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INFECTIOUS DISEASES

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# *Haemophilus influenzae* b-vaccination: the urgency for timely vaccination

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**Abstract** In Germany the annual number of systemic *Haemophilus influenzae* cases in unvaccinated children aged 3–60 months has recently been exceeded by the number of cases in children vaccinated at least once with the PRP-D, HbOC or OMP vaccines, which until 1995 have almost exclusively been used for *H. influenzae* b (Hib) vaccination. Most of the vaccinated children however could already have had more vaccinations at onset of disease. How much does an age-related suboptimal vaccination status increase the risk for systemic *H. influenzae* infections? A case control study was performed in West Germany. Cases with systemic *H. influenzae* infections were ascertained between 7/92 and 8/94 with an ongoing active hospital surveillance programme. Six age-matched population controls per case were recruited at random. Only vaccinated cases and controls were included in the study. The main exposure analysed in this study was suboptimal vaccination at censoring; for censoring ages (age at disease onset in cases and corresponding age in matched controls) > 6 months: one vaccination in 1st year only; > 18 months: two (three for combined vaccines with Hib + DT or DPT in one syringe) vaccinations in the 1st year of life but no booster vaccination. Suboptimal vaccination for age increased the risk for systemic *H. influenzae* infections by a factor of 4.74 (95%-CI 2.17–10.34). Following adjustment for confounders the odds ratio was 4.39 (95%-CI 1.74–11.07). Subgroup analyses showed that this risk was not related to the type of vaccine used. The risk for "no booster vaccination" in children aged > 18 months appeared even greater than the risk associated with one vaccination in the 1st year only.

**Conclusions** On schedule and complete Hib vaccinations are essential for an optimal effectiveness of Hib vaccination programmes. Booster vaccinatons between 12 and 18 months are important if the PRP-D, HbOC and OMP vaccines are used for primary vaccination.

**Key words** Vaccination · *Haemophilus influenzae* b vaccines · Vaccine efficacy · Compliance with vaccination schedules · Case control study

**Abbreviations** *DPT* diphteria pertussis tetanus · DT diphteria tetanus · *Hb-OC* Hib polysaccharide and diphtheria CRM 197 protein conjugate · Hib *Haemophilus influenzae* b · *IgG* immunglobulin G · OR odds ratio · *PRP-D* Hib polysaccharide conjugated to diphtheria toxoid · *PRP-OMP* Hib polysaccharide covalently bound to *Neisseria meningitidis* outer membrane protein complex

## Introduction

The introduction of *Haemophilus influenzae* b (Hib) vaccination programmes has dramatically reduced the rate of systemic Hib infections in several populations [1, 3, 5, 11, 13]. The annual number of systemic *H. influenzae* infections in non Hib vaccinatated children in Germany in the age spectrum from 3 months to five years was only 23 in a population of about 4 million children under the age of five from July 94 to June 95 [8]. This number was clearly exceeded by 33 cases in children, who had been vaccinated at least once. According to the national recommendations most of these cases however could already have had at least one further vaccination, at onset of disease.

How much does a suboptimal age related vaccination status increase the risk for systemic Hib infections? A

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case control study was carried out in Germany to anwer this question.

## Methods

Cases have been reported in a national active surveillance programme for systemic *H. influenzae* infections in Germany [16]. The case definition required the typical clinical condition in the form of epiglottitis plus culture-isolation of *H. influenzae* from an intratracheal or throat swab or blood culture and the culture isolation of *H. influenzae* from a physiologically sterile site for all other conditions. Serotyping was recommended but not mandatory.

For the cases included in this study the following criteria were met: at least one vaccination > = 14 days before onset of the disease, age < 10 years and treatment in a hospital in one of the federal states of the former Republic of West Germany. The hospital physicians, who had treated these cases were asked to invite the respective parents to collaborate in this study. By consent these parents revealed their identity and telephone number to the study group.

Six age-matched controls per case were recruited with the help of the local government offices for registration of residents from a municipality in the former Republic of West Germany. The municipality was selected at random with use of a population weighted sampling scheme to account for differences in the population sizes of the different municipalities. The respective parents of the selected controls were invited to collaborate in the study.

The data on the vaccination status including the type of vaccine used were obtained using a questionnaire. The vaccination status on the date of onset of illness and on the same date in the respective age-matched controls was assessed. The parents' report of the vaccination status was verified by an additional telephone interview with the physician who had carried out the vaccinations. Additional information on potential confounders e.g. the number of children and smoking habits in the household, parent social status and prematurity was collected on the questionnaire.

All telephone interviews were carried out by two persons who were not aware of the study hypothesis (they believed the purpose of the study was to find out differences in the efficacy of Hib vaccines used in Germany).

The following case definitons for suboptimal (delayed) vaccination were used: one vaccination within the 1st year of life only and censoring age (defined by the age at onset of patient illness and the same date in the corresponding age matched controls) > 6 months; or two (three for combined Hib + DT or DPT vaccines) vaccinations within the 1st year of life and censoring age > = 18 months. The German recommendations are to vaccinate twice within the first 6 months (three vaccinations for combined Hib + DT or DPT vaccines) and to give a booster vaccine between the 14th and the 18th month [17]. For children not vaccinated in the 1st year one vaccination in the 18th month or later is recommended [18].

All children who had been vaccinated at least once and who were younger than 6 months at censoring and those who had been vaccinated two or three times within the 1st year of life and were less than 18 months old at censoring and those who had received one vaccine in the 18th month or later or two or three vaccines in the 1st year plus a boster in the 2nd year of life at any censoring time were considered to be optimally vaccinated for their age.

The risk of systemic *H. influenzae* infections in children with a suboptimal vaccination status for their age was compared with the risk of disease in those with an optimal age-related vaccination status. The respective odds ratios (OR) for suboptimal vaccination for age in uni- and multivariate conditional logistic regression models using age as the matching variable were calculated in SAS release 6.11 (Proc PHREG). Because of inconstant numbers of matching controls m:n matching was used.

The selection of confounders for the multivariate regression model was carried out according to standard criteria [4, 15]. The criteria for the inclusion of covariates as confounders in the final logistic regression model were: (1) prior considerations; (2) "significant" ($P < 0.2$; Fisher's exact test, $\chi^2$ test or Wilcoxon's rank sum test) associations with both the exposure and outcome and an at least 5% change in crude OR when the covariates were introduced into the logistic regression model or an at least 10% change in crude OR in the logistic regression model irrespective of associations in the tests for independence and (3) significant associations with the outcome only ($P < 0.1$) in the uni- and multivariate analyses.

## Results

Of 212 cases reported in the study region from July 1992 to August 1994, 61 had been vaccinated (Table 1). Serotyping had been performed in 17 of the cases. In 14 of these, serotype b was confirmed and there were 3 non b serotype cases (type a, f and one uncapsulated case). Two additional cases in children with immundeficiency syndromes (one case with IgG 2 deficiency and common variable immundeficiency each), had to be excluded from further anlyses. The confirmed serotype b cases and the non serotyped cases were invited for the study. Informative questionnaires were returned for 50 of 56 cases (89%). The response in controls was lower: out of 342 invited controls 215 completed the questionnaire (63%). Of these controls 174 were vaccinated and had matching cases and could therefore be included in the further analyses.

The distribution of the potential confounders in the informative cases and controls is demonstrated in Table 2. The matching variable age was slightly higher in cases than than in controls (median/quartiles in cases: 16.8 months/9.8 and 20.8; in controls: 16.3/9.0 and 20.8) due to chance (for small communities children with the closest date of birth within a 3-month margin were selected) and due to relatively more controls for younger cases respectively. The vaccinated cases and controls were very similar with respect to sex, use of antibiotics to date and the use of day care or nursery school. There were more premature deliveries, multiple births and children sharing the bedroom with other children among the cases, whereas breastfeeding was more common in controls. Smoking was more common in the affected families as were more persons/children living in house-

**Table 1** Selection of cases and controls

| Population | *n* |
|---|---|
| Cases reported in ESPED (07/92–08/94) treated in West Germany | 212 |
| – vaccinated cases | 61 |
| – excluded (immundeficiency syndroms) | 2 |
| – not elegible (non b cases) | 3 |
| → invited cases for study | 56 |
| – informative questionnaires | 50 |
| Invited controls for study | 342 |
| – informative questionnaires | 215 |
| – vaccinated controls | 183 |
| – no matching case | 9 |
| Cases/controls included in study | 50/174 |

**Table 2** Distribution of covariables, considered as potential confounders

| Covariables | Cases | | Controls | |
|---|---|---|---|---|
| Age at censoring (median) | 16.8 months | | 16.3 months | |
| Sex (male) | 27 | (54%) | 92 | (53%) |
| Prematures | 3 | ( 6%) | 5 | ( 3%) |
| Multiple births | 4 | ( 8%) | 0 | ( 0%) |
| Breastfeeding (longer than 2 weeks) | 30 | (60%) | 124 | (71%) |
| At least one smoking household member | 23 | (46%) | 55 | (32%) |
| Persons in household, including the case/control (> 3) | 39 | (78%) | 84 | (48%) |
| Number of children <5 years in household, including the case/control: | | | | |
| 1 child | 21 | (43%) | 125 | (72%) |
| 2 children | 20 | (41%) | 44 | (26%) |
| 3 children | 8 | (16%) | 4 | (2%) |
| Sleeping habits: | | | | |
| – own bedroom | 20 | (40%) | 78 | (45%) |
| – parents' bedroom | 13 | (26%) | 61 | (35%) |
| – bedroom shared with other children | 17 | (34%) | 34 | (20%) |
| Day care or nursery school | 14 | (28%) | 39 | (23%) |
| Highest education level of either parent: | | | | |
| – no or lowest school leaving certificate | 13 | (26%) | 33 | (19%) |
| – qualified for college study | 24 | (49%) | 76 | (44%) |
| – qualified for university study | 12 | (25%) | 64 | (37%) |
| Antibiotics in previous year: | | | | |
| – up to two times | 41 | (82 %) | 142 | (85%) |
| – up to three times | 6 | (12%) | 15 | ( 9%) |
| – more than three times | 3 | ( 6%) | 11 | ( 6%) |
| Type of vaccine: | | | | |
| – PRP-D | 41 | (82%) | 143 | (82%) |
| – OMP | 1 | ( 2%) | 16 | ( 9%) |
| – HbOC | 8 | (16%) | 15 | ( 9%) |

holds and parents with low education levels. The proportion of cases and controls vaccinated with PRP-D vaccine was identical, whereas there were fewer cases vaccinated with the OMP vaccine and a higher proportion vaccinated with the HbOC vaccine.

Of the informative cases 34 had meningitis, 7 epiglottitis and 9 had other sites of infection (e.g.cellulitis, septicaemia and arthritis). Of the cases 14 had only been vaccinated once, 25 twice and 2 three times in the 1st year of life. Only one case was observed in a child given an additional booster vaccination. Five cases occurred after one dose given in the 2nd year and the vaccination status of three cases did not fit into this pattern (Table 3).

Being suboptimally vaccinated for the respective age increased the risk of systemic *H. influenzae* infections by a factor of 4.74 (Table 4). When several confounders were included in the conditional logistic regression model the OR was 4.39. The potential confounders included in the model were: sex, age and prematurity because of prior biological/medical considerations and multiple births, smoking in household, numbers of persons in household, breastfeeding > 2 weeks, own bedroom, number of children younger then 5 years in

**Table 3** Infection site in cases vaccinated at least once by number and time of the vaccination

| Site of infection | Number and timing of vaccination | | | | | | |
|---|---|---|---|---|---|---|---|
| | $1x \leq 12$ months | $2x \leq 12$ months | $3x \leq 12$ months | $2/3x \leq 12$ months + booster | $1x > 12$ months | other | $\sum$ |
| Meningitis | 13 | 16 | 2 | 0 | 3 | 0 | 34 |
| Epiglottitis | 0 | 3 | 0 | 1 | 2 | 1 | 7 |
| other | 1 | 6 | 0 | 0 | 0 | 2 | 9 |

**Table 4** Influence of a suboptimal vaccination status for age on the risk for systemic *Haemophilus influenzae* infection

| Type of comparison | Cases | | Controls | | Odds ratio | $CI_{95\%}$ (OR) |
|---|---|---|---|---|---|---|
| | Sub-optimally vaccinated | Optimally vaccinated | Sub-optimally vaccinated | Optimally vaccinated | | |
| Univariate analysis: suboptimally vaccinated vs optimally vaccinated | 23 (46%) | 27 (54%) | 35 (20%) | 239 (80%) | 4.74 | 2.17–10.34 |
| Multivariate analysis[a]: suboptimally vaccinated vs optimally vaccinated | 22 (47%) | 25 (53%) | 35 (20%) | 137 (80%) | 4.39 | 1.74–11.07 |

[a]With adjustment for the following covariates: sex, prematures, multiple births, smoking household member, number of persons in household, own bedroom, breastfeeding and number of children under 5 years in household

household because of the statistical considerations outlined in the methods section.

A subgroup analysis by type of vaccine was carried out to assess whether the impact of suboptimal vaccination status for age differed for different vaccines. The number of children given the different vaccines was (cases/controls): PRP-D 149 (36/113) PRP-D combined vaccine (+ DT or DPT) 35 (5/30) Hb-OC 23 (8/15) PRP-OMP 17 (1/16). Due to the small number of cases and controls statistically valid OR's could only be calculated for the PRP-D subgroup: OR 2.24 95% CI 0.65–7.66. In the PRP-D combined Hib + DT or DPT vaccine subgroup the calulations of the OR based on five cases (three exposed two unexposed) gave a 95% CI of 0.98–57.14. The respective 95% CI's for the PRP-OMP vaccine was 0.23–323.4 (based on one case; one exposed, 0 unexposed) and for the Hb-OC vaccine 3.2–556.0 (based on eight cases; six exposed, two unexposed).

An additional subgroup analysis for potentially different effects for omitted second or booster vaccinations was performed. Four cases in children vaccinated once in the 1st year of life were observed within the first 6 months whereas eight children were aged 6–18 months and two were older than 18 months. For the children aged 6–18 months 2 or three vaccinations in the 1st year of life would have been considered optimal. The adjusted OR (5.93; 95% CI 1.52–23.06) for omission of the second vaccination did not differ much from that for the whole group (Table 5). Ten cases were observed in children > 18 months (age range 18–24 months), who had been vaccinated two or three times in the 1st year of life and not given a booster vaccination as compared to one case with an additional booster. The OR for the omission of the booster vaccination in children aged > 18 months was 24.38; 95% CI 4.70–126.5.

## Discussion

A lower vaccine efficacy related to an incomplete as compared to a complete Hib vaccination status is well known [6, 13, 19]. An incomplete Hib vaccination status however may either be an inherent problem of the vaccination protocol or to noncompliance with the protocol. This important distinction has never been made yet. A child aged 3 months e.g. can hardly be vaccinated more than once and an Hib infection acquired by this child cannot be attributed to a non- optimal age related

**Table 5** Impact of suboptimal vaccination on the risk for systemic *Haemophilus influenzae* infections at different ages by numbers of vaccinations

| Type of comparison | Age[a] | Cases | | Controls | | Odds ratio | $CI_{95\%}$ (OR) |
|---|---|---|---|---|---|---|---|
| | | Sub-optimally vaccinated | Optimally vaccinated | Sub-optimally vaccinated | Optimally vaccinated | | |
| 1x vaccinated in 1. year of life vs | 6–18 months | 8 (32%) | 17 (68%) | 9 (11%) | 75 (89%) | 4.55[b] | 1.47– 14.10 |
| 2/3x vaccinated in 1. year of life | | 8 (33%) | 16 (67%) | 9 (11%) | 74 (89%) | 5.93[c] | 1.52– 23.06 |
| 2/3x vaccinated in 1. year vs 2/3x vaccinated in 1. year +booster | > 18 months | 10 (91%) | 1 ( 9%) | 16 (29%) | 39 (71%) | 24.4[d] | 4. 7–126.5 |

[a]Age at censoring
[b]Calculation with univariate conditional logistic regression
[c]Calculation with conditional logistic regression, adjusted for confounders (same as in table 4) sex, prematures, multiple births, smoking household member, number of persons in household, own bedroom, breastfeeding and number of children under 5 years in household
[d]Unstratified Mantel-Haenszel analysis

vaccination status. A child aged 11 months with one Hib vaccination only however is not optimally vaccinated for it's age and a *Hib* infection in this child might have been prevented with an optimal age related vaccination status. A child aged 12 months cannot have more than the basic immunisations whereas a child aged from 18 months onwards should have had the booster vaccination. A *Hib* infection in the first case cannot be attributed to a suboptimal vaccination status for age, whereas an infection acquired in the latter case might have been prevented with an optimal vaccination status for age.

In 1994 we reported an unexpectedly high number of *H. influenzae* meningitis cases in incompletely vaccinated children in Germany [9]. Further analysis of the data from ongoing surveillance for systemic *H. influenzae* infections during a 3-year observation period has consistently shown that 50%–80% of the *H. influenzae* infections in partially vaccinated children were related to a suboptimal vaccination status for age [8].

The results of the case control study demonstrate that this high proportion of suboptimally vaccinated cases with systemic *H. influenzae* infections does not only reflect the size of the risk population of suboptimally Hib vaccinated children but also a considerable risk of a suboptimal vaccination status for age.

Some overestimation of the risk due to a lower compliance in the controls than in the cases cannot be definitely excluded. Data on all potential confounders considered in previous case control studies on the Hib vaccine efficacy [7, 19, 21] were collected in this study and included in the final analyses if appropriate. Several of these potential confounders were associated with a suboptimal vaccination status. Adjustment for these confounders accounted only for a minor decrease of the odds ratio for a suboptimal Hib vaccination status.

Underestimation of the risk from these data appears more likely, however. Some of the non serotyped systemic *H. influenzae* infection cases might have been caused by non b serotypes or uncapsulated *H. influenzae* accounting for a bias towards unity although the serotyping results suggest that the proportion of non-b serotypes among the non serotyped cases is unlikely to exceed 20%. Further bias towards unity might arise from the slightly older age in cases as compared to controls.

Major efforts were made to minimise information bias: the interviewers were unaware of the study hypotheses and the information on the vaccination status was obtained from two independent sources (the parents and the doctor who had vaccinated the child).

There is biological evidence for the plausibilty of these findings from the time course of protective Hib antibody titres following one or two basic vaccinations [13].

In the subgroup analyses of the vaccine-type we had expected to find the strongest effect of a suboptimal vaccination status on the risk for systemic *H. influenzae* infections in the PRP-D subgroup: The PRP-D vaccine is less immunogenic than the other Hib vaccines marketed in Germany [10] and the effect of the PRP-D vaccine in a high risk group (Alaska natives) has been low [20] whereas OMP vaccine proved very effective, even with only two vaccinations given within the 1st 6 months of life in Navajo indians, another high risk group [14]. The risk in the PRP-D subgroups was not particularly high, and was even exceeded by the effects found in the HbOC subgroup. All these subgroup analyses however must be interpreted with care due to the small number of cases. At least the results do not suggest, that the effect of a suboptimal Hib vaccination status is confined to children vaccinated with the PRP-D vaccine.

Another unexpected finding was the high risk attributable to "no booster vaccination" in children aged 18 months or older although again the number of cases was low. In England the Hib vaccination schedule with 3 Hib vaccinations at 2, 3 and 4 months does not include booster vaccinations. A nationwide surveillance programme for vaccination failures in England is about to be analysed and the results are expected soon [2]. In England however PRP-T is the only vaccine used for Hib vaccinations in the 1st year of life and a confirmation of the adequacy of the English Hib vaccination programme without boostering might not be valid for other vaccines as well.

The practical implications of these findings are that early and complete Hib vaccinations are essential for an optimal effectiveness of Hib vaccination programmes and that booster vaccinations between months 12 and 18 appear to be important at least for the German vaccination schedule with mainly two Hib vaccinations in the 1st year and the use of the PRP-D, HbOC and OMP vaccines. Under the assumption of a 99% vaccine efficacy of an optimal Hib vaccination status, the expected vaccine efficacy (calculated for an OR of 24.4) in children of 18 months or older with only two (three) Hib vaccinations in the 1st year of life and no booster vaccination would be only 75%. Under the assumption of an about 89% vaccine efficacy [6, 13, 19] after two or three Hib vaccinations in the 1st year of life, the expected vaccine efficacy (calculated for an OR of 5.9) in children of 6–18 months vaccinated only once in the 1st year of life would be 35.1%. These vaccine efficacy estimates for suboptimal Hib vaccination for age are considerably lower than the reported estimates for one, two or three Hib vaccinations in the 1st year of life [6, 13, 19].

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