 years were available for a total of 46 countries. These data were divided into quartiles, and a global map was created with increasing density as rates increased from the lowest to the highest quartile in the 46 countries (Figure 9).

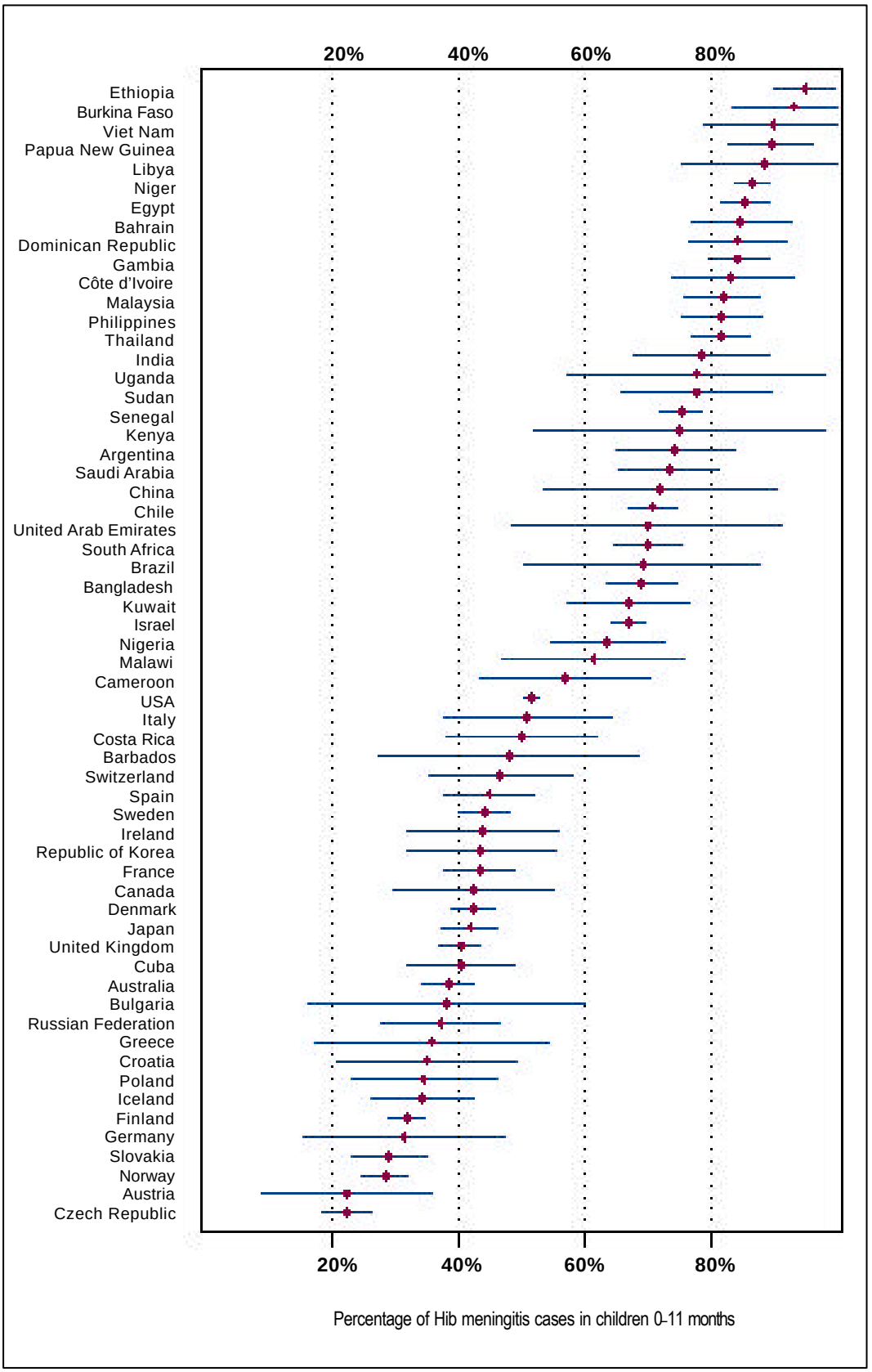
Figure 9: Country-specific incidence,* by quartile, of Hib meningitis per 100 000 children < 5 years of age for 46 countries in the pre-vaccine era



* Excludes studies of special-risk groups and those with < 15 cases.

The mean proportion of < 5 year Hib meningitis cases occurring in children aged 0-11 months was available for 60 countries (Figure 10). The proportion of Hib meningitis in children aged 0-11 months can provide a useful general indication of < 5 year Hib meningitis risk and should be taken into consideration when assessing the Hib disease burden. As the proportion of Hib meningitis in children 0-11 months increases, country < 5 year rates also tend to increase (r=.53, p=.0004).

Figure 10: Point estimate and 95% confidence interval for percentage of < 5 year Hib meningitis cases in children 0-11 months for 60 countries in the pre-vaccine era



3.11 Regional comparisons

The following five figures present comparisons for a variety of factors by region.

Figure 11 shows that the < 5 year Hib meningitis incidence rates are higher for AFR and AMR than for EUR or WPR ($p < 0.05$, Mann-Whitney). AFR has < 5 year Hib meningitis incidence rates significantly higher than those in EMR ($p = 0.01$) or AMR ($p = 0.053$, Mann-Whitney). Note that only a single point estimate is available for SEAR.

Figure 11: Incidence (median, quartiles, range) of Hib meningitis in children < 5 years of age, by WHO region (excludes studies in special-risk groups)

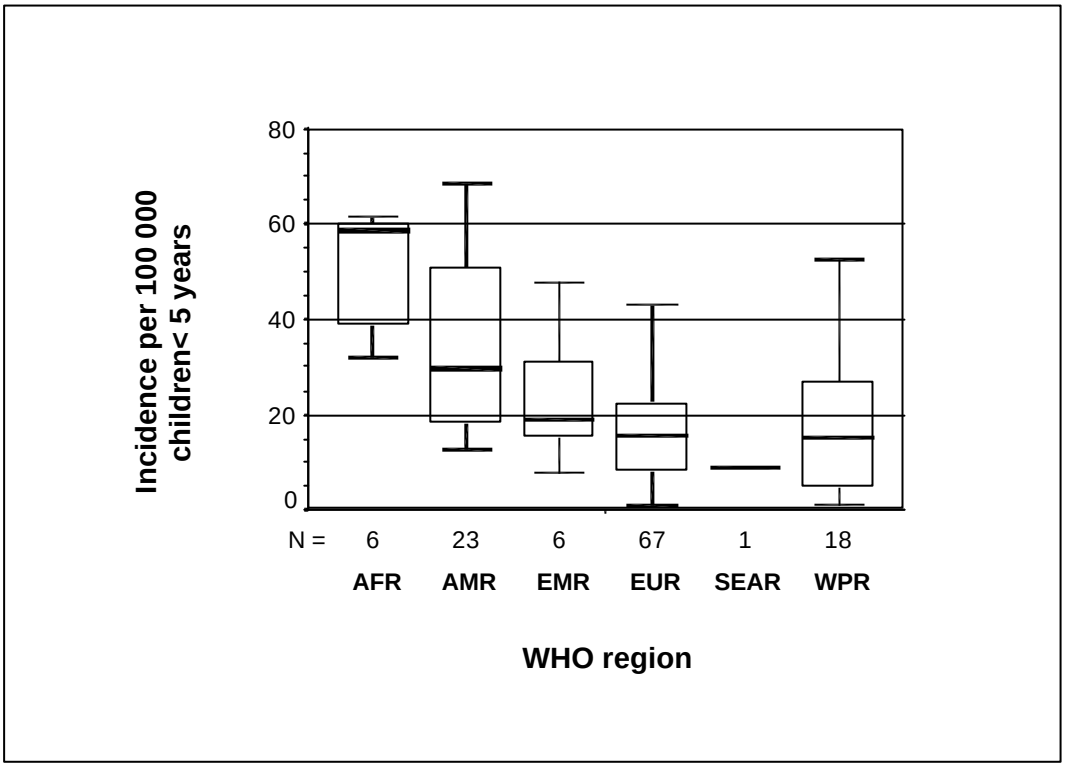


Figure 12 presents results of studies where Hib meningitis rates were available for children 0–11 months of age. In parallel with the < 5 year incidence findings, the rates for children 0–11 months of age in AFR and AMR are again significantly higher than in EUR ($p < 0.001$, Mann-Whitney). The rate for AFR is significantly higher than the rate for AMR ($p = 0.002$).

Figure 12: Incidence (median, quartiles, range) of Hib meningitis in children 0–11 months of age, by WHO region (excludes studies in special-risk groups)

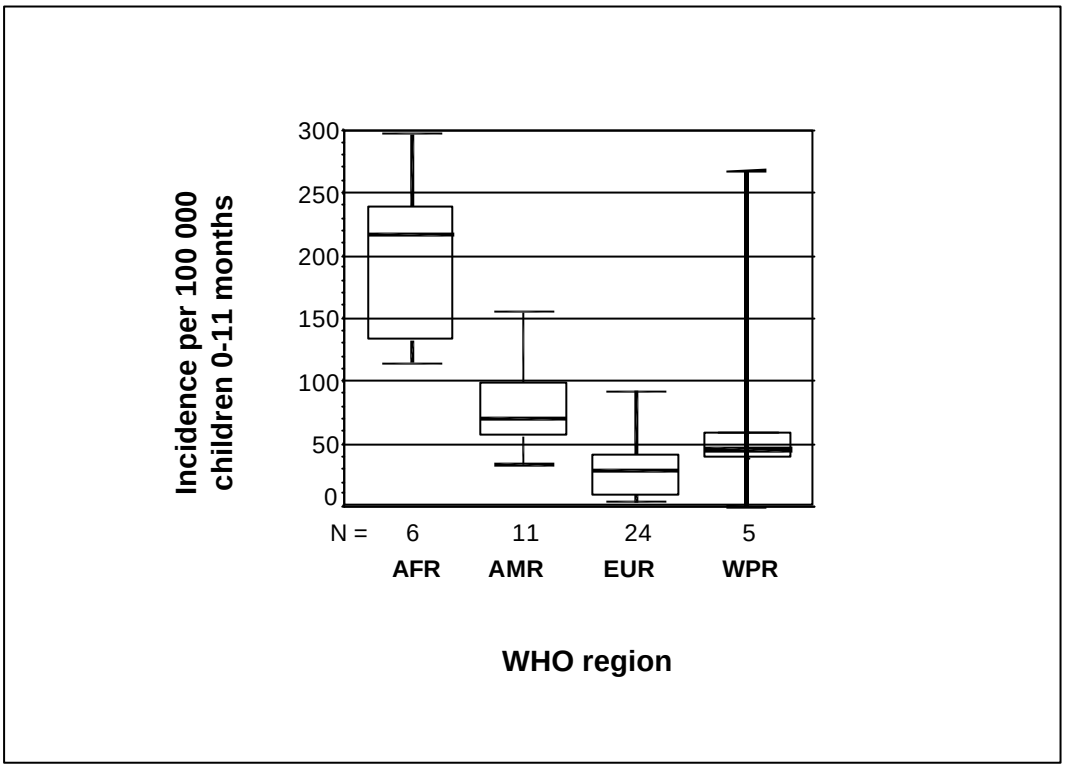


Figure 13 shows the proportion of < 5 year Hib meningitis cases that occurred in children 0–11 months of age. EUR has a significantly lower proportion than all other regions ($p < 0.003$, Mann-Whitney). The proportion in AMR is significantly lower than in AFR, EMR, and SEAR ($p < 0.005$, Mann-Whitney), which have similar values. The proportion of < 5 year Hib meningitis in WPR varied greatly from country to country, but is lower ($p < 0.005$) than in AFR.

Figure 13: Percentage (median, quartiles, range) of Hib meningitis in children < 5 years of age occurring in children 0–11 months of age, by WHO region (excludes studies in special-risk groups)

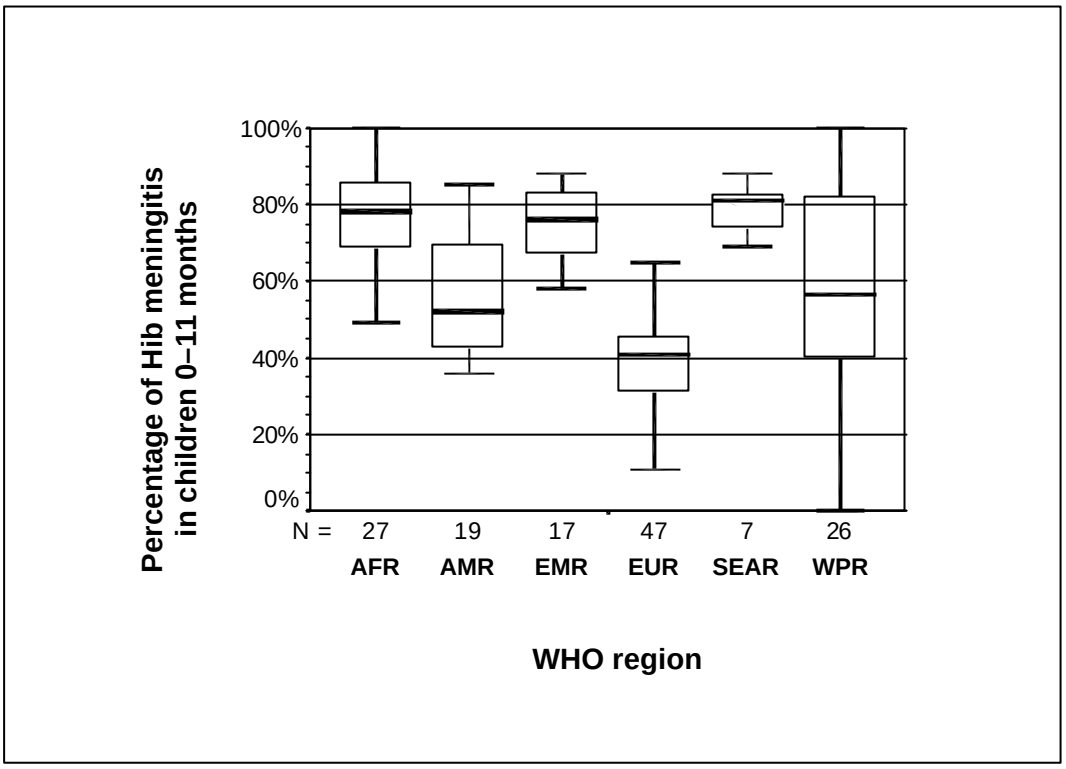


Figure 14 reveals that Hib represents a smaller proportion of < 5 year bacterial meningitis of known etiology in AFR than in any of the other regions. In AFR, this proportion is significantly less than in AMR and EMR ($p < 0.001$, Mann-Whitney), and this may reflect the high endemic levels of *Neisseria meningitidis* in AFR, even after data from epidemic years have been excluded. The values for EUR, SEAR and WPR are nearly identical.

Figure 14: Hib as a percentage (median, quartiles, range) of all bacterial meningitis with established etiology in children < 5 years of age, by WHO region (excludes studies in special-risk groups)

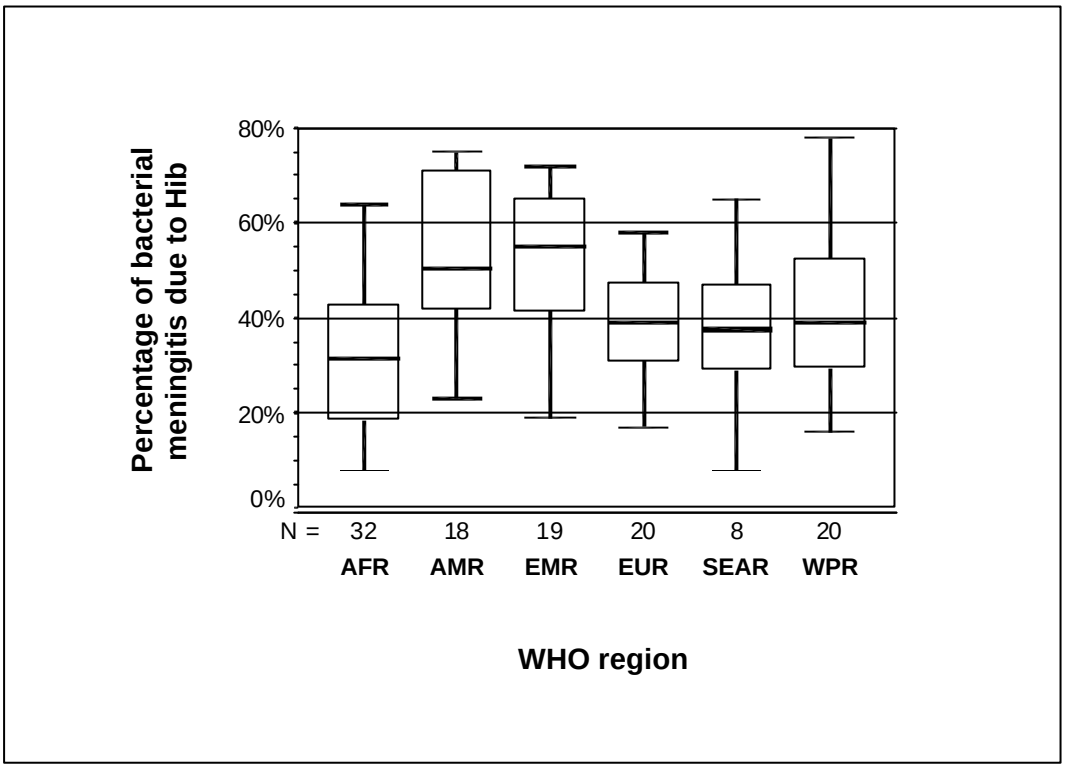
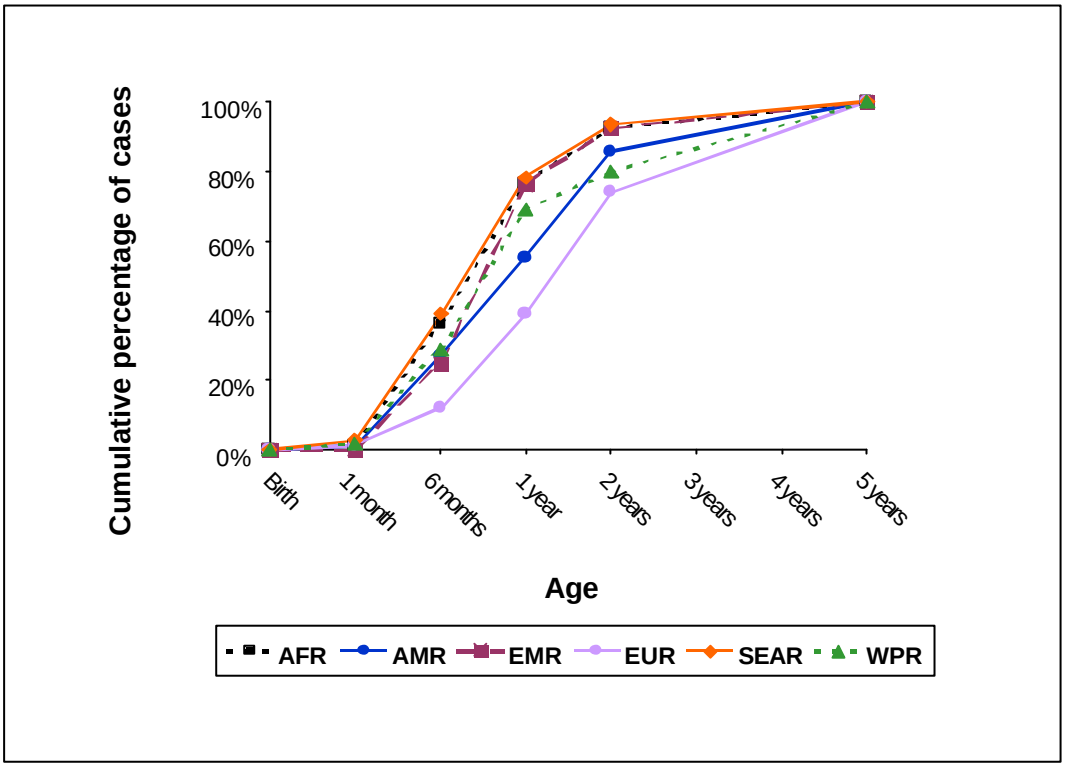


Figure 15 shows average values for the cumulative distribution of cases at different ages for each region. This figure excludes studies of special-risk groups and studies with < 15 total cases < 5 years. The numbers of studies included are 25, 59, 111, and 99 for 1 month, 6 months, 1 year, and 2 years of age, respectively. AFR, EMR, and SEAR are very closely similar to each other and have the youngest profile of cases. AMR and WPR are similar to each other and occupy an intermediate position. EUR has a much higher proportion of older cases, with a cumulative percentage of cases substantially lower than other regions at 6 months, 1 year, and 2 years.

Figure 15: Cumulative percentage of cases of Hib meningitis in children < 5 years of age, by WHO region

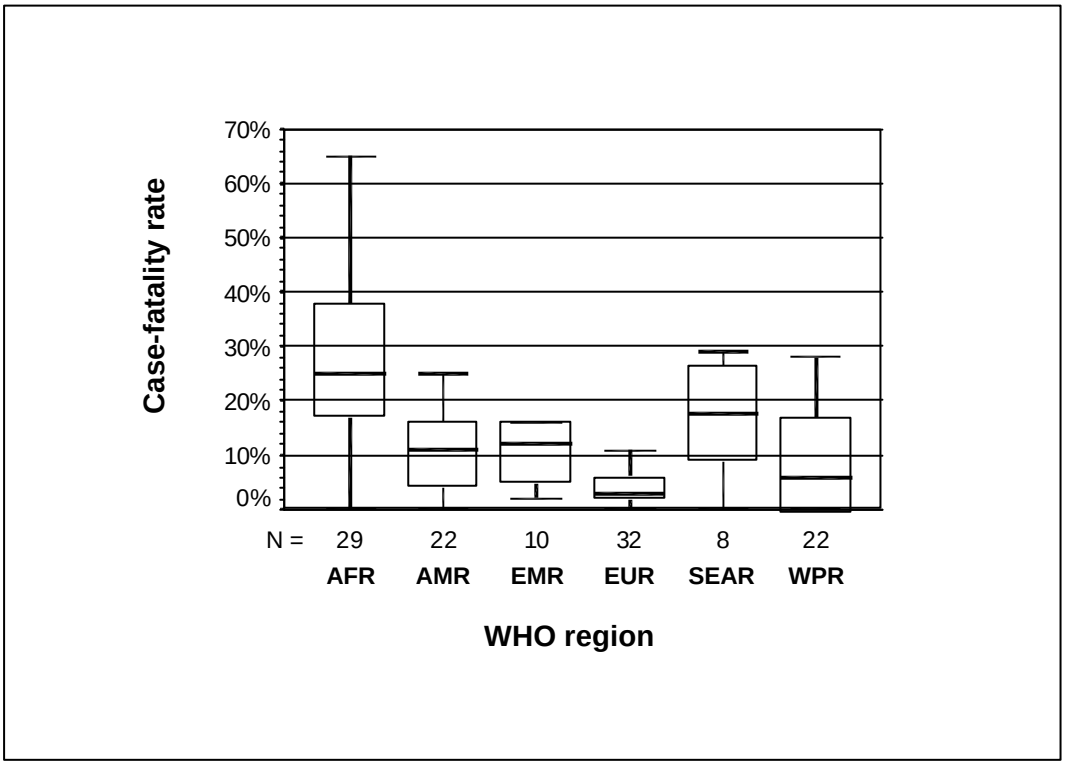


3.12 Deaths due to Hib meningitis

A total of 127 studies had information on case-fatality rates. The mean case-fatality rate for children with Hib meningitis was 13.8%, with a median of 10%, and a range of 0% to 65%. The mean case-fatality rate was 17.3% for developing countries, compared with 3.2% for industrialized countries. There was no significant trend in case-fatality rates by decade.

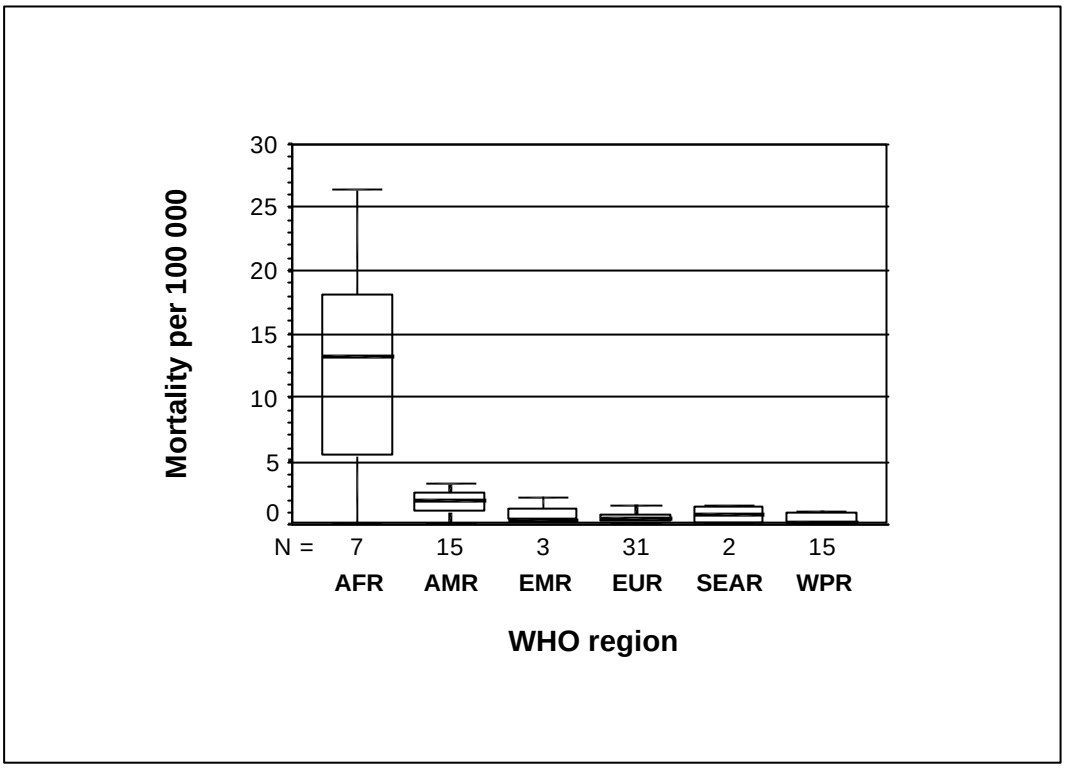
By region, mean case-fatality rates ranged from a low of 4.1% in EUR to a high of 27.6% in AFR. Case-fatality rates reflect the type and quality of medical treatment available for meningitis. The case-fatality rate is significantly higher in AFR than in AMR, EMR, EUR, and WPR ($p < 0.03$, Mann-Whitney) (Figure 16). The second highest case-fatality rate occurs in SEAR. The case-fatality rate in EUR is significantly lower than the rate in AFR, AMR, EMR, and SEAR ($p < 0.01$, Mann Whitney) and lower than the rate in WPR ($p = 0.08$).

Figure 16: Case-fatality rate of Hib meningitis in children < 5 years of age, by WHO region (excludes studies in special-risk groups)



AFR has by far the highest Hib meningitis mortality rate for children < 5 years of age (Figure 17). This comparison is based on 73 studies that reported both Hib meningitis incidence and case-fatality rates.

Figure 17: Estimated annual mortality rate from Hib meningitis in children < 5 years of age, by WHO region (excludes studies in special-risk groups)



Case-fatality rates for studies of special-risk groups have been excluded from these analyses. Despite the extremely high incidence of < 5 year Hib meningitis in these groups (mean 418.1/100 000), their case-fatality rates were low, with a mean of 6.5% for the four studies with this information. Low case-fatality rates in special-risk groups have been noted previously, with the explanation that such groups are living in industrialized countries where they have access to medical treatment *(Wright 1989)*. With such a high incidence of < 5 year Hib meningitis, clinicians are likely to have a high level of suspicion about the possible presence of Hib meningitis, and this could be expected to result in more rapid diagnosis and prompt treatment, helping reduce fatality rates.

4. Discussion

Our search identified 229 studies of Hib meningitis in children < 5 years of age, occurring in the pre-vaccine era. In all, these studies reported some 30 000 cases and more than 2100 deaths due to Hib meningitis. The compilation of these studies is attributable in part to the efforts of WHO regional staff in seeking data. Our search reveals more than 40 years of interest in the scientific study of Hib epidemiology. Our database demonstrates changes in the types of studies being conducted, with increasing emphasis on population-based studies, and a decreasing duration of studies. Both factors may relate to the use of studies to obtain information that can aid countries in deciding whether to introduce Hib vaccine. The population-based studies provide a more robust assessment of risk of Hib meningitis than passive surveillance or hospital-based studies.

4.1 Limitations of Hib meningitis incidence studies

Our review identified 132 studies of Hib meningitis incidence. These population-based studies represent the gold-standard method for assessing < 5 year Hib meningitis incidence. Nevertheless, there are a number of limitations to this type of study.

We considered each of the 121 incidence studies not conducted for special-risk groups to reflect the country risk. However, only 44 (36%) of the 121 studies were carried out nationwide or covering at least 50% of the population in a particular country. The rest of the studies covered one or more large cities (usually the capital) or one or more regions of the country, and thus may not fully reflect the national picture of Hib disease.

For patients admitted to health care facilities, a high index of clinical suspicion is needed for the diagnosis of meningitis, since presenting signs can be nonspecific, especially in neonates. Parents or guardians must be willing to approve the collection of specimens, and clinicians must be willing and able to obtain cerebrospinal fluid and/or blood samples for diagnostic evaluation. Once collected, CSF samples must be cultured promptly on a medium suitable for the fastidious *Haemophilus* bacterium, which requires both X and V factors for growth. Chocolate (heated blood) agar supplemented with X and V factors is preferred. Blood from sheep or horses may be used, but human blood is unsuitable because it may contain bactericidal components. Hib identification is also hindered by failure to use and properly perform antigen detection tests.

Pre-admission events also influence the likelihood of detecting Hib. Foremost among these is antibiotic treatment, which substantially reduces the likelihood of identifying an etiologic agent. Some children with bacterial meningitis may be treated successfully in the community without the proper diagnosis ever being made. Other children with bacterial meningitis may die without being admitted to hospital, with the cause of death never determined. Some families living in a specific study area may seek care from health facilities not within the study area.

These factors conspire to reduce the numbers of Hib meningitis cases detected – the numerator for incidence studies – and can thus result in substantial underestimates of the true incidence in some studies. In addition to problems in detecting Hib meningitis cases, the denominator for incidence studies also introduces further variation. Having a recent census of the < 5 year population is ideal, but in some of the studies we analysed, the actual size of the population served was not clearly defined.

4.2 Age distribution of Hib meningitis cases

For special-risk groups, an age distribution with a greater proportion of younger cases was first noted more than 20 years ago *(Ward et al. 1981)*. Others have used age distribution of cases in children < 5 years of age to suggest similarities between countries in Hib meningitis risks *(Wright 1989, Bijlmer 1991, Funkhauser et al. 1991, Peltola 1997–2001)*. The present analysis more fully quantifies this relationship. Rates increase as the proportion of cases in children 0–5 months, 0–11 months, and 0–23 months of age increases; rates decrease as the proportion of cases in children aged 24–59 months increases.

The bimodal distribution in the proportion of < 5 year cases occurring in children 0–11 months of age (Figure 3), whether special-risk groups are included or excluded, is not readily explained. It seems unlikely to be a totally spurious finding, but its relationship to < 5 year incidence is more complex than a simple linear relationship. One possible interpretation is that there are really only two different types of populations – those with lower < 5 year Hib meningitis risk and lower proportions of cases in children 0–11 months of age, and those with higher risk and higher proportions of cases in children 0–11 months of age. Such an explanation is not supported by the available incidence data (Figure 1), which contain no suggestion of bimodality after studies in special-risk groups are removed. However, as noted above, many factors can cause important variations in incidence rates, and incidence rates may simply be an imperfect "gold standard" for assessing these results. If the likelihood of identifying Hib in specimens from children is not age-related, then age distributions should be free of many of the problems affecting the incidence determinations listed above, and should be far more easily and reliably obtained than incidence data itself.

Incidence data are especially likely to be underestimated when the sensitivity in detecting Hib meningitis cases is suboptimal. It is possible that such phenomena underlie the 13 studies in cluster No. 4 (high proportion of cases aged 0-11 months and low < 5 year Hib meningitis incidence), all from developing countries. Studies in cluster No. 4 were significantly less likely to use antigen test results than

the developing countries in cluster No. 2 (5/13 versus 6/7, p=0.05). Four studies in cluster No. 4 raise specific concerns about undetected cases (Annex 2, studies number 48, 92, 138, and 140). Frequent use of antibiotics prior to collection of specimens appears to have been a problem in three studies where antigen detection tests were not used (Annex 2, studies number 88, 89, and 92). One study excluded culture-negative, antigen-positive specimens (Annex 2, study number 139). One study was based on cases admitted to a district referral hospital, but did not investigate possible admissions of cases to other district hospitals and health centres (Annex 2, study number 207). One study was based on cases passively reported to a health department, but no estimates of reporting completeness were provided (Annex 2, study number 45). Reporting completeness was also not investigated in another study where standard report forms were supposed to be completed by multiple participating hospitals (Annex 2, study number 6). Finally, in one study nearly half of abnormal cerebrospinal fluid specimens from children with clinically diagnosed meningitis did not have culture or antigen tests (Annex 2, study number 51). In sum, data from cluster No. 4 suggest that the observation of a high proportion of Hib meningitis cases in children 0-11 months of age coupled with a low < 5 year Hib meningitis incidence should lead to careful and critical scrutiny of factors possibly responsible for underdetection of cases.

Conversely, scrutiny of case finding methods in the 5 studies involving industrialised countries in cluster No. 3 (low proportion of cases in children 0-11 months and high < 5 year Hib meningitis incidence) reveals vigorous case detection efforts in 4 of the 5 studies, all from the USA (Annex 2, study numbers 54, 55, 61, and 66). Antigen detection tests were used in all 4 studies.

For most analyses we excluded studies with fewer than 15 cases of Hib meningitis, as this generally increased the strength of the associations we found. Studies with small numbers of cases can reflect a small relative size of the < 5 year population under study, insufficient duration of a study, or reduced sensitivity in detecting cases. Studies with small numbers of cases may also reflect truly low incidence, although data available to us was generally insufficient to choose between the latter two alternatives.

Assuming equal-sized yearly cohorts of children permitted remarkably accurate rates to be estimated from < 5 year rates and the proportion of < 5 year cases in particular age groups. The predicted and actual rates for studies where this could be assessed were nearly identical for children 0–11 months of age (r = 0.99). This very strong correlation can be partially attributed to deriving one of these parameters from the other because we assumed equal-sized yearly cohorts in 8 of the 90 qualifying studies. Some authors probably also relied on this assumption in calculating rates within the < 5 year group. While this method was expected to work well in countries with low childhood mortality and vertical population pyramids, it also performed well in locations where substantial childhood mortality was expected. It can be shown that even high infant mortality will have only small effects on the proportion of < 5 year children that are 0–11 months of age. For example, in a population with an high infant mortality of 100 deaths per 1000 live births, or 10% (and assuming no additional < 5 year deaths for simplification), the proportion of < 5 year children that are infants changes trivially from 20% to 21%. This occurs because each of the four succeeding cohorts after infancy will have the equivalent of only 90% of the annual births. If annual births are represented by the quantity 1.0, then the size of

the remaining cohorts will be represented by 0.9 times 4, and the total < 5 year population will be represented by 4.6. Annual births will represent only 1.0/4.6, or 22% of this < 5 year population (and infant deaths further reduce the size of the infant population to result in the 21% cited above). Any two of the three factors used in these estimates allow the remaining variable to be determined. Determining the annual rate of Hib meningitis per 100 000 children 0–11 months of age and the proportion of < 5 year cases occurring in children 0–11 months of age will allow the rate of < 5 year Hib meningitis to be estimated. This suggests an alternate approach to obtaining < 5 year Hib meningitis incidence data when the population of children 0–11 months of age is reliably available, and may also be used to assess internal consistency when both < 1 year and < 5 year Hib rates are available.

4.3 Ratio of Hib meningitis to pneumococcal meningitis

Neither Hib nor pneumococcal meningitis has a propensity for epidemics, and the ratio of < 5 year Hib meningitis cases to < 5 year pneumococcal cases should reflect in part laboratory proficiency in identifying Hib. The increasing ratios over time in regions other than AMR and EUR are consistent with improvements in the ability to identify Hib. Increasing proficiency in identifying Hib by laboratories in these regions might offset other factors, such as increasing antibiotic use, with opposite effects on rates of < 5 year Hib meningitis. A striking decline in < 5 year pneumococcal meningitis rates appears to have accompanied the above changes (data to be presented elsewhere). Too few data were available to permit a meaningful assessment of these changes by region.

4.4 Antibiotic pre-treatment

Another factor possibly influencing the observed trends in rates of both pneumococcal and Hib meningitis in children < 5 years of age is the likely increasing community use of antibiotics, although available evidence of trends in global usage patterns does not seem adequate to address this fully. Frequency of prior antibiotic use was not significant in regression analysis, but this information was reported in only 28 studies. Analysis of 13 studies where the effects of antibiotic treatment on CSF cultures could be determined showed a very substantial influence on the ability to isolate bacterial agents. The inability to show an effect of magnitude of prior antibiotic use on < 5 year Hib meningitis incidence in regression analysis (only 11 complete records), or a quantitative relationship between antibiotic use and the frequency with which the etiology was determined in < 5 year bacterial meningitis cases, probably reflects both small numbers and inaccuracies in this variable. Parents may be reluctant to admit that they have administered antibiotics available either over-the-counter or as leftovers of earlier prescriptions for household members. Parents also may be uncomfortable in acknowledging that they sought outpatient care from a different physician who was responsible for starting antibiotics. In the Philippines, assay of urine for antibacterial activity in children admitted with respiratory infections showed activity in virtually all of the 55% of children whose guardians reported such use, but also found antibacterial activity in 34% of children for whom such use had not been acknowledged *(Sombrero et al. 1999)*. In China, only 36% of children admitted to hospital were acknowledged to have taken antibiotics before admission, but direct evidence of antibacterial activity was found in 70% of blood samples and 43% of CSF samples obtained from children with clinically diagnosed bacterial meningitis *(Yang et al. 1993)*.

Despite the importance of prior treatment with antibiotics, separate reporting of results for those with and without prior treatment was infrequent. Isolation of bacteria was about 50% more frequent from clinical specimens from children without histories of antibiotic use. The available information on isolation of Hib is limited to only three of our studies, but overall results suggest an effect of roughly this magnitude (Table 2). As noted above, however, histories are likely to underestimate use, and many children thought not to have received antibiotics probably had in fact received them. This would produce an underestimate of the actual magnitude of the effects of prior antibiotics. If the average frequency of prior treatment is about 37% (the mean for 28 studies that reported this information) and prior use of antibiotics reduces Hib isolation by about 50%, then the total number of Hib isolations in the studies in our database would be expected to be at least 1.23-fold higher than if no prior antibiotics had been used. However, as noted above, the actual frequency of use is likely to exceed the reported frequency. Prior antibiotics are thought to have more of an effect on culture results than on antigen-test results.

4.5 Antigen tests

Some authors have questioned the utility of latex tests *(Perkins et al. 1995, Tarafdar et al. 2001)*; however, their studies were carried out in industrialised countries many years after Hib vaccine had been introduced and the number of cases of Hib meningitis had fallen to negligible levels. In contrast, our data set was based on studies in countries prior to Hib vaccine introduction. The data from studies conducted in the pre-vaccine era show substantial evidence of in-use effectiveness, increasing identifications of Hib by 31% (Table 3). Latex tests were reportedly used in only 58 (25%) of 229 studies, but may well have been used without notation in many others, thus accounting for lack of significance of this variable in logistic regression. If antigen tests had been used in all studies, this would be expected to increase overall identifications of Hib by at least 1.25 fold. A much higher percentage of Hib infections in CSF can be identified by antigen tests alone (range 86% to 92% depending on method of analysis) compared with culture alone. This suggests that for countries assessing the burden of Hib meningitis prior to vaccine introduction, given the option of using only one of these tests, antigen tests alone are likely to produce significantly larger yields than culture alone.

Our present observations are based on studies that were selected on the basis of Hib content, and not designed for specific study of pneumococcal infections, or the effects of antibiotics, or antigen tests. We have sought to understand the effects of these factors within our data set, but do not know how representative the results may be for studies specifically designed to more broadly study these other issues.

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Annex 1:
Countries and territories, by WHO region

WHO African Region (AFR)

Algeria, Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Namibia, Niger, Nigeria, Reunion, Rwanda, Saint Helena, Sao Tome and Principe, Senegal, Seychelles, United Republic of Tanzania, Zambia, Zimbabwe

WHO Region of the Americas (AMR)

Anguilla, Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Bermuda, Bolivia, Brazil, British Virgin Islands, Canada, Cayman Islands, Chile, Colombia, Costa Rica, Cuba, Dominica, Dominican Republic, Ecuador, El Salvador, French Guyana, Grenada, Guadeloupe, Guatemala, Guyana, Haiti, Honduras, Jamaica, Martinique, Mexico, Montserrat, Netherlands Antilles, Nicaragua, Panama, Paraguay, Peru, Puerto Rico, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and The Grenadines, Suriname, Trinidad and Tobago, Turks and Caicos Islands, United States of America, United States Virgin Islands, Uruguay, Venezuela

WHO Eastern Mediterranean Region (EMR)

Afghanistan, Bahrain, Cyprus, Djibouti, Egypt, Iran (Islamic Republic of), Iraq, Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Morocco, Oman, Pakistan, Qatar, Saudi Arabia, Somalia, Sudan, Syrian Arab Republic, Tunisia, United Arab Emirates, UNWRA (United Nations Relief and Works Agency for Palestine Refugees in the Near East), West Bank and Gaza, Yemen

WHO European Region (EUR)

Albania, Andorra, Armenia, Austria, Azerbaijan, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Luxembourg, Malta, Monaco, Netherlands, Norway, Poland, Portugal, Republic of Moldova, Romania, Russian Federation, San Marino, Slovakia, Slovenia, Spain, Sweden, Switzerland, Tajikistan, The former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Ukraine, United Kingdom, Uzbekistan, Yugoslavia

WHO South-East Asia Region (SEAR)

Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand

WHO Western Pacific Region (WPR)

American Samoa, Australia, Brunei Darussalam, Commonwealth of the Northern Mariana Islands, Cambodia, China, Cook Islands, Federated States of Micronesia, Fiji, French Polynesia, Guam, Japan, Kiribati, Lao People's Democratic Republic, Malaysia, Marshall Islands, Micronesia (Federated States of), Mongolia, Nauru, New Caledonia, New Zealand, Niue, Palau, Papua New Guinea, Philippines, Republic of Korea, Samoa, Singapore, Solomon Islands, Toklau, Tonga, Tuvalu, Vanuatu, Viet Nam, Wallis and Futuna Islands

Annex 2:

Tables summarizing information from 229 studies of *Haemophilus influenzae* type b (Hib) meningitis in children < 5 years of age, by WHO region

Note: Please refer to Section 2 "Methods" for details about variables in these tables.

WHO region and study number	Country	Study site	Year started	Duration (years)	Reference	Type of study	Estimated midpoint census of children <5 years for incidence studies	Hib meningitis														Bacterial meningitis			
								Number of cases <5 years, by age group (in months)						Annual incidence per 100 000 <5 years	Case-fatality rate in <5 years	Percent of cases <5 years, by age group (in months)						Percent of cases with antibiotic pre-treatment	Percent of cases <5 years with established etiology	Number of cases <5 years with established etiology	Percent of cases <5 years with established etiology due to Hib
								<1	0-5	0-11	0-23	24-59	0-59			<1	0-5	0-11	0-23	24-59					
AFRICAN REGION (AFR)																									
AFR studies with incidence data																									
1	Burkina Faso	Bobo-Dioulasso	1989	1	Tall 1992	Population-based Prospective	47 136	_	_	27	_	_	29	61.5	23	_	_	93	_	_	_	_	_	_
2	Gambia	Half of the Country	1985	2	Bijlmer 1990	Population-based Prospective	64 311	1	_	64	72	5	77	60.0	37	1	_	83	94	6	_	_	_	_
3	Gambia	Western Region	1990	3	Adegbola 1996	Population-based Prospective	82 000	4	_	120	135	6	141	57.3	16	3	_	85	96	4	_	_	_	_
4	Niger	Niamey	1981	11	Campagne 1999	Population-based Retrospective	92 346	_	_	530	566	45	611	60.0	44	_	_	87	93	7	_	83	1 507	41
5	Senegal	Dakar	1970	10	Cadoz 1981	Population-based Retrospective	168 000	_	_	490	_	_	651	38.8	34	_	_	75	_	_	_	73	1 599	41
6	South Africa	Cape Town	1991	1	Hussey 1997	Population-based Prospective	228 000	_	_	51	69	4	73	32.0	5	_	_	70	95	5	_	_	174	42
AFR studies without incidence data																									
7	Algeria	Alger	1966	2	Benallegue 1970	Hospital-based Retrospective		_	_	_	_	_	20		65	_	_	_	_	_	_	63	58	34
8	Cameroon	Yaounde	1982	2	Bernard-Bonnin 1985	Hospital-based Retrospective		_	_	29	42	9	51		24	_	_	57	82	18	_	80	152	34

WHO region and study number	Country	Study site	Year started	Duration (years)	Reference	Type of study	Estimated midpoint census of children <5 years for incidence studies	Hib meningitis														Bacterial meningitis			
								Number of cases <5 years, by age group (in months)						Annual incidence per 100 000 <5 years	Case-fatality rate in <5 years	Percent of cases <5 years, by age group (in months)						Percent of cases with antibiotic pre-treatment	Percent of cases <5 years with established etiology	Number of cases <5 years with established etiology	Percent of cases <5 years with established etiology due to Hib
								<1	0-5	0-11	0-23	24-59	0-59			<1	0-5	0-11	0-23	24-59					
9	Côte d'Ivoire	Dabou	1985	1	DeBary 1990	Hospital-based Prospective		_	_	54	_	_	65		_	_	_	83	_	_	_	92	130	50
10	Democratic Republic of the Congo	Kinshasa	1958	20	Omanga 1980	Hospital-based Prospective		_	_	_	_	_	111		14	_	_	_	_	_	_	46	239	46
11	Democratic Republic of the Congo	Kinshasa	1959	13	Lontie 1973	Hospital-based Prospective		_	_	_	_	_	91		18	_	_	_	_	_	_	_	320	28
12	Democratic Republic of the Congo	Lubumbashi	1973	3	Talleyrand 1979	Hospital-based Prospective		_	_	12	_	_	_		_	_	_	_	_	_	_	45	_	_
13	Ethiopia	Addis Ababa	1975	2	Hailemeskel 1978	Hospital-based Retrospective		_	_	49	49	0	49		19	_	_	100	100	0	_	_	_	_
14	Ethiopia	Addis Ababa	1993	3	Muhe 1999	Hospital-based Retrospective		_	_	_	_	_	74		38	_	_	_	_	_	_	_	116	64
15	Ethiopia	Gondar	1990	5	Gedlu 1995	Hospital-based Retrospective		_	17	27	_	_	31		48	_	55	87	_	_	_	68	65	48
16	Gambia	Banjul	1991	4	Palmer 1999	Hospital-based Prospective		1	43	91	_	_	109		17	1	39	83	_	_	_	68	244	45
17	Ghana	Accra	1991	1.4	Commey 1994	Hospital-based Prospective		_	_	_	_	_	7		_	_	_	_	_	_	_	_	_	_
18	Ghana	Kumasi	1983	1.7	Zadik 1986	Hospital-based Prospective		_	_	11	11	0	11		63	_	_	100	100	0	_	_	_	_
19	Ghana	Kumasi	1989	0.7	Mackie 1992	Hospital-based Prospective		_	_	_	5	5	10		30	_	_	_	50	50	_	_	34	29

WHO region and study number	Country	Study site	Year started	Duration (years)	Reference	Type of study	Estimated midpoint census of children <5 years for incidence studies	Hib meningitis													Bacterial meningitis			
								Number of cases <5 years, by age group (in months)						Annual incidence per 100 000 <5 years	Case-fatality rate in <5 years	Percent of cases <5 years, by age group (in months)					Percent of cases with antibiotic pre-treatment	Percent of cases <5 years with established etiology	Number of cases <5 years with established etiology	Percent of cases <5 years with established etiology due to Hib
								<1	0-5	0-11	0-23	24-59	0-59			<1	0-5	0-11	0-23	24-59				
20	Kenya	Nairobi	1985	1	Nesbitt 1988	Hospital-based Prospective		_	_	18	24	_	_		38	_	_	_	_	_	31	_	_	_
21	Kenya	Nairobi	1995	0.6	Mirza 1998	Hospital-based Prospective		_	_	12	14	1	16		7	_	_	75	93	7	_	71	96	17
22	Malawi	Blantyre	1972	2	Brown 1975	Hospital-based Retrospective		_	_	_	_	_	23		14	_	_	_	_	_	_	52	45	51
23	Malawi	Blantyre	1996	1	Molyneux 1998	Hospital-based Prospective		_	_	27	_	_	44		44	_	_	61	_	_	22	76	167	26
24	Malawi	Lilongwe	1989	1	Cuevas 1991	Hospital-based Retrospective		1	4	7	8	2	10		_	10	40	_	80	20	_	60	118	8
25	Mozambique	Maputo	1989	0.6	Ciana 1995	Hospital-based Prospective		_	_	_	_	_	12		_	_	_	_	_	_	_	73	51	24
26	Nigeria	Benin City	1974	5.4	Obi 1980	Hospital-based Retrospective		_	_	4	_	_	4		0	_	_	100	_	_	_	_	25	16
27	Nigeria	Benin City	1985	5.9	Akpede 1994a	Hospital-based Retrospective		_	_	28	37	1	38		_	_	_	74	97	3	_	_	164	23
28	Nigeria	Calabar	1981	2.8	Asindi 1986	Hospital-based Retrospective		_	_	3	6	_	6		17	_	_	50	100	_	_	_	46	13
29	Nigeria	Eastern Nigeria	1989	2	Onyemelukwe 1994	Hospital-based Prospective		0	_	19	35	4	39		_	0	_	49	90	10	_	_	93	42
30	Nigeria	Ibadan	1976	1.3	Montfiore 1978	Hospital-based Prospective		0	_	21	_	_	30		20	0	_	70	_	_	_	_	89	34

WHO region and study number	Country	Study site	Year started	Duration (years)	Reference	Type of study	Estimated midpoint census of children <5 years for incidence studies	Hib meningitis													Bacterial meningitis			
								Number of cases <5 years, by age group (in months)						Annual incidence per 100 000 <5 years	Case-fatality rate in <5 years	Percent of cases <5 years, by age group (in months)					Percent of cases with antibiotic pre-treatment	Percent of cases <5 years with established etiology	Number of cases <5 years with established etiology	Percent of cases <5 years with established etiology due to Hib
								<1	0-5	0-11	0-23	24-59	0-59			<1	0-5	0-11	0-23	24-59				
31	Nigeria	Ibadan	1976	5	Nottidge 1985	Hospital-based Prospective		2	_	108	120	_	_		26	_	_	_	_	_	_	_	_	_
32	Nigeria	Lagos	1970	4	Ogubemi 1975	Hospital-based Retrospective		_	10	_	_	_	42		_	_	24	_	_	_	_	_	208	20
33	Nigeria	Maiduguri	1988	4.9	Akpede 1994b	Hospital-based Prospective		_	5	7	8	1	9		_	_	56	78	89	11	_	68	64	14
34	Nigeria	Sokoto	1987	5	Emele 2000	Hospital-based Prospective		0	_	2	_	_	12		_	0	_	17	_	_	_	_	142	8
35	Rwanda	Kigali	1983	8	Salaun-Saraux 1995	Hospital-based Retrospective		_	_	_	78	19	97		28	_	_	_	80	20	_	_	241	40
36	South Africa	Western Cape	1981	3	Donald 1986	Hospital-based Prospective		1	12	30	43	2	45		_	2	27	67	96	4	_	_	_	_
37	South Africa	Western Cape	1985	9	Donald 1996	Hospital-based Prospective		_	_	108	138	14	152		_	_	_	71	91	9	_	_	566	27
38	Swaziland	National	1991	1.5	Ford 1994	Population-based Prospective		_	_	_	_	_	8		25	_	_	_	_	_	7	_	_	_
39	Uganda	Kampala	1965	0.7	Foster 1966	Hospital-based Retrospective		_	_	14	17	1	18		39	_	_	78	94	6	_	_	41	44
40	Zambia	Lusaka	1973	1	Chintu 1975	Hospital-based Prospective		_	_	6	7	0	7		_	_	_	86	100	_	_	56	34	21
41	Zambia	Lusaka	1978	1	Bhushan 1979	Hospital-based Prospective		0	_	4	_	_	7		14	_	_	57	_	_	_	58	54	13

WHO region and study number	Country	Study site	Year started	Duration (years)	Reference	Type of study	Estimated midpoint census of children <5 years for incidence studies	Hib meningitis														Bacterial meningitis			
								Number of cases <5 years, by age group (in months)						Annual incidence per 100 000 <5 years	Case-fatality rate in <5 years	Percent of cases <5 years, by age group (in months)						Percent of cases with antibiotic pre-treatment	Percent of cases <5 years with established etiology	Number of cases <5 years with established etiology	Percent of cases <5 years with established etiology due to Hib
								<1	0-5	0-11	0-23	24-59	0-59			<1	0-5	0-11	0-23	24-59					
42	Zambia	Lusaka	1980	2	Dube 1983	Hospital-based Prospective		_	_	11	_	_	13		_	_	_	85	_	_	_	_	141	9
43	Zambia	Lusaka	1967	1	Johnston 1970	Hospital-based Prospective		_	_	_	14	0	14		33	_	_	_	100	0	_	55	29	48
AMERICAS REGION (AMR)																									
AMR studies with incidence data																									
44	Argentina	Tucuman	1993	2	Fernandez 1996	Population-based Retrospective	135 368	_	_	61	78	4	82	30.3	18	_	_	74	95	5	_	_	109	75
45	Brazil	Campinas	1997	2	Weiss 2001	Population-based Prospective	76 473	_	9	18	24	2	26	17.0	15	_	35	69	92	8	8	52	92	28
46	Brazil	Salvador	1973	10	Bryan 1990	Population-based Retrospective	203 000	3	271	_	758	95	853	42.0	37	0	32	_	89	11	44	73	1 611	53
47	Canada	Manitoba	1981	3	Hammond 1988	Population-based Prospective	77 124	_	9	25	49	10	59	25.5	_	_	16	42	83	17	_	70	_	_
48	Chile	Santiago	1985	3	Ferreccio 1990	Population-based Retrospective	594 043	_	63	188	263	28	291	16.0	16	_	22	65	90	10	_	_	_	_
49	Cuba	National	1992	6	Tamargo 1999	Surveillance	816 605	_	_	_	_	_	765	15.6	_	_	_	_	_	_	_	_	_	_
50	Cuba	National	1994	5	Dickinson 2001	Population-based Prospective	735 133	_	_	51	93	34	127	15.5	_	_	_	40	73	27	_	_	_	_

WHO region and study number	Country	Study site	Year started	Duration (years)	Reference	Type of study	Estimated midpoint census of children <5 years for incidence studies	Hib meningitis														Bacterial meningitis			
								Number of cases <5 years, by age group (in months)						Annual incidence per 100 000 <5 years	Case-fatality rate in <5 years	Percent of cases <5 years, by age group (in months)						Percent of cases with antibiotic pre-treatment	Percent of cases <5 years with established etiology	Number of cases <5 years with established etiology	Percent of cases <5 years with established etiology due to Hib
								<1	0-5	0-11	0-23	24-59	0-59			<1	0-5	0-11	0-23	24-59					
51	Dominican Rebublic	National District	1998	2	SESPAS 2000	Population-based Prospective	329 000	_	36	71	79	5	84	12.8	_	_	43	85	94	6	_	38	200	42
52	Guatemala	Guatemala City	1996	2.3	Asturias 2001	Population-based Prospective	121 003	_	24	_	_	_	71	13.8	14	_	32	_	_	_	44	44	157	45
53	Jamaica	Kingston & St Andrew Region	1990	4	Barton-Forbes 2000	Population-based Retrospective	67 615	_	_	_	_	_	65	29.5	11	_	_	_	_	_	_	_	_	_
54	USA	Alaska	1980	3	Ward 1986	Population-based Retrospective	31 585	2	11	33	53	12	65	68.6	_	3	17	51	82	18	_	_	_	_
55	USA	Fresno County, California	1976	2.4	Granoff 1980	Population-based Prospective	39 090	_	_	23	_	_	59	62.9	_	_	_	39	_	_	_	_	_	_
56	USA	Colorado	1981	0.5	Istre 1985	Population-based Prospective	_	_	_	_	_	_	_	68.0	_	_	_	_	_	_	_	_	_	_
57	USA	Atlanta, Georgia	1983	1	Cochi 1986	Population-based Prospective	139 024	_	_	_	_	_	79	57.0	_	_	_	_	_	_	_	_	_	_
58	USA	Baltimore, Maryland	1965	11	Santosham 1979	Population-based Retrospective	125 134	_	_	142	_	_	267	19.3	4	_	_	53	_	_	_	_	_	_
59	USA	Minnesota	1983	2	Murphy 1992	Population-based Prospective	335 714	_	_	_	_	_	282	42.0	4	_	_	_	_	_	_	_	_	_
60	USA	Olmsted County, Minnesota	1959	12	Fraser 1973	Population-based Retrospective	8 700	1	_	_	_	_	42	40.0	5	2	_	_	_	_	_	_	57	74
61	USA	Monroe County, New York	1982	2	Redmond 1984	Population-based Retrospective	45 579	_	_	20	32	15	47	52.0	_	_	_	43	68	32	_	_	_	_

WHO region and study number	Country	Study site	Year started	Duration (years)	Reference	Type of study	Estimated midpoint census of children <5 years for incidence studies	Hib meningitis													Bacterial meningitis			
								Number of cases <5 years, by age group (in months)						Annual incidence per 100 000 <5 years	Case-fatality rate in <5 years	Percent of cases <5 years, by age group (in months)					Percent of cases with antibiotic pre-treatment	Percent of cases <5 years with established etiology	Number of cases <5 years with established etiology	Percent of cases <5 years with established etiology due to Hib
								<1	0-5	0-11	0-23	24-59	0-59			<1	0-5	0-11	0-23	24-59				
62	USA	Rhode Island	1970	5	Tarr 1978	Population-based Retrospective	73 880	_	_	_	_	_	99	26.8	3	_	_	_	_	_	_	_	_	_
63	USA	Tennessee	1963	9	Floyd 1974	Population-based Retrospective	52 839	_	_	51	_	_	107	22.5	8	_	_	48	_	_	20	_	255	42
64	USA	Dallas County, Texas	1983	2	Murphy 1992	Population-based Prospective	152 551	_	_	_	_	_	177	58.0	4	_	_	_	_	_	_	_	_	_
65	USA	20 states	1980	5	Adams 1993	Surveillance	7 109 000	_	_	3994	6131	1486	7617	21.4	4	_	_	52	80	20	_	_	10 584	72
66	USA	King County, Washington	1977	10	Sherry 1989	Population-based Retrospective	84 274	_	56	168	324	94	418	49.6	2	_	13	40	78	22	_	_	_	_
AMR studies with incidence data for special-risk groups																								
67	Canada	Keewatin District, Inuits	1981	3	Hammond 1988	Population-based Prospective	566	_	2	8	8	1	9	530.0	_	_	22	89	89	11	_	_	_	_
68	Canada	Manitoba, Native Indians	1981	3	Hammond 1988	Population-based Prospective	21 256	0	7	17	22	0	22	34.5	_	_	32	77	100	0	_	_	_	_
69	USA	Alaska, Eskimos	1971	6.5	Ward 1981	Population-based Prospective	1 881	1	23	46	50	0	50	409.0	_	2	46	92	100	0	_	_	69	72
70	USA	Alaska, Natives	1980	3	Ward 1986	Population-based Retrospective	7 321	1	22	43	58	4	62	282.3	_	2	35	69	94	6	_	_	_	_
71	USA	Alaska, Southwest, Natives	1971	3	Gilsdorf 1977	Population-based Retrospective	1 830	_	13	23	_	_	26	474.0	0	_	50	88	_	_	49	92	33	79

WHO region and study number	Country	Study site	Year started	Duration (years)	Reference	Type of study	Estimated midpoint census of children <5 years for incidence studies	Hib meningitis													Bacterial meningitis			
								Number of cases <5 years, by age group (in months)						Annual incidence per 100 000 <5 years	Case-fatality rate in <5 years	Percent of cases <5 years, by age group (in months)					Percent of cases with antibiotic pre-treatment	Percent of cases <5 years with established etiology	Number of cases <5 years with established etiology	Percent of cases <5 years with established etiology due to Hib
								<1	0-5	0-11	0-23	24-59	0-59			<1	0-5	0-11	0-23	24-59				
72	USA	Apache Indians	1973	10	Losonsky 1984	Population-based Retrospective	947	1	6	26	26	0	26	264.0	_	4	23	100	100	0	_	_	26	_
73	USA	Navajo Indians	1968	6	Coulehan 1984	Population-based Retrospective	15 721	_	_	_	_	_	144	152.3	_	_	_	_	_	_	_	_	_	_
74	USA	Navajo Indians	1974	7	Coulehan 1984	Population-based Retrospective	19 204	0	70	167	196	9	205	152.5	4	0	34	81	96	4	_	_	291	70
AMR studies without incidence data																								
75	Barbados	Queen Elizabeth Hospital	1974	6	St. John 1981	Hospital-based Retrospective		_	_	12	15	10	25		0	_	_	48	60	40	28	_	34	74
76	Bolivia	LaPaz	1992	0.8	Arteaga-Bonilla 1997	Hospital-based Retrospective		_	_	_	_	_	12		25	_	_	_	_	_	_	63	19	63
77	Chile	Santiago	1972	10	Juliet 1983	Hospital-based Retrospective		0	_	128	148	6	154		11	_	_	83	96	4	_	_	330	47
78	Chile	Santiago	1973	9	Herrera 1983	Hospital-based Retrospective		_	_	_	_	_	342		12	_	_	_	_	_	58	_	_	_
79	Chile	Santiago	1980	7	Guerrero 1988	Hospital-based Retrospective		0	_	21	28	0	28		6	0	_	75	100	_	33	60	95	29
80	Chile	Santiago	1983	10	Chavez 1994	Hospital-based Retrospective		0	_	_	154	17	171		19	_	_	_	90	10	_	79	369	46
81	Chile	Temuco	1988	3	Boehme 1993	Hospital-based Prospective		_	_	21	29	4	33		18	_	_	64	88	12	_	84	64	52

WHO region and study number	Country	Study site	Year started	Duration (years)	Reference	Type of study	Estimated midpoint census of children <5 years for incidence studies	Hib meningitis														Bacterial meningitis			
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								<1	0-5	0-11	0-23	24-59	0-59			<1	0-5	0-11	0-23	24-59					
82	Colombia	Medellin	1984	2	Otero 1988	Hospital-based Retrospective		2	11	_	31	8	39		_	5	28	_	79	21	32	95	79	49
83	Colombia	Cartagena	1991	2.1	Chacon 1995	Hospital-based Prospective		0	_	_	_	_	43		15	_	_	_	_	_	_	79	79	54
84	Costa Rica	San Jose	1992	1	Alvarez 1994	Hospital-based Retrospective		_	_	33	_	_	61		_	_	_	54	_	_	_	_	_	_
85	Ecuador	Quito	1988	6.2	Zurita 1995	Hospital-based Retrospective		_	_	_	156	1	157		_	_	_	_	99	1	_	_	_	_
86	Mexico	La Raza	1985	4	Games-Eternod 1991	Hospital-based Retrospective		_	75	_	207	24	231		_	_	32	_	90	10	_	48	326	71
87	Venezuela	Caracas	1976	5	Apollonia 1986	Hospital-based Retrospective		_	_	7	8	2	10		_	_	_	70	80	20	_	29	44	23
EASTERN MEDITERRANEAN REGION (EMR)																									
EMR studies with incidence data																									
88	Kuwait	Al-Kabeer, Al-Amiri, Al-Jahra Hospitals	1981	5.5	Shaltout 1989	Population-based Prospective	98 000	0	11	28	33	9	42	7.8	5	0	26	67	79	21	_	90	73	58
89	Kuwait	Farwania Health District	1981	7	Zaki 1990	Population-based Prospective	46 082	0	15	33	44	5	49	15.2	2	0	31	67	90	10	_	_	87	56
90	Qatar	National	1987	2	Novelli 1989	Population-based Prospective	41 000	_	4	8	12	1	13	15.9	_	_	31	62	92	8	_	_	_	_

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								<1	0-5	0-11	0-23	24-59	0-59			<1	0-5	0-11	0-23	24-59					
91	Saudi Arabia Riyadh		1996	2	Almuneef 2001	Population-based Retrospective	22 000	_	_	25	33	4	37	47.7	_	_	_	68	89	11	_	_	65	57
92	United Arab Emirates	Eastern Region	1990	2.5	Uduman 1994	Population-based Retrospective	36 475	_	7	14	19	1	20	21.9	10	_	35	70	95	5	_	_	32	63
93	United Arab Emirates	Eastern Region	1996	1	Uduman 2000	Population-based Prospective	41 935	_	_	_	_	_	13	31.0	_	_	_	_	_	_	_	78	18	72
EMR studies without incidence data																									
94	Bahrain	Salmaniya Medical Centre	1970	17	Khan 1988	Hospital-based Retrospective		_	12	67	73	6	79		10	_	15	85	93	7	44	_	187	42
95	Egypt	Cairo	1966	22.5	Girgis 1993	Hospital-based Retrospective		_	_	246	_	_	287		39	_	_	86	_	_	_	66	919	31
96	Egypt	Cairo	1977	2	Guirguis 1983	Hospital-based Prospective		_	_	35	_	_	42		57	_	_	83	_	_	_	_	168	25
97	Iran	Tehran	1968	8	Moazami 1977	Hospital-based Retrospective		_	1	9	11	1	12		_	_	8	75	92	8	_		62	19
98	Libyan Arab Jamahiriya	Benghazi	1994	1.2	Rao 1998	Hospital-based Prospective		_	_	23	25	1	26		_	_	_	88	96	4	_	84	56	46
99	Morocco	Casablanca	1994	2.5	Moustaoui 2000	Hospital-based Retrospective		_	_	_	_	_	82		_	_	_	_	_	_	_	_	_	_
100	Saudi Arabia	Al-Baha	1982	8	Al-Jurayyan 1992	Hospital-based Retrospective		_	_	21	25	1	26		4	_	_	81	96	4	_	78	52	50

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								<1	0-5	0-11	0-23	24-59	0-59			<1	0-5	0-11	0-23	24-59				
101	Saudi Arabia	Eastern Province	1982	3	Abomelha 1988	Hospital-based Retrospective		_	7	34	42	0	42		14	_	17	81	100	0	_	_	94	45
102	Saudi Arabia	Elmadina Elmunawara	1988	1	El-Amin 1991	Hospital-based Retrospective		_	_	11	_	_	19		_	_	_	58	_	_	_	65	46	41
103	Saudi Arabia	Qatif	1988	4	Srair 1992	Hospital-based Retrospective		_	1	7	8	0	8		_	_	13	88	100	0	45	_	25	32
104	Saudi Arabia	Riyadh	1980	2	Babiker 1984	Hospital-based Prospective		_	_	_	_	_	_		_	_	_	_	_	_	24	_	_	_
105	Saudi Arabia	Riyadh	1983	1	Talukder 1987	Hospital-based Prospective		_	_	4	6	0	6		_	_	_	67	100	0	_	_	9	67
106	Saudi Arabia	Riyadh	1984	11	Almuneef 1998	Hospital-based Retrospective		_	_	_	44	2	46		_	_	_	_	96	4	_	_	68	68
107	Saudi Arabia	Riyadh	1989	5	Abdullah 1997	Hospital-based Prospective		_	_	_	_	_	9		_	_	_	_	_	_	_	_	_	_
108	Saudi Arabia	Tabuk	1982	6	Azubuike 1990	Hospital-based Retrospective		_	_	_	24	3	27		15	_	_	_	89	11	45	78	38	71
109	Sudan	Khartoum	1985	1.5	Salih 1990	Hospital-based Prospective		_	_	19	_	_	24		16	_	_	79	_	_	_	_	36	67
110	Sudan	Khartoum	1989	1.5	Ahmed 1996	Hospital-based Prospective		_	_	16	20	1	21		_	_	_	76	95	5	34	_	38	55

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								<1	0-5	0-11	0-23	24-59	0-59			<1	0-5	0-11	0-23	24-59					
EUROPEAN REGION (EUR)																									
EUR studies with incidence data																									
111	Austria	Leoben	1983	10	Rauter 1994	Population-based Retrospective	17 600	_	_	8	24	12	36	20.5	6	_	_	22	67	33	25	94	67	54
112	Austria	National	1990	3	Vutuc 1995	Population-based Retrospective	453 074	_	_	_	_	_	146	10.7	_	_	_	_	_	_	_	_	_	_
113	Bulgaria	6 regions	1992	5	Kojouharova 2001	Population-based Retrospective	149 431	_	5	_	31	13	44	5.9	_	_	11	_	70	30	_	65	137	32
114	Bulgaria	6 regions	1997	2.5	Kojouharova 2002	Population-based Prospective	137 705	_	2	8	10	11	21	6.1	10	_	10	38	48	52	_	73	88	24
115	Croatia	National	1995	5	Borcic 2000	Surveillance	280 056	_	_	15	36	7	43	3.1	2	_	_	35	84	16	_	_	_	_
116	Czech Republic	National	1987	4	Kriz 2000	Surveillance	662 848	_	_	22	_	_	133	5.0	2	_	_	17	_	_	_	_	_	_
117	Czech Republic	National	1992	4	Kriz 2000	Surveillance	622 090	_	_	40	_	_	153	6.2	0	_	_	26	_	_	_	_	_	_
118	Czech Republic	National	1997	3	Kriz 2000	Surveillance	486 810	2	16	35	80	72	152	10.0	2	1	11	23	53	47	_	_	_	_

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								<1	0-5	0-11	0-23	24-59	0-59			<1	0-5	0-11	0-23	24-59				
119	Denmark	National	1975	10	Peltola 1990	Surveillance	261 616	_	71	213	388	130	518	19.8	_	_	14	41	75	25	_	_	_	_
120	Denmark	National	1985	2	Kristensen 1990	Population-based Retrospective	281 481	_	12	63	123	29	152	27.0	3	_	8	41	81	19	_	_	_	_
121	Denmark	National	1991	2	Hansen 1997	Population-based Retrospective	306 029	_	13	74	141	18	159	26.0	_	_	8	47	89	11	_	_	_	_
122	Finland	Helsinki	1946	5	Peltola 1992	Population-based Retrospective	39 936	_	_	_	_	_	32	16.0	_	_	_	_	_	_	_	_	_	_
123	Finland	Helsinki	1966	5	Peltola 1992	Population-based Retrospective	51 788	_	_	_	_	_	59	23.0	_	_	_	_	_	_	_	_	_	_
124	Finland	Helsinki	1976	5	Peltola 1992	Population-based Retrospective	49 494	_	_	_	_	_	105	43.0	_	_	_	_	_	_	_	_	_	_
125	Finland	National	1975	10	Peltola 1990	Surveillance	350 357	_	88	282	602	283	885	25.3	_	_	10	32	68	32	_	_	_	_
126	Finland	National	1976	5	Valmari 1987	Population-based Retrospective	_	_	_	_	_	_	_	27.0	_	_	_	_	_	_	_	_	_	_
127	Finland	National	1985	2	Takala 1989	Population-based Prospective	288 462	_	7	44	90	50	140	24.3	4	_	5	31	64	36	_	_	_	_
128	France	Val-de-Marne and Haute Garonne	1980	7	Livartowski 1989	Population-based Retrospective	119 500	_	7	56	95	28	123	14.7	3	_	6	46	77	23	_	_	_	_
129	France	Val-de-Marne and Haute Garonne	1980	10	Reinert 1993	Population-based Retrospective	118 000	_	11	74	138	39	177	15.0	_	_	6	42	78	22	_	_	_	_

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								<1	0-5	0-11	0-23	24-59	0-59			<1	0-5	0-11	0-23	24-59					
130	Germany	Bochun City Area	1971	21.5	Severien 1994	Population-based Retrospective	16 537	_	_	10	21	11	32	9.0	_	_	_	31	66	34	_	_	_	_	
131	Germany	Former East Germany	1989	1	Noack 1991	Surveillance	1 100 000	_	_	_	_	_	88	8.0	_	_	_	_	_	_	_	_	505	_	
132	Greece	Greater Athens Area	1992	2	Tsolia 1998	Population-based Prospective	175 395	_	4	10	25	3	28	8.0	_	_	14	36	89	11	_	62	73	38	
133	Greece	Southwestern Greece	1990	5	Syrogiannopoulos 1995	Population-based Retrospective	35 000	_	4	8	11	3	14	8.0	0	_	29	57	79	21	_	74	34	41	
134	Hungary	National	1998	1	Hungary MOH 2000	Surveillance	663 661	_	_	4	7	2	9	1.4	0	_	_	44	78	22	_	_	53	17	
135	Iceland	National	1974	15	Olafsson 1990	Surveillance	_	_	13	46	99	36	135	45.0	_	_	10	34	73	27	_	_	_	_	
136	Iceland	National	1974	11	Peltola 1990	Surveillance	_	_	_	_	_	_	_	46.3	_	_	8	31	72	28	_	_	_	_	
137	Ireland	National	1991	2	Fogarty 1995	Population-based Prospective	272 727	_	_	29	52	14	66	12.1	_	_	_	44	79	21	_	_	_	_	
138	Israel	National	1981	10	Slater 1990-91	Surveillance	464 955	_	130	540	784	50	834	17.9	3	_	16	65	94	6	_	_	_	_	
139	Israel	National	1988	2	Dagan 1992	Population-based Prospective	496 540	_	_	129	167	7	174	17.5	1	_	_	74	96	4	_	_	_	_	
140	Israel	Negev Region	1984	5	Halfon-Yaniv 1990	Population-based Retrospective	37 273	_	9	34	41	0	41	22.0	7	_	22	83	100	0	_	_	_	_	

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								<1	0-5	0-11	0-23	24-59	0-59			<1	0-5	0-11	0-23	24-59				
141	Italy	Florence	1993	2	Squarcione 1999	Population-based Prospective	35 148	_	_	_	6	0	6	8.5	_	_	_	_	100	0	_	_	_	_
142	Italy	Genoa	1993	2	Squarcione 1999	Population-based Prospective	25 952	_	_	_	4	2	6	11.5	_	_	_	_	67	33	_	_	_	_
143	Italy	Latium	1994	1	Squarcione 1999	Population-based Prospective	240 161	_	_	_	19	8	27	11.2	_	_	_	_	70	30	_	_	_	_
144	Italy	Naples	1987	9	Pizzuti 1998	Population-based Retrospective	210 432	_	_	28	50	5	55	2.9	_	_	_	51	91	9	_	57	142	39
145	Italy	Apulia	1994	1	Chironna 1998	Population-based Retrospective	243 529	_	_	3	6	0	6	2.5	_	_	_	50	100	0	_	61	14	43
146	Italy	Apulia	1995	1	Chironna 1998	Population-based Retrospective	240 959	_	2	9	11	3	14	5.8	_	_	14	64	79	21	_	64	18	78
147	Latvia	National	1997	1	Latvia MOH 2000	Surveillance	108 842	_	1	1	1	0	1	0.9	_	_	100	100	100	0	_	_	_	_
148	Latvia	National	1999	1	Latvia MOH 2000	Surveillance	96 268	0	0	0	1	0	1	1.0	_	0	0	0	100	0	_	_	_	_
149	Luxembourg	National	1980	13	DeJonghe 1995	Poplation-Based Retrospective	22 462	_	_	_	_	_	37	12.7	3	_	_	_	_	_	_	_	_	_
150	Malta	National	1990	5	Sciberras 1999	Population-based Retrospective	23 913	_	_	_	_	_	11	9.2	_	_	_	_	_	_	_	_	19	58
151	Netherlands	National	1980	2	Spanjaard 1985	Population-based Retrospective	887 670	_	_	_	_	_	335	22.0	_	_	_	_	_	_	_	_	735	46

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								<1	0-5	0-11	0-23	24-59	0-59			<1	0-5	0-11	0-23	24-59				
152	Norway	National	1975	10	Peltola 1990	Surveillance	266 950	_	72	160	309	258	567	21.2	_	_	13	28	55	45	_	_	_	_
153	Poland	2 districts (Kielce, Bydgoszcz)	1998	2	Zielinski 2001	Population-based Prospective	130 267	_	_	4	12	5	17	6.5	6	_	_	24	71	29	_	75	56	30
154	Poland	7 districts	1998	1	Tomaszunas 1999	Population-based Prospective	319 568	_	_	_	_	_	19	6.0	_	_	_	_	_	_	_	63	65	29
155	Russian Federation	Moscow	1999	1	Platonov 2001	Population-based Prospective	344 000	_	_	2	11	8	19	5.5	11	_	_	11	58	42	44	77	88	22
156	Slovakia	National	1996	2	Novakova 1999	Population-based Prospective	101 156	_	5	15	_	_	35	17.3	_	_	14	43	_	_	_	_	_	38
157	Slovakia	National	1991	8	Hudeckova 2000	Population-based Retrospective	375 176	_	10	51	114	79	193	6.4	17	_	5	26	59	41	_	59	391	49
158	Slovenia	National	1993	1	Cizman 1995	Population based Prospective	102 804	_	1	_	11	0	11	10.7	8	_	9	_	100	0	_	_	_	_
159	Spain	Barcelona	1994	2	Beni 1999	Population-based Retrospective	55 195	_	_	_	_	_	12	10.9	_	_	_	_	_	_	_	_	_	_
160	Spain	12 regions	1993	2	CNE 1997	Population-based Retrospective	1 230 982	_	31	86	157	35	192	7.8	2	_	16	45	82	18	_	_	_	_
161	Spain	Basque Region	1993	2	Perez-Trallero 1995	Population-based Retrospective	80 000	_	_	_	_	_	29	18.0	_	_	_	_	_	_	_	_	_	_
162	Spain	Valencia	1984	7	Asensi 1995	Population-based Retrospective	36 310	_	_	_	_	_	56	22.0	8	_	_	_	_	_	_	_	_	_

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								<1	0-5	0-11	0-23	24-59	0-59			<1	0-5	0-11	0-23	24-59				
163	Sweden	Gotenberg	1971	10	Claesson 1984	Population-based Retrospective	45 755	1	16	46	80	42	122	26.7	_	1	13	38	66	34	_	_	_	_
164	Sweden	National	1979	6	Peltola 1990	Surveillance	_	_	_	_	_	_	_	16.6	_	_	13	39	73	27	_	_	_	_
165	Sweden	National	1981	3	Trollfors 1987	Population-based Retrospective	477 461	_	72	202	325	115	440	30.7	2	_	16	46	74	26	_	_	_	_
166	Sweden	National	1987	3	Berg 1996	Population-based Retrospective	508 430	7	71	_	318	105	423	27.7	2	2	17	_	75	25	_	_	559	76
167	Sweden	Orebro County	1987	6	Hugosson 1995	Population-based Prospective	16 666	_	_	_	_	_	31	31.0	3	_	_	_	_	_	_	_	_	_
168	Switzerland	Geneva	1976	14	Gervaix 1993	Population-based Retrospective	19 578	_	_	35	55	20	75	27.4	0	_	_	47	73	27	_	_	_	_
169	Switzerland	National	1980	11	Muhlemann 1996	Population-based Retrospective	365 942	_	_	_	_	_	1041	25.9	_	_	_	_	_	_	_	_	_	_
170	UK	England, Cambridge	1975	7	Broughton 1984	Population-based Retrospective	_	_	_	11	22	16	38	18.0	3	_	_	29	58	42	_	_	_	_
171	UK	England, Northwest Region	1969	5	Goldacre 1976	Population-based Retrospective	314 545	_	25	56	103	70	173	11.0	6	_	15	32	60	40	_	83	510	34
172	UK	England, Northwest Region	1989	1	Quigley 1993	Population-based Prospective	292 555	_	_	_	_	_	50	17.0	2	_	_	_	_	_	_	_	_	_
173	UK	England, 5 regions	1990	2	Anderson 1995	Population-based Prospective	1 196 000	1	57	161	279	96	375	15.7	_	_	15	43	74	26	_	_	_	_

WHO region and study number	Country	Study site	Year started	Duration (years)	Reference	Type of study	Estimated midpoint census of children <5 years for incidence studies	Hib meningitis													Bacterial meningitis			
								Number of cases <5 years, by age group (in months)						Annual incidence per 100 000 <5 years	Case-fatality rate in <5 years	Percent of cases <5 years, by age group (in months)					Percent of cases with antibiotic pre-treatment	Percent of cases <5 years with established etiology	Number of cases <5 years with established etiology	Percent of cases <5 years with established etiology due to Hib
								<1	0-5	0-11	0-23	24-59	0-59			<1	0-5	0-11	0-23	24-59				
174	UK	Scotland	1991	1	Brewster 1993	Population-based Retrospective	326 087	_	_	_	_	_	60	18.4	_	_	_	_	_	_	_	_	_	_
175	UK	Scotland, Glasgow	1981	10	Coggins 1993	Population-based Retrospective	60 924	_	20	64	109	36	145	23.8	3	_	14	44	75	25	_	_	_	_
176	UK	Wales	1980	11	Howard 1991	Population-based Prospective	13 917	_	_	20	34	13	47	30.7	_	_	_	43	72	28	_	_	_	_
177	UK	Wales	1988	3	Howard 1991	Population-based Prospective	178 788	_	_	48	78	40	118	22.0	2	_	_	41	66	34	_	_	_	_
EUR studies without incidence data																								
178	Belarus	Minsk	1997	2.9	Astapov 2000	Surveillance		0	0	1	2	7	9		0	0	0	11	22	78	_	_	_	_
179	Italy	National	1994	3	Squarcione 1999	Surveillance		_	_	_	241	39	280		_	_	_	_	86	14	_	_	_	_
180	Poland	National	1997	2	Skoczynska 2000	Surveillance		_	_	18	37	10	47		_	_	_	38	79	21	_	_	114	41
181	Russian Federation	4 Cities	1996	1.1	Diomina 1999	Hospital-based Prospective		_	_	_	_	_	54		11	_	_	_	_	_	_	77	140	39
182	Russian Federation	Moscow	1980	4	Demina 1986	Hospital-based Retrospective		_	8	34	68	10	78		_	_	10	44	87	13	_	_	_	_

WHO region and study number	Country	Study site	Year started	Duration (years)	Reference	Type of study	Estimated midpoint census of children <5 years for incidence studies	Hib meningitis													Bacterial meningitis			
								Number of cases <5 years, by age group (in months)						Annual incidence per 100 000 <5 years	Case-fatality rate in <5 years	Percent of cases <5 years, by age group (in months)					Percent of cases with antibiotic pre-treatment	Percent of cases <5 years with established etiology	Number of cases <5 years with established etiology	Percent of cases <5 years with established etiology due to Hib
								<1	0-5	0-11	0-23	24-59	0-59			<1	0-5	0-11	0-23	24-59				
SOUTH-EAST ASIA REGION (SEAR)																								
SEAR studies with incidence data																								
183	India	Vellore	1998	2	Steinhoff 2001	Population-based Prospective	56 153	_	3	7	8	0	8	8.9	17	_	38	88	100	0	32	25	24	33
SEAR studies without incidence data																								
184	Bangladesh	Dhaka	1987	8	Saha 1997	Hospital-based Retrospective		8	97	191	257	20	277		_	3	35	69	93	7	_	_	582	48
185	India	Chandigarh	1972	2.3	Kumar 1980	Hospital-based Retrospective		_	_	14	_	_	17		_	_	_	82	_	_	41	_	50	34
186	India	Delhi, Culcutta, Jodhpur, Jaipur	1989	1	Kabra 1991	Hospital-based Retrospective		_	_	5	_	_	7		29	_	_	71	_	_	_	14	93	8
187	India	Madras	1989	1.3	Deivanayagam 1993	Hospital-based Prospective		_	_	25	_	_	_		18	_	_	_	_	_	26	_	_	_
188	India	6 referral hospitals	1993	2.1	Steinhoff 1998	Hospital-based Prospective		_	12	34	_	_	44		25	_	27	77	_	_	_	_	_	_
189	India	Vellore	1987	4.3	Singh 1992	Hospital-based Retrospective		_	_	_	38	1	39		28	_	_	_	97	_	_	_	_	_
190	Indonesia	Jakarta and Tangerang	1995	1.2	Pusponegoro 1998	Hospital-based Prospective		_	_	_	_	_	2		_	_	_	_	_	_	_	73	8	25

WHO region and study number	Country	Study site	Year started	Duration (years)	Reference	Type of study	Estimated midpoint census of children <5 years for incidence studies	Hib meningitis													Bacterial meningitis			
								Number of cases <5 years, by age group (in months)						Annual incidence per 100 000 <5 years	Case-fatality rate in <5 years	Percent of cases <5 years, by age group (in months)					Percent of cases with antibiotic pre-treatment	Percent of cases <5 years with established etiology	Number of cases <5 years with established etiology	Percent of cases <5 years with established etiology due to Hib
								<1	0-5	0-11	0-23	24-59	0-59			<1	0-5	0-11	0-23	24-59				
191	Nepal	Khatmandu	1993	0.5	Sharma 1996	Hospital-based Prospective		_	_	_	_	_	15		0	_	_	_	_	_	_	_	23	65
192	Thailand	Bangkok, Childrens Hospital	1980	11	Chotpitayasunondh 1994	Hospital-based Retrospective		0	84	186	216	13	229		11	0	37	81	94	6	_	88	503	46
193	Thailand	Bangkok, Chulalongkorn Hospital	1980	13	Likitnukul 1994	Hospital-based Retrospective		2	24	35	38	4	42		7	5	57	83	90	10	_	_	_	_
194	Thailand	Bangkok, Ramathibodi Hospital	1983	5	Charuvanij 1990	Hospital-based Retrospective		_	_	_	_	_	7		_	_	_	_	_	_	_	_	17	41
WESTERN PACIFIC REGION (WPR)																								
WPR studies with incidence data																								
195	Australia	N. Territory	1985	3	Hanna 1990	Population-based Retrospective	10 135	_	_	_	_	_	16	52.6	0	_	_	_	_	_	_	_	_	_
196	Australia	Canberra	1984	7	McGregor 1992	Population-based Retrospective	22 382	_	_	18	37	11	48	30.6	0	_	_	38	77	23	_	_	_	_
197	Australia	Sydney	1985	3	McIntyre 1991	Population-based Retrospective	229 165	_	21	54	98	37	135	19.7	4	_	16	40	73	27	_	_	_	_
198	Australia	Victoria State	1985	3	Gilbert 1990	Population-based Retrospective	295 051	_	25	79	166	58	224	25.4	3	_	11	35	74	26	_	_	_	_
199	Australia	W. Australia	1984	5	Hanna 1991	Population-based Retrospective	108 680	_	_	_	_	_	146	26.9	4	_	17	42	71	29	_	94	187	78

WHO region and study number	Country	Study site	Year started	Duration (years)	Reference	Type of study	Estimated midpoint census of children <5 years for incidence studies	Hib meningitis													Bacterial meningitis			
								Number of cases <5 years, by age group (in months)						Annual incidence per 100 000 <5 years	Case-fatality rate in <5 years	Percent of cases <5 years, by age group (in months)					Percent of cases with antibiotic pre-treatment	Percent of cases <5 years with established etiology	Number of cases <5 years with established etiology	Percent of cases <5 years with established etiology due to Hib
								<1	0-5	0-11	0-23	24-59	0-59			<1	0-5	0-11	0-23	24-59				
200	China	Anhui Province, Hefei City	1990	3	Yang 1996	Population-based Prospective	78 163	_	_	18	_	_	25	10.7	10	_	_	72	_	_	99	_	46	54
201	China	Hong Kong	1986	5	Lau 1995	Population-based Retrospective	384 800	_	_	_	_	_	34	1.8	_	_	_	_	_	_	_	_	_	_
202	China	Hong Kong SAR, Chinese	1984	9	Sung 1997	Population-based Retrospective	73 882	_	_	1	4	3	7	1.1	0	_	_	14	57	43	_	68	23	30
203	China	Hong Kong SAR, Viet Namese Refugees	1984	9	Sung 1997	Population-based Retrospective	4 360	_	_	2	2	0	2	5.2	0	_	_	100	_	_	_	_	7	29
204	Japan	6 Prefectures	1994	1	Kamiya 1998	Population-based Retrospective	1 411 000	_	14	27	39	27	66	4.7	3	_	21	41	59	41	_	_	_	_
205	Japan	Aichi Prefecture	1984	9	Ishikawa 1996	Population-based Retrospective	426 427	0	17	35	66	23	89	2.3	3	0	19	39	74	26	_	_	232	38
206	Japan	Mie Prefecture	1997	2	Nakano 2001	Poplation-based Prospective	90 868	_	_	_	_	_	11	6.1	_	_	_	_	_	_	_	_	_	_
207	Malaysia	Kelantan	1985	2.5	Choo 1990	Population-based Retrospective	180 000	_	14	22	_	_	29	6.4	14	_	48	76	_	_	29	_	54	54
208	New Zealand	National	1978	9	Lennon 1989	Population-based Retrospective	_	_	_	_	_	_	_	22.0	_	_	_	_	_	_	_	_	_	_
209	New Zealand	N. Auckland	1981	7	Voss 1989	Population-based Retrospective	64 459	_	_	_	_	_	122	27.0	_	_	_	_	_	_	_	_	_	_
210	Philippines	Manila	1994	3	Limcangco 2000	Population-based Retrospective	41 592	_	58	95	108	10	118	94.6	11	_	49	81	92	8	_	_	_	_

WHO region and study number	Country	Study site	Year started	Duration (years)	Reference	Type of study	Estimated midpoint census of children <5 years for incidence studies	Hib meningitis													Bacterial meningitis			
								Number of cases <5 years, by age group (in months)						Annual incidence per 100 000 <5 years	Case-fatality rate in <5 years	Percent of cases <5 years, by age group (in months)					Percent of cases with antibiotic pre-treatment	Percent of cases <5 years with established etiology	Number of cases <5 years with established etiology	Percent of cases <5 years with established etiology due to Hib
								<1	0-5	0-11	0-23	24-59	0-59			<1	0-5	0-11	0-23	24-59				
211	Singapore	Singapore	1990	6	Lee 2000	Population-based Retrospective	223 403	_	2	2	3	4	7	2.5	0	_	29	29	43	57	21	48	17	41
212	Vanuatu	Tana	1988	3	Carroll 1993	Population-based Prospective	4 378	9	9	9	9	0	9	68.5	22	_	_	100	100	0	_	73	36	25
WPR studies with incidence data for special-risk groups																								
213	Australia	Central Australia Aboriginal	1985	1	Hansman 1986	Population-based Retrospective	1 540	_	_	_	7	0	7	454.5	_	_	_	_	100	0	_	_	_	_
214	Australia	N. Territory Aboriginal	1985	3	Hanna 1990	Population-based Retrospective	5 041	_	_	_	24	0	24	158.6	8	_	_	_	100	0	_	_	_	_
215	Australia	W. Australia Aboriginal	1984	5	Hanna 1991	Population-based Retrospective	5 348	_	24	37	40	0	40	149.5	10	_	59	93	100	0	_	91	64	63
WPR studies without incidence data																								
216	China	Tainan, Taiwan	1988	4	Liu 1993	Hospital-based Retrospective		_	0	6	9	3	12		25	_	0	50	75	25	_	_	27	44
217	Japan	11 Prefectures	1979	6	Fujii 1986	Hospital-based Retrospective		4	33	124	218	73	291		_	1	11	43	75	25	_	79	917	32
218	Malaysia	Kelantan	1985	9.6	Khairulddin 1999	Hospital-based Retrospective		_	15	37	43	5	48		15	_	31	77	90	10	_	_	_	_
219	Malaysia	Kuala Lumpur	1971	7.8	Thong 1983	Hospital-based Prospective		2	12	32	37	2	39		8	5	31	82	95	5	_	_	_	_

WHO region and study number	Country	Study site	Year started	Duration (years)	Reference	Type of study	Estimated midpoint census of children <5 years for incidence studies	Hib meningitis													Bacterial meningitis			
								Number of cases <5 years, by age group (in months)						Annual incidence per 100 000 <5 years	Case-fatality rate in <5 years	Percent of cases <5 years, by age group (in months)					Percent of cases with antibiotic pre-treatment	Percent of cases <5 years with established etiology	Number of cases <5 years with established etiology	Percent of cases <5 years with established etiology due to Hib
								<1	0-5	0-11	0-23	24-59	0-59			<1	0-5	0-11	0-23	24-59				
220	Malaysia	Kuala Lumpur	1975	10	Navaratnam 1988	Hospital-based Retrospective		0	_	40	_	_	44		_	0	_	91	_	_	_	_	140	31
221	Papua New Guinea	Goroka Hospital	1980	4.6	Gratten 1985	Hospital-based Retrospective		3	49	69	75	2	77		28	4	64	90	97	3	_	_	151	51
222	Philippines	Bohol	1994	2	Lupisan 2000	Hospital-based Prospective		_	_	_	_	_	11		_	_	_	_	_	_	35	_	17	65
223	Philippines	Manila	1972	6	Reyes 1979	Hospital-based Retrospective		0	2	5	_	_	7		_	0	29	71	_	_	61	54	43	16
224	Philippines	Manila	1982	6.5	Santana 1992	Hospital-based Retrospective		0	_	21	_	_	24		21	0	_	88	_	_	51	_	71	34
225	Republic of Korea	Seoul	1977	6	Choi 1983	Hospital-based Retrospective		0	_	5	7	1	8		0	0	_	63	88	12	_	46	31	26
226	Republic of Korea	Seoul, Incheon, Suwon	1986	10	Kim 1998	Hospital-based Retrospective		_	_	19	32	14	46		17	_	_	41	70	30	_	_	114	40
227	Republic of Korea	Seoul	1986	11	Lee 1998	Hospital-based Retrospective		_	_	11	_	_	23		_	_	_	48	_	_	_	_	37	62
228	Singapore	Tan Tock	1984	4	Lim 1989	Hospital-based Retrospective		0	_	0	_	_	2		50	0	_	0	_	_	_	46	12	17
229	Viet Nam	Ho Chi Minh City	1995	1.6	Tram 1998	Hospital-based Prospective		_	_	27	28	2	30		_	_	_	90	93	7	_	76	65	46

Annex 3:
References for Annex 2, by WHO region

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Annex 4

Studies by cluster number, WHO region, and case-fatality rate

Cluster No. 1	<5 year Hib meningitis incidence < 35/100 000; proportion of < 5 year Hib cases in children 0–11 months of age < 60%; case-fatality rate (%) in WHO region column						
	Study number	Country and year study started	AFR	AMR	EMR	EUR	WPR
	47	Canada–1981		–			
	50	Cuba–1994		–			
	63	USA–1963		8%			
	58	USA–1965		4%			
	65	USA–1980		4%			
	111	Austria–1983				6%	
	114	Bulgaria–1997				10%	
	115	Croatia–1995				2%	
	116	Czech Republic–1987				2%	
	117	Czech Republic–1992				0%	
	118	Czech Republic–1997				2%	
	119	Denmark–1975				–	
	120	Denmark–1985				3%	
	121	Denmark–1991				–	
	125	Finland–1975				–	
	127	Finland–1985				4%	
	128	France–1980				3%	
	129	France–1980				–	
	130	Germany–1971				–	
	132	Greece–1992				–	
	137	Ireland–1991				–	
	144	Italy–1987				–	
	152	Norway–1975				–	
	153	Poland–1998				6%	
	155	Russian Federation–1999				11%	
	157	Slovakia–1991				17%	
	156	Slovakia–1996				–	
	160	Spain–1993				2%	
	163	Sweden–1971				–	
	165	Sweden–1981				2%	
	168	Switzerland–1976				0%	

Cluster No. 1	<5 year Hib meningitis incidence < 35/100 000; proportion of < 5 year Hib cases in children 0–11 months of age < 60%; case-fatality rate (%) in WHO region column						
	Study number	**Country and year study started**	**AFR**	**AMR**	**EMR**	**EUR**	**WPR**
	171	UK–1969				6%	
	170	UK–1975				3%	
	176	UK–1980				–	
	175	UK–1981				3%	
	177	UK–1988				2%	
	173	UK–1990				–	
	196	Australia–1984					0%
	199	Australia–1984					4%
	197	Australia–1985					4%
	198	Australia–1985					3%
	205	Japan–1984					3%
	204	Japan–1994					3%
Cluster No. 2	**< 5 year Hib meningitis incidence > 35/100 000; proportion of < 5 year Hib cases in children 0–11 months of age > 60%; case-fatality rate (%) in WHO region column**						
	Study number	**Country and year study started**	**AFR**	**AMR**	**EMR**	**EUR**	**WPR**
	1	Burkina Faso–1989	23%				
	2	Gambia–1985	37%				
	3	Gambia–1990	16%				
	4	Niger–1981	44%				
	5	Senegal–1970	34%				
	91	Saudi Arabia–1996			–		
	210	Philippines–1994					11%
Cluster No. 3	**< 5 year Hib meningitis incidence > 35/100 000; proportion of < 5 year Hib cases in children 0–11 months of age less than 60%; case-fatality rate (%) in WHO region column**						
	Study number	**Country and year study started**	**AFR**	**AMR**	**EMR**	**EUR**	**WPR**
	55	USA–1976		–			
	66	USA–1977		2%			
	54	USA–1980		–			
	61	USA–1982		–			
	135	Iceland–1974				–	

Cluster No. 4	< 5 year Hib meningitis incidence < 35/100 000; proportion of < 5 year Hib cases in children 0–11 months of age > 60%; case-fatality rate (%) in WHO region column						
	Study number	**Country and year study started**	**AFR**	**AMR**	**EMR**	**EUR**	**WPR**
	6	South Africa–1991	5%				
	44	Argentina–1993		18%			
	45	Brazil–1997		37%			
	48	Chile–1985		16%			
	51	Dominican Republic–1998		–			
	88	Kuwait–1981			5%		
	89	Kuwait–1981			2%		
	92	United Arab Emirates–1990			10%		
	138	Israel–1981				3%	
	140	Israel–1984				7%	
	139	Israel–1988				1%	
	200	China–1990					10%
	207	Malaysia–1985					14%
Cluster No. 5	**Studies in special-risk groups; case-fatality rate (%) in WHO region column**						
	Study number	**Country and year study started**	**AFR**	**AMR**	**EMR**	**EUR**	**WPR**
	68	Canada–1981		–			
	69	USA–1971		–			
	71	USA–1971		0%			
	72	USA–1973		–			
	74	USA–1974		4%			
	70	USA–1980		–			
	215	Australia–1984					8%

The Department of Vaccines and Biologicals was established by the World Health Organization in 1998 to operate within the Cluster of Health Technologies and Pharmaceuticals. The Department's major goal is the achievement of a world in which all people at risk are protected against vaccine-preventable diseases.

Five groups implement its strategy, which starts with the establishment and maintenance of norms and standards, focusing on major vaccine and technology issues, and ends with implementation and guidance for immunization services. The work of the groups is outlined below.

The *Quality Assurance and Safety of Biologicals team* team ensures the quality and safety of vaccines and other biological medicines through the development and establishment of global norms and standards.

The *Initiative for Vaccine Research* and its three teams involved in viral, bacterial and parasitic diseases coordinate and facilitate research and development of new vaccines and immunization-related technologies.

The *Vaccine Assessment and Monitoring team* assesses strategies and activities for reducing morbidity and mortality caused by vaccine-preventable diseases.

The *Access to Technologies team* endeavours to reduce financial and technical barriers to the introduction of new and established vaccines and immunization-related technologies.

The *Expanded Programme on Immunization* develops policies and strategies for maximizing the use of vaccines of public health importance and their delivery. It supports the WHO regions and countries in acquiring the skills, competence and infrastructure needed for implementing these policies and strategies and for achieving disease control and/or elimination and eradication objectives.

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