Review

Burden of Invasive Disease Caused by *Haemophilus influenzae* Type b in Asia

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SUMMARY: Globally, *Haemophilus influenzae* type b (Hib) is one of the leading causes of childhood meningitis and pneumonia. Vaccines against Hib have been developed and introduced into routine immunization programs in most industrialized nations, in which the burden of Hib disease has been clearly demonstrated. In Asia, the burden of Hib disease has been perceived as relatively low compared with other parts of the world. However, the results of several recent studies have allowed for a more cautious assessment of the disease burden in different populations and settings throughout Asia. These studies suggest that the true burden of Hib disease may have been underestimated, and point to several key factors that may have contributed to this problem, such as antibiotic use prior to the analysis of blood and cerebrospinal fluid in infants and children suspected of having invasive Hib disease. Trials evaluating Hib vaccines in Asian populations have shown that they are effective and safe. These results may aid in the decision about whether to implement routine Hib vaccination in Asia and help to track the impact of Hib vaccination in the future.

1. Introduction

*Haemophilus influenzae* type b (Hib) is the leading cause of bacterial meningitis in infants and children and the second leading cause of bacterial pneumonia worldwide (1). Invasive Hib disease is associated with high rates of mortality and long-term morbidity, including hearing loss, seizures, and motor and mental deficits. Globally, Hib causes approximately 3 million cases of serious illness in children aged less than 5 years and is responsible for 386,000 deaths each year (1). In Asia, preliminary reports suggested that the incidence of invasive Hib disease is relatively low, compared with industrialized countries in Europe and North America (2). Several factors, such as widespread use of antibiotics in infants and children, may have led to an underestimation of the true burden of Hib disease in Asia.

Standard treatments for invasive Hib disease include chloramphenicol and penicillin, although the prevalence of Hib strains that are resistant to these antibiotics may be increasing (3-6). Third-generation cephalosporins are more effective, but are also more expensive (3). Vaccines have been developed that effectively prevent Hib-related illness. In 1990, Hib vaccination was incorporated into routine infant immunization in the United States and most Western industrialized countries introduced Hib vaccination thereafter. In 2006, the World Health Organization (WHO) strengthened and clarified its position on routine Hib vaccination, stating that “conjugate Hib vaccines should be included in all routine infant immunization programmes” (1). The WHO further noted that “lack of local surveillance data should not delay the introduction of these vaccines”. In recent years, a growing amount of data has emerged that is leading to a more accurate estimation of the burden of Hib disease in Asia. Steady progress is being made as more countries introduce routine Hib vaccination, including some lower income countries thanks to the support of the GAVI Alliance, a unique organization that aligns public and private resources in a global effort to create greater access to the benefits of immunization (http://www.gavialliance.org) (Table 1) (7). The following is a review of some of the key data that have recently emerged on the burden of Hib disease in Asia and the potential impact of vaccination.

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in 17% of samples and in 35% of CSF samples. The causative agent was *H. influenzae* in 12% of *S. pneumoniae* infections, including 22 who developed meningitis. Patients with meningitis caused by Hib were sicker than those with only suspected bacterial meningitis: they were hospitalized for longer periods, and were more likely to develop inflammation and neurological sequelae, compared with those with other types of meningitis. During the study period, uptake and distribution of Hib vaccines in the surveillance area increased. Among children who received the vaccine, only 16% underwent complete immunization and 27% had partial immunization in the final month of the study. However, increased use of conjugate Hib vaccines in the population corresponded with a 25%-decline in the number of children with confirmed or probable Hib meningitis.

### 2. Southeast Asia

#### 2-1. Bangladesh

The prevalence of Hib isolates was evaluated in a large pediatric hospital in Bangladesh (4). Between 1993 and 2003, 1,412 meningitis cases and 2,434 pneumonia cases were reported. Hib disease accounted for 455 cases, of which 425 were meningitis. Most cases (91%) occurred during the first year of life. The case fatality rate and rate of sequelae were high (22 and 24%, respectively), suggesting that Hib infection is associated with severe disease. Notably, 21.5% of Hib isolates were resistant to chloramphenicol and 32.5% were resistant to ampicillin. Resistance to both chloramphenicol and ampicillin was common and associated with an increased risk of developing sequelae, compared with patients affected by sensitive isolates.

Sahai et al. (8) reviewed cerebrospinal fluid (CSF) culture results from 100 children aged less than 12 years who were treated for bacterial meningitis at an urban hospital in Bangladesh in 1994-1996. Organisms were successfully isolated from 35% of CSF samples. The causative agent was *H. influenzae* in 17% of samples and *Streptococcus pneumoniae* in 12% of samples. The fatality rate was 25%. The authors concluded that, in India, culture-negative bacterial meningitis accounts for most cases of meningitis. Prior antibiotic use may be partly responsible for the high rate of negative CSF cultures.

#### 2-2. India

The Invasive Bacterial Infections Surveillance (IBIS) study prospectively determined the incidence of Hib disease based on data collected in 1993-1997 from six tertiary hospitals in India (5). A total of 5,798 cases of infection likely related to *H. influenzae* were identified; 75% involved patients aged less than 5 years. Hib was detected in 125 cases, 62% of which were meningitis. The case-fatality rate was 11%. Among those patients with Hib meningitis, the mortality rate was 20% in those aged less than 1 year and 16% in those aged less than 5 years. Chloramphenicol resistance was found in 60% of cases, and 32% were resistant to 3 or more antibiotics. However, all cases were sensitive to third-generation cephalosporins.

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#### 2-3. South Korea

A prospective, population-based surveillance study was conducted to determine the incidence of invasive Hib disease in a defined population in Jeonbuk Province, South Korea in 1999-2001 (9). The annual incidence of invasive Hib disease in children aged less than 5 years was 6.8 per 100,000. The highest age-specific rate was found in children aged 12-23 months (13.6 per 100,000). The case-fatality rate was 7%. Patients with meningitis caused by Hib were sicker than those

### 3. Western Pacific geographic region

#### 3-1. Hong Kong

In Hong Kong, a retrospective survey was conducted to determine the incidence of invasive Hib disease (12). A total of 57 cases of invasive Hib disease were reported in children less than 12 years of age between 1986 and 1990, including 12 children with meningitis. The annual incidence of invasive Hib disease was 2.7 per 100,000 children aged less than 5 years. The authors discussed this relatively low incidence rate and indicated that widespread use of antibiotics in Hong Kong and China may have interfered with bacterial culture and identification of the causative agent.

#### 3-2. New Caledonia

Anglaret et al. (13) determined the incidence of *H. influenzae* infections in children aged less than 16 years in New Caledonia, an island in the Pacific Ocean. Between 1989 and 1991, 32 children had *H. influenzae* infections, including 22 who developed meningitis. Most meningitis patients were aged less

### Table 1. Hib vaccination status in GAVI-eligible countries

<table>
<thead>
<tr>
<th>Region</th>
<th>Using Hib vaccine in 2004</th>
<th>Using Hib vaccine in 2007</th>
<th>Planning to introduce Hib vaccine in 2008</th>
<th>Total using Hib vaccine by 2008</th>
<th>Decided to introduce Hib vaccine</th>
<th>Decision pending</th>
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<td>Bangladesh</td>
<td>4 of 9</td>
<td>Indonesia</td>
<td>India</td>
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<td>Vietnam</td>
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<td>None</td>
<td>Somalia</td>
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</table>

Data from reference (7).
than 2 years (93%). The annual incidence was 54.6 per 100,000 children aged less than 5 years (94 per 100,000 for Melanesian children and 13.8 per 100,000 for Caucasian children). The case-fatality rate was 3.2%. However, isolates were not serotyped, and it was not determined whether the non-serotype b strain may be more frequent in New Caledonia than in Western countries. The incidence of *H. influenzae* was in the range of reported rates in Western European populations.

3-3. Japan

The incidence of invasive Hib disease was evaluated in a 10-year study prior to the introduction of vaccine in Kamikawa, a sub-prefecture in Hokkaido, Japan (14). A total of 52 patients had invasive Hib disease, including 30 with meningitis (57.7%). Most patients were aged less than 2 years. Between 1996 and 2005, the annual incidence of invasive Hib disease ranged from 4.3 to 56.8 per 100,000 in children aged less than 5 years. A marked increase in incidence was seen in the last 2 years studied (2004 and 2005). No deaths occurred, but two patients developed long-term sequelae (epilepsy and developmental delays).

A related study has confirmed that children in Japan do not have protective levels of antibodies against Hib (>0.15 μg/mL) (15). The same study found that natural immunity is lowest during the first year of life and increases with age: only 4% of young adults did not have protective levels of antibody. Ampicillin resistance also appears to be increasing in Japan. In one study, the prevalence of ampicillin-resistant strains increased from 41.9% in 2000 to 60.1% in 2005, surpassing the 50%-mark in 2002 (16).

3-4. Papua New Guinea

Wandi et al. (17) collected data from a single hospital in rural Papua New Guinea to determine rates of long-term neurological sequelae in survivors of bacterial meningitis. Between 1992 and 2000, 120 cases of bacterial meningitis were recorded, of which 80 were available for a follow-up evaluation. Thirteen patients had evidence of *H. influenzae* infection. The rate of complications in this group of patients was high (54%), and many had multiple complications (31%). One-half of the patients were treated with chloramphenicol alone, despite the fact that more than 20% of Hib strains isolated in Papua New Guinea are resistant to chloramphenicol (3).

3-5. Philippines

To assess the epidemiology of Hib meningitis and associated sequelae, a population-based study was carried out in central Manila using data collected in 1994-1996 (18). Of the more than 41,500 children aged less than 5 years who were studied, 118 developed Hib meningitis and 15% developed sequelae. The case fatality rate was 11%. The annual incidence was 95 per 100,000 children. Peak incidence occurred between the ages of 4 and 6 months. Nearly one-half (49%) of affected children were aged less than 6 months (412 per 100,000), and 80% were aged less than 12 months. The authors concluded that Hib meningitis infection is an important health problem that affects children aged less than 5 years in central Manila and that is associated with a relatively high mortality rate and a high rate of sequelae.

In a prospective, single-center study conducted in a rural area (Bohol Island), Hib was found to be the most common cause of bacterial meningitis in children aged less than 5 years (19). In this study, 989 infants were suspected of having meningitis, and 54 (5%) of these patients showed the bacterial aetiology and developed bacterial meningitis. Twenty patients (37%) had confirmed Hib disease, all of whom were aged less than 1 year. Ten isolates were *S. pneumoniae* (18.5%). Twelve of the 54 patients with bacterial meningitis died (22%).

3-6. Singapore

In a retrospective analysis of data from 1994-2003 derived from a single hospital in Singapore, the annual incidence of invasive Hib disease was estimated to be 4.4 per 100,000 children aged less than 5 years (20). The most common manifestations of Hib disease were meningitis (58%) and pneumonia (26%). Of those children with invasive Hib disease, 46% developed significant long-term morbidity or mortality (case fatality rate: 3.8%). The incidence of Hib disease peaked in 1998-2001 (incidence rate ranging from 5.9 to 8.1 per 100,000 children <5 years of age) and then declined sharply (1.8 per 100,000 children <5 years of age in 2003), probably due to increased uptake of Hib vaccine in the private and public sectors secondary to active promotion by individual health practitioners. The reduction was attributed primarily to a reduction in cases of Hib meningitis. It was suggested that the partial vaccine uptake may already have been sufficient to confer some benefit by reducing nasopharyngeal carriage and inducing herd immunity. The authors estimated that 50% of infants born in 2003 received two doses of Hib vaccine.

3-7. Taiwan

In a population-based study conducted in Taiwan based on national insurance records, the annual incidence of Hib meningitis in children aged less than 5 years was 5.6 per 100,000 in 1997 (21). In 2000, the incidence had declined to 3.2 per 100,000 children—possibly due to increased use of Hib conjugate vaccines, which were introduced in 1993 in the private sector. Overall, 87.5% of Hib cases occurred in the first 24 months of life and 58.3% occurred during the first 12 months of life, with a peak between the ages of 6 and 13 months.

3-8. Vietnam

A population-based study was conducted in Hanoi and northern provinces of Vietnam to determine the incidence of Hib meningitis in children aged less than 5 years based on data collected in 2000-2002 (22). In this study, Hib was the most common bacterial aetiology. The annual incidence of confirmed or probable Hib meningitis was 12 per 100,000 children aged less than 5 years and 26 per 100,000 in children aged less than 2 years. The highest age-specific rate was seen in infants aged 7-11 months (44 per 100,000). Neurological sequelae were observed in 10%, and the overall case-fatality rate in children with confirmed or probable Hib meningitis was 4%. Based on recent census data in Vietnam, the authors calculated that, nationally, 1,005 children aged less than 5 years are hospitalized each year for Hib meningitis and an additional 5,107 are hospitalized for Hib pneumonia. Among the 1,005 with Hib meningitis, at least 100 will develop neurological sequelae and 40 will die as a result of the disease.

4. Eastern Mediterranean geographic region

4-1. Saudi Arabia

A prospective, population-based surveillance study was conducted to determine the incidence of Hib disease in Saudi Arabia (23). Hib was implicated in 58 of the 208 cases of bacterial meningitis found (28%), resulting in an incidence of 17 per 100,000 children aged less than 5 years.

A second study reported a much higher incidence (40 per 100,000), based on a retrospective chart review conducted
at a tertiary hospital in Riyadh (24). The study covered the period between 1995 and 2000. Notably, a reduction in incidence was seen after the Hib vaccine became commercially available in 1998 and was introduced in the Riyadh area (from 10 cases in 1996 to only 2 cases in 2000).

4-2. Turkey

The lack of Hib disease surveillance and epidemiological data on the throat carriage of Turkish children has caused a delay in the introduction of conjugated Hib vaccination into a proposed national vaccination program. The carriage rate of Hib was evaluated in preschool children (aged 5 - 7 years) in Middle Anatolia, Turkey (25). Of the 683 healthy children (up to 6 years of age) evaluated, 107 (15.6\%) carried Hib. Risk factors for *H. influenzae* carriage included male gender and sharing a room with multiple people. The prevalence of Hib disease remains unclear in Turkey.

4-3. United Arab Emirates

Mahmoud et al. (6) retrospectively determined the incidence of *H. influenzae*-related meningitis in the eastern region of the United Arab Emirates in the decade before Hib vaccine became commercially available in 1999. The annual incidence rate of meningitis ranged from 2.6 per 100,000 to 5.9 per 100,000 inhabitants for the period from 1990 to 1999. Of the 128 cases of meningitis identified, 59 (46\%) were caused by *H. influenzae*. Twenty-seven patients developed long-term neurological sequelae, including seizures (33\%) and deafness (26\%). Resistance to chloramphenicol was found in 3 of 51 isolates (6\%) and resistance to ampicillin in 10 of 53 isolates (19\%). The mortality rate was 3.1\%.

5. Hib incidence in Asian countries compared to incidence found globally

Reported incidences of Hib-related disease in children aged less than 5 years are summarized in Table 2 (9,10,12-14,18,20-24,26). The range of Hib disease incidence found in Asian countries is generally lower than that reported from other countries before Hib vaccine was introduced. In Europe, the United States, and Australia, for example, the annual incidence of Hib meningitis in children aged less than 5 years ranged from 20 to 60 per 100,000 (27). Even higher rates were seen in some subpopulations within industrialized nations, such as US Apache and Australian Aboriginal populations, where the incidence ranged from 150 to 250 cases per 100,000 (27). It is known from a number of studies carried out in Asia that a high proportion of children were pretreated with antibiotics, (8,9,21,26) and it is known from previous studies that the analysis of CSF from patients who have received antibiotic treatment may lead to a significant proportion of undetected Hib disease, especially when PCR is not used (28). Unmonitored antibiotic use is common practice in many Asian countries, and may contribute to the frequency of negative culture findings in cases of bacterial meningitis. Consequently, additional Hib meningitis cases may have remained unidentified. It is also unclear how many children with mild cases of Hib meningitis were treated with antibiotics and not admitted. Therefore, the reported incidence of invasive Hib disease may have been underestimated in some of the studies cited.

6. Hib vaccines: effectiveness in various countries

In some of the epidemiological reports described above, it was noted that the incidence of Hib disease appeared to decrease after Hib vaccine became commercially available (but did not decrease further after Hib vaccine was introduced as a routine immunization). These findings suggest that partial uptake of Hib vaccine may be effective—but suboptimal—in reducing the burden of Hib disease (9,20,21,29). The following studies have specifically evaluated the efficacy and safety of Hib vaccination in populations in Asia.

6-1. Bangladesh

Baqui et al. (29) evaluated the effectiveness of Hib vaccine in preventing pneumonia and meningitis in children aged less than 2 years in Dhaka, Bangladesh. Approximately 68,000 infants received a combined diphtheria, tetanus, and pertussis (DTP)-Hib vaccine. In this study, use of one or more doses of Hib vaccine was 90\% effective in preventing confirmed Hib meningitis. Two or more doses of vaccine offered significant protection against pneumonia with radiologically confirmed alveolar consolidation (34 - 44\% reduction). The advantage of radiology is that it is not dependent on blood culture, which can underestimate the burden of Hib pneumonia. The study demonstrated the feasibility of introducing a combined DTP-Hib vaccine within the framework of an existing infrastructure.

6-2. India

The efficacy and safety of a combined DTP-Hib vaccine...
were evaluated in 225 infants at three hospitals in India (30). Infants received three doses at 6, 10, and 14 weeks of age. Seroprotection was achieved in 99% of the 219 infants who received all three doses. The vaccine was well tolerated: redness and swelling at the injection site occurred after 2.7 and 11.5% of injections, respectively. Severe pain within 4 days was reported after 3.6% of injections, and one patient developed fever.

6-3. Indonesia

The efficacy and safety of Hib vaccination was evaluated in a double-blind, randomized trial conducted in 818 hamlets in Lombok, Indonesia (26). Between 1998 and 2002, over 55,000 children aged less than 2 years were enrolled and received either DTP vaccination alone or a combined DTP-Hib vaccination. The incidence of vaccine-preventable pneumonia was high (1,561 per 100,000 child-years of follow-up) but was comprised mainly of non-severe cases treated in the outpatient setting. In contrast to other studies, vaccination did not prevent pneumonia (defined by alveolar consolidation) in this study. There are a number of possible causes for these negative findings, such as masking in the radiological image by prior antimicrobial drug use, prompt administration of antimicrobial agents in the outpatient setting, and the high frequency of respiratory syncytial virus in cases of severe lower-respiratory tract infection (26,31). The incidence of vaccine-preventable bacterial meningitis ranged from 67 to 158 per 100,000 child-years of follow-up, and Hib vaccination did in fact prevent a large proportion of meningitis cases. The authors concluded that Hib vaccination should be considered due to its ability to prevent meningitis, but vaccination may have less impact on acute respiratory disease in children.

6-4. Thailand

In Bangkok, 119 infants received three doses of Hib vaccine (32). Geometric mean titers of anti-polyribosylribitol phosphate (PRP) antibody increased from 0.15 μg/mL at baseline to 1.3 μg/mL after two doses of vaccine and 8.8 μg/mL after the final dose. Local and systemic reactions to the vaccine were mild and transient: the most common reactions were local tenderness and redness (48 and 37%, respectively). No swelling was reported. Fever occurred in 5% of patients.

7. Barriers to introduction

In Asia, introduction of Hib vaccine has been hindered not only by the paucity of data verifying the burden of Hib disease, but also by the high costs associated with vaccination (31). Duke (3) has argued that Hib vaccination may be more cost-effective than standard therapies, based on data collected in a province in Papua New Guinea. Hib vaccination was estimated to save 61 more lives each year than chloramphenicol at a cost of US $1,216 per additional life saved. In contrast, third-generation cephalosporins would save only 8 more lives than chloramphenicol at a cost of US $1,514 per additional life saved.

Gessner et al. (33) reported a similar benefit based on their study of Hib vaccination in Lombok, Indonesia. They found a cost savings of US $74 per disability-adjusted life-year (DALY) averted. According to WHO criteria, an intervention is cost-effective if it averts DALY for less than the per capita gross national income (http://www.who.int/choice/costs/CER_thresholds/en). Given that the per capita income in Indonesia was US $1,280 in 2005, Hib vaccination appears to be highly cost-effective in this setting.

Limcancogo et al. (34) performed a cost-benefit analysis of Hib vaccine implementation in the Philippines. The model was based on a three-dose vaccination program and accounted for costs associated with long-term health effects due to Hib meningitis. This study showed that introduction of a Hib vaccination program would have a possible economic benefit for Philippine society.

Shin et al. (35) also performed a cost-benefit analysis of Hib vaccination in South Korea, but found an unfavorable cost-benefit ratio, assuming a cost of 26,000 won per immunization. They noted that, if costs per immunization were reduced to 20,000 won or less, the cost-benefit ratio would favor routine immunization.

Taken together, these pharmacoeconomic analyses illustrate the complexity of determining the benefits and risks of introducing a new vaccine across a heterogeneous region. However, reduced cost of vaccination and increased awareness regarding the possible underestimation of the impact of Hib disease are likely to further tip the balance in favor of routine immunization throughout Asia.

8. Conclusion

Based on the available evidence, it appears that most counties in Asia have a low-to-moderate burden of invasive Hib disease, although it is widely acknowledged that the true burden of Hib disease may be underestimated. It appears that the burden of Hib disease varies widely in this region, depending on a number of geographic, environmental, ethnic and genetic factors (20). Several recently reported studies have contributed to a more cautious assessment of the burden of Hib disease in Asia. Observations made during epidemiological studies indicate that even partial uptake of Hib vaccine in areas of low disease burden correspond with reductions in the incidence of Hib-related disease. These observations are supported by prospective studies of the efficacy and safety of Hib vaccines in various populations in Asia. Although the WHO has stated that a lack of local surveillance data should not delay the introduction of these vaccines, these studies may help to accelerate the introduction of Hib vaccines in routine immunization programs and aid in further study of the effects and cost-effectiveness of Hib vaccination in Asia.

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