

# Spectrum and burden of severe *Haemophilus influenzae* type b diseases in Asia

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The validity of the commonly held view that *Haemophilus influenzae* type b (Hib) diseases are rare in Asia is challenged in this article by a thorough analysis of the data available, often in languages other than English. The entire spectrum of Hib disease, not only meningitis, was taken into account, and over 100 reports from 25 countries were explored. Hib was the leading agent among nontuberculous childhood meningitis cases in two-thirds of 48 studies from 22 countries. Data from six countries showed that all the classical manifestations of invasive Hib diseases are also found in Asia, except epiglottitis, which was nearly absent. In Hong Kong Special Administrative Region of China Hib disease is rare, but otherwise the incidences seemed not to deviate much from those in Europe until recently, around 25 per 100 000 for meningitis and at least 40 per 100 000 per year for the classical Hib manifestations combined at age 0–4 years. In total, more than 200 000 cases of Hib disease are estimated to occur annually in Asia. Because nonbacteraemic Hib pneumonia remains mostly undetected, the total burden is probably significantly greater. The issue will be fully elucidated only by prospective epidemiological and clinical studies, but awaiting them should not delay large-scale vaccinations against Hib throughout Asia.

**Keywords:** Asia; *Haemophilus influenzae* type b, pathogenicity; *Haemophilus* infections, epidemiology, ethnology; meningitis; pneumonia; septicaemia.

Voir page 884 le résumé en français. En la página 884 figura un resumen en español.

## Introduction

Only a decade ago, *Haemophilus influenzae* type b (Hib) diseases devastated children in the USA as much as poliomyelitis had during the peak epidemic years of the early 1950s (1). Conjugate vaccines are now changing the picture entirely (2), but they are not utilized globally.

In Asia one of the obstacles to their use is the generally held view that Hib diseases are uncommon (3–8). This impression can be only partly explained by a questionable ability to culture *H. influenzae* (9). Reference is often made to Hong Kong Special Administrative Region of China, where no Hib strains were found among 0–4-year-old Chinese children (621 throat swabs), as opposed to 1.3% of Vietnamese children (10). Ethnic group was the only predictor suggesting Hib carriage, and this finding may explain the low incidence of Hib disease in Hong Kong, where different populations often live in rather dissimilar conditions (6–8).

Data from Asian populations living elsewhere are controversial. In Sydney, Australia, Hib disease is

uncommon among Chinese and Vietnamese populations (11). In California, the risk of Hib disease among Hispanic children used to be slightly lower, and in Asian children significantly ( $P < 0.001$ ) lower, than that among Caucasian and Black populations (12). However, a high incidence of Hib disease has been observed among Vietnamese refugees in Hong Kong Special Administrative Region of China (7), and among Bangladeshi, Indian, and Pakistani populations in the United Kingdom (13). One may argue that crowding and better surveillance may have contributed to the findings, but whatever the reasons, even the views of experts differ considerably.

This study attempts to look at a complex issue in its entirety, i.e. not just meningitis (14), which occupies only a part of the Hib disease spectrum. It was sought to determine whether all of Asia really does enjoy a low incidence of severe Hib diseases, and what the global burden is for these life-threatening infections against which effective vaccines are already available.

## Methods

A detailed literature search was undertaken to trace existing information on invasive Hib diseases in Asia. As defined by the World Bank (15), Asia was taken to be a geographical entity that extends from the

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Mediterranean Sea in the west to the Pacific Ocean in the east, including the Middle East and Japan but not Turkey, Russian Federation, or Papua New Guinea.

The great majority of the data used here were obtained from the published literature, but some originated from international scientific meetings. A considerable amount of information was published in languages other than English. Inclusion of all reports, irrespective of language, was deemed essential to increase precision and perhaps to reduce systematic errors (16, 17). Because bacteriological methods have improved considerably over the last 30 years or so, earlier studies were not included.

It was expected that the quality of studies would vary, and that the majority of surveys would be retrospective; prospective studies were thus a search priority. The analysis particularly focused on incidence data obtained from population studies, rather than from official reports, which tend to be unreliable. Attention was paid not only to children under 5 years of age — who account for the majority of cases of Hib disease (1, 18) — but to all age groups and the entire spectrum of manifestations of Hib. A total of more than 100 reports in six languages from 25 countries throughout the continent were scrutinized.

Demographic calculations were made using World Bank data (15). Actual numbers of cases were calculated from the incidences.

## Results

### Clinical manifestations

**Meningitis.** As expected, bacterial meningitis captured the most attention. In some reports (8) *Mycobacterium tuberculosis* was a common agent, but because of its special characteristics, tuberculous meningitis was excluded from this analysis.

Positive bacteriological findings (positive culture or antigen detection in cerebrospinal fluid) were reported in at least 48 meningitis studies from 22 countries (7, 8, 19–62). A comparison between the most common agents — *H. influenzae*, pneumococcus, meningococcus, and *Salmonella* spp. (fairly common in some countries) — is presented in Table 1.

*H. influenzae* was not always typed, but when it was, type b was identified almost exclusively (7, 20, 58, 60, 63, 64). The role of Hib as a major pathogen was evidenced beyond doubt. In 32 (67%) of the 48 studies with proven etiology, in two instances with pneumococci, Hib was the leading agent isolated; in 9 (19%) studies it was second; and in only 5 studies (10%) third. Only pneumococcus challenged Hib in importance. Up to two-thirds (33, 40, 47) of cases of meningitis may be due to Hib.

In two series, one from India (5) and another from Indonesia (3), Hib was not isolated at all. This might have occurred by chance or more likely by defective culture technique, because in six other studies from the same countries Hib was prominent.

For Asia as a whole, of the total of 5172 cases with defined etiology, 34% were caused by Hib, 23% by pneumococci, 14% by meningococci, 4% by salmonellae, and 25% by other bacteria (Table 1). The proportion of bacteriologically negative cases varied but was usually in the range of 25–30% of the entire series.

**Pneumonia.** All known manifestations of invasive Hib diseases were also encountered in Asia. Six studies (Fig. 1) (7, 58, 63, 65–67) indicated that pneumonia (mostly diagnosed by blood culture) was the second most common entity. The importance of Hib in pneumonia was reflected by the studies in the Philippines: initially, pneumococcal etiology proved to be only 30% more common than Hib among bacteraemic children (68). Some years later, however, *H. influenzae* (not always serotyped) was the commonest blood isolate at age 0–4 years (69). Finally, 148 *H. influenzae* isolates obtained from normally sterile body sites in 1985–96 were shown to be pneumonia in 75% of cases but meningitis in only 25% (64). In all, 68% of strains (101/148) were Hib.

Since blood culture is rarely positive for cases of pneumonia (70–72), these studies poorly reflect the true role of Hib or other *H. influenzae* strains in lower respiratory infections. Hence, of special interest were the over 10 studies from India or the Philippines (not all cited here) in which lung tap was used (64, 70–75). Unfortunately, serotyping was carried out only in one small series (six cases, two of which were Hib) (64). In India, *H. influenzae* accounted for 0–86% of cases in which an agent was identified; methodological problems were likely, however, since sometimes not even pneumococcus was detected (72). Hib is obviously an important agent in childhood pneumonia, but its true role will be disclosed only by more reliable studies.

**Septicaemia.** Information on Hib bacteraemia or septicaemia somewhat overlapped with that on Hib pneumonia. Three studies dealt with bacteraemia in various diseases. A Kuwaiti series (76) included adults; Hib was identified in 3.6% of 140 home-acquired bacteraemic infections. Interestingly, a yield of around 3% was also found in a prospective study on preschool children ( $n = 56$ ) in Hong Kong (77) and among 0–5-year-old Bangladeshi children with suspected septicaemia (78). In Israel in 1980–86, pneumococci caused 35%, *H. influenzae* 19%, *Escherichia coli* 12%, and *Salmonella* spp. another 12% of bacteraemia in 0–13-year-old children ( $n = 138$ ) (79).

**Cellulitis and osteoarticular infections.** Cellulitis represented up to 13–14% of the Hib cases (66, 67). This entity appeared to be more common in the western than eastern parts of Asia (Fig. 1). Up to 5% of cases were osteoarticular infections, more often septic arthritis than osteomyelitis.

**Epiglottitis.** Acute epiglottitis, which used to be the second most common manifestation of Hib disease in Australia (among non-Aboriginals), Europe, and North America, is rare in Asia; often not a single case was detected (7, 58, 63, 65–67). In

## Research

Table 1. Role of *Haemophilus influenzae* (Hib), pneumococci, meningococci, and *Salmonella* spp. in the etiology of bacterial meningitis in Asia

Country	Year(s)	Age range	No. of bacteriologically confirmed cases	% of bacteriologically confirmed cases					Reference
				Hib	Pneumococci	Meningococci	<i>Salmonella</i> spp.	Others <sup>a</sup>	
Bangladesh	1986	0–6 y	40	43	23	15	0	19	19
	1987–94	≤10 y	587	47	32	8	NA <sup>b</sup>	13	20
China	1988–89	<15 y	117	32	14	53	NA	NA	21
	1990–92	≤15 y	60	52	8	38	0	2	22
China (Province of Taiwan)	1980–84	3 mo–4 y	44	39	16	NA	NA	45	55
	1988–92	≤13 y	41	29	22	5	5	39	56
Hong Kong Special Administrative Region of China	1981–88	≤12 y	67	21	21	NA	24	34	7
	1984–93	1 mo–14 y	31	29	16	16	NA	39	8
India	1977–79	≤15 y	65	17	25	0	NA	23	23
	1982	≤12 y	20	40	20	0	5	35	24
	1985–86	1 mo–12 y	55	2	25	62	0	11	25
	late 1980s	≤12 y	20	10	15	0	5	70	26
	1989–90	≤11 y	55	51	27	2	NA	20	27
Indonesia	1990	≤15 y	39	0	13	0	0	87	5
	1976–77	≤15 y	74	11	12	1	27	49	28
	1979–81	≤15 y	20	0	35	0	10	55	3
Iran (Islamic Republic of)	1968–75	≤15 y	126	10	50	11	NA	29	30
Iraq	1988–89	All ages	181	25	7	68	0	0	29
Israel	1981–85	≤7 y	100	42	29	20	0	9	31
Japan	1979–84	≤15 y	824	35	23	2	<1	39	32
	1986–94	≤15 y	196	59	20	2	NA	19	33
Jordan	1992	2 mo–12 y	14	50	21	3	NA	26	34
Kuwait	1981–87	≤12 y	110	45	21	13	1	20	35
Malaysia	1970–77	≤12 y	52	50	35	0	2	13	36
	1983–86	≤12 y	56	16	14	13	0	57	37
	1985–87	≤12 y	58	50	24	9	0	17	38
	1991–92	≤15 y	79	43	23	3	1	30	39
	1993–94	5 mo–5 y	23	65	9	26	0	0	40
Pakistan	1990–92	2 mo–12 y	40	50	15	20	NA	15	41
Philippines	1980–85	2 mo–10 y	21	5	5	10	10	70	42
	1982–88	1 mo–19 y	74	34	28	7	10	21	43
Republic of Korea	1977–82	≤15 y	37	22	19	30	3	26	50
	1972–81	≤15 y	32	6	53	19	0	22	51
	1973–86	<15 y	78	22	33	17	0	28	52
	1979–86	≤15 y	34	18	12	21	0	49	53
	1986–95	3 mo–15 y	114	42	42	8	NA	8	54
Saudi Arabia	1982–85	≤12 y	105	42	24	11	2	21	44
	1988–89	≤15 y	59	36	12	39	0	13	45
	1982–90	1 mo–12 y	55	47	35	4	2	12	46
	ca.1983–94	≤15 y	70	66	24	4	0	6	47
	1988–91	≤15 y	27	30	22	30	NA	18	48
Singapore	1977–83	≤12 y	16	19	13	13	0	55	49
Thailand	1978–82	≤10 y	42	37	30	5	9	19	57
	1990	≤15 y	389	43	30	5	12	0	58
	1980–90	1 mo–15 y	478	48	25	4	14	9	59
United Arab Emirates	1990–93	1 mo–12 y	32	63	9	3	0	16	60
Viet Nam	1990s	All ages	281	30	31	20	NA	19	61
	1990s	≤15 y	34	53	18	11	NA	5	62

<sup>a</sup> May include *Salmonella* if not separated as own group.

<sup>b</sup> NA = data not available.

this regard Asia has much in common with Africa and the indigenous populations of Australia and North America. The peak age for the occurrence of epiglottitis was a few months later than that of Hib meningitis, as is characteristic of epiglottitis in other countries.

## Incidence

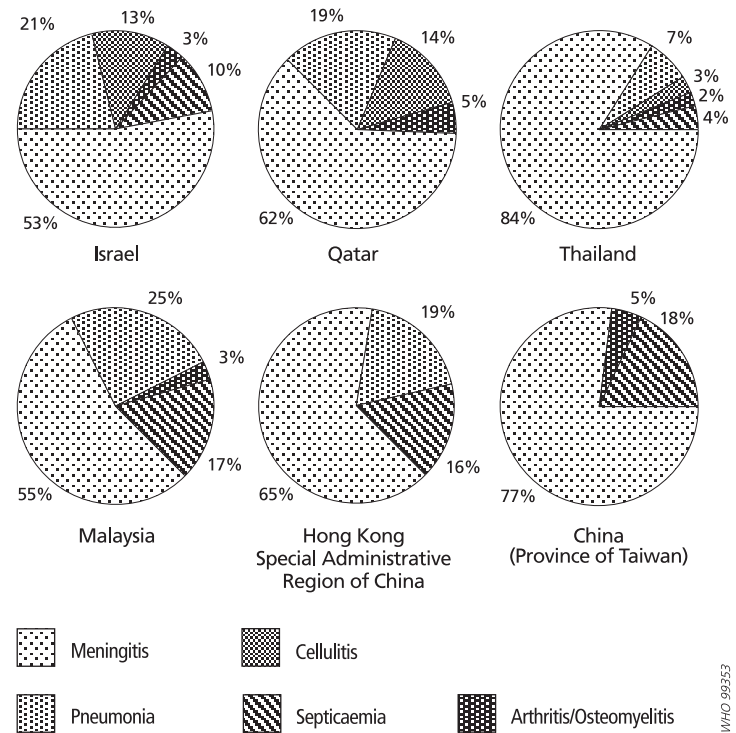
Distribution of etiology tells little about the impact of various agents in a community. Unfortunately, except for Israel (80) and the Philippines (81), prospective and population-based incidence studies have not yet been carried out in Asia; prospectively collected data were also obtained from China (22). However, relevant information was available from 14 countries or populations overall (Fig. 2) (7, 8, 21, 33, 35, 58, 60, 66, 80–90).

**Hib meningitis.** Specific rates for Hib meningitis were available from 13 countries (Fig. 2). The lowest annual rates were from Hong Kong Special Administrative Region of China; only 1.1 and 5.2 per 100 000 at age 0–4 years for Chinese and Vietnamese children, respectively (8). In contrast, a retrospective analysis from Malaysia estimated an incidence of 38 per 100 000 for Hib meningitis at age 0–4 years (86). This is remarkably close to the estimation from a hospital survey in Vellore, India (84), which suggested a minimum rate of 39 per 100 000. Another Indian survey (90) proposed a rate of 50–66 cases per 100 000 among 0–4-year-olds. It is likely that a prospective approach would have concluded even higher rates.

Listing the annual rates per 100 000 at age 0–4 years from west to east Asia (Fig. 2) indicates that the incidence in prevaccination Israel varied between 19 and 22 per 100 000 (31, 80). In Saudi Arabia the incidence was around 13 (89), in Kuwait (rate extrapolated from ref. 35) around 15, in Bahrain 21 (83), in Qatar 16 (66), in the United Arab Emirates 19–22 (60), in India between 39 and 66 (84, 90), and in Malaysia around 40 per 100 000 (86). In Thailand an incidence of 5.2 per 100 000 was published (85), but many clinicians consider the true rate to be considerably greater (58; Chotpitayasonondh, personal communication, 1996). In the Philippines the incidence was 18 per 100 000 (81), whereas in China (22) and Japan (87, 88), the rate was no more than around 10 and 8 per 100 000, respectively. Again, the workers concerned repeated that their calculations were probably underestimates. The prospective nature of the study in the Chinese city of Hefei (population, 1.1 million) adds to its value (22). As has been well publicized, the rates in Hong Kong Special Administrative Region of China were lower than in the nearby regions (6–8).

Nevertheless, the incidence of Hib meningitis was quite similar — between 15 and 21 per 100 000 at age 0–4 years (Fig. 2) — in four of five countries in the Middle East from which information was obtained. Considerably greater variation was observed between other regions of Asia: the rates were

Fig. 1. Spectrum of *Haemophilus influenzae* type b (Hib) disease among under-5-year-olds (age group 0–4 years) in Asia, from west to east. The distribution found is common to Africa and the indigenous populations of North America, Australia, and Papua New Guinea. The Malaysian series (63) also included foci other than those depicted here.

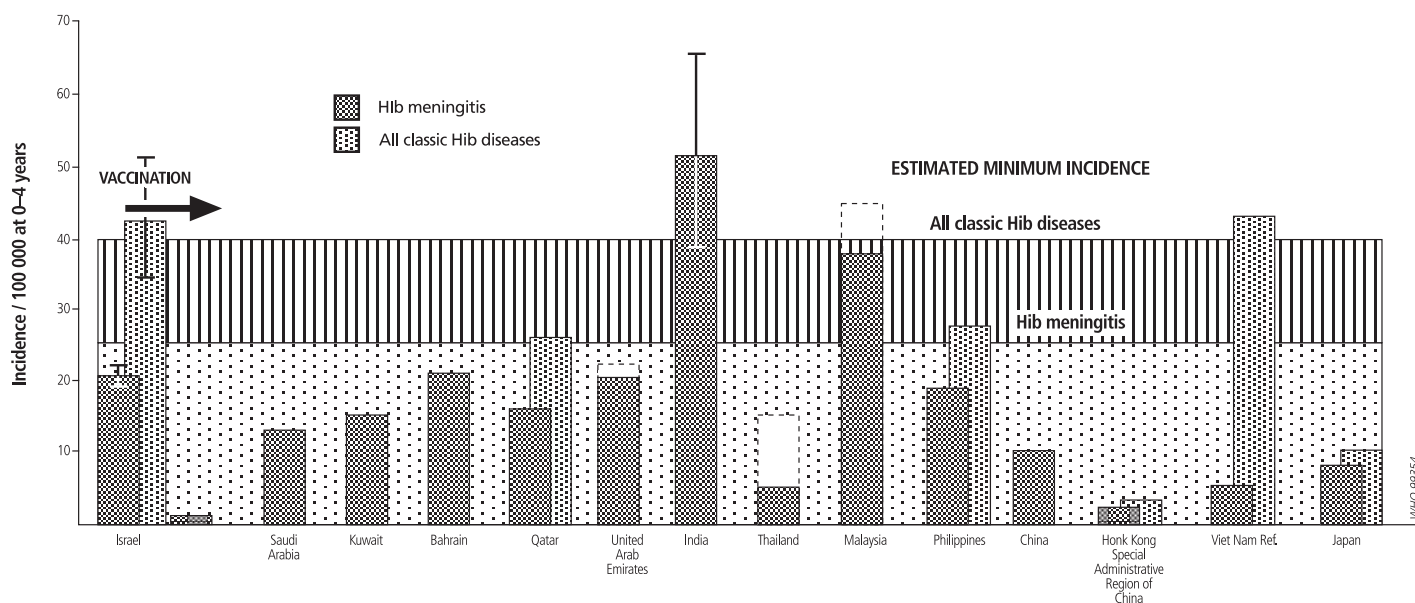


about twice that of the Middle East in populous India and Malaysia, but considerably less in the Far East. In general, rates in Asia seem to be little different from those of prevaccination Europe, particularly southern Europe, where the prevaccination incidence at age 0–4 years used to be 20–40 per 100 000 for meningitis and 40–60 per 100 000 for all classical (nonbacteraemic Hib pneumonia excluded) manifestations (91) — a third lower than in the USA (92).

Besides suboptimal case finding in some studies, Hib meningitis seems to be increasing in frequency in some regions (20, 56, 93). In Dhaka, Bangladesh, a 700% increase in the annual number of cases occurred in the national paediatric hospital over the period 1987–94 (20). This highly significant proportional increase ( $P < 0.001$ ) could not be ascribed to factors such as improved laboratory technique or greater activity in sample taking, since isolates of other bacteria remained similar over this period.

**Other manifestations.** Annual rates for some nonmeningitis manifestations at age 0–4 years were available from Israel (67). The prevaccination incidence was 7 per 100 000 for bacteraemic Hib pneumonia, 4 per 100 000 for cellulitis, 3 per 100 000 for septicaemia, and <1 per 100 000 for epiglottitis. The nonmeningitis manifestations combined added more than 80% to the incidence of Hib meningitis in Israel, and a very similar trend was also

Fig. 2. Incidence of *Haemophilus influenzae* (Hib) meningitis and all Hib diseases in different populations of Asia at age 0–4 years, from west to east (7, 8, 22, 33, 35, 58, 60, 66, 80–90). "Viet Nam Ref." refers to the refugee population in Hong Kong Special Administrative Region of China, whose rate may not be directly applicable to Viet Nam itself. Note: "All Hib diseases" refers to the classic manifestations (Fig. 1) and mostly neglects Hib pneumonia. Pre vaccination data in Israel (31, 80) for this no longer represent the current situation (82).



observed (Fig. 1) in Malaysia (63). Evidently, counting only meningitis cases gives a very false picture of even classic Hib diseases, not to mention nonbacteraemic Hib pneumonia. Nevertheless, the information agrees well with the clinical data throughout the continent (Fig. 1); the classic entities other than meningitis added 20–80% to the proportion of meningitis.

**All Hib manifestations.** Data on the classic Hib diseases combined were available from seven reports. In Israel, the annual incidence per 100 000 at age 0–4 years was between 34 and 51 (31, 80), in Qatar it was 26 (66), in the Philippines 28 (81), in Hong Kong 3 (7), and in Japan around 10 (87, 88). Including the cases of nonbacteraemic pneumonia would have increased the rates significantly. This was not done because the information on this important Hib manifestation was so meagre (*see below*).

A spectacular difference between populations in the same area was observed in Hong Kong Special Administrative Region of China: a small series showed an incidence of Hib disease among Vietnamese refugees of 43 per 100 000 (95% confidence interval (95% CI) = 17.2–87.9) versus 2.67 per 100 000 (95% CI = 2.0–3.5) in all Hong Kong residents of this age (7). Also, in Israel there was some difference between two populations: among Jews the rate was 48 per 100 000 versus 58 per 100 000 among Bedouins (80).

### Burden caused by Hib diseases

**Total number of cases.** Besides incomplete reporting, there were clearly several other causes for presumed underestimation of the true rates. Indiscriminate use of antibacterials in Asia is common; for example, over

98% of children with respiratory symptoms (common also in meningitis) attending Beijing Children's Hospital have received such drugs (94). In Bangladesh (78) and Thailand (58) over-the-counter sales of such drugs are equally liberal, and in India 40% of meningitis patients are taking antibacterials when they present at hospital (23). Such policies almost certainly suppress the yield of cultures, as shown in Dhaka (78).

Against the background situation described above, an extrapolation of the data from individual countries to the whole of Asia was entertained — fully realizing that extending local rates to a large continent is a risky procedure, and even more so since pneumonia (probably the commonest Hib entity in developing countries (95, 96)) was mostly not detected because of diagnostic problems. While we are awaiting better studies, some speculative calculations (Table 2) still seemed worth while.

An overall incidence of around 25 per 100 000 for Hib meningitis appears reasonable (Fig. 2). If this rate is accepted, there would be 100 000 cases per year among under-5-year-olds throughout Asia, where 11% — more than 385 million — of the total population ( $3.4 \times 10^3$ ) are children of this age (15). Countless other Hib entities must have occurred without etiological diagnosis, and since meningitis represents only 50–80% of the entire clinical spectrum (Fig. 1), a considerably higher rate would reflect all classic manifestations of Hib. An incidence of around 40 cases per 100 000 per year is probably a reasonable estimate (Fig. 2) — a rate which would result in 150 000 cases per annum for this age group.

Furthermore, Hib infections do not exclusively affect small children; 9–12% occur in adults (63, 97, 98). If we arbitrarily apply the overall Scandinavian or

US prevaccination Hib incidence (4–5 cases per 100 000 in all age groups (92, 98)), the annual number of cases in Asia would be 175 000–200 000.

However, Hib pneumonia has to be taken into account in its entirety, not merely the few cases (Fig. 1) detected by culture of blood or, occasionally, pleura fluid. The lung tap studies (64, 70–75) clearly show that *H. influenzae* is a major agent. Serotyping was only rarely performed, but the tiny series (64) available with this information from Asia supports the African experience (99) that the role of Hib in severe childhood pneumonia in developing countries is not negligible. Our own serological data from China support this view (unpublished results).

**Mortality.** Until Hib pneumonia is better characterized, meningitis remains the leading killer Hib disease. One-third of patients in a teaching hospital could succumb (57, 100, 101), and fatality rates around 50% are not uncommon in poor conditions (58). In addition, many children die at home (20, 101) and, surprisingly, also after initially successful treatment: in Bangladesh one-quarter (11/45) of children who “survived” died at home within 110 days of discharge (102). A 20-year analysis of causes of death of Chinese children ( $n = 891$ ) showed that pneumonia was the number one killer (40%), and central nervous system infections the number two (100); undoubtedly Hib infection played a role in these conditions.

We can assume that at least 25 000 lives are lost every year in Asia because of Hib meningitis and that over 30 000 patients die from all classic Hib diseases (Table 2). The toll of Hib pneumonia is probably even greater.

**Sequelae.** Information on Hib infection sequelae was almost nonexistent. In Jordan, 29% of 17 children with postmeningitis hearing impairment had Hib meningitis, and even loss of vision was observed (103). There is no reason to assume sequelae would develop in fewer than 30% of surviving patients (41, 86). This would imply that at least 23 000 patients per year who survive Hib meningitis are left with sequelae, mostly hearing impairments (Table 2). In situations devoid of rehabilitation facilities, the results could be catastrophic.

**Drug resistance.** The increasing resistance of Hib to conventional and inexpensive antibacterials adds to the problem. In one study from India, a costly third-generation cephalosporin was required in 43% of Hib meningitis cases (104). On the other hand, all *H. influenzae* isolates tested in the Philippines in 1985–96 were sensitive to ampicillin, chloramphenicol, co-trimoxazole (trimethoprim + sulfamethoxazole), and tetracycline (64). This indicates that these standard drugs may still be used in many countries.

### Hib vaccination in Asia

Although all Hib conjugate vaccines are available in Asia, they are mostly used in private practice. Israel and some states in the Gulf on the Arabian Peninsula are the only countries to date that have initiated large-

Table 2. Proven and assumed characteristics of *Haemophilus influenzae* (Hib) disease in Asia

<b>No. of countries or regions</b>	<b>51</b>
<b>Population (ref. 15)</b>	
Total	3 433 274 000
No. aged <5 years	385 639 000
<b>Hib disease</b>	
Meningitis	
Annual incidence at age <5 years <sup>a</sup>	25 per 100 000
No. of cases per year	100 000
% fatality rate	25
No. of lives lost per year	25 000
Incidence of sequelae	30%
No. of sequelae per year	23 000
<b>All Hib manifestations<sup>b</sup></b>	
Annual incidence at age <5 years	40 per 100 000
No. of cases per year	150 000 000
No. of cases in all age groups per year	175 000–200
No. of lives lost per year	>30 000
<b>Resistance of Hib to conventional antibacterials</b>	0–50%
<b>Conjugate vaccines</b>	
Availability	Reasonable
Exploitation	Poor

<sup>a</sup> No large community-based and prospective incidence studies have been carried out in Asia so far, but estimations were made using the data available from 14 countries or regions (Fig. 2).

<sup>b</sup> The role of Hib pneumonia is probably grossly underestimated.

scale vaccinations. In such countries where these large-scale vaccinations have been initiated, Hib diseases have virtually disappeared (82) (Fig. 2).

## Discussion

No doubt the scientific quality of the studies reviewed varied, and some of the estimates may be disputable; but this should not hide the fact that Hib is indeed a significant problem in Asia, surpassing some other vaccine-preventable diseases. A total of 175 000–200 000 cases of classic manifestations of Hib occur each year (Table 2), and especially countless numbers of pneumonia cases pass without recognition. Hundreds of thousands, perhaps a few million, of Hib cases develop each year on this populous continent.

Oropharyngeal carriage (10) and the incidence of Hib disease (7, 8) are low in affluent Hong Kong Special Administrative Region of China, but this obviously is not the case throughout Asia (Fig. 2). Studies should be performed in other Asian countries, but approximately 100 reports from 25 countries throughout the continent do not support claims of a sparsity of Hib infections, and they may even be increasing in frequency (20, 56, 93). The problem has not been revealed to its true extent, and sometimes its importance is not

realized. Hib meningitis was repeatedly deemed of minor importance in the Republic of Korea until the records of 14 hospitals in Seoul over 10 years were checked. This indicated that Hib had been responsible for 52% of meningitis cases among 0–4-year-olds, and was the principal pathogen among this age group (54). Higher rates than expected are often found once they are investigated (105). With Hib infection, disclosure of the entire disease spectrum is difficult because of the variety of manifestations (Fig. 1). Making all the manifestations of the disease reportable would aid in its recognition.

In nearby Papua New Guinea, the annual incidence of Hib pneumonia (“acute lower respiratory infection”) among 0–4-year-olds is 2860 cases per 100 000 (106). If this extremely high rate (based admittedly on a small series) has any relevance for Asia, pneumonia is the key disease, despite full realization that not all lower respiratory *H. influenzae* cases are of type b (64, 107, 108). The role of Hib in pneumonia was underlined in a prospective study in the Gambia reported in 1997, which suggested that up to 25% of severe childhood pneumonia in developing countries is due to Hib (96). This figure is more than double the previous estimate from the same country (5–10%) (95). The findings from Asia are in agreement with data from the Gambia, but population-based studies are urgently needed.

A seroepidemiological study in China (Province of Taiwan) (109) showed that antibody concentrations in various age groups were close to

those in Finland and the USA prior to mass vaccination. This is good news, since it suggests that each one of the costly Hib conjugates would be immunogenic enough to be used in adjacent countries. In this respect, the situation in these countries coincides with that in the Middle East (14). In contrast, the same analysis of Hib meningitis in 14 countries also revealed that infants in south and south-east Asia (Bangladesh, Malaysia, Philippines, Thailand, and Viet Nam) fall ill earlier. These children may thus be in need of the most immunogenic vaccines available (14).

The number of doses seems not critical. Except for Iceland, all Scandinavian countries give only two primary Hib vaccinations with a late booster (instead of the generally recommended four doses) — and the results are excellent (110). Benefits of vaccination, so far reported only in Israel (82) (Fig. 2), will probably be considerable in Asia where treatment may be delayed, resulting in high case fatality and morbidity rates (102) (Table 2). Some Arab countries have begun the general Hib immunization of children, but many other parts of Asia have yet to start. This costs lives and has numerous tragic sequelae. ■

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### Résumé

#### Spéctre des maladies graves à *Haemophilus influenzae* type b en Asie et charge de morbidité

L'opinion courante selon laquelle les maladies à *Haemophilus influenzae* type b (Hib) sont rares en Asie est remise en cause dans cet article qui fait suite à une analyse approfondie des données disponibles dans des langues souvent autres que l'anglais. On a tenu compte de tout le spectre des maladies à Hib et pas seulement de la méningite, et plus d'une centaine d'observations de 25 pays ont été étudiées. Sur 48 études concernant 22 pays, les deux tiers montraient que Hib était l'agent principal responsable des méningites non tuberculeuses de l'enfant. Les données de six pays montraient que toutes les manifestations classiques des affections invasives à Hib se retrouvent aussi en Asie, à l'exception de l'épiglottite qui est pratiquement absente. A Hong Kong, région administrative spéciale de la Chine, les

pathologies à Hib sont rares, mais, par ailleurs, l'incidence jusqu'à récemment ne semblait pas s'écarter notablement des niveaux observés en Europe, c'est-à-dire environ 25 pour 100 000 pour la méningite et au moins 40 pour 100 000 par an pour l'ensemble des manifestations classiques à Hib de 0 à 4 ans. En tout, on estime à plus de 200 000 le nombre annuel de cas d'affections à Hib en Asie. Les pneumopathies à Hib en l'absence de bactériémie n'étant le plus souvent pas décelées, la charge de morbidité totale est probablement bien plus importante. La question ne pourra être totalement éclaircie qu'au moyen d'études épidémiologiques et cliniques prospectives, mais, en attendant, il ne faut pas retarder la vaccination à grande échelle contre le Hib dans l'ensemble de l'Asie.

### Resumen

#### Espectro y carga de morbilidad asociados a las infecciones graves por *Haemophilus influenzae* tipo b en Asia

La validez de la muy extendida opinión según la cual las enfermedades por *Haemophilus influenzae* tipo b son infrecuentes en Asia es cuestionada en el presente artículo a partir de un exhaustivo análisis de los datos

disponibles, publicados a menudo en idiomas distintos del inglés. Se tuvo en cuenta todo el espectro de enfermedades por Hib, no sólo la meningitis, y se analizaron más de cien informes de 25 países. Se observó

que Hib era la principal causa de los casos de meningitis infantil no tuberculosa considerados en las dos terceras partes de 48 estudios de 22 países. Los datos de seis países mostraron que en Asia se dan todas las manifestaciones clásicas de las enfermedades invasivas por Hib, a excepción de la epiglotitis, prácticamente inexistente. En la Región Administrativa Especial de Hong Kong, en China, las afecciones por Hib son raras, pero por lo demás hasta hace poco su incidencia no se desviaba mucho de la observada en Europa: cada año, unos 25 casos de meningitis por 100 000, y al menos 40 por 100 000 para el conjunto de las manifestaciones

clásicas por Hib, en el grupo de edad de 0-4 años. En total, se estima que anualmente se registran en Asia más de 200 000 casos de enfermedad atribuible a Hib. Dado que la mayoría de los casos de neumonía por Hib no bacteriémica pasan desapercibidos, la carga total es probablemente mucho mayor. Sólo mediante estudios epidemiológicos y clínicos prospectivos se podrá esclarecer por completo esa cuestión, pero el hecho de estar a la espera de esas conclusiones no debería demorar las iniciativas de vacunación a gran escala contra el Hib en toda Asia.

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