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Invasive *Haemophilus influenzae* type b disease in German children:

Epidemiology and vaccine effectiveness in the era of hexavalent vaccines

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1 SUMMARY (ENGLISH)

Background: Following the introduction of conjugate vaccines against invasive *Haemophilus influenzae* type b (Hib) disease in Germany, the incidence of Hib disease dramatically decreased. Hib conjugate vaccines were combined with diphtheria, tetanus and acellular pertussis antigens (DTaP/Hib) and gradually replaced by higher-valent vaccines, additionally incorporating inactivated polio virus and - since the end of 2000 - hepatitis B (DTaP-IPV-HB/Hib or hexavalent vaccines). Recently, an increasing incidence of invasive Hib disease in children and an increasing number of vaccine failures have been reported from some European countries, which coincided with the introduction of combination vaccines containing the acellular pertussis component. Previous data in Germany showed no such increase and vaccine effectiveness (VE) of DTaP/Hib and DTaP-IPV/Hib combination vaccines against invasive Hib disease was estimated to be high. Since Germany is the first country who introduced hexavalent vaccines, insufficient data on the impact of hexavalent vaccines on invasive Hib disease and on the VE against invasive Hib disease in children exist.

Aim: To assess (1) annual numbers of Hib cases and vaccine failures of Hib vaccines before and after the introduction of hexavalent vaccines in German children, (2) annual incidences of invasive Hib disease before and after the introduction of hexavalent vaccines in German children and to estimate (3) VE of hexavalent vaccines against invasive Hib disease in German children.

Subjects and Methods: Invasive *Haemophilus influenzae* (Hi) infections in children less than 10 years were ascertained from 1998 to 2004 through two independent nation-wide active surveillance systems, one hospital- and one laboratory-based. Species confirmation and capsular testing was performed in the national consulting laboratory for Hi. Cases were defined by any hospitalisation due to a systemic infection clinically compatible with an invasive Hi disease and with isolation of Hi from a normally sterile body site. Annual case numbers and incidences were adjusted for underreporting and for differences in the proportion of typed cases over time. VE was determined with a case-cohort approach using Cox regression with time-dependent covariates. In this analysis, Hib cases born between August 2000 and June 2003, aged 2 months or older and ascertained from August 2000 to December 2003 were included for case-cohort analysis and a ‘sub’-cohort of children born in the same time frame as the cases was randomly sampled in a nationwide immunisation survey. Children receiving two/three Hib doses (depending on vaccine type) in the first year of life, without booster, were defined as ‘fully primed’, children receiving a single dose in the

second year of life, regardless of priming, as receiving a '2nd year dose' and children receiving a booster dose at the age of 11 months or later following full priming as receiving the 'full immunisation'.

Results: In the two surveillance systems annual response rates since 1998 were >90%, the proportion of untyped Hi cases decreased from 25% of all reported cases in 1998 to 15% in 2004 and the proportion typed in the national consulting laboratory increased from 55% of all reported cases in 1998 to 70% in 2004. The annual number of Hi cases decreased from 51 in 1998 to 27 cases in 2004. Hib cases fluctuated between 28 in 1998 and 4 in 2004. Of all 117 Hib cases detected since 1998, 64 were not vaccinated and 52 were vaccinated at least once. 92% of the unvaccinated Hib cases and 53% of the vaccinated Hib cases could have received at least one (additional) dose if timing of general recommendations would have been followed. Of all vaccinated Hib cases, 12 had been vaccinated with at least one dose of a hexavalent vaccine. Overall annual incidence rates of Hi disease were relatively constant throughout the years 1998 through 2004 (0.8-0.4/100,000). Annual incidences of Hib disease ranged between 0.3 and 0.1 per 100,000 in 1998 and 2004, respectively, with the highest incidence in the 3-11 month age-group (1.7/100,000 in 2003). Adjustment for underreporting and differences in typing gave no evidence of an increasing trend of Hib disease in German children. Twenty-seven cases were eligible for VE calculation; 17 were unvaccinated and 10 vaccinated with hexavalent vaccines; of these, 5 received an incomplete primary series, 5 received the full primary series and none a 2nd year dose or the full immunisation before disease onset. In the immunisation survey, response rate was 63% and interviewed households were representative for age-eligible children in Germany according to geographical and social distributions. 1303 valid interviews of children born from 1 August 2000 onwards were available. Median age at vaccination with the complete primary series of hexavalent vaccines was 6.0 months and 14.4 months for the full immunisation. Effectiveness of hexavalent vaccines against invasive Hib infection was 75.5% (95% CI: 31.4-91.3) for incomplete primary series and 91.8% (95% CI: 73.6-97.5) for the full primary series. For the 2nd year dose - but no full immunisation - and full immunisation vaccine effectiveness was 100.0% (95% CI: 99.5-100.0 and 99.9-100.0, respectively).

Conclusion: Four years after the introduction of hexavalent vaccines in Germany, there was no indication of increasing incidence of invasive Hib disease or increasing number of vaccine failures in children. Hexavalent vaccines continue to show the high effectiveness against invasive Hib disease observed for other DTaP-containing Hib vaccines in Germany. Sustained surveillance – especially for fully immunised children - should confirm protection induced by hexavalent vaccines.

2 SUMMARY (GERMAN)

Einleitung

In Deutschland ist die Inzidenz von invasiven *Haemophilus influenzae* Typ b (Hib) Erkrankungen nach der Einführung von Konjugatimpfstoffen gegen Hib drastisch gesunken. Hib-Impfstoffe wurden daraufhin mit anderen Antigenen zu Kombinationsimpfstoffen zusammengefasst: zu Beginn mit Diphtherie-, Tetanus- und azellulären Pertussis-Antigenen (DTaP/Hib), dann zusätzlich mit inaktivierte Polioviren und – seit Ende 2000 – mit Hepatitis B-Antigenen (DTaP-IPV-HB/Hib; hexavalente Impfstoffe). Kürzlich wurden aus anderen europäischen Ländern steigende Hib-Inzidenzen und Hib-Impfversager berichtet, die in Zusammenhang mit der azellulären Pertussiskomponente von Kombinationsimpfstoffen stehen. In Deutschland konnte bislang kein solcher Anstieg festgestellt werden und die Wirksamkeit von DTaP/Hib und DTaP-IPV/Hib Kombinationsimpfstoffen gegen invasive Hib Erkrankungen ist hoch. Da Deutschland das erste Land war, in dem hexavalente Impfstoffe eingeführt wurden, gibt es bislang noch ungenügend Daten über deren Einfluss auf die Epidemiologie von invasiven Hib Erkrankungen und die Wirksamkeit dieser Impfstoffe im ‚Feld'. Ziel dieser Studie war es (1) die Anzahl von Hib Fällen und von Hib-Impfversagern und (2) die Jahresinzidenzen von invasiven Hib-Erkrankungen vor und nach der Einführung von hexavalenten Impfstoffen bei Kindern in Deutschland zu bestimmen und (3) die Wirksamkeit der hexavalenten Impfstoffe gegen invasive Hib Erkrankungen zu berechnen.

Methoden

Invasive *Haemophilus influenzae* (Hi) Erkrankungen bei Kindern unter 10 Jahren wurden zwischen 1998 und 2004 über zwei unabhängige aktive Surveillance-Systeme in Deutschland erhoben. Die Typisierung der Erreger erfolgte im Nationalen Konsiliarlabor für Hi in Mainz. Ein Fall wurde definiert als jede Hospitalisierung aufgrund einer systemischen Infektion, die klinisch vereinbar mit einer invasiven Hi Infektion war und einen Erregernachweis aus normalerweise sterilen Körperflüssigkeiten hatte. Jährliche Fallzahlen und Inzidenzen wurden für Untererfassung und Unterschiede im Anteil der typisierten Fälle korrigiert. Die Impfstoff-Wirksamkeit wurde mit der ‚Case-Cohort' Methode und zeitabhängigen Kovariablen im Cox-Modell ermittelt. Hierbei wurden alle Hib Fälle, die zwischen August 2000 und Juni 2003 geboren und mindestens 2 Monate alt waren, eingeschlossen und deutschlandweite Telephoninterviews zum Impfstatus von Kindern, die im selben Zeitrahmen geboren wurden, durchgeführt. Kinder, die je nach Impfstofftyp zwei oder drei Hib-Impfdosen im ersten Lebensjahr ohne nachfolgenden ‚Booster' erhielten, werden als ‚vollständig grundimunisiert', Kinder, die eine Dosis im zweiten Lebensjahr, unabhängig von der Anzahl vorangegangener Dosen, als ‚immunisiert mit Dosis im 2.

Lebensjahr', und Kinder, die die vollständige Grundimmunisierung und einen Booster im Alter von 11 Monaten oder später erhielten als ‚vollständig immunisiert' definiert.

Ergebnisse

Die jährlichen Response-Raten der beiden Surveillance-Systeme betrugen >90%, der Anteil untypisierter Hi Fälle sank von 25% im Jahr 1998 auf 15% im Jahr 2004 und der Anteil der Fälle, die im Nationalen Konsiliarlabor typisiert wurden stieg von 55% aller Fälle im Jahr 1998 auf 70% im Jahr 2004. Die jährliche Anzahl der Hi Fälle sank zwischen 1998 und 2004 von 51 auf 27 Fälle, die der Hib Fälle schwankte zwischen 28 und 4 pro Jahr. Von allen 117 Hib Fällen, die seit 1998 detektiert wurden, waren 64 nicht und 52 zumindest einmal gegen Hib geimpft. 92% der ungeimpften und 53% der geimpften Hib Fälle hätten mindestens eine weitere Dosis zum Zeitpunkt ihrer Erkrankung erhalten sollen, wenn die Empfehlungen der Ständigen Impfkommission in Deutschland eingehalten worden wären. Zwölf der geimpften Hib Fälle erhielten mindestens eine Dosis eines hexavalenten Impfstoffes. Die Jahresinzidenzen von Hi blieben zwischen 1998 und 2004 relativ konstant (0,8-0,4/100.000), Die Jahresinzidenzen von Hib schwankten zwischen 0,3 und 0,1 pro 100.000, mit den höchsten Werten für die Altersgruppe der 3-11 Monate alten Kinder (1,7/100.000 im Jahr 2003). Auch Korrekturen bezüglich Untererfassung oder Typisierungs-Anteil gaben keinen Anhalt für eine Zunahme von invasiven Hib-Infektionen in Deutschland. Für die Berechnung der Wirksamkeit von hexavalenten Impfstoffen konnten 17 ungeimpfte und 10 geimpfte Kinder (5 unvollständig grundimmunisiert, 5 vollständig immunisiert) mit Hib Erkrankung aufgenommen werden. Die Responserate aus den Telephoninterviews betrug 63% und die interviewten Haushalte waren bezüglich geographischer und sozialer Parameter repräsentativ für entsprechende Kinder in Deutschland. Insgesamt waren 1303 Interviews verfügbar. Das mediane Alter zur vollständigen Grundimmunisierung betrug 6,0, das zur vollständigen Immunisierung 14,4 Monate. Die Wirksamkeit der hexavalenten Impfstoffe gegen invasive Hib-Erkrankungen betrug 75,5% (95% CI: 31,4-91,3) für unvollständig grundimmunisierte Kinder und 91,8% (95% CI: 73,6-97,5) für vollständig grundimmunisierte Kinder. Für Kinder, die vollständig oder im 2. Lebensjahr immunisiert wurden, war der Impfstoff zu 100,0% wirksam (95% CI: 99,5-100,0 bzw. 99,9-100,0).

Schlussfolgerung

Vier Jahre nach der Einführung von hexavalenten Impfstoffen in Deutschland gibt es keinen Hinweis für steigende Hib-Inzidenzen oder steigende Anzahl von Hib-Impfversagern. Hexavalente Impfstoffe weisen eine hohe Wirksamkeit gegen invasive Hib Erkrankungen bei Kindern auf, die vergleichbar mit denen anderer DTaP-enthaltender Hib-Impfstoffe ist. Eine längere Surveillance-Periode erscheint jedoch insbesondere zur Beurteilung der Wirksamkeit von vollständig immunisierten Kindern sinnvoll.

3 INTRODUCTION

Prior to the development of effective vaccines, *Haemophilus influenzae* type b (Hib) was the most common single organism causing invasive bacterial infections in children in the developed world (Tudor-Williams et al., 1989; Murphy et al., 1992; Wenger et al., 1992). In most European countries, the annual incidence rate of invasive Hib in children less than five years ranged between 20 and 50 per 100,000 (e.g. Reinert et al., 1993; Hargreaves et al., 1996; Takala et al., 1989; Tozzi et al., 1997; van Alphen et al., 1997). Following the introduction of conjugate vaccines against Hib in July 1990 in Germany, the incidence of Hib disease decreased sharply (von Kries et al., 1997). Similar patterns were observed in other European countries (Garpenholt et al., 1996; Hargreaves et al., 1996), the US (Adams et al., 1993) and Australia (Herceg, 1997).

Because Hib conjugate 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. The first diphtheria-tetanus-acellular pertussis (DTaP) / Hib conjugate combination vaccines were licensed for primary vaccination and have been available to physicians in Germany since October 1996. Other DTaP/Hib conjugate vaccines in combinations incorporating inactivated poliovirus vaccine (IPV) have subsequently been registered in 1998 in response to a recommendation of the German Vaccine Advisory Board (*Ständige Impfkommission am Robert-Koch Institut* = STIKO) to switch from oral polio virus (OPV) to IPV in January 1998. DTaP-based Hib vaccines were widely used in Germany: within one year of availability, over 70% of all Hib vaccinations in children were being given as combinations containing DTaP (Institute for Medical Statistics, Munich, personal communication, 2005).

Concerns have been raised in some countries over the use of DTaP/Hib conjugate combinations following the demonstration that DTaP/Hib conjugate combination vaccines elicit lower antibody levels to Hib polysaccharide after the primary vaccination series when compared with administration of the same Hib conjugate vaccine injected separately, either as a separate injection concomitantly with DTaP or alone. Nevertheless, 95% of DTaP/Hib conjugate vaccines had an antibody response to Hib >0.15µg/mL, the minimum protective concentration for anti-Hib antibody level which is generally correlated to protection against Hib (Eskola et al., 1996; Pichichero et al., 1997; Schmitt, 1995; Shinefield et al., 1997). A comparison of anti-Hib antibody titres achieved with Hib conjugate vaccines in recent combination vaccines to those seen in studies with licensed monovalent Hib conjugate vaccines suggest that slightly lower

titres may not translate into reduced clinical efficacy (Eskola et al., 1999). In addition, other markers of Hib immunity (functional capacities of antibodies, immune memory, booster responses, etc.) showed no difference between separate and combined administration of this component (Eskola et al., 1999; Bell et al., 1998; Zepp et al., 1997; Poolman et al., 2001). The clinical relevance of this lower antibody response has therefore been questioned (Eskola et al., 1999).

Despite the spectacular success of Hib conjugate vaccines in the developed world (Peltola, 2000), an increasing number of vaccine failures have recently been reported from the Netherlands (Rijikers et al., 2003) and the United Kingdom. In the UK, the incidence of invasive Hib disease at age 0-4 years increased from 0.65 per 100,000 in 1998 to 4.58 per 100,000 in 2002 (Ramsay et al., 2003). This increase has been seen to coincide with the change from whole cell pertussis to acellular pertussis Hib combination vaccines and with the introduction of concomitant meningococcal group C vaccine (Trotter et al., 2003). The effectiveness of these DTaP/Hib vaccines following full priming was only 56.7% (Ramsay et al., 2003). This resulted in the withdrawal of DTaP/Hib vaccines and implementation of a national immunisation catch-up campaign for children younger than 4 years in the UK (Health Protection Agency, 2004). In Germany, however, the effectiveness of DTaP/Hib and DTaP-IPV/Hib vaccines has been estimated to be high (Schmitt et al., 2001; Kalies et al., 2004).

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. Again, these vaccines gained rapid acceptance; the average market share of the two licensed vaccines (Hexavac®; Infanrix hexa®) increased from 63% of all Hib vaccines in 2001, 83% in 2002 and 87% in 2003 to 88% in 2004 (Institute for Medical Statistics, Munich, personal communication, 2005). Apart from two conference abstracts (Kalies et al., 2003, 2005), there are no data published describing numbers of Hib cases or Hib incidences or estimating the effectiveness of hexavalent vaccines against invasive Hib disease after licensure of these vaccines. Therefore, evaluating whether hexavalent Hib vaccines are as effective as lower-valent Hib vaccines in preventing invasive Hib disease in Germany remains an important issue, not only for regulatory authorities but also for the public.

This study aims to assess the impact of the introduction of the two hexavalent DTaP-IPV-HBV/Hib conjugate combination vaccines on invasive Hib disease in Germany, and to estimate the effectiveness of hexavalent vaccines against invasive Hib disease in children. The objectives of this study are presented in detail in the following section.

4 OBJECTIVES OF THE STUDY

(1) To describe annual numbers of Hib cases and vaccine failures of Hib vaccines against invasive Hib disease in German children before and after the introduction of hexavalent combination vaccines on the German market.

(2) To describe annual incidence of invasive *H. influenzae* and Hib disease in German children before and after the introduction of hexavalent combination vaccines on the German market.

(3) To estimate the effectiveness of hexavalent combination vaccines against invasive Hib disease in German children:

(a) after incomplete primary series;
(b) after complete primary series;
(c) after complete primary series followed by a booster dose at the age of 11 months or later ('fully immunised');
(d) after receiving a dose in the second year of life regardless of priming ('2nd year dose'), excluding category c;

(e) after any number of vaccinations but not according to the recommended schedule;
(f) after an immunisation according to the recommended schedule.

Definitions of vaccine effectiveness, the different categories of vaccination status and the recommended Hib vaccination schedule are given in detail in chapters 6.1 and 6.4.4.

5 STRUCTURE OF THE DOCUMENT

This study is structured in a 'material and methods' section (chapter 6) where general definitions, the surveillance system for detection of *H. influenzae* (Hi) cases, the national immunisation survey for evaluation of the immunisation status in the German population and the statistics used are described.

The 'results' section is subdivided into five chapters. In the first chapter (chapter 7.1), the quality of the surveillance system to detect *H. influenzae* cases and of the national immunisation survey to detect the Hib immunisation status of German children – which is necessary to answer objective 3 – will be described. In the second chapter (chapter 7.2), a general description of the data derived from these two systems is given; to reflect a situation where hexavalent combination vaccines dominated the German market, this section is restricted to the time period of the years 2001-2004 for the case surveillance system and to children born after 30 July 2000 for the immunisation survey. In the next three chapters, the above objectives of the study will be answered; in chapters 7.3 and 7.4, cases or incidences of cases detected in the years 2001-2004 will be compared to a time period before hexavalent combination vaccines have been licensed. In chapter 7.5 the effectiveness of hexavalent vaccines against invasive Hib disease is reported; here, cases detected in 2004 could not be considered for effectiveness calculations because the national immunisation survey collected data on children born up to 31 December 2003 only.

The 'discussion' section (chapter 8) debates meanings of these results in the context of other data.

6 MATERIAL AND METHODS

6.1 Definitions

6.1.1 Recommended Hib vaccination schedule

In Germany, the immunisation calendar is recommended by the German Standing Committee on Vaccination (*Ständige Impfkommission am Robert Koch-Institut*; STIKO). Children are vaccinated by paediatricians or family physicians who can choose any of the vaccines licensed for immunisation of infants and children. In the study period, 15 different products were available for Hib vaccination in children. The recommended schedule for all Hib vaccines containing acellular pertussis components is a 3-dose primary series at age 2, 3 and 4 months with a booster dose scheduled at 11-14 months. For vaccines not containing acellular pertussis a 2-dose primary series at age 2 and 4 months is recommended (Robert Koch Institute, 2003). As brand names were asked for a distinction between the completion of these two primary schedules could be made. For children vaccinated with Hib vaccines who did not receive full priming and booster by the age of 12 months, a single Hib dose in the second year of life is recommended.

6.1.2 Categories of vaccination status

According to the recommended German vaccination schedule for Hib the following two definitions with mutually exclusive vaccination categories were defined:

(1) Completeness of vaccination schedule

- Incomplete primary series: after receiving one dose of a Hib vaccine not containing acellular pertussis or after receiving 1-2 doses of a Hib vaccine containing acellular pertussis in the first year of life and no further doses at age 11 or later.
- Complete primary series: after receiving at least two doses (vaccines not containing acellular pertussis) or three doses (vaccines containing acellular pertussis) of Hib vaccines in the first year of life and no further doses at age 11 or later.
- 2nd year dose: after receiving a booster dose at the age of 11 months or later following complete primary series, or any dose in the second year of life regardless of priming.

  A specification of the latter category is:

  - *Full immunisation: after receiving a booster dose at the age of 11 months or later following complete primary series (=full priming).*

(2) Age-eligibility of vaccination schedule

- Immunised according to recommended schedule:
    - Receiving a 2nd year dose or full immunisation;
    - Receiving full primary series and less than 16 months old at disease onset;
    - Receiving incomplete primary series and less than 6 month old at disease onset;
    - Not immunised and less than 2 months old at disease onset.
- Immunised not according to recommended schedule:
    - Receiving a full primary series and 16 or more months old at disease onset;
    - Receiving incomplete primary series and 6 month or more old at disease onset;
    - Not vaccinated with a Hib vaccine and 2 months or older at disease onset.

  This definition is less stringent than the recommended vaccination schedule: for the incomplete primary series, children were defined as being immunised age-appropriate if they were less than 6 months old at disease onset, even if they should have received more doses until this age by applying the exact timing of the recommended vaccination schedule.

6.1.3 Vaccine failures

The following definition for vaccine failures with mutually exclusive categories was chosen:

- Vaccine failure of the incomplete primary schedule: invasive Hib disease in a child occurring at least 1 week after incomplete primary Hib vaccine series (single doses given at least 1 month apart) and prior to a dose completing primary schedule or a 2nd year dose.

- Vaccine failure of the complete primary schedule: invasive Hib disease in a child occurring at least 1 week after complete primary Hib vaccine series (single doses given at least 1 month apart) and prior to a booster dose given at an age ≥ 11 months.

- Vaccine failure of a 2nd year dose: invasive Hib disease occurring at least 1 week after a dose of vaccine given at the age of 11 months or later following full priming or any dose in the second year of life, irrespective of the total number of doses given.

A specification of the latter category is:

- *Vaccine failure of the primary and booster regimen: invasive Hib disease occurring at least 1 week after complete primary Hib vaccine series (single*

doses given at least 1 month apart) and after a booster dose given at an age of 11 months or later.

6.2 *H. influenzae* cases in Germany

To assess valid numbers and incidences of invasive Hib disease in Germany a reliable nationwide surveillance system was used: national active surveillance of invasive *Haemophilus influenzae* disease in children less than 16 years of age was performed through the *'Erhebungseinheit für Seltene Pädiatrische Erkrankungen in Deutschland (ESPED)'* (Schmidt et al., 1993).

6.2.1 Case definition

A case of invasive *Haemophilus 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 [all cases of bacteraemia without a reported focus were classified as septicaemia since they were all hospitalised], cellulitis, arthritis) and with isolation of *H. influenzae* from a normally sterile body site such as blood or cerebrospinal fluid. All cases occurring in children less than 10 years of age are analysed in this study.

6.2.2 ‚Erhebungseinheit für Seltene Pädiatrische Erkrankungen in Deutschland' *(ESPED)*

ESPED was established in July 1992, adapted from the British Paediatric Association Surveillance Unit (Schmidt et al., 1993) with the primary purpose of epidemiological surveillance. ESPED evaluated the effect of vaccination on invasive *H. influenzae* disease incidence over the period from July 1992 to December 1995. As shown in other countries, vaccination against Hib greatly reduced the incidence of disease in Germany (von Kries et al., 1997) to such an extent that Hib surveillance was dropped from the ESPED programme at the end of 1995. National active surveillance of invasive *H. influenzae* disease was reintroduced in 1998.

Before 1998, the active surveillance system was based on monthly report cards sent to all hospital paediatric departments in Germany; from 1998 onwards an additional system was established based on reports from laboratories performing microbiological analyses.

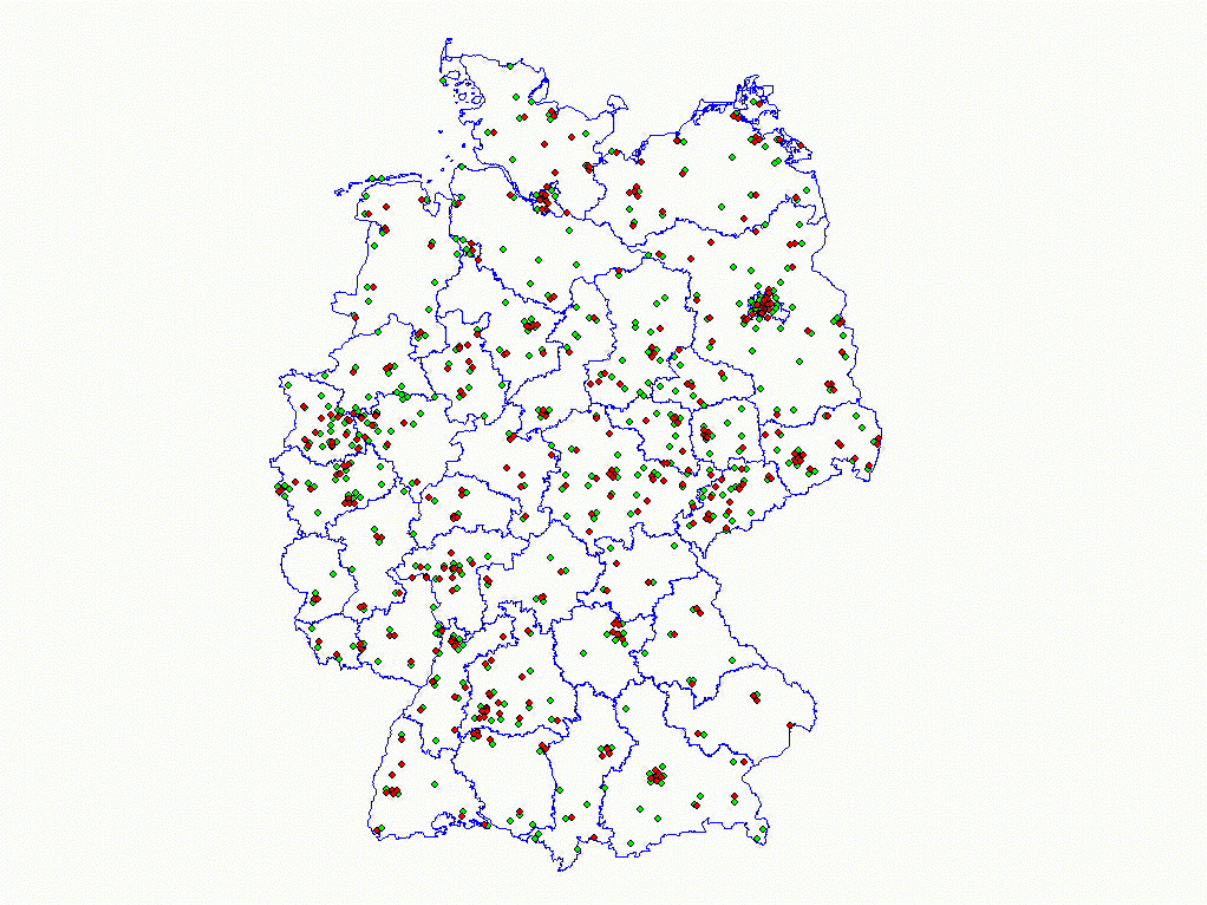
6.2.2.1 Clinical ESPED

As part of the established national clinical surveillance system, monthly report cards were routinely sent to the heads of all known hospital paediatric departments in Germany (range: 388-393 hospital departments per year). The geographic distribution of these hospitals in 1998 to 1999 is shown in figure 1 (green dots). The cards solicit information on the number of patients hospitalised with any one of up to 12 listed rare diseases / serious adverse events (annex A.1, chapter 15.1). Invasive *H. influenzae* disease was reinstated to this list in January 1998. Case reports were followed up by means of a questionnaire mailed to the reporting paediatrician, requesting information on age, sex, and nationality of the patient, the clinical history including any underlying risk factors for invasive Hib disease, results of diagnostic procedures including serotyping of *H. influenzae* isolates, clinical management, outcome and Hib vaccination history with type / brand of vaccine and number of doses administered (annex A.2, chapter 15.1). If necessary, additional information was obtained through telephone interviews of paediatricians.

6.2.2.2 Laboratory ESPED

In 1997, the Robert-Koch-Institute of the German Ministry of Health, located in Berlin, established an independent laboratory surveillance system (Laboratory ESPED). The surveillance mechanism was similar to that of Clinical ESPED with monthly report cards being sent to all laboratories known at that time to be performing microbiological analysis on specimens of any origin from paediatric hospital departments throughout Germany (range: 290-295 laboratories per year). The geographic distribution of these hospitals in 1998 to 1999 is shown in figure 1 (red dots). Invasive *H. influenzae* disease, defined as isolation of *H. influenzae* from a normally sterile body fluid such as blood or cerebrospinal fluid, was added to the report card in January 1998. The monthly report card requested details about the age of the patient, the clinical origin of the specimen, and bacterial serotype (annex A.3, chapter 15.1). In addition vaccination histories and, from 2001 onwards, information on concomitant medical conditions as well as outcome was obtained by questionnaire or telephone calls to the respective paediatrician for all reported cases of invasive *H. influenzae* disease.

Figure 1: Clinics and laboratories involved in the ESPED surveillance in 1998-1999. (Hospitals are marked in Green, laboratories in Red)



Response rates for both Clinical ESPED and Laboratory ESPED surveillance surveys were measured by the number of surveillance cards/questionnaires returned over the number of cards/questionnaires sent out.

6.2.2.3 Matching of the two sources and identification of the duplicates

Cases reported to Clinical- and Laboratory-ESPED were matched using personal identifiers (initials, sex, birth date, geographical region, type of isolate and time of recording) to exclude any duplicate reporting of the same cases by the two systems. Matching was performed by Robert Koch Institute (Berlin, Germany) and Institute of Social Paediatrics (University Munich, Germany) independently. Cases with discordant matching results were double checked by both parties and final decision was agreed upon full information of the two possible duplicates.

6.2.2.4 Serotyping and final classification

Culture, identification and serotyping of clinical isolates by slide agglutination were performed in the local laboratories participating in the ESPED programme according to their routine procedures. Local laboratories also performed Polymerase Chain Reaction testing (PCR) 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 (Prof. Dr. H-J. Schmitt), where typing of *H. influenzae* isolates is performed by slide agglutination using a commercial kit (*Haemophilus influenzae* Agglutinating Sera (a-f); Murex Biotech Ltd., Dartford, UK) and by the PCR method described by Falla et al. (1994). This method was recommended by Dr. Mary Slack (project leader of the European Union Invasive Bacterial Infections Surveillance Network [EU-IBIS]), to be used in all European reference laboratories. If slide agglutination and PCR results are discordant, PCR results are considered final.

Cases are classified as type b based on the following criteria: if samples for the case were not sent to the national consulting laboratory, local typing results are considered final; if samples for the case were sent to the reference laboratory, the national consulting laboratory results are considered final.

6.3 National immunisation survey

To estimate the effectiveness of hexavalent DTaP-HBV-IPV/Hib combination vaccines against invasive Hib disease during the surveillance period the number of Hib cases and estimates of vaccination coverage in the study population are needed. No precise vaccine coverage data are routinely available in Germany.

The only available representative routine data on vaccination coverage in childhood derive from school health examinations. Although these data cover most children at a certain age, they have some limitations: they lag 5 to 6 years behind the current vaccination practice and do not assess types of vaccine or timing of vaccination. Furthermore, each of the 16 states in Germany is responsible for its own school health examination and has different definitions for fully immunised children.

Therefore, representative nationwide immunisation surveys were conducted to assess precise vaccine information of children applying the random digit dialling method using computer assisted telephone interviews (Schulte, 1997). To bridge between telephone

interviews on parents with children born between 1 June 1996 and 30 June 1999 (Laubereau et al., 2002; Kalies et al., 2004), parents with children born between 1 July 1999 and 30 June 2003 were chosen for this survey and interviewed between July 2002 and January 2004 using identical methods (Kalies et al., 2006).

Figure 2 illustrates the different steps of the telephone interviewing process from first call to population for analysis: in an initial interview 22,266 households were screened for the presence of a child born in the respective birth years (point 0) and asked if they were willing to receive a second telephone call concerning questions about the health of their child and possible vaccinations (point 1). On request, a letter with the purpose and the names and affiliations of the principal investigators of the study was sent to the families. Of all 3,286 households with children born in the respective years, 2,421 households were willing to answer to a second telephone call. Informed consent was obtained from all participating parents. 865 households refused participation (point 2); main reasons for non-participation were 'no interest' (27%), 'no time to answer' (20%) and 'concerns about data safety' (19%). In addition, fourteen households refused participation because their child was not vaccinated, although interviewers encouraged them to participate.

In the second telephone call, parents were asked by a team of trained interviewers to provide all dates and brand names of vaccinations from the relevant pages of their child's vaccination booklet. If records were unreadable, parents were asked to send a photocopy of the relevant pages, to give contact details of their paediatrician and to sign a declaration authorising the paediatrician to release vaccination information. If no vaccination booklet was available and the child had been vaccinated at least once, parental consent was sought to approach the paediatrician for the vaccination information. Additionally, birth date, sex and place of residence of the child and socio-economic status of the parents (education, occupation and household income) were collected.

Out of all 2,421 households who initially agreed to participate, 262 households could not be contacted in the second stage (point 3) due to quality neutral drop outs; main reasons were a change of the family's telephone number in the time between first and second call (48%), no child born in the respective year - despite former information - (20%) and no person reached at this telephone number within the maximum number of twelve telephone calls (19%).

Out of the 2,421 households who initially agreed to participate, 232 households declined to participate in the second stage when contacted (point 4); main reasons were 'no interest on subject of survey' (18%) and 'no time' (15%).

Response rates to the telephone interviews were calculated according to international standards (Smith et al., 2001): '*number of completed interviews*' divided by the result of the '*number of screened households with children born in the respective years*' minus the '*number of households which could not be reached at the second telephone call because of reasons unlikely to be related to the exposure of interest*' (change of family's telephone number in the time between first and second telephone call; no person reached at this telephone number within a maximum number of twelve telephone calls; child not belonging to eligible age group [in contrast to first telephone call's information]). This corresponds to: point 5 / (point 1 – point 3) in figure 2.

Data of the immunisation survey were compared with official data for the German population regarding geographical and socio-economic variables. For this purpose, data of the '*Mikrozensus*' were used (Federal Statistical Office Germany, 2002): the '*Mikrozensus*' is conducted annually on a representative sample of one percent of the German population. It collects data on working life, education as well as social and family life stratified by marital status and number and age of children in the respective family. The data of the telephone survey were compared with data on families with at least one child under the age of three years.

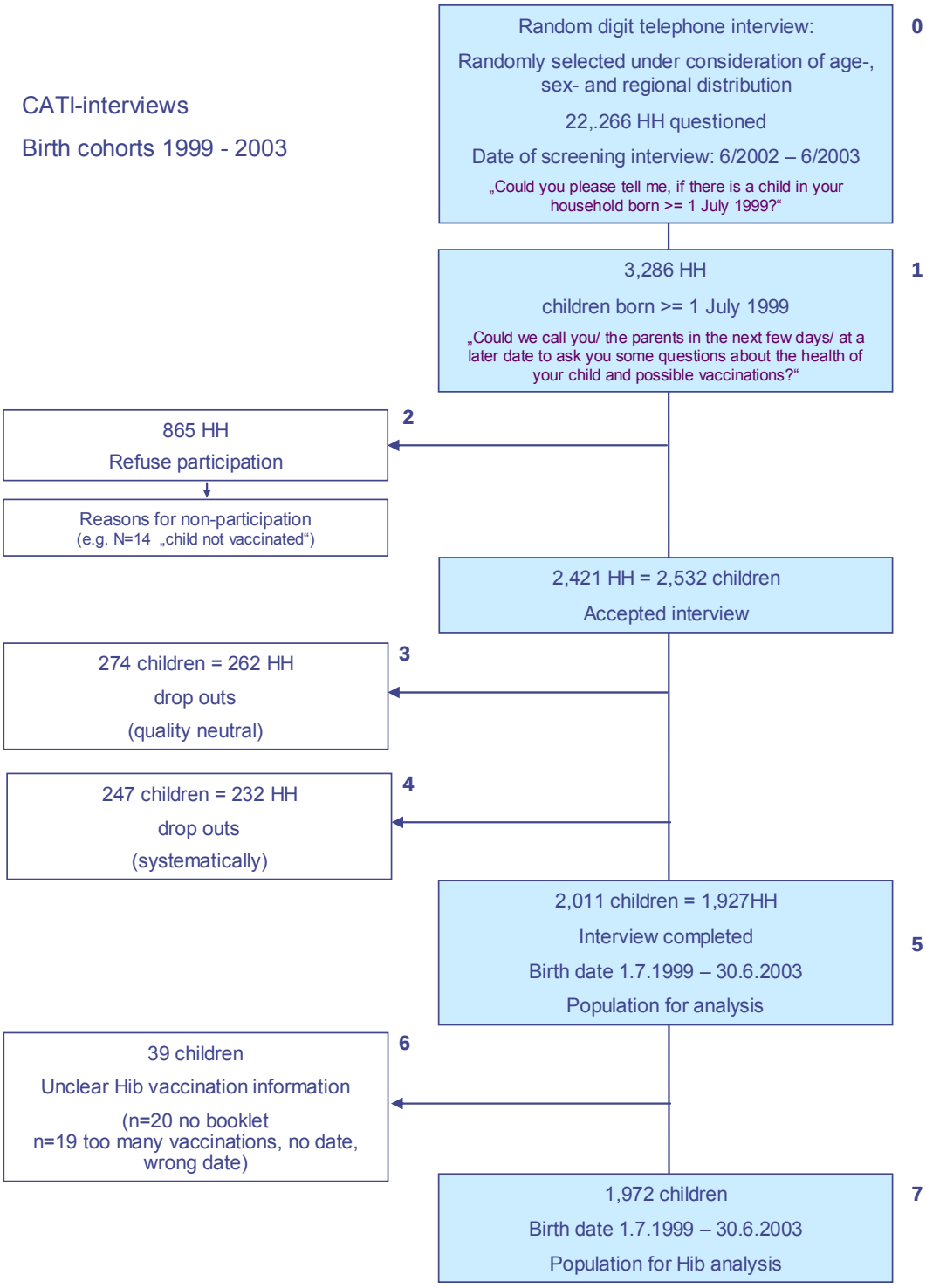


Figure 2: Telephone interviews to assess vaccination coverage of children in Germany. HH = number of households

6.4 Data analysis

6.4.1 Incidence rates

Age-specific annual incidence rates were calculated for the following age groups:

- 0-2 months
- 3-11 months
- 1.0-4.9 years
- 5.0-9.9 years.

The denominators used for the calculation of the annual incidence rates were extracted from the official population data of the Federal Statistical Office Germany (2005). Table 1 shows these denominators by year. At the time of this study, data on age groups under one year were not available for the year 2004. They were estimated by using 2003 data.

Table 1: German official population data ('*Statistisches Bundesamt*') used for calculation of annual incidence rates

Age-group	2004	2003	2002	2001	2000	1999	1998
0-2 months	176,612 *	176,612	179,813	183,939	191,638	193,235	197,441
3-11 months	529,837 *	529,837	539,438	551,816	574,916	579,705	592,325
1.0-4.9 years	2,945,564	3,017,871	3,085,271	3,157,229	3,177,290	3,178,090	3,171,126
5.0-9.9 years	3,974,875	3,984,183	4,005,842	4,017,158	4,073,345	4,255,004	4,417,203
All age groups	7,626,888	7,708,503	7,810,364	7,910,142	8,017,189	8,206,034	8,378,095

* 2004 official data not available at the time of this report. 2003 numbers provided here.

6.4.2 Survival analysis for uptake and timing of immunisations

Uptake and timing of immunisation by age in months was calculated according to the Kaplan-Meier method. 'Time of survival' was defined as the period from birth to receipt of the respective dose or series. The inverse survival is the probability of being vaccinated at time t, which is the coverage rate at a certain age. 95% confidence intervals (CI) were calculated using the Greenwood formula (Cox & Oakes, 1984). The Kaplan-Meier method for vaccine uptake is described in detail by Laubereau et al. (2002). Figure 3 demonstrates possible interpretations of an inverse Kaplan-Meier curve: this fictive vaccination is recommended at age 2 months.

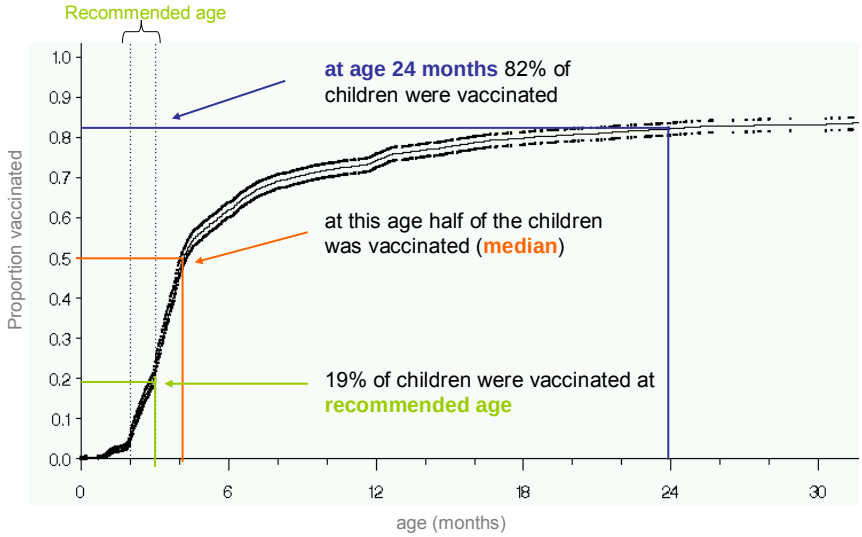


Figure 3: Proportion of children vaccinated with a fictive vaccination by child's age. Inverse Kaplan-Meier curves with 95% confidence intervals. Recommended age-period lies between vertical lines. Blue, red and green lines illustrate proportion vaccinated at 24 months, median age and proportion vaccinated at recommended age, respectively.

6.4.3 Adjustments for underreporting and proportion serotyped

For a proper interpretation of number of cases or changed incidences over time one must be sure that the two ESPED systems report the 'true' number of invasive Hi and Hib cases in Germany. Since identification of all cases can rarely be achieved in any disease monitoring system, estimates of completeness and eventual corrections for incompleteness are essential. In addition, changed proportions of typed Hi cases - and therefore the possibility to detect a type b case - may result in changing numbers of Hib cases reported and should be adjusted for.

6.4.3.1 Adjustment for underreporting of Hi cases through the reporting systems

Approaches to correct for incompleteness of case ascertainment are referred to as capture-recapture method. An estimate of the 'true' number of cases (N) can be calculated based on the number of cases ascertained by each single source (here: two sources A and B), the number of cases present in both sources (AB), with a correction factor for small samples (McCarty et al., 1993):

$$estimated\ number\ of\ cases\ (N) = \left[\frac{\left(cases_{source\ A} + 1\right) \times \left(cases_{source\ B} + 1\right)}{\left(cases_{source\ AB} + 1\right)} \right] - 1$$

with variance (var) estimated by

$$\mathrm{var}\ (N) = \left[\frac{\left(cases_A + 1\right) \times \left(cases_B + 1\right) \times \left(cases_A - cases_{AB}\right) \times \left(cases_B - cases_{AB}\right)}{\left(cases_{AB} + 1\right)^2 \times \left(cases_{AB} + 2\right)} \right]$$

and confidence intervals constructed by

$$\left[N - \tau_{\alpha/2} \sqrt{\mathrm{var}(N)};\quad N + \tau_{1-\alpha/2} \sqrt{\mathrm{var}(N)} \right]$$

with τ_k as the respective k-quantile of the standard normal distribution.

An assumption to calculate reliable capture-recapture estimators is that the different sources have to be independent of each other. No dependency of these two sources was assumed because the two ESPED systems rely on two different reporting systems working independent of each other.

6.4.3.2 Adjustment for differences in the proportion of typed cases over time

The following formula was used to correct for changes in the proportion of Hib isolates typed over time (McVernon et al., 2004):

$$adjusted\ Hib\ reports = known\ Hib\ reports + \left[\left(\frac{known\ Hib\ reports}{all\ typed\ Hi\ reports} \right) \times untyped\ Hi\ reports \right]$$

6.4.4 Vaccine effectiveness

Before a vaccine is licensed, its efficacy normally had been investigated in randomised double-blinded clinical trials. If the efficacy of a vaccine is investigated 'in the field', under more complex and unpredictable natural conditions this efficacy in the field is called effectiveness. Therefore, the term vaccine effectiveness (VE) is used throughout this document.

6.4.4.1 Theory

The analytic approach of this vaccine effectiveness study was that of a case-cohort study (Prentice, 1986; Barlow et al., 1999) describing a study design which is a mixture between case-control and cohort study. Case-cohort studies are of relevance if disease occurrence is rare and assessment of vaccine status and other covariables is hard or expensive to collect. In a defined population all cases with their vaccination status and interesting covariables are assessed; in a subcohort, which is a representative fraction of the whole population, accurate information on the same variables is assessed. In contrast to case-control studies a case can also be found in the subcohort. This is demonstrated by figure 4.

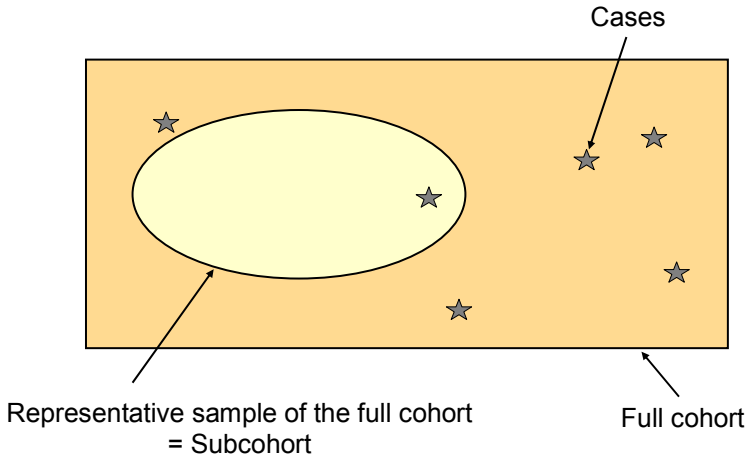


Figure 4: Schematic description of case-cohort design

Vaccine effectiveness is generally measured as 1 minus some measure of relative risk (RR) in the vaccinated group compared to the unvaccinated group (Halloran et al., 1997):

$$VE = 1 - RR$$

Analysis of case-cohort design is relatively complex as no standard software exists that provides appropriate analyses. Nevertheless, the advantage of case-cohort design over other designs is that time until disease outbreak and timing of vaccinations or differing immunisation status with repeated vaccinations can be considered.

6.4.4.2 Hib vaccine effectiveness

According to the date of introduction of DTaP-HBV-IPV/Hib combination vaccines (October 2000) and to the German immunisation schedule (three doses given at the age of 2, 3 and 4 months, with a booster dose given at the age of ≥ 11 months), cases born from 1 August 2000 onwards and aged two months or more were considered eligible to have received a hexavalent vaccine in the primary series.

Therefore all infants in Germany born between 1 August 2000 and 30 June 2003 were defined to be eligible for main calculations of effectiveness of hexavalent vaccines and therefore constitute the full cohort. The Lexis diagram in figure 5 displays these at-risk periods for the case and cohort children.

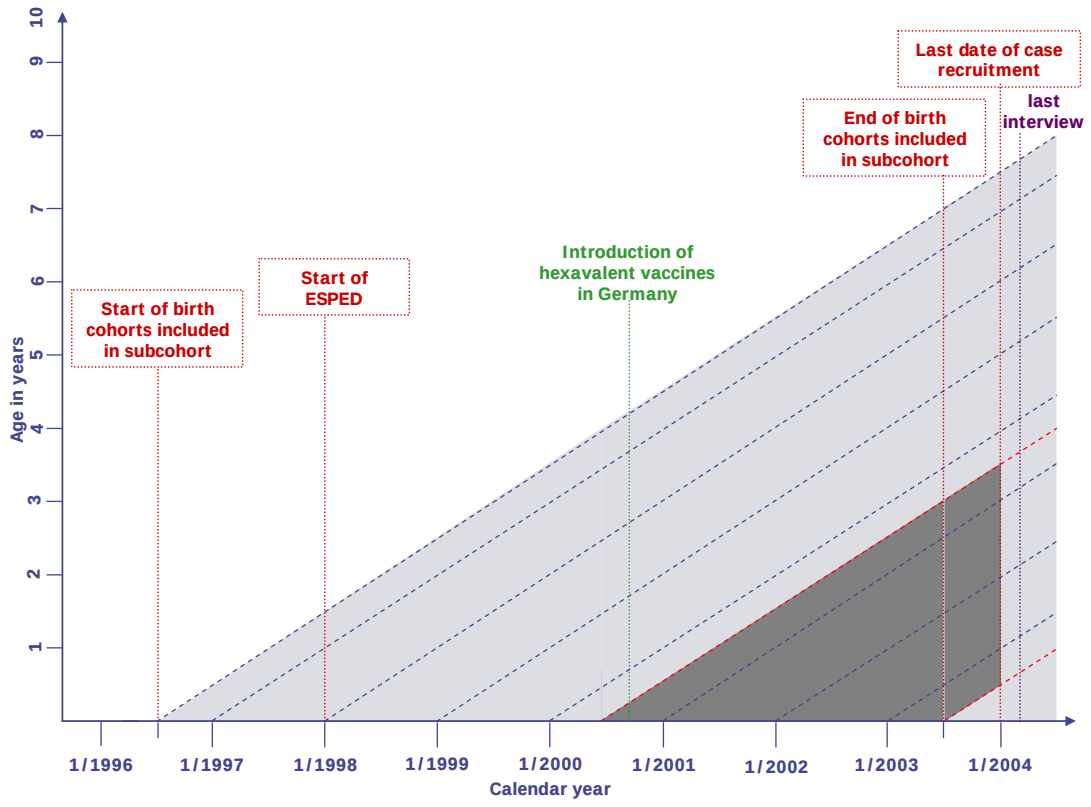


Figure 5: Lexis diagram displaying the at-risk periods for cases and sub-cohort members. Children within the dark polygon will be eligible for main calculations of hexavalent vaccine effectiveness.

Cases with confirmed systemic Hib infections were ascertained by the ESPED-system as described in chapter 6.2.2 and contributed to main vaccine effectiveness calculations if born between 1 August 2000 and 30 June 2003, aged 2 months or more at disease onset and detected by the ESPED system until 31 December 2003. Cases with untyped invasive Hi

disease – and therefore potentially belonging to serogroup b – were included as Hib cases in sensitivity analysis.

From the full cohort, a representative sub-cohort was randomly sampled in the nationwide immunisation survey as described in chapter 6.3 and contributed to main vaccine effectiveness calculations if born between 1 August 2000 and 30 June 2003.

Since uptake of vaccine information in the nationwide immunisation survey was assessed until January 2004 only, cases contributed to vaccine effectiveness calculations only if detected until a comparable date, 31 December 2003.

Hib vaccine effectiveness was assessed for both DTaP-IPV-HB/Hib combination vaccines (Hexavac®; Infanrix hexa®) together. In Germany, physicians are free to choose any of the licensed vaccines for immunisation of infants and children. Therefore, children can receive a mixed schedule with different types of Hib vaccines. Children receiving mixed schedules of DTaP-IPV-HB/Hib combination vaccines and other Hib vaccines were not considered for the main effectiveness calculations, but considered in sensitivity analysis.

The case-cohort study was analysed using Cox regression as suggested by Barlow (1994) and Prentice (1986), and as first applied to vaccine effectiveness studies by Moulton et al. (1995). Children in the sub-cohort became at risk at birth or at the start of the surveillance period if the latter was later in time. They were censored on the date of their last interview. Cases became at risk only on the date of positive Hib culture. It was assumed that no child in the sub-cohort later became a case: with an annual incidence of approximately 0.2 / 100,000 invasive Hib cases in the German population, only 0.005 cases would be expected in the sub-cohort. This assumption seems therefore realistic. Age was used as the analysis timeline. The vaccine status of subcohort members was defined by the child's age at each dose and was included as a time-dependent covariate. To assess the estimates of vaccine effectiveness, two models with mutual exclusive covariates indicating (1) completeness of vaccination schedule (receipt of first to second primary series / full primary series / 2nd year dose but no full immunisation / full immunisation of DTaP-IPV-HB/Hib combination vaccine) and (2) age-eligibility of the vaccination schedule (immunised according to / not according to recommended schedule) was used. Figures 6a and 6b visualise the concept of time-dependent variables for both models. For robust variance estimation an infinitesimal jackknife estimator of the influence function variance was used (Barlow, 1994).

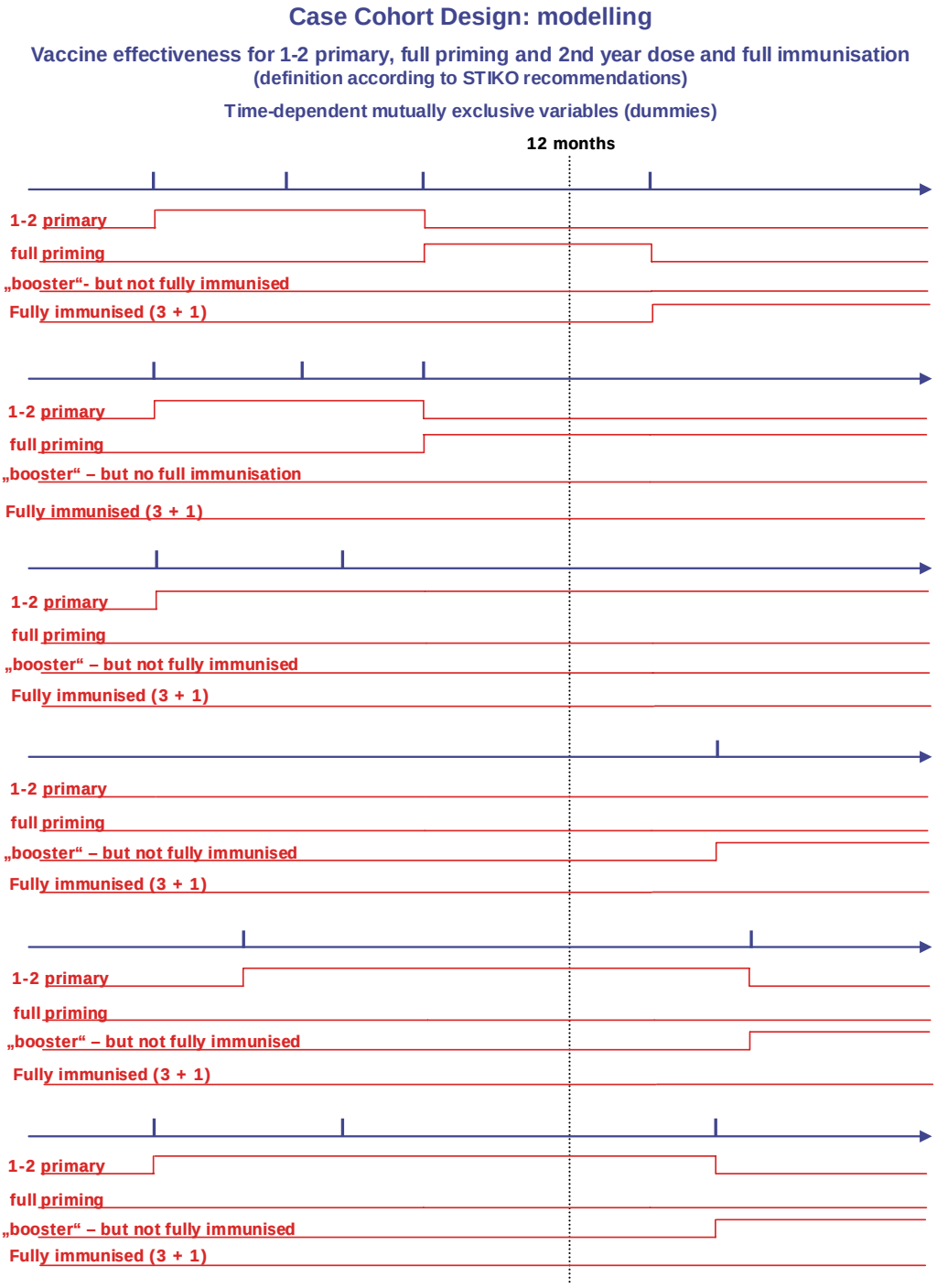


Figure 6a: Example of the changing vaccination status of six children by time (blue line) **defined by 'completeness of the vaccination schedule'.** Each vertical bar represents a Hib vaccination. The time-dependent mutual exclusive variables used in the model (so-called dummies) are represented by the four red lines below each child. Upward steps mark the change from zero to 1 and vice versa at this time in the model.

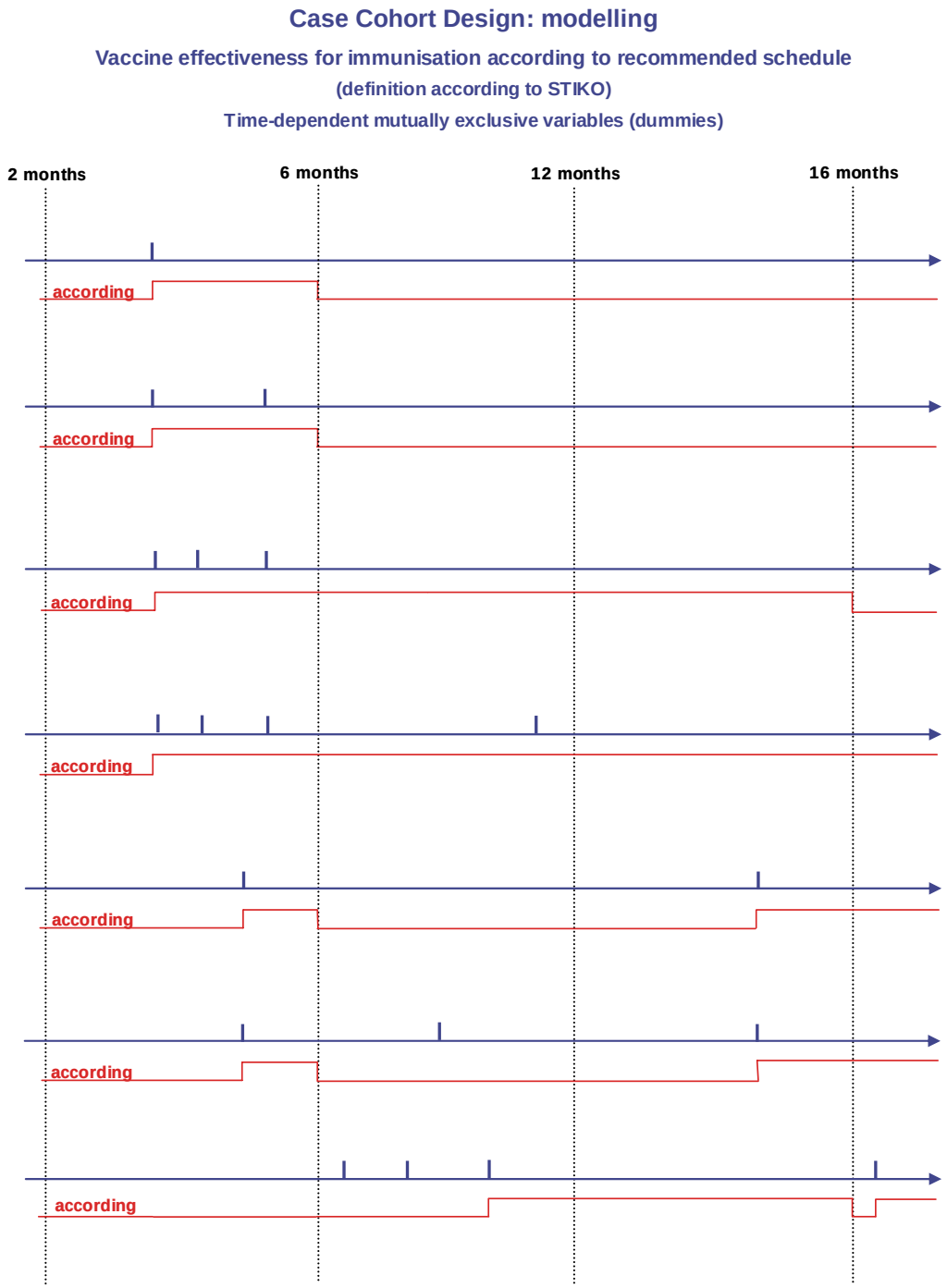


Figure 6b: Example of the changing vaccination status of seven children by time (blue line) **defined by 'age-eligibility of the vaccination schedule'.** Each vertical bar represents a Hib vaccination. The time-dependent variable used in the model is represented by the red line below each child. Upward steps mark the change from zero to 1 and vice versa at this time in the model.

6.4.4.3 Sensitivity analysis

For the sensitivity analysis the effect on vaccine effectiveness was evaluated if

(1) children with mixed vaccine schedules (mixture of other DTaP-containing or non-DTaP containing vaccines with hexavalent vaccines within a child) were included as having received hexavalent Hib combination vaccines only,

(2) cases with untyped invasive Hi disease - and therefore potentially belonging to the serotype b group - were included as Hib cases.

For all statistical analysis SAS (SAS Institute, Cary, NC) version 9.1 was used.

7 RESULTS

7.1 Data quality

7.1.1 ESPED surveillance system

7.1.1.1 Response rates

In the years 2001 through 2004, the annual number of Clinical ESPED cards sent out was 5419, 5339, 5473, and 5544 of which 5301, 5238, 5339, and 5420 cards were returned, respectively. Per year, 42, 45, 48, and 35 follow-up questionnaires were sent out to paediatricians and 41, 44, 45, and 31 of these questionnaires were returned.

In the years 2001 through 2004, the annual number of Laboratory ESPED cards sent out was 3535, 3474, 3502 and 3402 of which 3392, 3311, 3336 and 3280 cards were returned, respectively. Per year, 40, 23, 29, 23 follow-up questionnaires were sent out or telephone calls were made and 38, 23, 26 and 21 of these questionnaires were returned or answered.

The resulting response rates are high and do not differ from the years before the introduction of hexavalent vaccines (Table 2).

Table 2: Response rates to Clinical and Laboratory ESPED from 1998 to 2004

Year of surveillance	Response rate			
	Clinical ESPED cards	Clinical ESPED questionnaires	Laboratory ESPED cards	Laboratory ESPED questionnaires / telephone calls
1998-99	95%	99%	96%	*
2000	98%	100%	100%	*
2001	98%	98%	96%	95%
2002	98%	98%	95%	100%
2003	98%	94%	95%	90%
2004	98%	89%	96%	91%

* Laboratory ESPED questionnaires / telephone calls were routinely added in year 2001.

There were no substantial differences between response rates of the 16 federal states in Germany (‘*Bundesländer*’) for either Clinical or Laboratory ESPED cards (table 3). Lowest

response rates were observed in the city state 'Hamburg' for Laboratory ESPED cards in 2001 (83%) and for Clinical ESPED cards in 2004 (85%).

Table 3: Response rates of Clinical and Laboratory ESPED cards by German federal states ('*Bundesland*') in 2001 through 2004.

'*Bundesland*'	Response rate							
	2001		2002		2003		2004	
	Lab ESPED	Clinical ESPED	Lab ESPED	Clinical ESPED	Lab ESPED	Clinical ESPED	Lab ESPED	Clinical ESPED
Baden-Württemberg	97%	99%	96%	100%	93%	98%	98%	99%
Bayern	97%	100%	95%	100%	97%	98%	92%	98%
Berlin	97%	92%	94%	97%	88%	92%	96%	100%
Brandenburg	95%	99%	100%	99%	99%	96%	95%	100%
Bremen	100%	100%	100%	100%	89%	100%	92%	97%
Hamburg	83%	97%	87%	100%	92%	94%	99%	85%
Hessen	100%	94%	98%	99%	93%	100%	91%	100%
Mecklenburg-Vorpommern	99%	100%	99%	100%	100%	100%	100%	100%
Niedersachsen	99%	99%	95%	96%	100%	98%	100%	98%
Nordrhein-Westfalen	94%	96%	91%	97%	94%	98%	96%	96%
Rheinland-Pfalz	99%	97%	97%	95%	100%	93%	95%	97%
Saarland	100%	100%	97%	100%	100%	100%	100%	100%
Sachsen	99%	100%	99%	100%	99%	100%	97%	100%
Sachsen-Anhalt	88%	100%	89%	100%	88%	99%	99%	100%
Schleswig-Holstein	86%	86%	94%	86%	87%	86%	98%	86%
Thüringen	97%	100%	99%	99%	99%	100%	99%	100%

7.1.1.2 Completeness of case reporting

Through both surveillance systems, a total of 51, 39, 63, 50, 42, 41 and 27 cases of invasive *H. influenzae* (Hi) disease were reported annually in 1998 through 2004.

The proportions of reported cases have been consistently lower for Clinical compared to Laboratory ESPED for every year of surveillance since 1998 (table 4). However, more dramatic manifestations (meningitis, epiglottitis, septic arthritis) of invasive Hi disease are more likely to be reported to the Clinical ESPED system. The proportion of these cases among all Clinical ESPED cases was 66% in 2001, 62% in 2002, 66% in 2003 and 50% in 2004 as compared to 49% in 2001, 56% in 2002, 51% in 2003 and 36% in 2004 in Laboratory ESPED. Similar findings could be observed in the 1998 to 2000 data on *H. influenzae* surveillance.

Table 4: Number and proportion of detected cases by data source from 1998 to 2004

Year of surveillance	Data source				Duplicates (detected in both sources)	Total N cases
	Clinical ESPED		Lab ESPED			
	number	% of total	number	% of total		
1998	30	59%	45	88%	24	51
1999	21	54%	32	82%	14	39
2000	32	51%	50	79%	19	63
2001	29	58%	49	98%	28	50
2002	26	62%	39	93%	23	42
2003	27	66%	39	95%	25	41
2004	14	52%	22	81%	9	27

Applying capture-recapture methodology, the proportion of all 'true' Hi cases in German children that has been captured by each single source ranged between 38.5% and 64.1% for Clinical ESPED and between 59.1% and 96.6% for Laboratory ESPED. Both sources together captured 75.7% to 97.4% of Hi cases per year (table 5).

Table 5: Observed number of cases and estimated completeness of the two ESPED systems by year of surveillance using capture-recapture method.

	1998	1999	2000	2001	2002	2003	2004
Clinical ESPED	30	21	32	29	26	27	14
Laboratory ESPED	45	32	50	49	39	39	22
Duplicates	24	14	19	28	23	25	9
total number of cases	51	39	63	50	42	41	27
% captured by both systems	91.1%	82.3%	75.7%	98.6%	95.5%	97.4%	80.6%
% captured by Clinical ESPED	53.6%	44.3%	38.5%	57.2%	59.1%	64.1%	41.8%
% captured by Lab ESPED	80.4%	67.5%	60.1%	96.6%	59.1%	92.6%	65.7%

7.1.1.3 Proportion of cases typed

The percentage of untyped cases decreased from 25% of all reported invasive Hi cases in 1998 to 15% in 2004 (table 6).

In concordance to the increasing proportion of cases typed, serotyping in the national consulting laboratory of Hi increased from 1998 to 2004: 55% of all reported cases were typed in the national consulting laboratory in 1998, 58% in 1999, 63% in 2000, 70% in 2001, 74% in 2002, 73% in 2003 and 70% in 2004.

Table 6: Total number of cases and proportion of untyped cases from 1998 to 2004

Year of surveillance	N Cases	Total untyped
1998	51	13 (25%)
1999	39	11 (28%)
2000	63	13 (21%)
2001	50	10 (20%)
2002	42	8 (19%)
2003	41	7 (17%)
2004	27	4 (15%)

Adjustments to correct for changes in the proportion of Hib isolates typed over time (see chapter 6.4.3.2) are presented in chapter 7.3.1.

7.1.1.4 Serotyping: concordance between local and reference laboratories

Of all 131 cases serotyped in 2001 through 2004, 77 were serotyped in both, local laboratories and the national consulting laboratory for Hi in Mainz, 19 were serotyped in local laboratories only and 35 in the national consulting laboratory only. Of the 77 specimens typed by both laboratories, eight specimens presented discordant serotype results. Of these, seven specimens were typed as type b in the local laboratory but as non-type b in the reference laboratory (5 as a-f negative, 1 as type f, 1 as type a) and one was typed as non-type b (a-f negative) in local laboratories but as type b in the reference laboratory. According to chapter 6.2.2.4, these eight specimens were classified according to the results of the national consulting laboratory for Hi (table 7).

Table 7: Concordance of typing results between local laboratories and the reference laboratory in 2001 through 2004. The eight cases with discordant typing results are marked in green.

Local laboratories	Reference laboratory		
	Type b	Non-type b	Untyped
Type b	28	7	15
Non-type b	1	41	4
Untyped	8	27	29
Final typing results	37	75	48

7.1.2 National immunisation survey

7.1.2.1 Response rates and data validity

Out of all 3286 contacted households with children in the respective birth cohorts, 262 households could not be reached in the second stage of the interview. In total, 1927 houshoulds with 2011 children born between 1 July 1999 and 30 June 2003 were interviewed. The resulting response rate was 63%. For analyses 20 children with no vaccination booklet available and 19 children with implausible immunisation data (too many vaccinations, no vaccination date, implausible dates) were excluded (figure 2; point 6). For the remaining 1972 children median age at interview was 26.0 months. The number of telephone interviews and child's age at interview by birth year of the respective child is shown in table 8.

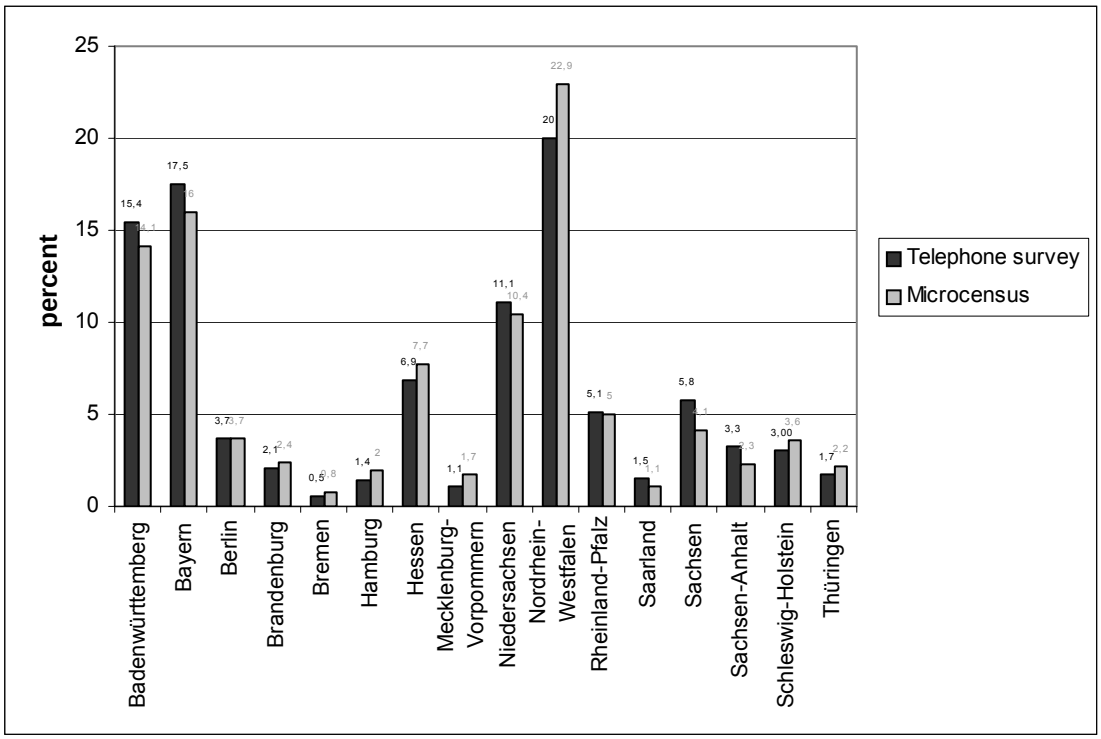
Table 8: Number of telephone interviews and child's age at interview by birth year of the child.

Age at interview	Year of birth				
	1999	2000	2001	2002	2003
0-<6 months	-	-	-	2	-
6-<12 months	-	-	2	4	65
1-<2 years	-	1	91	451	3
>= 2 years	320	577	453	3	-
total	320	578	546	460	68
Median (month) (10^{th}-90^{th} perc)	38.6 (33.4-52.4)	30.9 (24.7-43.9)	25.0 (19.5-32.5)	12.8 (12.3-21.4)	6.5 (6.2-11.6)
Range (min-max)	30.6-54.4	22.7-48.0	9.1-36.4	1.2-24.5	6.1-12.3

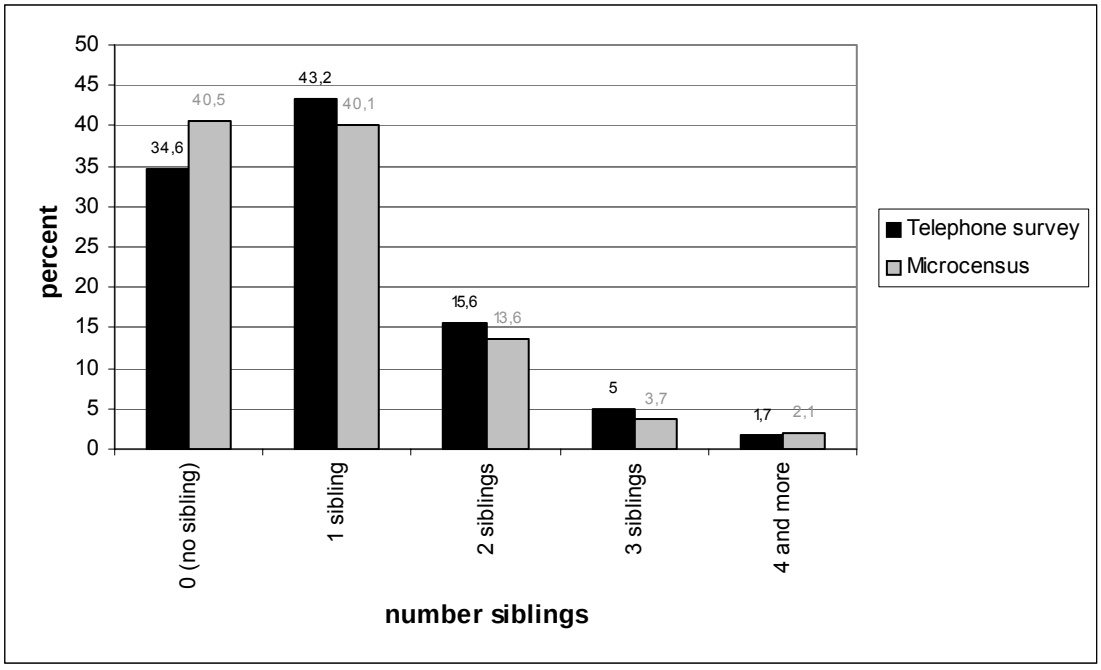
For the description of the immunisation status in German children (chapter 7.2.2) and vaccine effectiveness calculations (chapter 7.5), data of all 1303 children born from 1 August 2000 onwards will be presented as these children belong to the birth cohorts which could have received a hexavalent vaccine in the primary series.

7.1.2.2 Representativeness

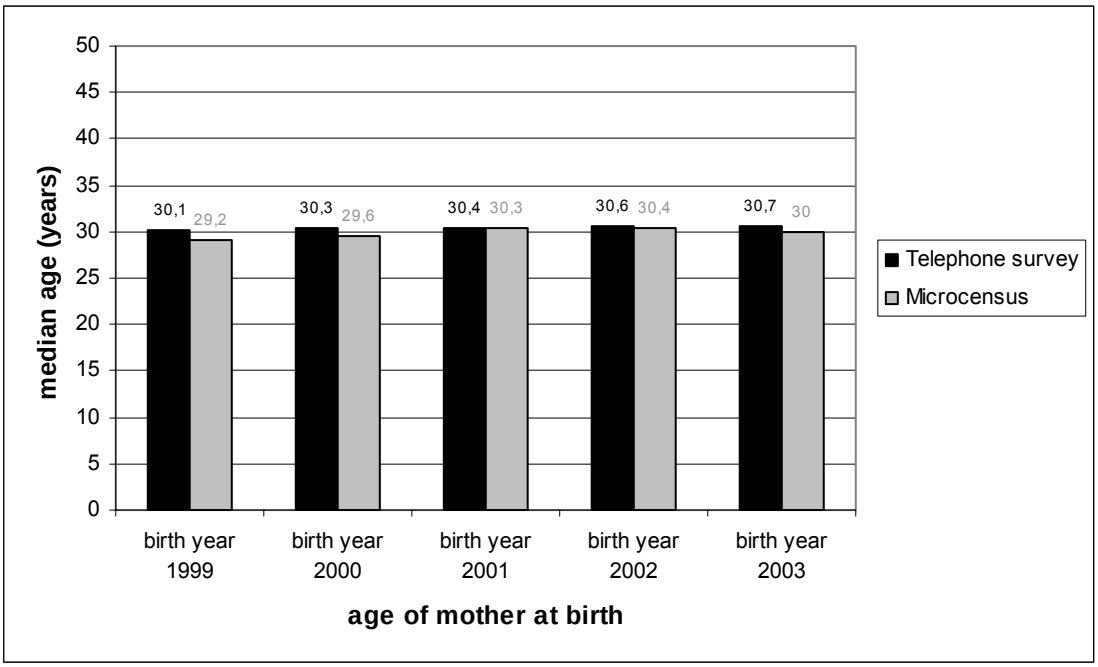
Comparisons with data of the 'Mikrozensus' revealed that the sampled telephone interviews are representative for age-eligible children in Germany according to geographical and social distributions (figures 7a-c). Children from households with higher income are slightly over-represented (figure 7d).



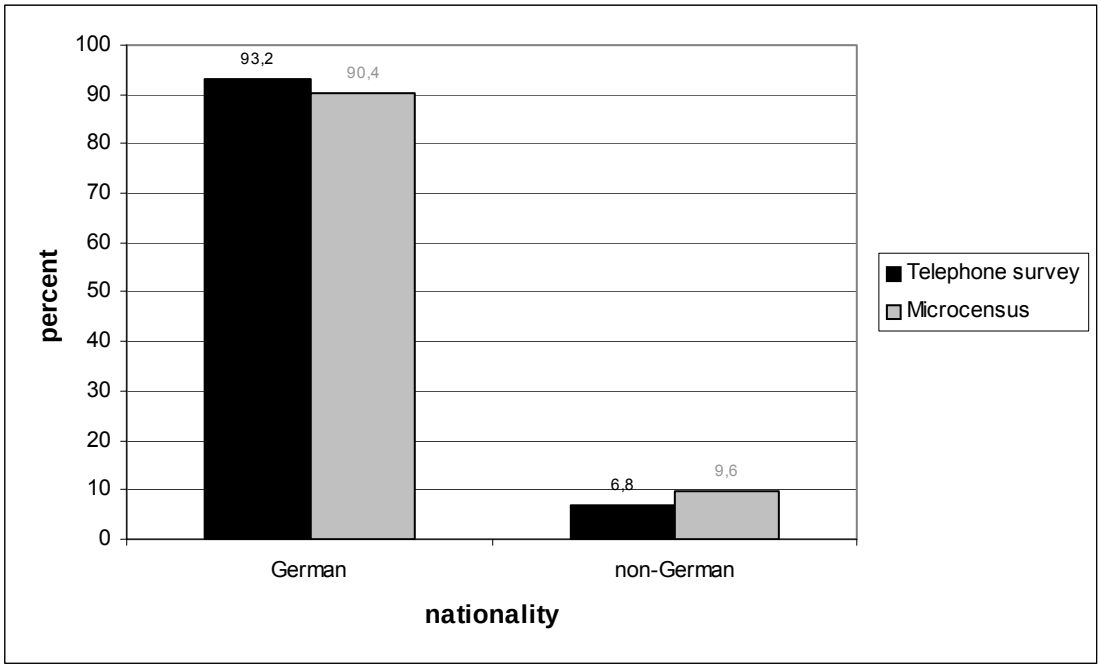
a. by ‚*Bundesland*'



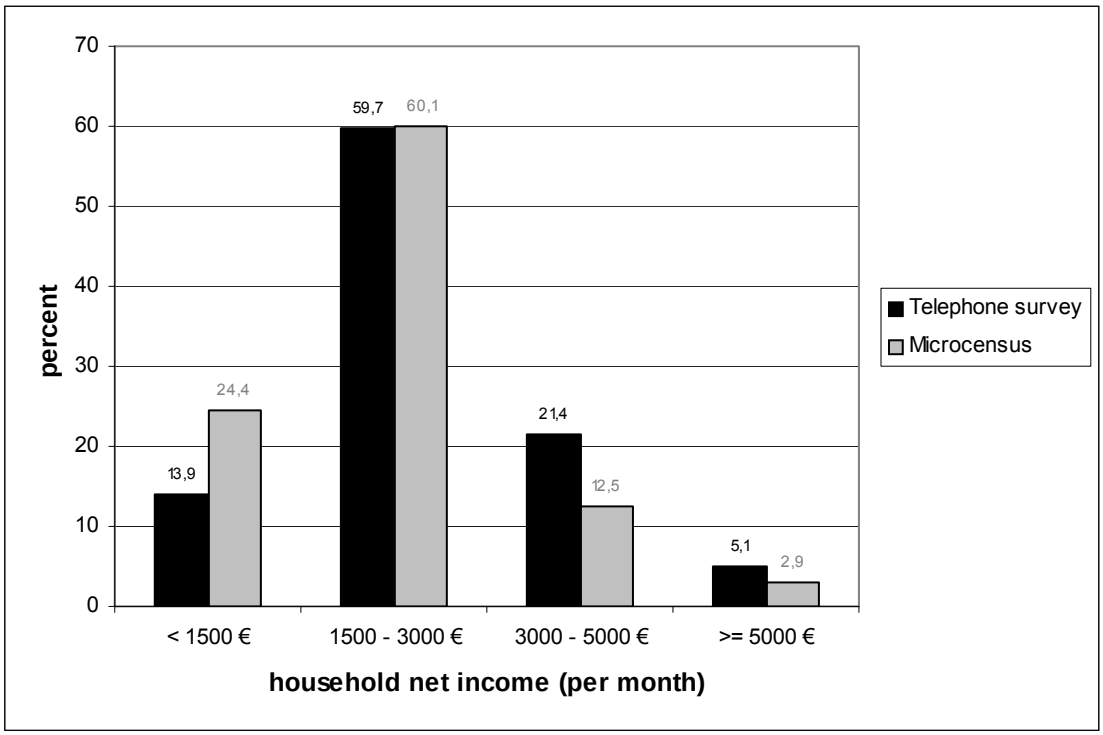
b. **by number of siblings**



c. **by age of mother at birth of child**



d. by nationality of the child



e. **by household net income**

Figure 7: Comparison of sociodemographic characteristics between families taking part in the national immunisation survey and official data of the Statistical Office in Germany ('Mikrozensus').

7.2 General description of the data

7.2.1 H. influenzae cases 2001-2004

7.2.1.1 Seasonal distribution

Out of all 160 invasive Hi cases in children under 10 year of age detected in the ESPED surveillance system from 2001 through 2004, the majority of cases were reported in autumn and winter: most cases occurred in December, January and October (22, 19, 19 cases each). In the remaining months, 6-16 cases were reported every month (table 9).

Table 9: Number of invasive *H. influenzae* cases reported by month in 2001 through 2004.

Month	N Cases
January	19
February	12
March	16
April	11
May	11
June	14
July	6
August	11
September	6
October	19
November	13
December	22

7.2.1.2 Distribution by age, sex and nationality

Of the 160 reported invasive Hi cases

- 25 cases (16%) occurred in children aged 0 to 2 months,
- 42 cases (26%) occurred in children aged 3 to 11 months,
- 74 cases (46%) occurred in children aged 12 months to 4 years and
- 19 cases (12%) occurred in children aged 5 to 10 years.

There were 96 cases of invasive Hi disease in boys and 64 cases in girls (60% vs. 40%).

Information about nationality of the child was available for 153 of the 160 cases. Of these, 78% had a German and 22% a non-German nationality; most children with non-German nationality (n=34) were from other European countries (n=14) or from Turkey (n=6).

7.2.1.3 Clinical description

Haemophilus influenzae pathogens were isolated

- in the cerebrospinal fluid for 29 cases (18%),
- in blood for 80 cases (50%),
- in both blood and cerebrospinal fluid for 43 cases (27%),
- in peritoneal fluid for 3 cases (2%) and
- in other physiologically sterile material for 5 cases (3%).

Information about the primary diagnosis was available for all 160 cases. The most common clinical presentation of invasive Hi infection in children was meningitis, constituting almost one half of all reports (46%). Table 10 shows the distribution of all primary diagnoses by age group. The category 'other' includes 6 cases of epiglottitis. The most common clinical presentation in the very young (0-2 months) was septicaemia (40%) whereas this changed to meningitis (42-52%) in the older age groups.

Table 10: Distribution of invasive *H. influenzae* disease by primary diagnosis and age group in 2001 through 2004.

Primary diagnosis	Age groups				Total N (%)
	0 - 2 months N (%)	3 - 11 months N (%)	1.0 - 4.9 years N (%)	5.0 - 9.9 years N (%)	
Meningitis	7 (28%)	22 (52%)	36 (49%)	8 (42%)	73 (46%)
Pneumonia	7 (28%)	6 (14%)	14 (19%)	2 (11%)	29 (18%)
Septicaemia	10 (40%)	6 (14%)	8 (11%)	3 (16%)	27 (17%)
Other	1 (4%)	8 (19%)	16 (22%)	6 (31%)	31 (19%)
Total	25	42	74	19	160

The clinical outcome of Hi disease was known for 138 of the 160 cases; of the 138 cases

- 9 children (6%) died,
- 121 children (88%) recovered from the acute infection without any obvious sequelae and
- 8 (5%) had serious sequelae (e.g. hygroma, hydrocephalus).

Information on underlying medical conditions was reported for 153 of all 160 children. Fifteen of these children (10%) were born prematurely before 37 weeks gestation (median gestation: 32 weeks; range 25-36 weeks). Three children had Down's syndrome (2%) and four children had immunodeficiency or received immunosuppressive therapy (3%). For 32 children (20%) other possible clinical risk factors for Hi infection were reported (malignancies, other

syndromes, severe injuries). Some children had more than one risk factor; when combined, 44 children (29%) had at least one possible clinical risk factor.

7.2.1.4 Serotypes

Serotyping was performed in 131 of the 160 (82%) cases reported from 2001 through 2004. Overall 52 cases were determined to be type b and 79 to be non-type b. Of the 79 non-type b cases, 15 were capsulated, 60 were non-capsulated (a-f negative) and 4 cases were not further specified. Of the 15 capsulated non-b cases, 13 were type f, 1 was type e, and 1 was type a. Whereas type b was predominantly a cause of serious infections in the age group 3-11 months (55%), all other age groups were dominated by non-type b infections (table 11).

Table 11: Distribution of invasive *H. influenzae* disease by serotype and age group in 2001 through 2004

Serotype	Age groups				Total N (%)
	0-2 months N (%)	3-11 months N (%)	1.0-4.9 years N (%)	5.0-9.9 years N (%)	
Type b	4 (16%)	23 (55%)	23 (31%)	2 (11%)	52 (33%)
Non-type b	16 (64%)	13 (31%)	37 (50%)	13 (68%)	79 (49%)
capsulated	*0*	*5*	*8*	*2*	*15*
non-capsulated	*16*	*7*	*26*	*11*	*60*
not specified	*0*	*1*	*3*	*0*	*4*
Untyped	5 (20%)	6 (14%)	14 (19%)	4 (21%)	29 (18%)
Total	25	42	74	19	160

Almost one half of all meningitis cases were due to type b infections, whereas children with a clinical presentation of pneumonia or septicaemia were predominantly infected by non-capsulated Hi bacteria (table 12).

Table 12: Distribution of invasive *H. influenzae* disease by serotype and primary diagnosis in 2001 through 2004

Serotype	Primary diagnosis				Total N (%)
	Meningitis N (%)	Pneumonia N (%)	Septicaemia N (%)	Other N (%)	
Type b	34 (47%)	4 (14%)	3 (11%)	11 (35%)	52 (33%)
Non-type b	30 (41%)	17 (59%)	19 (70%)	13 (42%)	79 (49%)
capsulated	*10*	*2*	*1*	*2*	*15*
non-capsulated	*19*	*14*	*17*	*10*	*60*
not specified	*1*	*1*	*1*	*1*	*4*
Untyped	9 (12%)	8 (28%)	5 (19%)	7 (23%)	29 (18%)
Total	73	29	27	31	160

7.2.1.5 Vaccination status

Vaccination status was reported in 156 of the 160 (98%) cases reported from 2001 through 2004. Twenty-one of all 52 (40%) children with known type b disease had been vaccinated at least once before disease onset in contrary to 56 of all 79 (71%) children with non-type b disease. There were no fatal cases occurring in vaccinated Hib cases. Figure 8 summarises these results.

Figure 8: Description of vaccination status by serotype and outcome of all invasive *H. influenzae* cases reported in the German ESPED surveillance system in the years 2001 through 2004

Serotype	Type b			Untyped			Non-type b								
							capsulated			uncapsulated			not specified		
	52			29			15			60			4		
Vaccination Status*	**V**	**NV**	**UK**	**V**	**NV**	**UK**	**V**	**NV**	**UK**	**V**	**NV**	**UK**	**V**	**NV**	**UK**
	21	**31**	**0**	**13**	**12**	**4**	**13**	**2**	**0**	**39**	**21**	**0**	**4**	**0**	**0**
Outcome=death	0	3	0	1	2	0	1	0	0	0	2	0	0	0	0

*: **V** = **v**accinated; **NV** = **n**ot **v**accinated; **UK** = vaccination **un**known

Of the 21 vaccinated Hib cases detected in the ESPED surveillance system from 2001 through 2004, seven children were vaccinated with 4 Hib doses, another seven children were vaccinated with 3 Hib doses, two children were vaccinated with 2 Hib doses and four children were vaccinated with one dose of a Hib containing vaccine before disease onset. For one child numbers of Hib containing vaccines given was unclear. Hexavalent vaccines were involved in 12 of the 21 children. Of these, four children received one dose of a hexavalent Hib vaccine, two children received 2 doses of a hexavalent Hib vaccine, five children received 3 doses of a hexavalent Hib vaccine and one child received the last of four Hib doses as a hexavalent Hib vaccine before disease onset. A detailed description of the 21 vaccinated cases with invasive Hib disease is shown in table 13.

Table 13: Vaccination history of the *H. influenzae* type b cases who received any Hib-containing vaccine. Age at disease onset and age at vaccination in months.

case	vaccine failure*	age at disease onset	N vaccination	vaccination history							
				vaccination 1		vaccination 2		vaccination 3		vaccination 4	
				age	vaccine	age	vaccine	age	vaccine	age	vaccine
11/01	pr+bo	28	4	3	5-valent	5	5-valent	7	5-valent	13	5-valent
32/01	incompl pr	6	1	5	hexavalent	-	-	-	-	-	-
36/01	pr+bo	38	4	3	4-valent	4	5-valent	5	5-valent	15	5-valent
48/01	pr+bo	41	4	4	5-valent	5	5-valent	6	5-valent	13	Hib mono
57/01	pr	17	4	4	5-valent	6	5-valent	6	5-valent	8	5-valent
2/02	pr	12	3	2	hexavalent	4	hexavalent	6	hexavalent	-	-
27/02	pr+bo	25	4	2	5-valent	3	5-valent	4	5-valent	12	5-valent
39/02	pr+bo	48	4	4	4-valent	5	4-valent	6	4-valent	12	4-valent
2/03	pr	17	3	3	hexavalent	5	hexavalent	7	hexavalent	-	-
6/03	incompl pr	8	1	6	hexavalent	-	-	-	-	-	-
25/03	incompl pr	4	1	3	hexavalent	-	-	-	-	-	-
32/03	2nd y dose	81	3	5	5-valent	7	5-valent	12	5-valent	-	-
34/03	pr+bo	40	4	2	4-valent	3	4-valent	4	4-valent	20	hexavalent
36/03	incompl pr	4	1	3	hexavalent	-	-	-	-	-	-
39/03	pr	7	3	2	hexavalent	3	hexavalent	4	hexavalent	-	-
44/03	pr	23	3	4	hexavalent	5	hexavalent	8	hexavalent	-	-
45/03	incompl pr	6	2	3	hexavalent	4	hexavalent	-	-	-	-
46/03	pr	17	3	3	hexavalent	5	hexavalent	8	hexavalent	-	-
9/04	unclear	25	unknown							-	-
10/04	incompl pr	4	2	2	hexavalent	3	hexavalent	-	-	-	-
29/04	pr	49	3	4	5-valent	5	5-valent	6	5-valent	-	-

* incompl pr: vaccine failure of the incomplete primary schedule; pr: vaccine failure of the complete primary schedule; pr+bo: vaccine failure of the primary and booster regimen; 2nd y dose: vaccine failure of a dose given after the age of 11 months.

Median age at disease onset differed between vaccinated and unvaccinated cases with invasive Hib disease: 17.0 months (minimum: 4.0; maximum: 81.0) vs. 9.0 months (minimum: 1.0; maximum: 104.0). There were more possible clinical risk factors for Hib infection present in vaccinated compared to unvaccinated children (19.0% vs. 12.9%). Differences in the clinical presentation were marginal (vaccinated Hib cases: 62% meningitis, 26% other focus, 7% no focus; unvaccinated Hib cases: 68% meningitis, 33% other focus, 5% no focus).

7.2.2 Immunisation status of children in the German population

7.2.2.1 Hib vaccine coverage

In the national immunisation survey, a total of 1303 valid interviews were realised on children born between 1 August 2000 and 30 June 2003. Figure 9a-d displays the time course of

completion of the first dose, full primary series, the 2nd year dose and the full immunisation against Hib for all these children (definitions for these categories are provided in chapter 6.1.2).

Figure 9a shows that 50% of all children received their first Hib vaccination at the age of 3.4 months. At the age of 1 year 91.9% of all children have received at least one Hib vaccination. At the end of the recommended age for the first dose (2.9 months) only 28.7% received the respective dose.

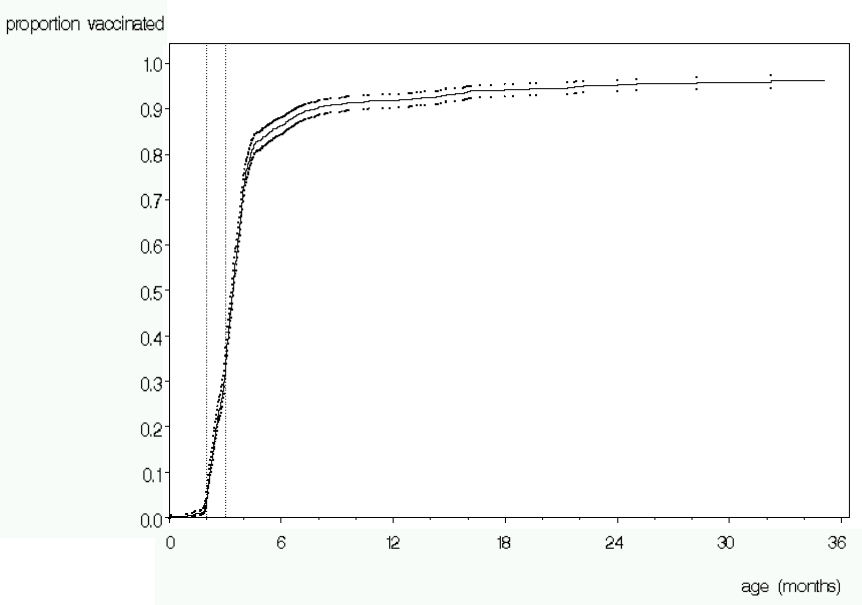


Figure 9a: Hib vaccine coverage in Germany: Proportion of children vaccinated with the first Hib dose by child's age. German national immunisation survey on birth cohorts 1 August 2000 through 30 June 2003 (N=1303). Inverse Kaplan-Meier curves with 95% confidence interval. Recommended age-period lays between vertical lines.

Figure 9b shows that completion of the primary series is only achieved by 80% of the children; at the end of the recommended age (4.9 months) only 16.6% of all children have received the complete primary series. Coverage of 75% is reached by the age of 9.1 months.

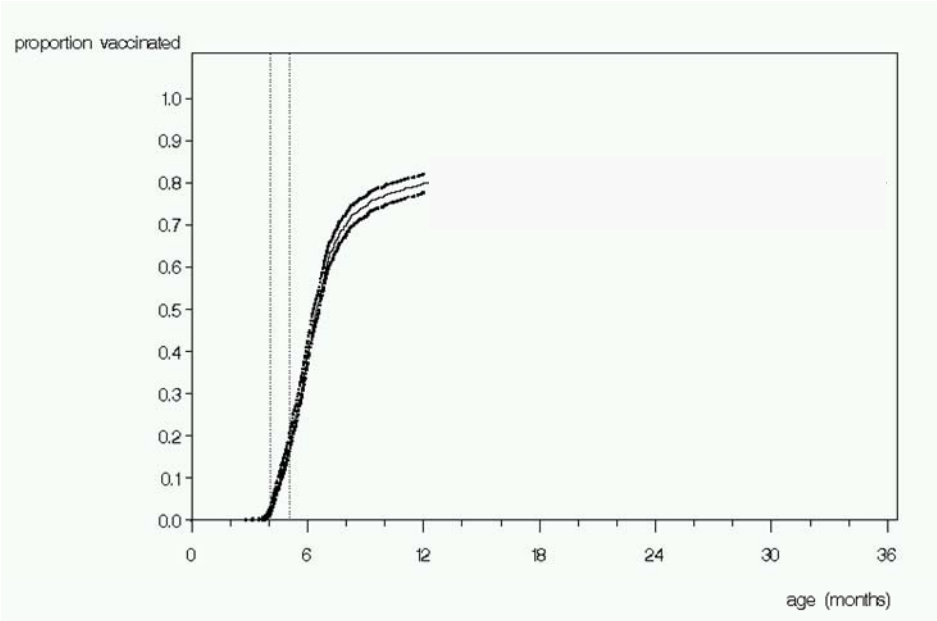


Figure 9b: Hib vaccine coverage in Germany: Proportion of children vaccinated with the full primary schedule by child's age. German national immunisation survey on birth cohorts 1 August 2000 through 30 June 2003 (N=1303). Inverse Kaplan-Meier curves with 95% confidence interval. Recommended age-period lays between vertical lines.

Figure 9c shows that completion of the 2nd year dose is only achieved by 5.5% of the children at the age of 1 year and by 78.8% at the age of 2 years; at the end of the recommended age (14.9 months) only 37.5% were adequately vaccinated. Coverage of 50% and 75% is reached by the age of 16.6 months and 23.1 months, respectively.

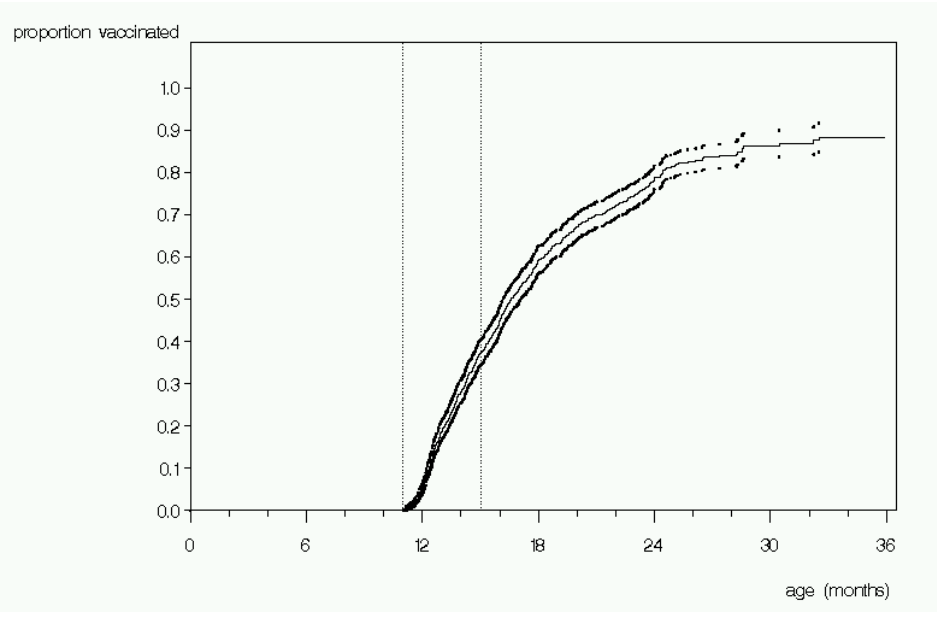


Figure 9c: Hib vaccine coverage in Germany: Proportion of children with 2nd year dose by child's age. Inverse Kaplan-Meier curves with 95% confidence interval. German national immunisation survey on birth cohorts 1 August 2000 through 30 June 2003 (N=1303). Recommended age-period lays between vertical lines.

Figure 9d shows that completion of the full immunisation schedule is only achieved by 64.1% at the age of 2 years; a coverage of 50% is reached by the age of 18.5 and a coverage of 75% or more is never reached.

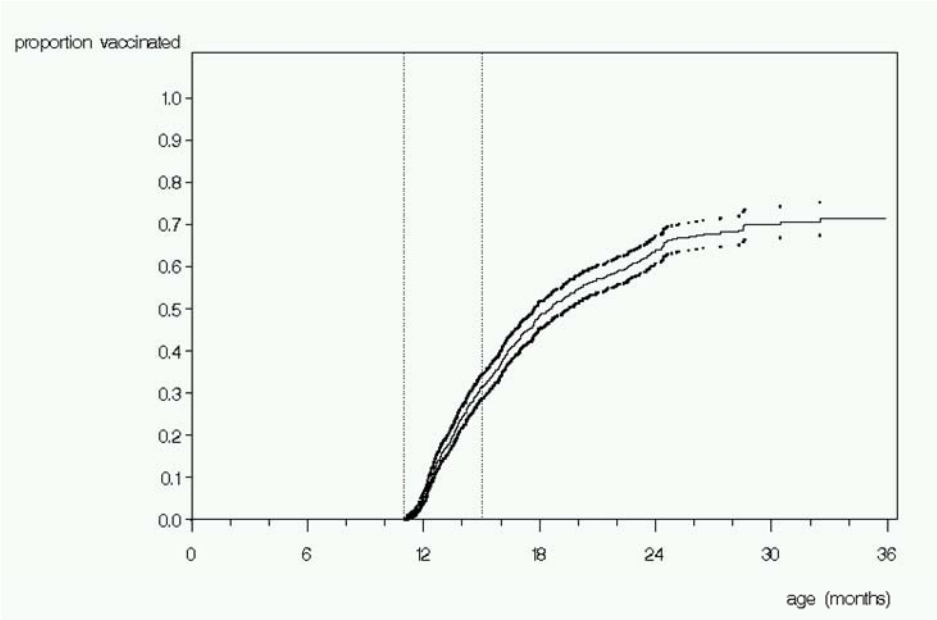


Figure 9d: Hib vaccine coverage in Germany: Proportion of children fully immunised by child's age. Inverse Kaplan-Meier curves with 95% confidence interval. German national immunisation survey on birth cohorts 1 August 2000 through 30 June 2003 (N=1303). Recommended age-period lays between vertical lines.

Table 14 summarises the results of figures 9a-d for age at defined coverage levels for Hib vaccination and coverage at defined ages.

Table 14: Age of children at defined coverage levels for Hib vaccination and Hib vaccination coverage at one / two years of age and at recommended age as calculated by Kaplan-Meier method (95% confidence intervals)**.** German national immunisation survey on birth cohorts 1 August 2000 through 30 June 2003 (N=1303).

	Age (months) at coverage of			Proportion (%) vaccinated at		
	25%	50% =median age	75%	age 1 year	age 2 years	recommended age*
First dose	2.8 (2.6-2.9)	3.4 (3.4-3.5)	4.1 (4.0-4.2)	91.9 (90.3-93.3)	95.3 (94.0-96.5)	28.7 (26.3-31.3)
Full priming#	5.4 (5.3-5.5)	6.5 (6.3-6.6)	9.1 (8.4-10.1)	80.0 (77.7-82.1)	-	16.6 (14.7-18.7)
2nd year dose#	13.7 (13.4-13.9)	16.6 (16.2-17.0)	23.1 (21.9-23.9)	5.5 (4.4-6.9)	78.8 (75.9-81.6)	37.5 (34.6-40.6)
Full immunisation#	14.1 (13.8-14.4)	18.5 (17.7-19.4)	not reached	5.5 (4.4-6.9)	64.1 (60.8-67.3)	31.6 (28.8-34.5)

see definitions in methods section

* proportion of children vaccinated within the age-frame recommended by the STIKO: at least one dose at <3 months, the full primary series at <5 months and the 2nd year dose/full immunisation at <15 months.

7.2.2.2 Use of hexavalent vaccines

Of all 1303 children with valid data, 72 (5.5%) had never been vaccinated against Hib at the age of the interview, 890 (68.3%) had received DTaP-IPV-HB/Hib combination vaccines only, 158 (12.1%) had received DTaP-(IPV)/Hib combination vaccines only, 23 (1.8%) had received Hib vaccines without acellular pertussis component only, 158 (12.1%) had received mixed schedules of Hib vaccines and two children (0.2%) had received at least one vaccine where brand name was not reported.

Of those 158 children receiving mixed schedules of Hib vaccines, 151 (95.6%) had received mixed schedules of DTaP-IPV-HB/Hib combination vaccines and other Hib vaccines.

The use of hexavalent vaccines per child increased with the child's year of birth from 47.9% in 2000 to 76.6% in 2003, while the use of 4- and 5-valent Hib containing vaccines decreased from 24.9% in 2000 to 17.2% in 2003 (Table 15).

Table 15: Distribution of type of vaccine per child for children ever vaccinated with Hib containing vaccine by birth year. German national immunisation survey on birth cohorts 1 August 2000 through 30 June 2003 (N=1231).

Proportion ever vaccinated with …	Year of birth			
	2000	2001	2002	2003
Hib vaccines without Pa	2.8	2.9	0.5	0.0
DTaP-(IPV)/Hib	24.9	11.1	8.2	17.2
DTaP-IPV-HB/Hib	47.9	71.5	85.1	76.6
Mixed types*	24.4	14.4	6.1	6.3
Unknown types	0.0	0.2	0.2	0.0
Total number of children vaccinated	229	522	428	64

* Children receiving mixed schedules of the above categories of vaccines (including mixtures of DTaP-IPV-HB/Hib)

7.2.2.3 Timeliness of hexavalent vaccine uptake

Table 16 shows the median age of children vaccinated with hexavalent vaccines only in comparison to the recommended schedule. The first two doses were administered with a delay of approximately 0.5-1.5 months compared with national recommendations. The third dose was administered with a median age of 6.1 months; this is 1.2 months later than the upper limit of the national recommendations. The median age at which the fourth dose was administered was 14.3; this is near the upper limit of the national recommendations.

According to the definitions given in the methods section, the median age at full priming was 6.0 months, at 2nd year dose 14.4 months and at full immunisation (fully primed + booster) 14.3 months.

Table 16: Median age of children vaccinated with hexavalent vaccines in comparison to national recommendations in Germany (Kaplan-Meier estimates). German national immunisation survey on birth cohorts 1 August 2000 through 30 June 2003.

	Number vaccinated with respective dose	Median age (95% CI) at vaccination (month)	Range of age (months)	National recommendation (month)
1st dose	890	3.3 (3.2 - 3.4)	1.0 - 25.0	2.0 - 2.9
2nd dose	865	4.6 (4.5 - 4.7)	2.0 - 23.9	3.0 - 3.9
3rd dose	829	6.1 (5.9 - 6.2)	2.8 - 26.5	4.0 - 4.9
4th dose	477	14.3 (13.9 - 14.7)	4.0 - 30.4	11.0 - 14.9
Full priming	779	6.0 (5.8 - 6.1)	2.8 - 12.0	4.0 - 4.9
2nd year dose	516	14.4 (14.1 - 14.8)	11.0 - 30.4	11.0 - 14.9
Full immunisation (3+1)	446	14.3 (13.9 - 14.6)	11.0 - 30.4	11.0 - 14.9

7.3 Annual numbers of Hib cases and vaccine failures before and after licensure of hexavalent vaccines (Objective 1)

7.3.1 Annual numbers of Hib cases

In Clinical ESPED only, data on invasive *H. influenzae* cases were available from year 1993 onwards, with a gap in the years 1996 and 1997 where no data were collected (figure 10). The total number of Hi cases detected by Clinical ESPED decreased drastically by the factor 8, from 120 cases in 1993 to 14 cases in 2004. This decrease is not as obvious for Hib cases: they fluctuated from 15 cases in 1993, 29 in 1994 to 7 in 1999, 15 in 2000 and one in 2004. Here, the proportion of untyped cases – which probably could belong to type b cases – has to be taken into account for proper interpretation.

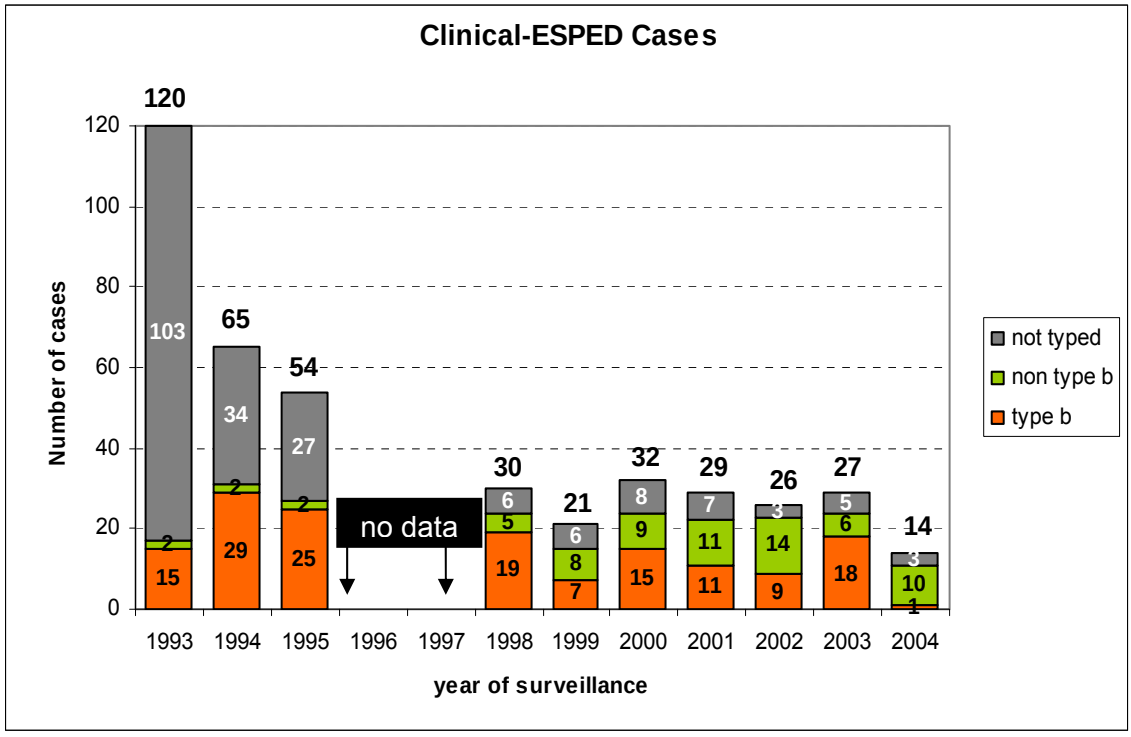


Figure 10: Annual number of *H. influenzae* cases by serotype detected in one surveillance system (Clinical ESPED) since 1993. In 1996 and 1997 no data on *H. influenzae* cases were collected. At the end of 2000 hexavalent vaccines were introduced on the German market.

In both surveillance systems together (Clinical and Laboratory ESPED), the total number of detected Hi cases decreased from 51 cases in 1998 to 39 in 1999, rose again to 63 cases in

2000 and decreased to 27 cases in 2004 (figure 11). The number of Hib cases fluctuated between 28 cases in 1998 and 4 cases in 2004.

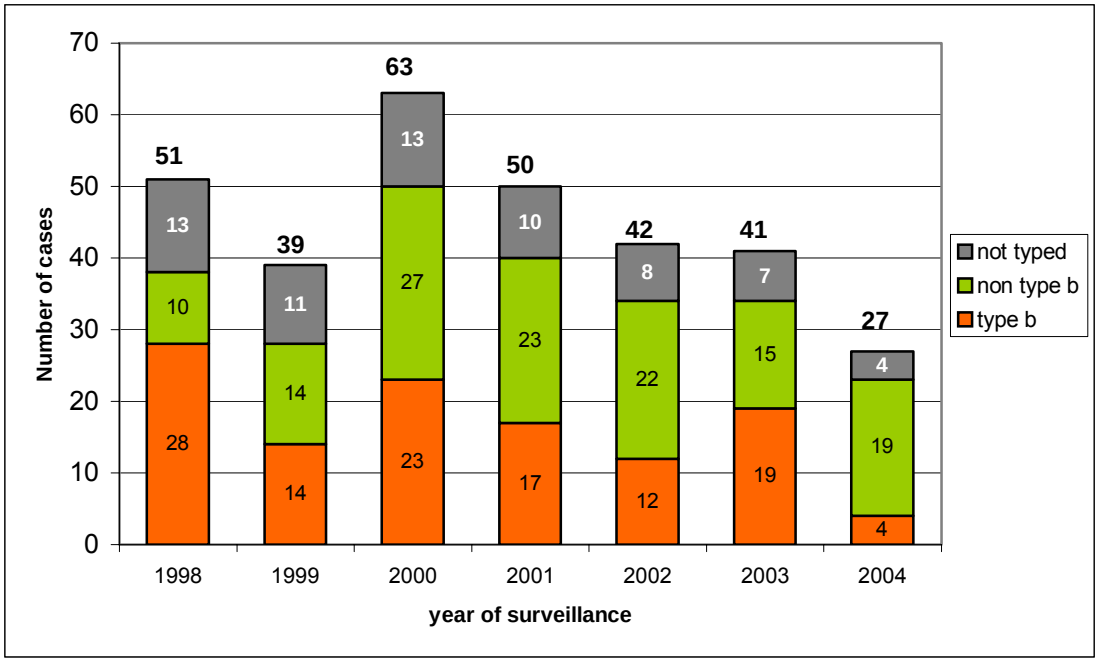


Figure 11: Annual number of *H. influenzae* cases by serotype detected in both surveillance systems (Clinical and Laboratory ESPED) since 1998. At the end of 2000 hexavalent vaccines were introduced on the German market.

Correcting these numbers for incompleteness of the surveillance system using capture-recapture estimates, the same pattern was found (table 17): highest estimated number of Hi cases in 2000 (83 cases), lowest in 2004 (34 cases); highest estimated number of Hib cases in 1998 (30 cases), lowest in 2004 (7 cases). In 2004, the number of estimated 'true' number of Hib cases nearly doubled using capture-recapture method compared to reported numbers as shown in figure 11.

Table 17: Estimated number of *H. influenzae* cases by year of surveillance and serotype using capture-recapture method.

Estimated number of cases by capture-recapture method (95% CI)	1998	1999	2000	2001	2002	2003	2004
All *H. influenzae*	56 (50-63)	47 (38-57)	83 (66-101)	51 (49-53)	44 (40-48)	42 (40-45)	34 (25-42)
Type b	30 (26-33)	15 (12-18)	23*	18 (16-19)	12 (11-14)	19 (19-20)	7 (0-14)
Non type b	10*	16 (13-18)	27*	23*	22*	15*	21 (17-25)

* Here, confidence intervals could not be calculated since all cases detected in one source were also present in the second source and therefore variance equates zero (see formula chapter 6.4.3.1).

When adjusting Hib cases for changes in the proportion of Hib isolates typed over time (see chapter 6.4.3.2), the above described fluctuation in Hib cases was more pronounced. Numbers decreased from 38 cases in 1998 to 5 cases in 2004, with intermediate peaks in 2000 (29 cases) and 2003 (23 cases) in all age groups. The overall decrease in Hib cases was mainly due to the age group 12 months to 4.9 years, the fluctuation mainly due to the age group 3-11 months (table 18).

Table 18: Number of Hib cases by year of surveillance and age at disease onset adjusted for differences in the proportion of typed cases over time.

	1998	1999	2000	2001	2002	2003	2004
All age groups	38	20	29	21	15	23	5
0-2 months	0	2	4	3	2	1	0
3-11 months	7	1	10	8	5	11	3
12 months – 4.9 years	25	13	12	8	8	10	2
5.0 – 9.9 years	4	4	2	2	0	1	0

Since the introduction of hexavalent vaccines at the end of 2000, no increase of invasive Hib cases in children could be detected in Germany.

7.3.2 Vaccine failures

Of all 117 invasive Hib cases detected in both surveillance systems since 1998, 52 were vaccinated at least once with a Hib vaccine, 64 were not vaccinated and for one case vaccination status was unknown. The annual distribution of vaccinated and unvaccinated Hib cases is shown in figure 12.

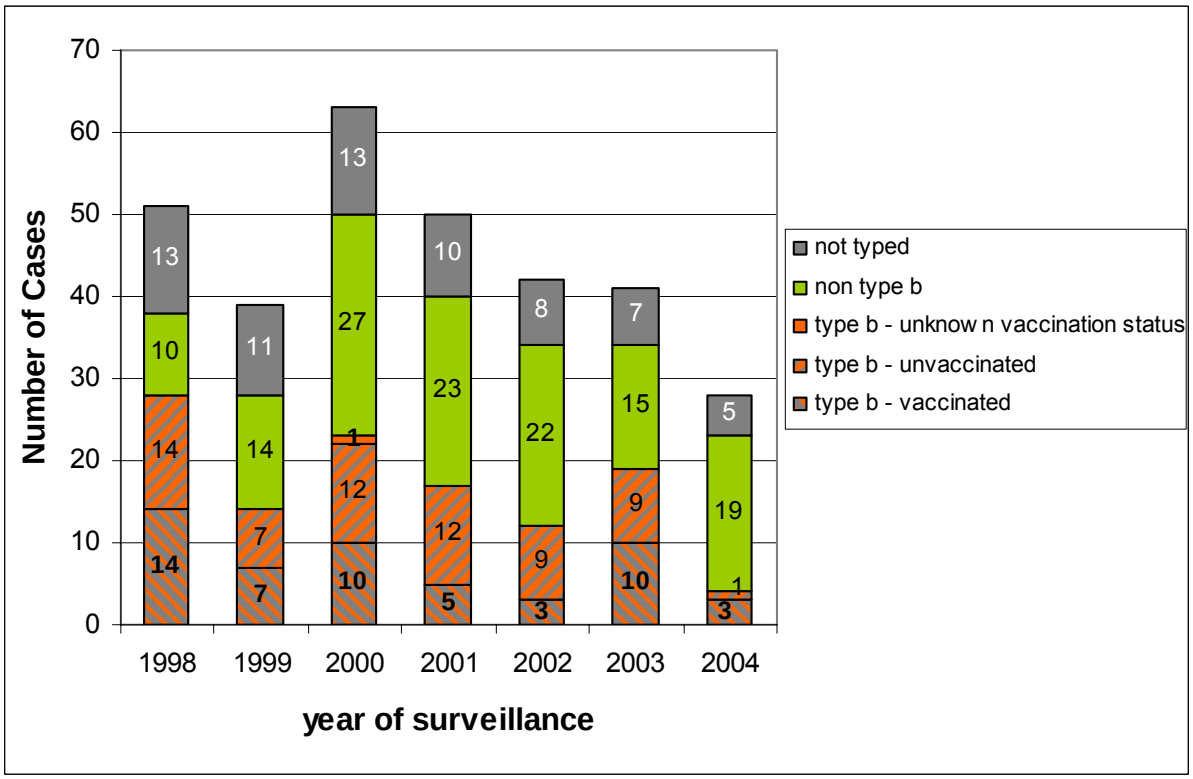


Figure 12: Annual number of *H. influenzae* cases by serotype and vaccination status detected in both surveillance systems (Clinical and Laboratory ESPED) since 1998. At the end of 2000 hexavalent vaccines were introduced on the German market.

The proportion of vaccinated Hib cases among all Hib cases was 50% in 1998, 50% in 1999, 45% in 2000, 29% in 2001, 25% in 2002, 52% in 2003 and 75% in 2004.

Of the 64 unvaccinated Hib cases detected since 1998, 59 were old enough to have received at least one shot of a Hib vaccine before disease onset if German vaccination recommendations would have been followed. Of the 52 vaccinated Hib cases, exact numbers of Hib vaccine doses given and age at receipt of Hib vaccines was known for 49 cases. Of these, 14 received incomplete priming, 19 complete priming, 10 full immunisation and 6 the 2nd year dose. Twenty-two of the 49 cases (44%) were not vaccinated according to German vaccination recommendations (see definition of 'age-eligibility of vaccination schedule', chapter 6.1.2); four additional cases immunised with an incomplete primary series could have received at least one additional shot of a Hib vaccine before disease onset if the exact timing of vaccination recommendations would have been considered.

Figure 13 shows the number of Hib cases by completeness of vaccination schedule and compliance with recommendations of the German Vaccine Advisory Board (STIKO).

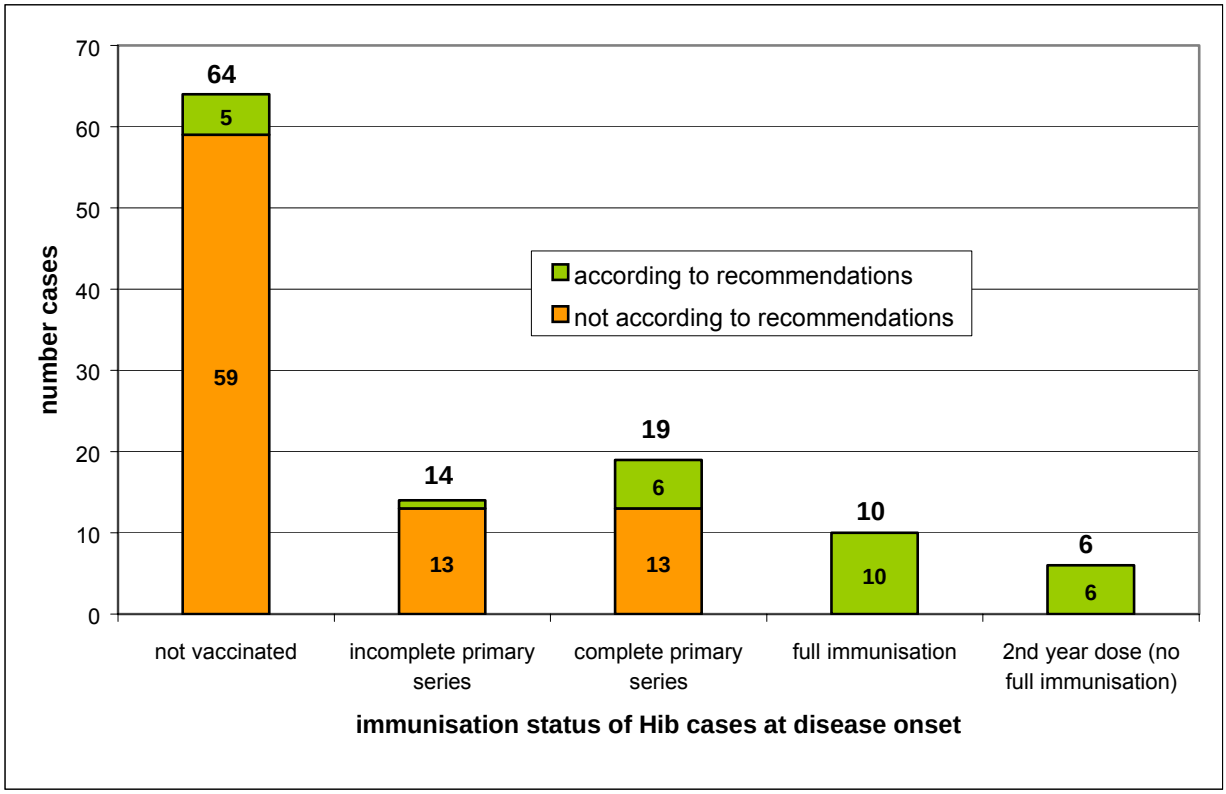


Figure 13: Number of Hib cases in both surveillance systems since 1998 (n=117) by completeness of vaccination schedule and compliance with the timing of the recommendations of the German Vaccine Advisory Board (STIKO). Invasive Hib cases marked in orange could have received more Hib vaccine doses before disease onset if vaccinated according to recommendations.

According to the definition of 'age-eligibility of the vaccination schedule' (chapter 6.1.2) - which is less stringent than the one described in figure 13 - five of the 14 Hib cases immunised with an incomplete primary series were 'immunised according to' and nine 'not immunised according to' the recommendations.

Of all vaccinated Hib cases, 12 had been vaccinated with at least one dose of a hexavalent vaccine. For these cases, number of Hib vaccine doses given and age at receipt of Hib vaccines is described in table 13 (chapter 7.2.1.5). One of these cases was detected in 2001, 2002 and 2004 each and 9 were detected in 2003.

7.4 Annual incidence rates of *H. influenzae* cases before and after licensure of hexavalent vaccines (Objective 2)

7.4.1 H. influenzae

Overall annual incidence rates of invasive *H. influenzae* disease were relatively constant throughout the years 1998 to 2004 (table 19). The highest incidence rates were found in the 0-2 month age group (7.3 and 5.4 per 100,000 in 2000 and 2001, respectively) and in the 3-11 month age group (2.6, 2.7 and 2.6 per 100,000 in 2000, 2001 and 2003, respectively). The increase in incidence was small, all confidence intervals overlapped and there was no evidence for an increasing trend.

Table 19: Age-specific annual incidence rates per 100,000 (95% CI) of invasive *H. influenzae* disease from 1998 to 2004

year	0-2 months		3-11 months		1.0 – 4.9 years		5.0 – 9.9 years		total	
	N	incidence	N	incidence	N	incidence	N	incidence	N	incidence
1998	6	3.0 (1.1-6.6)	8	1.4 (0.6-2.7)	31	1.0 (0.7-1.4)	6	0.1 (0.0-0.3)	51	0.6 (0.5-0.8)
1999	9	4.7 (2.1-8.8)	3	0.5 (0.1-1.5)	23	0.7 (0.5-1.1)	4	0.1 (0.0-0.2)	39	0.5 (0.3-0.6)
2000	14	7.3 (4.0-12.3)	15	2.6 (1.5-4.3)	22	0.7 (0.4-1.0)	12	0.3 (0.2-0.5)	63	0.8 (0.6-1.0)
2001	10	5.4 (2.6-10.0)	15	2.7 (1.5-4.5)	18	0.6 (0.3-0.9)	7	0.2 (0.1-0.4)	50	0.6 (0.5-0.8)
2002	5	2.8 (0.9-6.5)	8	1.5 (0.6-2.9)	24	0.8 (0.5-1.2)	5	0.1 (0.0-0.3)	42	0.5 (0.4-0.7)
2003	4	2.3 (0.6-5.8)	14	2.6 (1.4-4.4)	19	0.6 (0.4-1.0)	4	0.1 (0.0-0.3)	41	0.5 (0.4-0.7)
2004	6	3.4 (1.2-7.4)	5	0.9 (0.3-2.2)	13	0.4 (0.2-0.8)	3	0.1 (0.0-0.2)	27	0.4 (0.2-0.5)

7.4.2 H. influenzae type b

The same pattern was found when considering the annual incidences of invasive type b *H. influenzae* disease irrespective of the vaccination status (table 20). No substantial change - or even a decrease - was observed in incidences for children 1.0-4.9 and 5.0-9.9 years old but a possible increase in type b infection was seen among children younger than one year in 2000 and 2001. Again, incidence returned to previous levels in 2002, rose again in 2003 and fall in 2004. However, numbers were very small and all confidence intervals overlapped.

Table 20: Age-specific annual incidence rates per 100,000 (95% CI) of type b invasive *H. influenzae* disease from 1998 to 2004

year	0-2 months		3-11 months		1.0 – 4.9 years		5.0 – 9.9 years		total	
	N	incidence	N	incidence	N	incidence	N	incidence	N	incidence
1998	0	0.0 (0.0-1.9)	5	0.8 (0.3-2.0)	20	0.6 (0.4-1.0)	3	0.1 (0.0-0.2)	28	0.3 (0.2-0.5)
1999	1	0.5 (0.0-2.9)	1	0.2 (0.0-1.0)	9	0.3 (0.1-0.5)	3	0.1 (0.0-0.2)	14	0.2 (0.1-0.3)
2000	2	1.0 (0.1-3.8)	8	1.4 (0.6-2.7)	11	0.3 (0.2-0.6)	2	0.0 (0.0-0.2)	23	0.3 (0.2-0.4)
2001	2	1.1 (0.1-3.9)	7	1.3 (0.5-2.6)	7	0.2 (0.1-0.5)	1	0.0 (0.0-0.1)	17	0.2 (0.1-0.3)
2002	1	0.6 (0.0-3.1)	5	0.9 (0.3-2.2)	6	0.2 (0.1-0.4)	0	0.0 (0.0-0.1)	12	0.2 (0.1-0.3)
2003	1	0.6 (0.0-3.2)	9	1.7 (0.8-3.2)	8	0.3 (0.1-0.5)	1	0.0 (0.0-0.1)	19	0.2 (0.1-0.4)
2004	0	0.0 (0.0-2.1)	2	0.4 (0.0-1.4)	2	0.1 (0.0-0.2)	0	0.0 (0.0-0.1)	4	0.1 (0.0-0.1)

Annual incidences of vaccinated Hib cases were very low and did not show substantial changes over the years – with the exception of the years 2000 and 2003 (table 21): incidences for children 3-11 months old rose to 0.7 and 0.9 per 100,000 in 2000 and 2003, respectively. But again, numbers are very small and all confidence intervals overlap.

Table 21: Age-specific annual incidence rates per 100,000 (95% CI) of vaccinated type b invasive *H. influenzae* disease from 1998 to 2003

year	0-2 months		3-11 months		1.0 – 4.9 years		5.0 – 9.9 years		total	
	N	incidence	N	incidence	N	incidence	N	incidence	N	incidence
1998	0	0.0 (0.0-1.9)	1	0.2 (0.0-0.9)	12	0.4 (0.2-0.7)	1	0.0 (0.0-0.1)	14	0.2 (0.1-0.3)
1999	0	0.0 (0.0-1.9)	0	0.0 (0.0-0.6)	5	0.2 (0.1-0.4)	2	0.0 (0.0-0.2)	7	0.1 (0.0-0.2)
2000	0	0.0 (0.0-1.9)	4	0.7 (0.2-1.8)	5	0.2 (0.1-0.4)	1	0.0 (0.0-0.1)	10	0.1 (0.1-0.2)
2001	0	0.0 (0.0-2.0)	1	0.2 (0.0-1.0)	4	0.1 (0.0-0.3)	0	0.0 (0.0-0.1)	5	0.1 (0.0-0.1)
2002	0	0.0 (0.0-2.1)	0	0.0 (0.0-0.7)	3	0.1 (0.0-0.3)	0	0.0 (0.0-0.1)	3	0.0 (0.0-0.1)
2003	0	0.0 (0.0-2.1)	5	0.9 (0.3-2.2)	4	0.0 (0.1-0.3)	1	0.0 (0.0-0.1)	10	0.1 (0.1-0.2)
2004	0	0.0 (0.0-2.1)	1	0.2 (0.0-1.1)	2	0.1 (0.0-0.2)	0	0.0 (0.0-0.1)	3	0.0 (0.0-0.1)

7.4.3 Non-type b H. influenzae

No substantial changes were observed in annual incidences of non-type b Hi infection but a slight increase was seen in age groups 0-2 months in the years 1999 to 2001 and again in 2004, and in age group 3-11 months in the years 2000 to 2002 (table 22).

Table 22: Age-specific annual incidence rates per 100,000 (95% CI) of non-type b invasive *H. influenzae* disease from 1998 to 2004

	0-2 months		3-11 months		1.0 – 4.9 years		5.0 – 9.9 years		total	
	n	incidence	n	incidence	n	incidence	n	incidence	n	incidence
1998	**2**	**1.0 (0.1-3.7)**	**1**	**0.2 (0.0-0.9)**	**5**	**0.2 (0.1-0.4)**	**2**	**0.0 (0.0-0.2)**	**10**	**0.1 (0.1-0.2)**
Capsulated	0	0.0 (0.0-1.9)	0	0.0 (0.0-0.6)	0	0.0 (0.0-0.1)	0	0.0 (0.0-0.1)	0	0.0 (0.0-0.0)
Non-capsulated	2	1.0 (0.1-3.7)	1	0.2 (0.0-0.9)	5	0.2 (0.1-0.4)	2	0.0 (0.0-0.2)	10	0.1 (0.1-0.2)
Not specified	0	0.0 (0.0-1.9)	0	0.0 (0.0-0.6)	0	0.0 (0.0-0.1)	0	0.0 (0.0-0.1)	0	0.0 (0.0-0.0)
1999	**5**	**2.6 (0.8-6.0)**	**2**	**0.3 (0.0-1.2)**	**7**	**0.2 (0.1-0.5)**	**0**	**0.0 (0.0-0.1)**	**14**	**0.2 (0.1-0.3)**
Capsulated	0	0.0 (0.0-1.9)	2	0.3 (0.0-1.2)	1	0.0 (0.0-0.2)	0	0.0 (0.0-0.1)	3	0.0 (0.0-0.1)
Non-capsulated	5	2.6 (0.8-6.0)	0	0.0 (0.0-0.6)	6	0.2 (0.1-0.4)	0	0.0 (0.0-0.1)	11	0.1 (0.1-0.2)
Not specified	0	0.0 (0.0-1.9)	0	0.0 (0.0-0.6)	0	0.0 (0.0-0.1)	0	0.0 (0.0-0.1)	0	0.0 (0.0-0.0)
2000	**6**	**3.1 (1.1-6.8)**	**4**	**0.7 (0.2-1.8)**	**9**	**0.3 (0.1-0.5)**	**8**	**0.2 (0.1-0.4)**	**27**	**0.3 (0.2-0.5)**
Capsulated	0	0.0 (0.0-1.9)	1	0.2 (0.0-1.0)	1	0.0 (0.0-0.2)	0	0.0 (0.0-0.1)	2	0.0 (0.0-0.1)
Non-capsulated	6	3.1 (1.1-6.8)	3	0.5 (0.1-1.5)	7	0.2 (0.1-0.5)	8	0.2 (0.1-0.4)	24	0.3 (0.2-0.4)
Not specified	0	0.0 (0.0-1.9)	0	0.0 (0.0-0.6)	1	0.0 (0.0-0.2)	0	0.0 (0.0-0.1)	1	0.0 (0.0-0.1)
2001	**5**	**2.7 (0.9-6.3)**	**6**	**1.1 (0.4-2.4)**	**9**	**0.3 (0.1-0.5)**	**3**	**0.1 (0.0-0.2)**	**23**	**0.3 (0.2-0.4)**
Capsulated	0	0.0 (0.0-2.0)	3	0.5 (0.1-1.6)	0	0.0 (0.0-0.1)	0	0.0 (0.0-0.1)	3	0.0 (0.0-0.1)
Non-capsulated	5	2.7 (0.9-6.3)	3	0.5 (0.1-1.6)	8	0.3 (0.1-0.5)	3	0.1 (0.0-0.2)	19	0.2 (0.1-0.4)
Not specified	0	0.0 (0.0-2.0)	0	0.0 (0.0-0.7)	1	0.0 (0.0-0.2)	0	0.0 (0.0-0.1)	1	0.0 (0.0-0.1)
2002	**2**	**1.1 (0.1-4.0)**	**3**	**0.6 (0.1-1.6)**	**12**	**0.4 (0.2-0.7)**	**5**	**0.1 (0.0-0.3)**	**22**	**0.3 (0.2-0.4)**
Capsulated	0	0.0 (0.0-2.1)	1	0.2 (0.0-1.0)	3	0.1 (0.0-0.3)	2	0.0 (0.0-0.2)	6	0.1 (0.0-0.2)
Non-capsulated	2	1.1 (0.1-4.0)	1	0.2 (0.0-1.0)	9	0.3 (0.1-0.6)	3	0.1 (0.0-0.2)	15	0.2 (0.1-0.3)
Not specified	0	0.0 (0.0-2.1)	1	0.2 (0.0-1.0)	0	0.0 (0.0-0.1)	0	0.0 (0.0-0.1)	1	0.0 (0.0-0.1)
2003	**3**	**1.7 (0.4-5.0)**	**2**	**0.4 (0.0-1.4)**	**7**	**0.2 (0.1-0.5)**	**3**	**0.1 (0.0-0.2)**	**15**	**0.2 (0.1-0.3)**
Capsulated	0	0.0 (0.0-2.1)	0	0.0 (0.0-0.7)	2	0.1 (0.0-0.2)	1	0.0 (0.0-0.1)	3	0.0 (0.0-0.1)
Non-capsulated	3	1.7 (0.4-5.0)	2	0.4 (0.0-1.4)	5	0.2 (0.1-0.4)	2	0.1 (0.0-0.2)	12	0.2 (0.1-0.3)
Not specified	0	0.0 (0.0-2.1)	0	0.0 (0.0-0.7)	0	0.0 (0.0-0.1)	0	0.0 (0.0-0.1)	0	0.0 (0.0-0.0)
2004	**6**	**3.4 (1.2-7.4)**	**2**	**0.4 (0.0-1.4)**	**9**	**0.3 (0.1-0.6)**	**2**	**0.1 (0.0-0.2)**	**19**	**0.2 (0.1-0.4)**
Capsulated	0	0.0 (0.0-2.1)	1	0.2 (0.0-1.1)	3	0.1 (0.0-0.3)	0	0.0 (0.0-0.1)	4	0.1 (0.0-0.1)
Non-capsulated	6	3.4 (1.2-7.4)	1	0.2 (0.0-1.1)	4	0.1 (0.0-0.3)	2	0.1 (0.0-0.2)	13	0.2 (0.1-0.3)
Not specified	0	0.0 (0.0-2.1)	0	0.0 (0.0-0.7)	2	0.1 (0.0-0.2)	0	0.0 (0.0-0.1)	2	0.0 (0.0-0.1)

7.4.4 Adjusted incidence rates

Correcting incidences for incompleteness of case ascertainment through both surveillance systems using capture-recapture estimates, nearly identical rates to those described above were observed (table 23):

Table 23: Estimated annual incidence rates per 100,000 (95% CI) of invasive *H. influenzae* disease by serotype from 1998 to 2004 using capture-recapture method

year	Hib		Non type b		All Hi	
	N	incidence	N	incidence	N	incidence
1998	30	0.4 (0.2-0.5)	10	0.1 (0.1-0.2)	56	0.7 (0.5-0.9)
1999	15	0.2 (0.1-0.3)	16	0.2 (0.1-0.3)	47	0.6 (0.4-0.8)
2000	23	0.3 (0.2-0.4)	27	0.3 (0.2-0.5)	83	1.0 (0.8-1.3)
2001	18	0.2 (0.1-0.4)	23	0.3 (0.2-0.4)	51	0.6 (0.5-0.8)
2002	12	0.2 (0.1-0.3)	22	0.3 (0.2-0.4)	44	0.6 (0.4-0.7)
2003	19	0.2 (0.1-0.4)	15	0.2 (0.1-0.3)	42	0.5 (0.4-0.7)
2004	7	0.1 (0.0-0.2)	21	0.3 (0.2-0.4)	34	0.4 (0.3-0.6)

When adjusting Hib cases for changes in the proportion of Hib isolates typed over time (see chapter 6.4.3.2), higher incidences resulted, especially for the first two age groups (table 24). The highest estimated incidence rates were found in the 0-2 month age group (2.1 per 100,000 in 2000) and in the 3-11 month age group (2.1 per 100,000 in 2003).

Table 24: Age-specific annual incidence rates per 100,000 (95% CI) of type b invasive *H. influenzae* disease from 1998 to 2004 adjusted for differences in the proportion of typed cases over time.

year	0-2 months		3-11 months		1.0 – 4.9 years		5.0 – 9.9 years		total	
	N	incidence	N	incidence	N	incidence	N	incidence	N	incidence
1998	0	0.0 (0.0-1.9)	7	1.2 (0.5-2.4)	25	0.8 (0.5-1.2)	4	0.1 (0.0-0.2)	38	0.5 (0.3-0.6)
1999	2	1.0 (0.1-3.7)	1	0.2 (0.0-1.0)	13	0.4 (0.2-0.7)	4	0.1 (0.0-0.2)	20	0.2 (0.1-0.4)
2000	4	2.1 (0.6-5.3)	10	1.7 (0.8-3.2)	12	0.4 (0.2-0.7)	2	0.0 (0.0-0.2)	29	0.4 (0.2-0.5)
2001	3	1.6 (0.3-4.8)	8	1.4 (0.6-2.9)	8	0.3 (0.1-0.5)	2	0.0 (0.0-0.2)	21	0.3 (0.2-0.4)
2002	2	1.1 (0.1-4.0)	5	0.9 (0.3-2.2)	8	0.3 (0.1-0.5)	0	0.0 (0.0-0.1)	15	0.2 (0.1-0.3)
2003	1	0.6 (0.0-3.2)	11	2.1 (1.0-3.7)	10	0.3 (0.2-0.6)	1	0.0 (0.0-0.1)	23	0.3 (0.2-0.4)
2004	0	0.0 (0.0-2.1)	3	0.6 (0.1-1.7)	2	0.1 (0.0-0.2)	0	0.0 (0.0-0.1)	5	0.1 (0.0-0.2)

Since the introduction of hexavalent vaccines at the end of 2000, no increase in the incidence of invasive Hib disease in children could be detected in Germany. The highest estimated incidence rate since 1998 was seen in the 3-11 month age group in 2003, but confidence intervals were wide.

7.5 Effectiveness of hexavalent vaccines against invasive Hib disease (Objective 3)

7.5.1 Cases and subcohort members contributing to effectiveness calculations

7.5.1.1 Cases

As described in the methods section the analytic approach to assess vaccine effectiveness was that of a case-cohort study. Cases included in the effectiveness calculations of hexavalent vaccines met the following criteria:

- Born between 1 August 2000 and 30 June 2003
- Aged 2 months or older
- no vaccination or vaccination with hexavalent vaccines before onset of disease
- confirmed systemic *H. influenzae* infection (type b or untyped) detected by ESPED until 31 December 2003

Thirty-four cases met these definitions. Of these, 27 were identified as type b and 7 were not typed. Of the 27 Hib cases, 10 were vaccinated with hexavalent vaccines and 17 were unvaccinated; of the 7 untyped cases, 2 were vaccinated with hexavalent vaccines and 5 unvaccinated. There were no cases vaccinated with a mixture of hexavalent and other Hib vaccines before onset of disease.

Of the 10 cases vaccinated with hexavalent vaccines, 5 had received an incomplete primary series, and 5 had received the full primary series. None had received a booster or 2nd year dose. According to their age and to the German recommended vaccination schedule, 3 of the 5 partially primed children and 3 of the 5 fully primed children could have received at least one additional dose before disease onset. The other four children with invasive Hib disease and one of the two children with untyped H. influenzae disease were defined as immunised according to the recommended schedule (see ‘age-eligibility of the vaccination schedule’; chapter 6.1.2).

In table 25 vaccination histories of the 10 Hib and the 2 untyped *H. influenzae* cases vaccinated with hexavalent vaccines and eligible for effectiveness calculations are shown in detail.

Table 25: List of all Hib and untyped Hi cases vaccinated with hexavalent vaccines from the ESPED surveillance system in Germany, which contributed to vaccine effectiveness calculations.

case	birth date (mm/year)	age at disease (months)	serotype	N vaccination	vaccination history						age-eligibility of the vaccination schedule*
					vaccination 1		vaccination 2		vaccination 3		
					age	vaccine	age	vaccine	age	vaccine	
***Haemophilus influenzae* type b**											
32/01	8/2000	6	Type b	1	5	hexavalent	-	-	-	-	not according
6/03	7/2002	8	Type b	1	6	hexavalent	-	-	-	-	not according
25/03	11/2002	4	Type b	1	3	hexavalent	-	-	-	-	according
36/03	5/2003	4	Type b	1	3	hexavalent	-	-	-	-	according
45/03	5/2003	6	Type b	2	3	hexavalent	4	hexavalent	-	-	not according
2/02	11/2001	12	Type b	3	2	hexavalent	4	hexavalent	6	hexavalent	according
2/03	8/2001	17	Type b	3	3	hexavalent	5	hexavalent	7	hexavalent	not according
44/03	11/2001	23	Type b	3	4	hexavalent	5	hexavalent	8	hexavalent	not according
46/03	5/2002	17	Type b	3	3	hexavalent	5	hexavalent	8	hexavalent	not according
39/03	3/2003	7	Type b	3	2	hexavalent	3	hexavalent	4	hexavalent	according
Untyped *Haemophilus influenzae*											
34/02	5/2001	15	Untyped	2	2	hexavalent	12	hexavalent	-	-	according
27/03	11/2001	17	Untyped	3	4	hexavalent	5	hexavalent	6	hexavalent	not according

* 'not according' means not according to the vaccination schedule; 'according' means according to the vaccination schedule (definition 'age-eligibility of the vaccination schedule'; chapter 6.1.2)

Cases with unknown serotype (cases #34/02 and #27/03 from table 25 and 5 unvaccinated cases) were taken into account in sensitivity analyses. Case #34/03, a 40 month old boy vaccinated four times with the last dose given as a hexavalent vaccine (table 13; chapter 6.2.1.5), was not included in vaccine effectiveness calculations because he was born before 1 August 2000.

7.5.1.2 Subcohort

According to the analytic approach of a case-cohort study to assess vaccine effectiveness, all infants in Germany constitute the full cohort. From the full cohort, a representative sub-cohort was randomly sampled in the nationwide immunisation survey as described in the methods section.

Subcohort members included in the effectiveness calculations of hexavalent vaccines met the following criteria:

- Born between 1 August 2000 and 30 June 2003
- Aged 2 months or older at interview
- no vaccination or vaccination with hexavalent vaccines before onset of disease
- interviews done until 30 January 2004

1112 children from the telephone surveys met these definitions. Of these, 71 (6.4%) had never been vaccinated against Hib at the time of the interview, 890 (80.0%) had received hexavalent vaccines only, and 151 (13.6%) had received mixed schedules of hexavalent and other Hib vaccines.

Of those receiving hexavalent vaccines only, 334 (34.8%) were fully primed only and 517 (58.1%) received 2nd year dose at the time of the interview; of those receiving mixtures of hexavalent Hib vaccines and other Hib vaccines, 26 (17.2%) were fully primed and 121 (80.1%) received 2nd year dose (table 26).

Table 26: Children from the German national immunisation survey included in vaccine effectiveness calculations: type of vaccines used and number of doses administered at the time of the interview.

Vaccination status	**N**	**%**
Not Hib vaccinated	71	100
Hexavalent Hib vaccines	890	100
1 dose priming	*11*	*1.2*
2 doses priming	*28*	*3.2*
Full priming	*334*	*37.5*
2nd year dose	*517*	*58.1*
full immunisation	*447*	-
Mixed types	151	100
1 dose priming	*0*	*0.0*
2 doses priming	*4*	*2.6*
Full priming	*26*	*17.2*
2nd year dose	*121*	*80.1*
full immunisation	*99*	-
Total	1112	

For those children receiving hexavalent vaccines only, median age (95% CI) at vaccination with the complete primary series of hexavalent vaccines was 6.0 (5.8-6.1) months and median age at vaccination with the full immunisation was 14.4 (14.1-14.8) months. This is later than recommended by the national immunisation guidelines: 2.0-2.9 months later than recommended for the primary series and at the upper recommended end for the full immunisation.

All 151 children receiving a mixture of hexavalent and other Hib vaccines were taken into account in sensitivity analyses.

7.5.2 Estimates of hexavalent Hib vaccine effectiveness

7.5.2.1 Vaccine effectiveness for completeness of the vaccination schedule

The overall estimate of the effectiveness for DTaP-IPV-HB/Hib combination vaccines against invasive Hib was 75.5% (95% CI: 31.4-91.3) for an incomplete primary series and 91.8% (95% CI: 73.6-97.5) for the full primary series. For the 2nd year dose - but no full immunisation - and full immunisation vaccine effectiveness was 100.0% (95% CI: 99.5-100.0 and 99.9-100.0, respectively). Table 27 shows the results of the time-to-event analysis in detail.

Table 27: Vaccine effectiveness of *Haemophilus influenzae* type b immunisation with DTaP-IPV-HB/Hib on children born from 8/2000 through 6/2003 in Germany. Estimates, standard error and vaccine effectiveness from Cox regression model and robust variance estimates for completeness of vaccination schedule.

Completeness of vaccination schedule	N cases	Parameter estimate (ß)	Standard error	Vaccine effectiveness*	95% CI
No vaccination	17	0**	-	0.0%**	-
Incomplete primary series	5	-1.40631	0.52545	75.5%	31.4-91.3
Full primary series	5	-2.50494	0.59867	91.8%	73.6-97.5
2nd year dose, but not fully immunised	0	-16.83515	0.45130	100.0%	99.5-100.0§
Full immunisation	0	-16.81207	0.42775	100.0%	99.9-100.0§

* $(1-e^{ß}) \times 100\%$
** reference category
§ binominal exact confidence intervals

7.5.2.2 Vaccine effectiveness for age-eligibility of the vaccination schedule

The overall estimate of effectiveness for DTaP-IPV-HB/Hib combination vaccines against invasive Hib was 92.6% (95% CI: 77.7-97.5) for children vaccinated according to their age and to the German recommended vaccination schedule. Table 28 shows the results of the time-to-event analysis in detail.

Table 28: Vaccine effectiveness of *Haemophilus influenzae* type b immunisation with DTaP-IPV-HB/Hib on children born from 8/2000 through 6/2003 in Germany. Estimates, standard error and vaccine effectiveness from Cox regression model and robust variance estimates for age-eligibility of vaccination schedule.

Age-eligibility of vaccination schedule	N cases	Parameter estimate (ß)	Standard error	Vaccine effectiveness*	95% CI
Not according to schedule	23	0**	-	0.0%	-
according to schedule	4	-2.59791	0.55939	92.6%	77.7-97.5

* $(1-e^{ß}) \times 100\%$
** reference category

Adjusting for the number of Hib vaccine doses given, the relative risk of invasive Hib disease for those not vaccinated to the recommended schedule was 6.5 (95% CI: 1.1-38.0).

7.5.3 Sensitivity analyses

Inclusion of

- children with mixed vaccine schedules (mixture of DTaP-IPV-HB/Hib and other Hib vaccines within a child) as having received DTaP-IPV-HB/Hib vaccines (there were no cases but 151 children from the subcohort with mixed vaccine schedules)
  and / or
- cases with untyped invasive *H. influenzae* disease - and therefore potentially belonging to the serotype b group - as Hib cases (cases #34/02 and #27/03 [see table 25]; case #34/02 was defined as '2nd year dose' but is neither 'fully primed' nor 'fully immunised')

did not lower the point estimators of vaccine effectiveness described in the previous chapter for more than 0.2 percent; an exception is the point estimator for the 2nd year dose: if the one untyped Hi case is included in the model, point estimators were 75.9% and 81.6%, respectively; but confidence intervals were extremely wide, 0.0-98.4% and 0.0-98.0%, respectively.

The results of the sensitivity analyses are shown in detail in the annex, chapter 15.2 (tables A1-A6).

8 DISCUSSION

Four years after the introduction of hexavalent vaccines in Germany, there was no indication of increasing incidence of invasive Hib disease or increasing number of Hib vaccine failures in children. Hexavalent vaccines continue to show the high effectiveness against invasive Hib disease observed for other DTaP-containing Hib vaccines in Germany (Kalies et al., 2004).

8.1 *H. influenzae* type b disease before and after the introduction of hexavalent combination vaccines

8.1.1 Cases and incidences

The annual number of Hib cases in children under 10 year of age ranged between 14 and 28 for the years 1998 through 2000, compared to numbers of 4 to 19 cases per year in the years 2001 through 2004, a time period where hexavalent vaccines had been introduced and gained a rapid increase on the German market. Constant annual numbers might lead to false conclusions if denominators are decreasing – a fact which is true for the German birth cohorts; but, even if considering incidences, no increase in invasive Hib disease after the introduction of hexavalent vaccines was detectable: annual incidence rates of Hib disease ranged between 0.2 to 0.3 per 100,000 in 1998 through 2000 compared to 0.1 to 0.2 per 100,000 in 2001 to 2004 which is statistically inseparable. Considering an annual rate of 23 per 100,000 children with invasive Hib disease before the introduction of any Hib vaccines (von Kries, 1997), these rates again demonstrate the success of all Hib vaccines.

Data from most other European countries report comparable or slightly higher incidence rates (EU-Ibis, 2004). In the UK, however, an increase in the incidence of invasive Hib disease from 0.65 per 100,000 children younger than 5 years in 1998 to 4.6 per 100,000 in 2002 was observed, with most cases being vaccinated (Ramsey et al., 2003). A more pronounced increase coincided with a switch in the distribution of combination vaccines, from diphtheria-tetanus-whole cell pertussis (DTwP)/Hib to DTaP/Hib at the end of 1999, as well as with the introduction of a concomitant meningococcal C conjugate vaccination (Trotter et al., 2003). An increase in the incidence of Hib meningitis and epiglottitis among vaccinated children was also observed in the Netherlands in 2002 (Rijkers et al., 2003), despite the exclusive use of monovalent Hib vaccines and the recommendation of a booster dose since

the introduction of Hib vaccines in 1993. Causes for this increase are not yet clear and further surveillance has to confirm this trend.

8.1.2 Vaccine failures

In Germany, the absolute number of Hib vaccine failures was very small, between 7 and 14 cases per year for 1998 through 2000 and between 3 and 10 cases per year for 2001 through 2004. Although the proportion of vaccinated Hib cases ranged between 25% in 2002 and 75% in 2004, it should be noted that when most of the population is vaccinated, most cases will be vaccine failures, so a high proportion of vaccine failures is not necessarily indicative of declining vaccine effectiveness. Of particular importance when considering Hib vaccine failures in Germany is the fact that most Hib cases could have been avoided if they were vaccinated according to the German recommendations: almost all (92%) unvaccinated Hib cases were old enough to have received at least one shot of a Hib vaccine before disease onset if recommendations would have been followed, and 44% (definition made in this thesis) or even 53% (exact timing) of the vaccinated children were old enough to have received at least one additional shot if recommendation would have been followed. Data from the national immunisation survey showed that 70% - 80% of all German children were not vaccinated at the recommended age, are therefore under-protected and at risk of coming down with an invasive Hib disease. The relevance for German Health Policies to point at the importance of timely vaccination is evident since delayed vaccination is present for all other antigens as well (Kalies et al., 2006). Nevertheless, to date there are no national vaccination targets and implemented instruments to assess their achievements. Furthermore, there are no incentives or public health services to ensure that children have received recommended vaccinations.

8.1.3 Possible biases

Possible biases of case ascertainment were considered: response rates to both surveillance systems were high; nevertheless, Clinical ESPED reported fewer cases than Laboratory ESPED. Corrections for incompleteness of the surveillance systems using Capture Recapture method shows that both systems together captured a high proportion of all ‘true’ cases, between 75% and 97% per year. Accounting for this in the analysis, did not change the results. Better overall ascertainment from laboratories may reflect that laboratory results are coded by pathogens and not by clinical diagnosis and are therefore easier to report. The same observations were made in the 1998 to 2000 data on *H. influenzae* surveillance and in

another ESPED surveillance programme using the same two sources for pneumococcal surveillance (von Kries et al., 2000).

In many surveillance systems it is very difficult to ensure consistency of case ascertainment over long periods of time because reporting and typing of cases changed over time. In the presented data reporting of *H. influenzae* cases remained relatively constant, but typing of cases changed between 1998 and 2004. The latter could only then mask a ‚true' increase if typing rates would have decreased; the opposite was the case: typing rates increased between 1998 and 2004. In addition, after adjustment for changes in the proportion of cases typed over time no such increase was seen.

8.2 Effectiveness of hexavalent vaccines against invasive Hib disease

The vaccine effectiveness estimates for hexavalent vaccines confirm the high effectiveness of other DTaP-containing Hib combination vaccines previously reported applying the same analytic approach of a case-cohort design (Kalies et al., 2004); vaccine effectiveness for these DTaP-(IPV)/Hib combination vaccines was 89.6% (95% CI: 67.0-96.7) for an incomplete primary series, 96.7% (95% CI: 87.7-99.1) for the full primary series and 98.5% (95% CI: 94.5-99.6) for the 2nd year dose. Although estimates for the incomplete and complete primary series were slightly lower for hexavalent vaccines, there was no significant difference for vaccine effectiveness between hexavalent and DTaP/Hib or DTaP-IPV/Hib vaccines (figure 14).

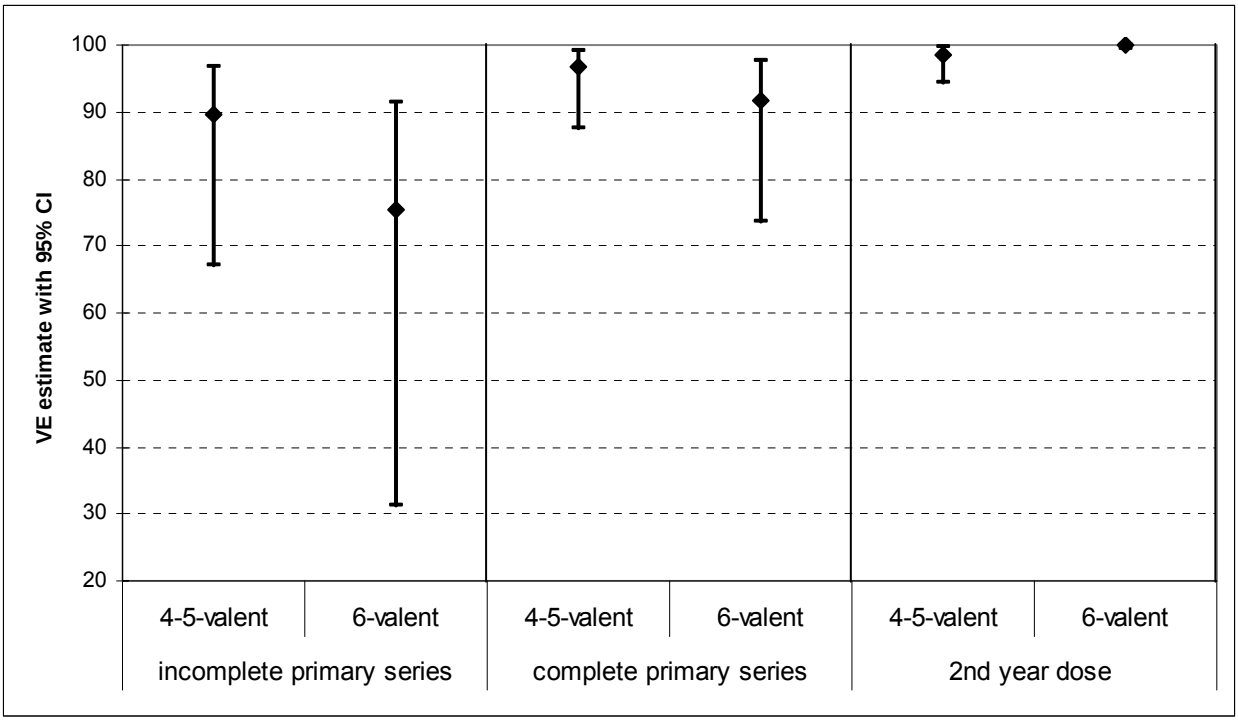


Figure 14: Effectiveness of DTaP-(IPV)/Hib and DTaP-IPV-HB/Hib vaccines (4-5-valent vs. 6-valent) against invasive Hib disease in German children. Point estimates with 95% confidence intervals; reference category = no vaccination; data for 4-5-valent vaccines derive from Kalies et al., 2004.

8.2.1 Superiority of case-cohort design

Information from a nationwide immunisation survey and on detailed Hib case reports was combined to study Hib vaccine effectiveness. Similar information was used in the UK to study the effectiveness of meningococcal C vaccination (Balmer et al., 2002) as well as Hib vaccination (Ramsey et al., 2003). In both UK studies, information on the cases was assumed to be complete and the analytical method was referred to as the screening method (Farrington, 1993). The screening method can be used in situations where it is not possible to obtain the exact vaccination status of each child in the healthy population. It falls back on external sources on proportions vaccinated, normally data routinely collected for vaccination status in the population. Furthermore, in the screening method, it is assumed that the proportion of vaccinated in the population is the 'true' value, without variation.

The present vaccine effectiveness study uses a case-cohort design where detailed information on Hib cases and on a subcohort of the German population through a nationwide immunisation survey was obtained. The utility of this approach has first been illustrated in analyses of Hib vaccine effectiveness among children living on a south-western Native American reservation during 1988-1993 (Moulton et al., 1995). This approach, which applies proportional hazard models to estimate the vaccine effectiveness, has the advantage of taking sampling variability of cases and controls into account. In addition, by modelling the vaccination status as a time-dependent variable, it is also possible to account for the wide variation in age at vaccination, the changing immunisation status of each child, and the overlap of age at vaccination with age at disease. This is especially important in Germany were a delay in vaccine uptake and a high individual variation in age at vaccination exists (Laubereau et al., 2001; Kalies et al., 2006) and has been confirmed by the present study; for example, median age at vaccination with the full primary series of hexavalent vaccines was 6.0 months, which is 1.2 months later than the upper limit of the national recommendations, and completion of the full immunisation schedule ranged between ages 11.0 and 30.4 months. The case-cohort method for estimation of vaccine effectiveness accounts for this high variance and delay of vaccine uptake in Germany. The case-cohort approach, however, requires detailed information on individuals. This information had to be obtained from the immunisation survey performed for this study, since the only routine estimation of vaccination coverage in Germany is based on school health examinations which do not assess types of vaccines or timing of vaccinations (Robert Koch Institute, 2005).

8.2.2 Possible biases

A number of possible sources of bias were considered. Incomplete ascertainment of cases could have led to bias if reporting was related to the vaccination status. For the reporting laboratories this is unlikely since they were unaware of the vaccination history of any patient. For hospitals vaccinated cases would be expected to be reported more reliably than unvaccinated cases as breakthrough cases are known to be of interest, which would lead to an underestimation of vaccine effectiveness. Bias could have occurred from overrepresentation of hexavalent vaccinated type b cases among those not sent for typing and therefore possibly type b. The sensitivity analysis showed, however, that the inclusion of all untyped cases as type b cases did not change the estimation of vaccine effectiveness substantially.

Response rates to the telephone surveys were 63%. These response rates are similar to response rates conducted in other telephone surveys in Germany or the US (Centre for Disease Control, 2003; Meyer et al., 2002; Rehmet et al., 2002). Comparisons with official data provided by the Federal Statistical Office, Germany, (2002) revealed that the sampled telephone interviews are representative for families with age-eligible children in Germany with regard to geographical and social distribution. However, children from households with higher income are slightly over-represented. Whether these children have differing Hib immunisation patterns is not known.

A selection bias while recruiting parents for the vaccination interview of their child cannot be excluded: parents of unvaccinated children could have refused to participate in the survey more frequently than parents of vaccinated children. This would lead to an overestimation of the vaccine coverage, and an overestimation of vaccine effectiveness. School entry health examinations in Germany – although not complete and only available for younger birth cohorts where the proportion of Hib vaccinated children is known to be lower – estimate the proportion of children not vaccinated against Hib at about 6.6% (personal communication, Dr. Anette Siedler, Robert Koch Institute, Berlin, personal communication, 2003). This is comparable with the 5% of unvaccinated children found in the national immunisation survey at 2 years of age.

8.2.3 Causes for differing vaccine effectiveness estimates between UK and Germany

In the UK, in addition to the described increase in the incidence of invasive Hib disease (chapter 8.1), a case-control study showed an increasing risk in fully vaccinated children with increasing number of DTaP/Hib doses (Mc Vernon et al., 2003). A decline of effectiveness over time following vaccination was shown in another study (Ramsey et al., 2003). The effectiveness of these DTaP/Hib vaccines following full priming was only 56.7%. In Germany however, a high vaccine effectiveness of DTaP-containing Hib combination vaccines was found (Schmitt et al., 2001; Kalies et al., 2004). As demonstrated in this thesis, effectiveness of hexavalent vaccines was 91.8% (95% CI: 73.6-97.5) for fully primed children.

In contrast to the UK, where a three dose regimen of Hib vaccine at 2, 3 and 4 months and no booster are recommended, the German Vaccine Advisory Board (STIKO) recommends a four dose regimen at age 2, 3, 4 and a booster at 11 months. Immunising a child according to these recommendations leads to the high vaccine effectiveness of 92.6% (95% CI: 77.7-97.5) found in this work, irrespective of the number of doses given. Children not vaccinated to these recommendations have a more than 6-fold risk (6.5 [95% CI: 1.1-38.0]) to come down with invasive *H. influenzae* disease, even if they received e.g. three hexavalent vaccine doses.

The present data have the statistical power to differentiate between the effect of full priming and the additional effect of the booster dose: vaccine effectiveness of hexavalent vaccines for the 2nd year dose and full immunisation were slightly higher than that for fully primed children, and confidence intervals do not overlap with those of full priming (100.0% [95% CI: 99.5-100.0] and 100.0% [95% CI: 99.9-100.0], respectively, vs. 91.8% [95% CI: 73.6-97.5]).

Given the high number of cases in the UK that occurred after the first year of life, the present results suggest that the absence of a booster dose in the UK immunisation schedule might be a potential explanation of the reduced effectiveness of the DTaP/Hib combination vaccines in that country (von Kries et al., 1997). The effect of the booster dose might not only be related to better protection of the individual child given the booster dose but also to a higher level of herd immunity, as the booster dose further reduces asymptomatic carriage of Hib (Zepp et al., 1997). Actual data on Hib carriage rates and vaccinations status are scarce for Germany. Presently available unpublished data indicate that Hib carriage in school age children is close to 0% (Dr. Britta Gröndahl, National *H. influenzae* Reference Centre at the

Department of Paediatric Infectious Diseases, Johannes-Gutenberg-University, Mainz, personal communication, 2005).

The recommended age for the primary series is identical in the UK and Germany, but considerable delay in vaccine administration has been observed in Germany (Laubereau et al., 2001; Kalies et al., 2006). In the subcohort described here, the median age at completion of the primary series of hexavalent combination vaccines was 6.0 months. It has been suggested that immune memory may increase with age at vaccination and with longer intervals between doses (Zepp et al., 1997; Vidor et al., 2001). Thus, the observed delay in the administration of the primary series might further influence vaccine effectiveness and explain the higher vaccine effectiveness in fully primed children in Germany compared with UK. It would have been of interest to investigate effects of age at receipt of primary or booster doses, but the number of immunised children was insufficient to support such estimates.

8.3 Conclusion

With the widespread use and rapid uptake of hexavalent combination vaccines in Germany, no increase in Hib cases, incidences or vaccine failures was found and high vaccine effectiveness against Hib for fully primed as well as for fully immunised children was observed.

The current data are based on a relatively short follow-up after the introduction of hexavalent vaccines. Sustained surveillance of *H. influenzae* type b disease in German children is planned until 2007 and should confirm the protection induced by hexavalent vaccines – especially for fully immunised children. This persistent monitoring of *H. influenzae* cases might appear redundant; however, without monitoring of Hib cases in the UK, the apparent problems related to a vaccination schedule without a booster dose would not have been detected.

9 NOTATION

CI	Confidence interval
DTaP/Hib	Diphtheria, tetanus and acellular pertussis containing Hib vaccine
DTwP/Hib	Diphtheria, tetanus and whole cell pertussis containing Hib vaccine
DTaP-IPV/Hib	DTaP plus inactivated poliovirus containing Hib vaccine (pentavalent vaccine)
DTaP-IPV-HB/Hib	DTaP-IPV plus hepatitis B containing Hib vaccine (hexavalent vaccine)
EMEA	European Agency for the Evaluation of Medicinal Products
ESPED	'Erhebungseinheit für seltene pädiatrische Erkrankungen in Deutschland'
Hi	*Haemophilus influenzae*
Hib	*Haemophilus influenzae* type b
PCR	Polymerase Chain Reaction
RR	Relative risk
STIKO	'*Ständige Impfkommission am Robert Koch-Institut*'; German Vaccine Advisory Board
UK	United Kingdom
US	United States
VE	Vaccine effectiveness

10 LITERATURE

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and all reporting paediatricians and interviewed parents for their time and efforts in fulfilling report cards / questionnaires or answering to telephone calls.

12 DECLARATION OF ORIGINALITY

I hereby declare that this study is an original study based on my own work and that I have not submitted it for any other course of degree. All quotations and paraphrases from other sources have been duly acknowledged by citation marks and in the reference list.

In detail, I have made the following substantial contributions to the study:

- Conception and design of the study
- Drafting of study protocols and contracts with sponsors (Glaxo SmithKline, Biologicals, Rixensart, and SanofiPasteur MSD, Lyon) and executing institutes (tns Healthcare)
- Coordination and supervision of the ongoing study
- Acquisition and management of the data
- Statistical expertise, analysis and interpretation of the data
- Drafting of the manuscript

Helen Kalies, July 2006

13 CURRICULUM VITAE

Name	Helen U. Kalies
Nationality	German, English
Date of birth	25.09.1970
Place of birth	London

Schooling

1973 - 1974	Ipstock Place School, London
1977 - 1981	Primary school Gauting
1981 - 1990	Otto-von-Taube Gymnasium Gauting Abitur =general qualification for university entrance (Grade: 1.8)

Tertiary education

1990 - 1996	Biology at Ludwig Maximilian University (LMU), Munich Diploma thesis at Max Planck Institute for Behavioural Physiology, Seewiesen Diploma examination (Grade: 1.1)
1997 - 1999	Public Health and Epidemiology, post-graduate study at LMU Munich Master thesis at the Department of Cardiology, 'Klinikum Innenstadt', Munich Master examination (Grade: 1.3)

Professional life

1999 - 2000	Scientist at tumour registry of LMU Munich: principal investigator of the study ‚*quality assessment of regional medical care in patients with rectum carcinoma (field study rectum carcinoma)*'.
since 1/2001	Scientist at Department of Epidemiology, Institute for Social Paediatrics and Adolescent Medicine, LMU Munich: principal investigator of the study ‚*Active surveillance of invasive Haemophilus influenzae disease in Germany: a study through the ESPED reporting system*', principal investigator of the study ‚*Use of health insurance data to estimate vaccination coverage in German children*' and of studies concerning health issues in children.

Awards

1999	‚*Bavarian Public Health – Lion*' for the best master theses
2004	‚*Best poster presentation*' of the Deutschen Gesellschaft für Pädiatrische Infektologie (DGPI) (see chapter 14, C13)
2005	'*Best poster presentation*' of the European Society for Pediatric Infectious Diseases (ESPID) (see chapter 14, C18)

Private life

Ski-touring, long-haul journeys, photographing
from 1993 to 1998 hut guardian, from 1999 to 2001 president of *‚Akademischer Skiclub München (ASCM)*'; since 2002 touring guide of the German Alpine Club

14 PUBLICATION LIST

A. Original papers

A1 Klauss V, Pethig K, Kalies H, Pichelmayer E, Heublein B, Rieber J, Spes CH, Reichart B, Siebert U, Haverich A, Mudra H. Intravascular ultrasound has a prognostic impact after heart transplantation: A multivariable analysis in a large patient cohort. J Heart Lung Transplant 1999; 18: 60.

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C2 Kalies H, Siebert U, Pethig K, Heublein B, Rieber J, Spes CH, Pichlmayer E, Reichart B, Haverich A, Mudra H, Klauss V. Prognostic model for cardiac events after heart transplantation using intravascular ultrasound in a large patient cohort. Public Health – Entwicklungen und Potentiale, Freiburg i.B. 6.-8.10.1999. Das Gesundheitswesen, 1999; 61: A184.

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C6 Siebert U, Kalies H, Pethig K, Pichlmayer E, Rieber J, Spes CH et al. Selection of optimal IVUS parameter for risk assessment in patients after heart transplantation. European Heart Journal 2000; 21: 90.

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C10 Kalies H, von Kries R. Durchimpfungsraten in den Schuleingangsuntersuchungen 1997-2000 in Bayern. Kinder- und Jugendmedizin 2002; 2: A19-A198.

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C12 Kalies H, Meyer N, Siedler A, H-J Schmitt, von Kries R. Effectiveness of DTPa / Hib and DTPa-IPV / Hib combination vaccines in Germany: four year follow-up. Annual meeting of the European Society for Pediatric Infectious Diseases, Sicily, Italy, 2003.

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C14 Kalies H, Gröndahl B, von Kries R, Zimmer K, Schmidt L, Rockahr S, Siedler A, Weißmann B, Heinrich B, H-J Schmitt und die ESPED Arbeitsgruppe. Invasive *Haemophilus influenzae* Infektionen bei Kindern in Deutschland: Ergebnisse der ESPED-Studie von 1998 bis 2002. 56. Jahrestagung der Deutschen Gesellschaft für Mikrobiologie und Hygiene, Münster, Germany, 2003.

C15 Steinmann A, Höppe P, von Kries R, Wanka E, Kalies H, Liebl B, Nowak D. UV-Strahlung im Kindesalter – Risiko, Risikowahrnehmung, Schutzverhalten. Allergo J 2004; 13.

C16 Kalies H, Grote V, Schmitt H-J, von Kries R. Durchimpfungsraten bei Kindern in Deutschland: Status quo und Trends. Symposium der Stiftung Kindergesundheit, des

Bayerischen Staatsministeriums für Umwelt, Gesundheit und Verbraucherschutz und des Klinikums der Universität München: Prävention von Anfang an - Wunsch und Wirklichkeit. München, 2004.

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C18 von Kries R, Reinert RR, Siedler A, Arenz S, Toschke AM, Kalies H. 7–valent pneumococcal vaccination: impact of the German at-risk strategy. Annual meeting of the European Society for Pediatric Infectious Diseases congress, Valencia, Spain, 2005. (awarded with 'best poster presentation')

C19 Kalies H, Grote V, Schmitt H-J, von Kries R. Did the introduction of combination vaccines improve on-time immunisations in children? Annual meeting of the World Society for Pediatric Infectious Diseases congress, Warsaw, Poland, 2005.

C20 von Kries R, Kalies H. Wirksamkeit von Kombinationsimpfstoffen gegen invasive *Haemophilus Influenzae* Type b Erkrankungen bei Kindern in Deutschland. Kinderärztekongress der Deutschen Gesellschaft für Kinder- und Jugendmedizin, Bremen, Germany, 2005.

C21 Arenz S, Kalies H, Toschke AM, Al-Lahham A, Siedler A, Reinert RR, von Kries R. Causes for a poor effectiveness of an at risk strategy for 7-valent pneumococcal vaccination in Germany. Annual meeting of the European Society for Pediatric Infectious Diseases congress, Basel, Switzerland, 2006.

C22 Kalies H, von Kries R. Use of health insurance data to estimate vaccination coverage in Germany. Annual meeting of the European Society for Pediatric Infectious Diseases congress, Basel, Switzerland, 2006.

D Diploma and master thesis

D1 Kalies H. Diploma thesis (Max-Planck-Institut für Verhaltensphysiologie Seewiesen). Werbung während der Eiablage - lästig und vermeidbar? Eine Verhaltensstudie an der Kleinlibelle Calopteryx virgo. 1996. (Grade: 1.0)

D2 Kalies H. Master thesis (Ludwig-Maximilians-Universität München). Prädiktive Wertigkeit von IVUS-Parametern für kardiale Ereignisse bei Patienten nach Herztransplantation. Ein Beitrag zu Health Technology Assessment. 1999. (Grade: 1.0; awarded with ‚Bavarian Public Health Lion' for the best master thesis 1999)

15 ANNEX

15.1 Questionnaires

Annex A.1: Monthly report card used by Clinical ESPED

ESPED – Meldekarte **März 1999**

Bitte **A n z a h l** Erkrankungen eintragen!

1. Multiple Sklerose / ADEM . . . . . ☐
2. Transientes Myeloproliferatives Syndrom bei NG mit M. Down . . . . ☐
3. Erstmanifest. Diab. mell. bei Kind unter 5 Jahren . . . . . ☐
4. Haemophilus influenzae-Infektionen . . . . . ☐
5. Organoazidopathien und Fettsäurenoxidationsdefekte. . . . . ☐
6. Vit.-K-Mangelblutungen . . . . . ☐
7. Neonatale Pilzsepsis . . . . . ☐
8. Systemische Pneumokokken-Infektionen . . . . . ☐
9. Pertussis-Komplikationen. . . . . ☐
10. Seröse Meningitis nach MMR-Impfung . . . . . ☐
11. Sinusvenenthrombose oder Ischämischer Schlaganfall . . . . . ☐
12. Hämolytisch-Urämisches Syndrom (HUS) . . . . . ☐

Keine der obigen Erkrankungen beobachtet: (Bitte ankreuzen!) . . . . . ☐

Erhebungseinheit für seltene pädiatrische Erkrankungen in Deutschland

ESPED – Meldekarte **März 1999**

Dieser Abschnitt ist für Ihre Unterlagen bestimmt!

(Tragen Sie hier Ihre Fallmeldungen ein; zur Identifikation eventuell mit Art der Erkrankung, Namen, Patientennr., Geb.-Datum u.ä.)

Bei Problemen und Unklarheiten sind wir für eine telefonische Rücksprache mit der Studienleitung dankbar.

ESPED-Tel.-Nr. 0211/81-16263 Fax: 0211/81-16262

Datei: ESPRUECK.DOC e-mail: esped@rz.uni-duesseldorf.de

Annex A.2: Questionnaire used by Clinical ESPED

Erhebungseinheit für seltene pädiatrische Erkrankungen in Deutschland

Forschungsstelle für pädiatrische Epidemiologie bei der Deutschen Gesellschaft für Kinderheilkunde und Jugendmedizin

Invasive *Haemophilus influenzae*-Infektion (Kinder < 16 Jahre)

ESPED Arbeitsgruppe der Kinderklinik der Heiunrich-Heine-Universität Düsseldorf Postfach 10 22 44 **40013 Düsseldorf**		⇦ ***Rücksendung an nebenstehende Adresse erbeten***
		Klinik-IDNO: ..... ESPED-LNR: ..... Aussendedatum: 13.10.2005 *Wird von ESPED ausgefüllt!* Eingangsdatum: .....

Berichtende Kinderklinik: Ansprechpartner für Rückfragen:
.....
..... Tel.:

..... Fax:

PATIENTENDATEN

Patienteninitialen: I_x_I____I / I_x_I____I Geburtsdatum: I____I . I_____I
2. Buchstabe *Familienname* *Vorname* *Monat* *Jahr*

Geschlecht: ○ weiblich Nationalität des Kindes: ○ deutsch
○ männlich ○ andere: .....

STATIONÄRE AUFNAHME I____I . I____I . I_____I

LOKALISATION

❍ Meningitis ❍ Epiglottitis ❍ Pneumonie
❍ sept. Arthritis ❍ Osteomyelitis ❍ Bakteriämie ohne Fokus
❍ sonstige, *welche*:.....

Kultureller Nachweis in: ❍ Blut ❍ Liquor ❍ sonstiges.....
Nachweis am: I____I . I____I . I_____I
Untersuchungsnr.:.....

ß-Lactamase-Bildner: ❍ ja ❍ nein ❍ nicht geprüft

SEROTYPISIERUNG

❍ Serotypisierung wurde nicht angestrebt
❍ erfolgte in dem Labor, in dem der Keim angezüchtet wurde
Name/Adresse des Labors: .....
❍ Keime weiterversandt
Name/Adresse des Labors: .....

Ergebnis der Typisierung

❍ Nicht typisierbar
❍ Typ b
❍ nicht Typ b, sondern: ❍ a ❍ c ❍ d ❍ e ❍ f ❍ a – f negativ

HIB-IMPFUNG

❍ ja ❍ nein

Name/Anschrift des Impfarztes:.....

	Datum (Tag/Monat/Jahr)	Name des (Kombinations-)Impfstoffes, Charge
1. Impfung:	I____I . I____I . I_____I	.....
2. Impfung:	I____I . I____I . I_____I	.....
3. Impfung:	I____I . I____I . I_____I	.....
4. Impfung:	I____I . I____I . I_____I	.....

Impfdaten erhoben aus:

❍ Elternbefragung ❍ Einsicht in Impfausweis ❍ Anruf beim Impfarzt

Wenn Haemophilus influenzae Typ B nachgewiesen und das Kind vollständig Hib-geimpft ist:

Wurde eine immunologische Abklärung durchgeführt?

❍ nein

❍ ja, welche:.....

ANAMNESE

Bestehen anamnestische Auffälligkeiten ? ❍ ja ❍ nein

Wenn ja, welche:

❍ Frühgeburt in der I___I___I. SSW

❍ erhält immunsupressive Therapie *welche:*.....

❍ bekannter Immundefekt *welcher:* .....

❍ angeborene Anomalien *welche:* .....

❍ Chromosomenaberration *welche:* .....

❍ sonstiges .....

ERGEBNIS

❍ Unklar (Befunde stehen noch aus)

❍ Völlige Ausheilung

❍ Hörvermögen: ❍ normal ❍ pathologisch ❍ nicht geprüft

❍ Überleben mit Restschäden (außer Hörvermögen), *welche*: .....
.....
.....

❍ Tod

Annex A.3: Monthly report questionnaire used by Laboratory ESPED

Falldefinition: **Anzucht aus *physiologisch sterilem Substrat (wie Blut, Liquor, Punktat)***		
bei Kindern < 16 Jahre ***Streptococcus pneumoniae*** ja ☐ nein ☐	bei Kindern < 16 Jahre ***Haemophilus influenzae*** ja ☐ nein ☐	bei Säuglingen < 4 Monate ***Streptococcus agalactiae*** ja ☐ nein ☐
Wenn nein, bitte Bogen trotzdem zurück! ***Wenn ja, bitte Bogen weiter ausfüllen:***		
Anzahl Kinder mit	**Streptococcus pneumoniae** _____ **Haemophilus influenzae** _____ **Streptococcus agalactiae** _____	
Für jedes Kind mit Befund aus o.g. sterilen Untersuchungsmaterialien werden folgende Angaben erbeten (weitere Bögen bitte unter o.a. Fax- bzw. Tel-Nr. anfordern oder kopieren):		
Ihre ***Untersuchungsnummer*** _____		
Vorname / Name (jeweils ***zweiter*** Buchstabe)	|_X_|___| / |_X_|___|	
Geschlecht	mnl. ☐ wbl. ☐ unbek. ☐	
Geburtsdatum (Monat und Jahr)	|_XX_| . |___| . |_____|	
Wohnort-PLZ (erste 3 Ziffern)	|___|___|___|_X_|_X_|	
Probenmaterial: **1** Blut **2** Liquor **3** Pleura-Punktat **4** sonstiges (bitte angeben)	1 ☐ 2 ☐ 3 ☐ 4 ☐→ _____	
Eingangsdatum der Probe	|___|. |___|. 2001	
Herkunft der Probe: **1** Kinderklinik **2** sonst. Klinik **3** niedergel. Arzt	1 ☐ 2 ☐ 3 ☐	
Materialeinsendung zur Typisierung und Resistenzbestimmung – Stämme von ...		
Strep. pneum. an NRZ Aachen ja ☐ nein ☐	Haem. infl. an Labor Kiel ja ☐ nein ☐ wenn ***nein***: Kapseltyp |___|	Strep. agalac. an Labor Freiburg ja ☐ nein ☐

15.2 Sensitivity analyses of vaccine effectiveness calculations

15.2.1 Inclusion of children with mixed vaccine schedules

Table A.1: Vaccine effectiveness of DTaP-IPV-HB/Hib vaccines against invasive *H. influenzae* type b disease (completeness of vaccination schedule). Inclusion of children with mixed vaccine schedules.

Completeness of vaccination schedule	N cases	Parameter estimate (ß)	Standard error	Vaccine effectiveness*	95% CI
No vaccination	17	0**	-	0.0%**	-
Incomplete primary series	5	-1.55792	0.53006	78.9	40.5-92.6
Full primary series	5	-2.62887	0.59257	92.8	77.0-97.7
2nd year dose, but not fully immunised	0	-17.23215	0.45387	100.0	99.5-100.0§
Full immunisation	0	-17.20428	0.43417	100.0	99.8-100.0§

* $(1-e^{ß}) \times 100\%$
** reference category
§ binominal exact confidence intervals

Table A.2: Vaccine effectiveness of DTaP-IPV-HB/Hib vaccines against invasive *H. influenzae* type b disease (age-eligibility of vaccination schedule). Inclusion of children with mixed vaccine schedules.

Age-eligibility of vaccination schedule	N cases	Parameter estimate (ß)	Standard error	Vaccine effectiveness*	95% CI
Not according to schedule	23	0**	-	0.0%	-
according to schedule	4	-2.61151	0.57835	92.7	77.2-97.6

* $(1-e^{ß}) \times 100\%$
** reference category

15.2.2 Inclusion of children with untyped invasive H. influenzae disease

Table A.3: Vaccine effectiveness of DTaP-IPV-HB/Hib vaccines against invasive *H. influenzae* type b disease (completeness of vaccination schedule). Inclusion of children with untyped invasive *H. influenzae* disease.

Completeness of vaccination schedule	N cases	Parameter estimate (ß)	Standard error	Vaccine effectiveness*	95% CI
No vaccination	17	0**	-	0.0%**	-
Incomplete primary series	5	-1.53921	0.50822	78.5	41.9-92.1
Full primary series	5	-2.57921	0.54595	92.4	77.9-97.4
2nd year dose, but not fully immunised	0	-1.42091	1.13766	75.9	0.0-98.4
Full immunisation	0	-16.58641	0.38481	100.0	100.0-100.0§

* $(1-e^{ß}) \times 100\%$
** reference category
§ binominal exact confidence intervals

Table A.4: Vaccine effectiveness of DTaP-IPV-HB/Hib vaccines against invasive *H. influenzae* type b disease (age-eligibility of vaccination schedule). Inclusion of children with untyped invasive *H. influenzae* disease.

Age-eligibility of vaccination schedule	N cases	Parameter estimate (ß)	Standard error	Vaccine effectiveness*	95% CI
Not according to schedule	23	0**	-	0.0%	-
according to schedule	4	-2.57842	0.500735	92.4	79.5-97.2

* $(1-e^{ß}) \times 100\%$
** reference category

15.2.3 Inclusion of children with untyped invasive H. influenzae disease and mixed vaccine schedules

Table A.5: Vaccine effectiveness of DTaP-IPV-HB/Hib vaccines against invasive *H. influenzae* type b disease (completeness of vaccination schedule). Inclusion of children with untyped invasive *H. influenzae* disease and mixed vaccine schedules.

Completeness of vaccination schedule	N cases	Parameter estimate (ß)	Standard error	Vaccine effectiveness*	95% CI
No vaccination	17	0**	-	0.0%**	-
Incomplete primary series	5	-1.69682	0.51195	81.7	50.0-93.3
Full primary series	5	-2.71082	0.53963	93.4	80.9-97.7
2nd year dose, but not fully immunised	0	-1.69318	1.14343	81.6	0.0-98.0
Full immunisation	0	-16.60254	0.39130	100.0	100.0-100.0§

* $(1-e^{ß}) \times 100\%$
** reference category
§ binominal exact confidence intervals

Table A.6: Vaccine effectiveness of DTaP-IPV-HB/Hib vaccines against invasive *H. influenzae* type b disease (age-eligibility of vaccination schedule). Inclusion of children with untyped invasive *H. influenzae* disease and mixed vaccine schedules.

Age-eligibility of vaccination schedule	N cases	Parameter estimate (ß)	Standard error	Vaccine effectiveness*	95% CI
Not according to schedule	23	0**	-	0.0%	-
according to schedule	4	-2.59458	0.50875	92.5	79.8-97.2

* $(1-e^{ß}) \times 100\%$
** reference category