Vaccine (2008) **26**, 2545–2552

available at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/vaccine

Effectiveness of hexavalent vaccines against invasive *Haemophilus influenzae* type b disease: Germany's experience after 5 years of licensure

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Received 23 October 2007; received in revised form 14 February 2008; accepted 2 March 2008
Available online 20 March 2008

KEYWORDS
Haemophilus influenzae type b;
Hexavalent combination vaccines;
Vaccine effectiveness;
Germany

Summary Vaccine effectiveness (VE) was determined with a case-cohort approach using Cox regression. Cases with confirmed systemic Hib infections in children born from 1 August 2000 to 31 December 2004 were ascertained through two independent nationwide active surveillance systems. A representative cohort of 1303 children born in the same time frame was randomly sampled in a nationwide immunisation survey. Thirty cases were eligible for VE calculation; 19 were unvaccinated and 11 vaccinated with hexavalent vaccines. VE was 68.4% (95% CI: 19.0–87.6) for incomplete primary series and 90.4% (95% CI: 70.6–96.8) for the full primary series. For full immunisation VE was 100.0% (95% CI: 52.7–100.0). Hexavalent vaccines show a high effectiveness against invasive Hib disease in Germany.

Introduction

Following the introduction of conjugate vaccines against *Haemophilus influenzae* type b (Hib) in Germany, the incidence of Hib disease decreased sharply [1]. Similar patterns were observed in other European countries [2–5].

As Hib vaccines are usually administered at the same time as diphtheria, tetanus and pertussis vaccines, combination vaccines were developed to improve compliance and reduce health care costs. Since 1996, diphtheria–tetanus–acellular pertussis (DTaP)-based Hib conjugate combination vaccines have been widely used in Germany.

DTaP/Hib conjugate combination vaccines have been shown to elicit lower antibody levels to Hib polysaccharide after three doses in the first year of life when compared with administration of the same monovalent Hib conjugate vaccine [6–9]. However, despite these findings Eskola et al. [10] neither found for conjugate combination vaccines a reduced clinical efficacy nor a reduced immunity against Hib. Once

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doi:10.1016/j.vaccine.2008.03.001

the booster dose is given, there is no difference in antibody levels to Hib polysaccharide between DTaP/Hib conjugate combination vaccines and monovalent Hib conjugate vaccines [11].

In Germany, the effectiveness of DTaP/Hib and DTaP-inactivated poliovirus (IPV)/Hib combination vaccines against Hib has been estimated to be high [12,13]. These findings contrast with observations in the UK, where an increasing number of Hib vaccine failures have been reported in 2002, which coincided with the change from whole cell pertussis to acellular pertussis Hib combination vaccines [14]. The effectiveness of these DTaP/Hib vaccines following three doses was estimated to be 56.7% [15].

These observations point to the need to closely monitor the effectiveness of DTaP-based combination vaccines. At the end of 2000, Germany was the first country where hexavalent vaccines were introduced by adding a hepatitis B (HBV) component to the previous pentavalent DTaP—IPV/Hib combination vaccine. These vaccines gained rapid acceptance; in the first year after its introduction the average market share of the two licensed vaccines (Hexavac®; Infanrix hexa®) among all vaccines containing Hib-antigens reached 63% of all Hib vaccines and increased to 86% in 2005 (Institute for Medical Statistics, Munich, personal communication, 2005). To our knowledge there are no data on field effectiveness of hexavalent vaccines against invasive Hib disease. This study therefore aims to estimate the effectiveness of hexavalent vaccines against invasive Hib disease in German children 5 years after licensure.

Subjects and methods

The analytic approach of this study was that of a case-cohort study [16,17]: in a defined population (full cohort) all cases with their vaccination status and co-variables of interest are assessed; in a subcohort, which is a representative fraction of the defined population, accurate information on the same variables is assessed. Cases with confirmed invasive Hib infections were ascertained by a nationwide active surveillance system. The subcohort was randomly sampled in a nationwide vaccine coverage survey. All infants in Germany constituted the full cohort. However, the cohort and, hence, the cases were restricted to those born between 1 August 2000 and 31 December 2004.

Case recruitment and definition

Since 1998 two established population-based prospective surveillance systems with active follow-up of reported cases, one hospital-based and one laboratory-based, were used to detect children less than 10 years of age with invasive *Haemophilus influenzae* disease [18]. In the present study cases contributed to the vaccine effectiveness calculations if aged 2 months or older at disease onset and with a confirmed invasive *H. influenzae* infection detected between 1 August 2000 and 31 December 2005.

A case of invasive *H. influenzae* infection was defined as any hospitalisation due to a systemic infection clinically compatible with an invasive *H. influenzae* disease (e.g., meningitis, pneumonia, epiglottitis, septicaemia, cellulites, and arthritis) and with the isolation of *H. influenzae* from a normally sterile body site such as blood or cerebrospinal fluid. Culture, identification and serotyping of clinical isolates by slide agglutination were performed in the local laboratories participating in the surveillance programme according to their routine procedures. Local laboratories also performed PCR testing when available. Laboratories were encouraged to send their specimens to the National *H. influenzae* Consulting Laboratory at the Department of Paediatric Infectious Diseases, Johannes-Gutenberg-University, Mainz, Germany, where typing of *H. influenzae* isolates was performed by slide agglutination using a commercial kit (*H. influenzae* agglutinating sera (a—f); Murex Biotech Ltd., Dartford, UK) and by a method recommended by the European *Haemophilus* Reference Unit [19]. If slide agglutination and PCR results were discordant, PCR results were considered final. If samples for the case were not sent to the reference laboratory, local typing results are considered final; if samples for the case were sent to the reference laboratory, the reference laboratory results are considered final. Of note, if no typing was performed, the case is considered ''untyped''.

The vaccination status of the cases was determined by a detailed questionnaire asking for the number and dates of Hib vaccinations before disease onset, and brand names of the vaccines used. The source of this information was obtained from vaccination booklets or vaccinating paediatricians.

National immunisation survey

A representative nationwide vaccine coverage survey was conducted between July 2002 and January 2006 applying the random digit dialling method using computer-assisted telephone interviews (CATI). At the initial interview, 78,266 persons were screened for the presence of a child in the household and asked if they were willing to participate in a second telephone call when questions would be asked about their child's health and possible vaccinations. Informed consent was obtained from all participating parents. Upon request, a letter explaining the purpose of the study and providing the names and affiliations of the principal investigators was sent to the families. In a second telephone call, parents were asked to read the dates and brand names of vaccinations from the relevant pages of the vaccination booklet. Additionally, birth dates, sex, socio-economic status, and place of residence of the child were ascertained. In the present study children contributed to the vaccine effectiveness calculations if aged 2 months or older at interview and interviewed until 31 December 2005.

Response rates to the telephone interviews were calculated according to international standards [20].

Data from the immunisation survey were compared with data of the national statistics office [21] for German families with at least one child under the age of 3 years regarding geographical and socio-economic variables.

The study was approved by the ethics committee.

Analytic approach and statistical methods

Hib vaccine effectiveness was assessed for both licensed DTaP—IPV—HB/Hib hexavalent combination vaccines