Available online at www.sciencedirect.com
ScienceDirect
Vaccine 25 (2007) 6482–6489
Vaccine
www.elsevier.com/locate/vaccine

Epidemiology of invasive *Haemophilus influenzae* type b disease in Singapore children, 1994–2003

Koh Cheng Thoon [a,1], Chia Yin Chong [a,*,1], Winston Yong Meng Ng [a,1], Paul E. Kilgore [b,2], Batmunkh Nyambat [b,2]

[a] *Infectious Disease Service, Department of Paediatric Medicine, KK Women's and Children's Hospital, Singapore*
[b] *Division of Translational Research, International Vaccine Institute, Seoul, South Korea*

Received 4 September 2006; received in revised form 8 June 2007; accepted 10 June 2007
Available online 24 July 2007

Abstract

Invasive *Haemophilus influenzae* type b (Hib) diseases are major causes of childhood morbidity and mortality. For the period from 1994 to 2003, we retrospectively identified 53 children with invasive Hib disease including 31 with meningitis, 14 with pneumonia, 2 with septic arthritis, 2 with epiglottitis, 1 with neutropenic sepsis, and 3 who were bacteraemic without a focus. Two children died and 22 had serious sequelae; significantly, survivors with sequelae had presented with meningitis (P-value < 0.001) or sepsis (P-value = 0.001). During the 11-year period, the annual incidence of invasive Hib disease was estimated to be 4.4/100,000 children <5 years old. With rising affluence, decreasing costs of vaccines, and increased costs in caring for survivors, universal infant immunization with Hib vaccine may need to be reconsidered in Singapore.

Keywords: *Haemophilus influenzae* type b; Invasive disease; Children; Singapore

1. Introduction

Haemophilus influenzae type b (Hib) is a Gram-negative aerobic coccobacilli that is an important cause of childhood morbidity and mortality, especially in children <5 years of age. Hib causes a wide spectrum of infections including respiratory tract infections, arthritis, meningitis, cellulitis as well as bacteraemia and septicemia; however, invasive disease such as septic arthritis, meningitis or septicemia is associated with significant morbidity. Hib was the most common cause of bacterial meningitis in children in North America prior to the introduction of widespread vaccination and has been suggested to be the commonest cause of bacterial meningitis in children <5 years of the age worldwide in the late 1970s and early 1980s [1–3]. With the development of the Hib conjugate vaccine, rates of invasive Hib disease in general have decreased dramatically in countries where universal infant immunization with Hib was practiced [4–6].

Although there is an abundance of data on the clinical spectrum of invasive Hib diseases in children in developed countries of North American and Europe, data from Asia (in particular Southeast Asia) remains scarce. Two previous series from Singapore on invasive Hib diseases yielded data on only a total of 11 patients in the pediatric age group; the rest were adult patients [7–8].

Hence, we decided to conduct a hospital-based retrospective analysis to report the incidence, characteristics and clinical sequelae of invasive Hib diseases in Singaporean children admitted over a 10-year period to the pediatric departments of Singapore General Hospital (SGH, 1994–1997), Tan Tock Seng Hospital (TTSH,

* Corresponding author. Tel.: +65 6394 1964; fax: +65 6394 1973.
E-mail address: Chong.Chia.Yin@kkh.com.sg (C.Y. Chong).

[1] Results reported in this manuscript were presented in part at the 1st Singhealth Annual Scientific Meeting, October 15–17, 2004, Singapore.

[2] Human experimentation guidelines of the authors' institution were followed in the conduct of clinical research.

0264-410X/$ – see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.vaccine.2007.06.037

1994–1997) and KK Women's and Children's Hospital (KKH, 1997–2003, after the merger of the two above departments). Our analysis also afforded the opportunity to correlate the incidence of invasive Hib disease with Hib vaccine sales in Singapore.

2. Material and methods

KK Women's and Children's Hospital was re-built in 1997 with the aim of not only providing improved obstetric and gynecological care, but also centralized pediatric services for Singaporean children. The Department of Pediatric Medicine at KKH was formed in 1997 after the pediatric departments in SGH and TTSH merged and relocated to KKH when it was newly built, and is based within the 300-bed Children's Tower which is an acute tertiary facility that sees up to 54% of pediatric admissions in Singapore (source: Business Office, KKH).

From January 1994 to December 2003, all children <16 years of age with laboratory-confirmed invasive Hib disease were first identified from microbiological records of the respective hospitals. Case records of all patients with laboratory-confirmed invasive Hib disease were subsequently retrieved from the medical records office for review. Laboratory-confirmed invasive Hib disease was defined as the isolation of the organism from blood, cerebrospinal fluid or other normally sterile sites such as bone and joints (aspirates) in microbiologic cultures. Sterile site specimens were plated on blood agar plates with staphylococcal streak as well as chocolate agar plates. *H. influenzae* was then identified by colony morphology and Gram stain (Gram-negative coccobacilli which were oxidase-positive, catalase-positive, and growth around factor XV discs but no growth around X or V or API Neisseria and Haemophilus (APINH), separately). Sensitivity testing was by disc diffusion calibrated dichotomous susceptibility (CDS) [9] method, with Nitrocefin disc used for β-lactamase testing (if negative by the Nitrocefin disc test, the Hib isolate was reported as sensitive to ampicillin). Latex agglutination was performed on sterile site specimens and isolates of *H. influenzae* to detect Hib, using the Bacterial Antigen Kit, Wellcogen (Remel, UK).

Definitions of clinical syndromes of invasive Hib disease included: (1) bacteraemia (presence of viable bacteria in blood); (2) sepsis (presence of bacteraemia and fulfilling the criteria of systemic inflammatory response syndrome [at least 2 of the following: fever >38 °C or hypothermia <36 °C, age-appropriate tachycardia, age-appropriate tachypnoea, age-appropriate white cell counts that are abnormally low or high], with or without organ dysfunction or shock); (3) meningitis (inflammation of cerebral meninges secondary to Hib infection, as confirmed by a positive growth on cerebral spinal fluid (CSF) culture, or positive Hib-specific latex agglutination test on CSF); (4) pneumonia (lung infection with fever/hypothermia, and cough, confirmed by radiographic evidence of new-onset pulmonary infiltrates or consolidation, together with either positive cultures for Hib in blood, bronchoalveolar lavage or pleural effusate, or positive Hib-specific latex agglutination test on bronchoalveolar lavage or pleural effusate); (5) epiglottitis (locally invasive infection of the epiglottis with or without infection of surrounding structures, together with positive cultures for Hib in blood); (6) arthritis (purulent inflammation of joint spaces secondary to bacterial infiltration, as evidenced by elevated polymorphonuclear counts in joint fluid aspirates and either positive cultures for Hib in blood or joint fluid, or positive Hib-specific latex agglutination test on joint fluid).

The following clinical data were collected for each patient: (1) demographics (age, sex and race); (2) clinical diagnosis/syndrome at presentation and complications during hospitalization; (3) significant past medical history; (4) location and resistance pattern of isolates as well as any relevant investigation results; (5) presence of subsequent long-term sequelae or mortality after illness episode.

Descriptive statistics were applied to continuous data, and non-parametric tests (Mann–Whitney tests) were performed to look for any significant differences in age between different populations (as age was not normally distributed). For categorical data, two-tailed chi-square analyses (with Fisher's correction for categories with less than 5 data points) were performed to look for significant associations between patient demographics, past medical history, clinical diagnosis, clinical sequelae and mortality. *P*-values were considered significant at a cutoff of <0.05. Data analysis was performed using SPSS for Windows, v10 (Chicago, IL, USA).

Annual adjusted incidence rates of invasive Hib disease in Singapore (in children <5 years of age) were calculated as:

$$(\text{Number of incident Hib cases}) \times \left(\frac{100}{54}\right) \times \left(\frac{100000}{N}\right)$$

Incident Hib cases refer to the number of children with newly diagnosed invasive Hib disease during one calendar year who are <5 years of age. *N* represents the annual number of children <5 years living in Singapore based on government population statistics (Population Trends 2005 report, Department of Statistics, Singapore) [10]. Our calculation of incidence rates assumes that: (1) all invasive Hib diseases are seen in an acute pediatric facility in Singapore and (2) KKH (and SGH and TTSH combined prior to 1997) admit 54% of all pediatric inpatients in Singapore.

To estimate the overall impact of conjugate Hib vaccines in Singapore, annual Hib vaccine sales data (including both mono-component Hib vaccine and combination vaccines containing Hib) were obtained from pharmaceutical sales data over the period from 1997 to 2003 (currently available Hib-containing vaccines in Singapore are listed in Table 1) [32]. These data were then plotted against the annual incidence rate of invasive Hib disease for comparison. The study was reviewed by the Institutional Review Board, KKH and approval was obtained for waiver of consent from patients.