

A REVIEW OF Hib EPIDEMIOLOGY IN ASIA

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On behalf of the Steering Committee for Prevention and Control of Infectious Diseases in Asia:

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Abstract. Meningitis due to an invasive *Haemophilus influenzae* type b (Hib) infection, has been previously perceived to be relatively uncommon in Asia. However, the incidence of disease and its impact may have been underestimated. In addition to a lack of microbiological facilities in some hospitals, difficulties in culturing the organism and the widespread use of antibiotics may have hidden the true incidence of the disease in some countries. Furthermore, the reported disease burden probably underestimates the incidence of Hib pneumonia.

The epidemiology of invasive Hib disease for various Asian nations is reviewed in this paper. Hospital-based studies show that Hib is a major cause of bacterial meningitis and/or pneumonia in the Philippines, India, Thailand, Malaysia, Indonesia and Vietnam. Singapore and Hong Kong have a low incidence of infection compared with Western and other Asian nations. This low incidence is not due to a higher level of natural protective antibodies, but may be related to an interaction between environmental and genetic factors. Therefore the widespread belief that Hib infection is unimportant in Asia does not refer to Asia as a whole and possibly to Chinese patients only, and failure to recognize this has serious implications.

The inclusion of Hib vaccine in the routine infant immunization schedule in many industrialized nations has significantly reduced the incidence of invasive disease. Recent studies have shown Hib vaccination is also effective in preventing invasive disease in children in developing countries.

While population-based data may be required to confirm the need for public-funded infant Hib immunization in Asia, its introduction in countries with a high incidence of Hib meningitis and/or pneumonia has the potential to significantly improve pediatric health and survival.

INTRODUCTION

Haemophilus influenzae type b (Hib) causes serious bacterial infections in children including meningitis, pneumonia, epiglottitis, septicemia and septic arthritis (Shapiro and Ward, 1991). Before the introduction of Hib vaccines, it was the major

cause of childhood bacterial meningitis in industrialized nations.

The epidemiology and the clinical pattern of Hib disease in developing countries differs from that seen in industrialized nations. Developing countries have a higher incidence of the disease, and it occurs in younger children, with most cases occurring before 12 months of age (Funkhouser *et al*, 1991; Bijlmer, 1994). In developing countries, pneumonia is a more common manifestation of infection than meningitis (Greenwood, 1992).

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Strains of *H. influenzae* other than type b, also called non-type b strains, cause less serious, mucosal infections including otitis media, sinusitis, bronchitis and urinary tract infections. Current Hib vaccines cannot prevent these non-type b infections (Anonymous, 1997). The incidence of Hib disease in children under 5 years of age ranged from 20 to 100 cases per 100,000 in most countries (Table 1) (Clements, 1994). The rate of infection in Australia and the USA before vaccination was introduced was estimated to be 50 to 60 cases per 100,000 (Wenger *et al*, 1992; Gilbert *et al*, 1990). Some populations, namely Eskimos, North American Indians and Australian Aborigines, have a significantly higher incidence of 200-450 cases/100,000. Asian countries on the other hand appear to have a low incidence – some population-based studies have reported an incidence as low as 2 cases per 100,000.

Hib has been recognized as a major public health problem worldwide, and it is now preventable by routine immunization of infants. In vaccinated populations, surveillance studies have shown more than a 95% decrease in the incidence of Hib disease, even before high immunization levels were achieved (Anonymous, 1997). Despite this worldwide success, Hib immunization is yet to be introduced in many Asian nations due in part to the apparent low incidence of the disease in the region.

The lack of population-based studies in most Asian countries has made it difficult to assess the actual incidence of the disease. This article reviews the epidemiology of Hib disease in various Asian countries in order to assess the need for the introduction of infant Hib immunization.

Table 1

Worldwide incidence of invasive Hib disease in children under 5 years of age (per 100,000), prior to the use of Hib vaccines (Clements, 1994).

Region	Years	Hib meningitis	All Hib disease
Australia/NZ	1985-87	25-53	39-92
US/Canada	1959-91	40-69	67-130
Europe	1985-90	15-26	33-60
Israel	1985-90	18	34
Africa	1980s	36-60	NA
South America	1989-90	15-25	21-43
Asia	1990s	1.3-1.9	1.9-27

Hib in Asia

Hib disease is perceived to be fairly unimportant in Asia, this is despite the fact that it is a major cause of bacterial meningitis. A review of 20 studies conducted in the region has shown that Hib is the most common of three major pathogens implicated in bacterial meningitis (Peltola, 1998).

While Singapore (Tee and Lin, 1996) and Hong Kong (Lau *et al*, 1995; 1998) do appear to have a genuinely low incidence of Hib disease, the incidence in other countries may be under-reported. Hib is an important cause of childhood pneumonia, particularly in developing countries (Greenwood, 1992). Due to the difficulty in obtaining an etiological diagnosis of bacterial pneumonia in children, the reported Hib disease burden in some Asian countries is likely to underestimate the incidence of Hib pneumonia (Anonymous, 1997). In addition, the widespread use of non-prescription antibiotics in some countries may make culture of *H. influenzae* difficult, thus hiding the true incidence of the disease.

The Philippines

In the Philippines, *H. influenzae* plays a role in acute respiratory infection and meningitis. Transmission of Hib appears to be higher during the dry months – December and January – than during the monsoon season – June, July and August (Santana-Arciaga *et al*, 1994).

A 1988 study conducted by the Research Institute of Tropical Medicine (RITM) in Manila showed that 63.3% of *H. influenzae* isolated from blood and/or pleural fluid from children with pneumonia was serotype b (Table 2) (Tupasi, 1988). In comparison, 93.3% of isolates from the cerebrospinal fluid (CSF) of children with meningitis were type b, thus in meningitis, Hib is the predominant serotype. For acute respiratory infections however, almost 30% of *H. influenzae* isolates were non-serotypable.

More recent data from the RITM (1985-1998) for children aged 1 month to 5 years has confirmed that serotype b is the predominant pathogen in invasive *H. influenzae* infection (Gatchalian, 1998 personnel communication). In the hospital-based study, there were a total of 148 isolates obtained from blood, pleural fluid, CSF and lung aspirate, of which 101 (68%) were type b, 10 (7%) were capsulated non-type b and 25 (17%) were non-serotypable.

The mean age of the 126 patients in the study was 9 months, and 86% were less than 12 months old. The clinical diagnosis was pneumonia in 75% of cases (94 patients) and meningitis in 25% of cases. There were 22 deaths in total – a 17% case fatality rate (Carlos, 1997).

What appears to be a low prevalence rate of *H. influenzae* infection in the Philippines may be due to factors such as difficulties in isolating the bacteria, as well as widespread use of antimicrobial drugs. Recent antimicrobial resistance surveillance data have revealed only slight resistance to conventional antibiotics for Hib infections in the Philippines (Carlos, 1997). There was no resistance to chloramphenicol, 1.8% resistance to cotrimoxazole and only 1.6% resistance to ampicillin. Thus, in the Philippines, *H. influenzae* organisms are still responding to less expensive, conventional drugs.

India

Hospital-based data suggests that Hib is the

Table 2
Serotypes of *H. influenzae* isolated from children with pneumonia and/or meningitis in the Philippines.

Serotype	Blood and/or pleural fluid No (%)	Cerebrospinal fluid (CSF) No (%)
A	5 (4.6)	1 (6.7)
B	69 (63.3)	14 (93.3)
C	2 (1.8)	-
E	1 (0.9)	-
non-serotypable	32 (29.3)	-
Total	109 (100)	15 (100)

predominant meningitis-causing agent in Indian children under 5 years of age (John *et al*, 1998). The estimated incidence of Hib meningitis in India is 50-66 cases/100,000 children under five years of age (John *et al*, 1998). The true incidence, however, is difficult to determine. Many laboratories in India have difficulty culturing *H. influenzae*, while antibiotic usage may also hide the true incidence of Hib disease (John *et al*, 1998).

A 1964 hospital-based study involving three centers – Delhi, Madras and Vellore – revealed 45% of isolates from CSF in children with pyogenic meningitis were *H. influenzae* (Ahmed *et al*, 1964). In Vellore, data on *H. influenzae* disease has been collected periodically from 1953-1991 (Table 3) (Ahmed *et al*, 1964; Venkatesh *et al*, 1985; Singh, 1992).

From 1953 to 1991, there has been a decline in the frequency of isolation of microbial agents, probably as a result of widespread antimicrobial use before children are seen by a clinician. In the past decade, there has been an increasing incidence of Hib resistant to antibiotics including chloramphenicol and ampicillin (John *et al*, 1998). The lower frequency of isolation of *H. influenzae* in studies in some centers in India may be caused by unsatisfactory media and culture methods (John *et al*, 1998).

More recent data from a surveillance study of invasive Hib disease conducted in six sites across the country from 1993-1995 revealed that Hib was the most frequent cause of bacterial meningitis in children under 5 years of age (Invasive Bacterial Infections Surveillance Group, 1998). The invasive bacterial infection surveillance study (IBIS) involved a total of 1,032 patients with suspected meningitis or pneumonia. Infants under 12 months of age accounted for 76% of all in-

Table 3
Etiological agents in childhood pyogenic meningitis, Vellore 1953-1991.

Organism	1953-1960	1967-1969	1974-1977	1982	1983-1984	1987-1991
<i>H. Influenzae</i>	38	24	11	18 (27) ^a	17 (21) ^a	25
<i>S. pneumoniae</i>	33	16	13	9	4 (6) ^a	NA
<i>Neisseria meningitidis</i>	2	0	1	0	0	NA
Other	9	17	14	18	21	NA
None	17	43	61	55 (46) ^a	58 (52)	NA
Total cases	87	75	90	44	48	157

^aIncluding results of culture and antigen detection by latex agglutination.

NA - not analysed.

vasive Hib infections, and the peak incidence was 6-9 months of age. The Hib case fatality rate for infants less than 12 months old was 29% (15-47%, 95% CI).

The seroprevalence of anti-Hib antibodies in Indian children is similar to other non-vaccinated populations. Antibody is rapidly acquired in the pre-school period; seroprevalence is less than 20% in infants under 12 months of age, but over 80% at 4 years of age (Acharya *et al*, 1997).

Thailand

Invasive Hib is recognised as the most frequent etiologic agent of bacterial meningitis in Thai infants, as well as an important cause of bacteremia, pneumonia, and septic arthritis (Chotpitayasunondh, 1998).

Although the absolute incidence of Hib disease is not known, recent data from the Children's Hospital in Bangkok show that Hib accounts for approximately 40% of cases of meningitis. In a retrospective study of 50 pediatric patients with systemic *H. influenzae* disease admitted to a University Hospital in Bangkok between 1980-1992, the peak incidence of infection was found to be in children between 4 and 6 months of age (Likitnukul, 1994). Meningitis (55.7%) and pneumonia (25.3%) were the main clinical consequences of infection and the overall mortality rate was 8%.

In a second retrospective study reported in 1996, the annual incidence of Hib disease in Thailand was estimated to be 5.8 per 100,000 in children younger than 5 years of age, calculated from hospital data (Sunakorn, 1996).

Malaysia

H. influenzae was the most common causative organism of bacterial meningitis in a study of infants and children admitted to the University Hospital in Kuala Lumpur between 1970 and 1977 (Lee *et al*, 1977). The organism accounted for 44% of cases, and 24 of 26 isolates were type b strains.

A 1990 study conducted in children hospitalized with pyogenic meningitis in the state of Kelantan confirmed that *H. influenzae* is the most commonly isolated organism. CSF cultures were positive for the organism in 50% of the 58 children studied (Choo *et al*, 1990).

A more recent study conducted during 1995 confirmed these findings. The study reviewed all cases of postneonatal meningitis in children 12

years of age or less admitted to five pediatric hospital departments across Malaysia in 1995.

During the study period, 435 cases of meningitis were admitted to the five centers, however only 71 cases fulfilled laboratory diagnostic criteria. Nearly one-half (48%) of all bacteriologically-proved cases of meningitis were caused by Hib (Hussain *et al*, 1998). A majority of the cases (76%) were in infants less than one year of age.

Indonesia

There has been a decline in the number of children admitted to hospital with bacterial meningitis in Indonesia since 1990, and this has been attributed to socioeconomic improvement including early treatment of infection with effective antibiotics (Pusponegoro *et al*, 1998).

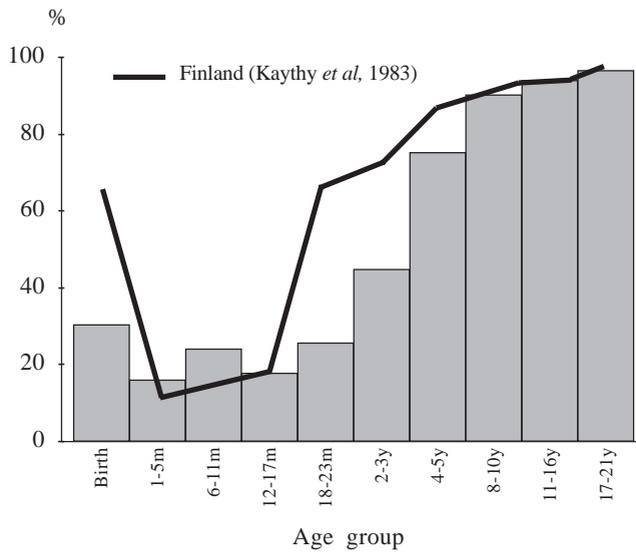


Fig 1—Percentage of individuals with anti-Hib antibody >0.15 µg/ml in Singapore.

