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Review

Haemophilus influenzae type b carriage and burden of its related diseases in Chinese children: Systematic review and meta-analysis

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ABSTRACT

Background: Haemophilus influenzae type b (Hib) is an important cause of invasive bacterial disease in children worldwide. The limited awareness of disease burden is a major barrier to the introduction of Hib vaccine into China's National Immunization Program. Therefore, we conducted a systematic review and meta-analysis to estimate carriage of Hib and burden of its related diseases in Chinese children.
Methods: We systematically searched Pubmed, Web of Science, Ovid, Chinese National Knowledge Infrastructure (CNKI), and Wanfang databases for studies published up to December 31, 2016, reporting Hib carriage and burden of Hib diseases among children in Mainland China. Pooled estimates were obtained using random-effects models.
Results: We included 27 studies with 15783 children across 14 provinces. The pooled carriage of Hib was 5.87% (95% CI 3.42–8.33) for healthy children. The pooled proportion of disease due to Hib were 4.06% (95% CI 3.29–4.83) for acute lower respiratory tract infection (ALRI) and 27.32% (95% CI 0.41–54.24) for bacterial meningitis. The proportion of ALRI caused by Hib was higher in northern China than that in the south. Significant heterogeneity was noted across and within regions ($P < 0.001$). After the induction of Hib vaccine, meta-regression showed that carriage of Hib changed little ($P = 0.725$), but the proportion of ALRI caused by Hib in children decreased ($P < 0.001$).
Conclusions: Hib carriage persists at low levels among children in China. The proportion of ALRI due to Hib infection decreased with year. Incorporation of Hib vaccine into the National Immunization Program could reduce the burden of Hib disease in China.

Contents

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1. Introduction

Haemophilus influenzae type b (Hib) is a global public health problem and is an important pathogen of invasive bacterial diseases in children. Invasive Hib diseases may manifest as bacterial pneumonia, meningitis, bacteraemia, cellulitis, epiglottitis, septic arthritis, osteomyelitis and pericarditis [1,2]. Hib is second only to *Streptococcus pneumoniae* as a common cause of bacterial pneumonia [3].

Even with adequate medical treatment, 5% of children with Hib meningitis die and 9.5% (IQR 7.1–15.3) of survivors suffer at least one major severe sequela after hospital discharge, including blindness, epilepsy, deafness, and learning disabilities [4,5]. The fatality rate is considerably higher in regions with limited health resources. In 2000, Hib caused about 8.11 million cases of serious illness and 371,000 deaths in children aged 1–59 months worldwide [2].

Vaccination with Hib vaccines is considered a highly effective public health intervention [6–9]. By the end of 2015, Hib vaccines had been part of the routine infant immunization program in 191 countries, accounting for over 98% of World Health Organization (WHO) member states [10]. China's National Immunization Program (NIP) was established in 1978 and provides efforts to accommodate the demands of children at risk of vaccine-preventable diseases [11]. Since 2016, the NIP has included 11 vaccines, which are offered to all children under 7 years of age free of charge at immunization clinics [12]. The Hib conjugate vaccine, Act-HIB® produced by Sanofi Pasteur, first became available in China in 1997. Domestic Hib conjugate vaccines have also been developed. However, this vaccine has not yet been included in the China's NIP and is purchased by caregivers' out-of-pocket expense at the immunization clinics.

The decision making about including Hib vaccine into the NIP has been impeded by several issues including uncertainty about the Hib disease burden, availability and cost of the vaccine, and public perception of vaccine benefits [9,13,14]. We therefore undertook a systematic review and meta-analysis to estimate the carriage of Hib and burden of its related diseases in Chinese children and provide evidence for the decision-making of Hib vaccine into China's National Immunization Program.

2. Methods

2.1. Literature search

We searched five databases (Pubmed, Web of Science, Ovid, CNKI and Wanfang) to identify studies reporting the prevalence of Hib in Chinese children. The following terms were used: "*Haemophilus influenzae type b*", "Hib", "prevalence", "carriage", "epidemiology", "infection rate" and "China". We restricted searches to human studies in Chinese and English published up to December 31, 2016. We also screened reference lists of selected studies and searched the internet for any potentially relevant studies that had not been identified through the searches. Carriage of Hib was defined as the proportion of studied healthy children who were confirmed by nasopharyngeal swab culture or molecular methods.

2.2. Inclusion criteria

Studies were included if they met the following criteria: (a) observational studies carried out in Mainland China; (b) sufficient data for calculating the pooled estimates; (c) reporting diagnostic methods including selective culture methods for isolation and identification of Hib or other molecular methods; (d) children aged <18 years; (e) total sample size >50; and (f) original research article describing data not published previously. We excluded articles from Hong Kong, Macao, and Taiwan due to separate infant immunization systems.

2.3. Data extraction and quality assessment

Two investigators (YaY and WC) independently extracted the information using a standardized form. Data were abstracted for the following study characteristics: author, year of publication, study period, study design, setting and location, study population, participants' sex and age, diagnostic methods, sample size, number of subjects with Hib. If needed, we also attempted to contact the authors for additional information. A five-item tool adopted from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline was used to assess the risk of bias for the individual studies [15,16]. Each study was scored for bias type (high risk = 0, moderate risk = 1, and low risk = 2), and the total score represented the summary assessment of bias risk. The assessment was performed by two authors independently, and any disagreement was solved by group discussion.

2.4. Statistical analysis

The pooled prevalence estimates with 95% confidence intervals were obtained by using random-effects models to account for between-study heterogeneity in study design and sample size. A number of 0.5 was added to event number and sample size of studies with zero events. Heterogeneity was measured using the Q test with a significance level of 5% and the I^2 statistic, which represents the proportion of variance due to between-study heterogeneity rather than sampling error (low: $I^2 < 25\%$ low, moderate: 25–50%, high: $I^2 > 50\%$). Forest plots were generated to show the prevalence with corresponding 95% CIs for each study and the overall random-effects pooled estimate. Potential sources of heterogeneity were further investigated by using subgroup analyses and meta-regression for studies with available data. Subgroup analyses included study period (before and after 1998), sex, age groups ($\leq$5 and >5 years) and regions separated by the Qinling Mountains-Huaihe River Line (South and North). Meta-regression was performed to explore effects of study period, sex, age group, region, sample size (as a continuous variable) and quality assessment score. Because only few covariates were individually significant, the multivariate meta-regression model was not developed. We used the funnel plots (prevalence vs. standard error) and Egger's test to detect publication bias. Sensitivity analyses were