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Haemophilus influenzae type b and cross-reactive antigens in natural Hib infection dynamics; modelling in two populations

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SUMMARY

Natural immunity to *Haemophilus influenzae* type b (Hib) invasive disease is based on antibodies arising in response to encounters with Hib or cross-reactive (CR) bacteria. The relative importance of Hib and CR contacts is unknown. We applied a statistical model to estimate the total rate of immunizing infections of Hib and CR prior to wide-scale vaccinations in Finland and the UK. The average rates of these contacts were 0·7 and 1·2 per year per child in Finland and the UK, respectively. Using a rough estimate of 0·1 Hib acquisitions per year per child in the UK based on carriage rates, the proportion of Hib among all immunizing contacts was in the order of 10%, suggesting that CR bacteria have a major role. In general, varying frequency of CR contacts may explain some differences in the pre-vaccination incidence and age-distribution of invasive disease in different countries.

INTRODUCTION

Haemophilus influenzae type b (Hib) was still the most common cause of invasive disease among children a decade ago. As a result of successful immunization programmes with the Hib conjugate vaccine, Hib disease has nearly been eliminated in a large number of countries, and WHO thus recommends it for consideration worldwide. To anticipate possible long-term effects of Hib conjugate vaccinations, epidemiological information from the pre-vaccination era can be of great value.

The pre-vaccination epidemiology of Hib disease varied considerably between populations [1–3]. In the industrialized world the peak incidence of Hib disease occurred around 12 months of age [4–6]. In developing countries and populations resembling them (Alaskan Inuites, North American Indians) the disease typically took place at an even younger age, the majority (up to 80%) occurring before the first birthday [7–9]. Although meningitis was the most common clinical manifestation world-wide, there were also differences between areas: pneumonia was common in developing countries [10, 11], whereas epiglottitis, with the peak incidence around 3 years of age, was common in industrial countries [5, 6, 12]. The reasons for the differences between populations in the incidence and in the age distribution of invasive Hib disease are not known, but differences in frequency of Hib contacts have been suggested as a possible cause [1, 13].

The present understanding of Hib immunity is based on the inverse relationship between a high serum Hib antibody concentration and a low incidence of invasive Hib disease at the population level. However, it was only after the polyribosylribitol-

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phosphate (PRP) capsular polysaccharide (PS) had been purified and used as a vaccine that protective immunity was conclusively shown to be associated with antibodies to PRP [14–18]. The disease is rare during the first months of life, as long as maternally derived antibodies persist, and starts increasing at approximately 6 months of age when their concentration has decreased to a very low level. Due to immature immunity, children under 18 months of age do not respond effectively to PRP, a T-cell independent antigen [19]. A high force of infection thus directly translates into a high incidence of disease among infants. Later in life the effect of the force of infection on disease incidence is complex: frequent encounters with Hib on the one hand increase the risk of invasive disease, and, on the other hand, contribute to protective immunity by increasing the antibody concentration. We have previously considered such dynamics between the force of infection and population immunity and showed that a high force of infection with sufficiently frequent stimuli of antibody production may in fact contribute to a low incidence of Hib disease [20].

Polysaccharides identical or similar (cross-reactive, CR) to the Hib polysaccharide PRP have been identified in several bacteria and shown to be able to induce protective antibodies to Hib [21–26]. The role of CR bacteria in Hib epidemiology and their effect on the outcome of vaccination interventions in the long run are not known. Mathematical modelling has provided suggestive evidence of the importance of CR bacteria in immunity towards Hib in unvaccinated populations [27]. Coen et al. have also studied the population epidemiology in an area where Hib conjugate vaccines were in wide use and concluded that the observed dramatic decrease in Hib disease incidence could best be explained if a majority of the natural immunizing contacts were attributed to CR bacteria [28].

As both Hib and CR contacts induce production of protective antibodies against Hib a key question concerning immunity focuses on the overall rate of such immunizing contacts. It is also crucial to estimate the proportion of Hib among all immunizing contacts because only contacts with Hib can progress to invasive disease. The impact of these indirect and direct effects of bacterial contacts on disease incidence is fundamental when studying population immunity. We have previously formulated a model for Hib immunity, including the age-dependent capability to respond to encounters with Hib and CR, and the rate of decline of antibodies after such an encounter [29]. In this paper we combine the immunity model and data on disease incidence to estimate the frequency of bacterial contacts with both Hib and CR bacteria that together determine the age-specific pattern of invasive Hib disease. We use a statistical model that treats the occurrence of invasive disease as a marker of susceptibility and thereby links disease to the frequency of immunizing encounters. Previously we have modelled data on invasive Hib disease in Finland [30]. In the present study, we extend the analysis to compare two different populations before the implementation of Hib vaccination: Finland with relatively late occurrence of the disease and the UK where invasive disease was typically seen earlier in life.

MATERIAL AND METHODS

Data

Finnish data on invasive disease

Data on invasive Hib disease were collected in Finland during June 1985–May 1986, before large scale Hib vaccinations started [12]. Ages of invasive Hib cases among children up to 15 years of age were recorded in an intensified surveillance, totalling 197 cases during 1 year. At the time of the surveillance, the size of the birth cohort in Finland was around 60000. In a retrospective review of the laboratory data it was shown that 98% of the diagnostic findings had been notified to the surveillance.

UK data on invasive disease

Prevaccination data on confirmed invasive Hib infections were collected in an enhanced surveillance during October 1990–September 1992 [31]. In this paper we consider cases in children up to 15 years old, totalling 555 cases from the East Anglian, Northern, North Western, Oxford and South Western regions of England during the 2 years. These data will be referred to as the 'UK data'. The cases of invasive Hib disease were related to the population under surveillance by using the 1991 census. The annual birth cohort size in the combined regions was roughly 200000.

In both study populations the annual birth cohort sizes had been approximately constant during the decade preceding the surveys. The annual age-specific incidence of invasive Hib disease had also remained stable over consecutive years in both countries [5, 32]. Due to these relatively constant epidemiological

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conditions, cross-sectional 1-year disease occurrence data (recorded ages) were interpreted as age-related occurrence of disease among a 1-year birth cohort followed in time.

Response to Hib vaccination

Hib antibodies were measured with radioimmunoassay from the sera of 464 children who had been vaccinated with Hib polysaccharide vaccine in an efficacy trial in Finland during 1974–7. The children received the polysaccharide vaccine as a single injection and antibodies were measured 3 weeks post vaccination [18, 33, 34].

Maternally derived antibodies

Hib antibody concentrations were measured with radioimmunoassay from serum samples of unvaccinated children at 2 days, and 2, 3, 4 and 7 months of age ($n = 164, 127, 366, 228, 66$), collected during several immunogenecity studies during recent decades [35–39].

A model for immunity and immunizing infections

Biological definitions and assumptions

The antibodies responsible for protective immunity to Hib are directed against the capsular polysaccharide PRP and referred to as *Hib antibodies*. All bacterial contacts which potentially induce production of Hib antibodies are termed *immunizing contacts*, irrespective of the actual age-specific ability of the child to produce sufficient (protective) quantity of antibodies. The immunizing contacts can be encounters with Hib as well as with bacteria with cross-reactive (CR) antigens. There is both direct and indirect evidence that Hib antibody concentrations above 0·15 μg/ml prevent a Hib contact progressing to invasive disease [21, 34, 40, 41]. This cut-off value of present Hib antibody concentration is used as an indicator of immunity to disease and is referred to as the *presumed protective concentration*. A *susceptible* refers to a child with Hib antibodies below this concentration.

Maternally derived immunity

The child receives antibodies passively from the mother in the later part of pregnancy and thereby may be protected from Hib disease. The duration of this maternally derived immunity was determined experimentally from sera of unvaccinated children. We assumed all Hib antibodies during the first 9 months of life to be of maternal origin, as PRP cannot elicit a response in infants of this age due to immunological immaturity. A logistic regression model with age as an explanatory variable was fitted to the data on antibody concentrations, dichotomized at a cut-off value of 0·15 μg/ml. The model was used to predict the proportion $V(a)$ of children with maternally derived immunity (antibodies $> 0{\cdot}15\,\mu$g/ml) at ages < 9 months.

Immunizing contacts

Recurrent immunizing encounters with Hib or CR bacteria occur as no permanent immunity is assumed to exist against such subclinical infections (carriage). The age-dependent rate of Hib and CR encounters per year per child is denoted by $\lambda(a)$. This rate is conditional on the age of the child and thus represents the age-specific force of infection of immunizing contacts, irrespective of the possibility of transient immunity to carriage.

At Hib or CR encounter, the child produces antibodies and, if their concentration reaches the presumed protective concentration of 0·15 μg/ml, transient immunity against invasive Hib disease is established. It is not possible in practice to obtain data on the age-specificity of antibody responses to subclinical Hib or CR encounters due to the low prevalence of Hib carriage and inability to identify CR stimuli. As a proxy, we therefore used data on antibody concentrations obtained 3 weeks after vaccination with Hib PRP vaccine in infants and young children. The age-specific logarithm of the antibody concentration at response to PRP stimulus was modelled by the following function:

$$R(a) = \left[1 + \eta - \frac{1}{1 - \exp(\varphi a)} \right] + w.$$

The expression in brackets represents the geometric mean response as an increasing function of age a; parameter η is the asymptotic mean response; φ controls the rate of convergence to the asymptotic. The variability in response across individuals is accounted for by w, a zero-mean normally distributed random variable with variance σ^2.

Duration of the acquired immunity after an immunizing contact

Duration of acquired immunity to Hib disease depends on the magnitude of antibody response at a

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contact with Hib or CR bacteria and the subsequent rate of decline of antibody concentration. Based on independence of the response and the rate of decline, a model for the duration of immunity in children $\geqslant 4$ years of age was developed by Auranen et al. [20, 29]. Function $R(a)$ was now used to modify the model to take into account age-dependence in the response of children < 4 years of age. The modified model was then applied to predict the proportion $f(a; u)$ of children susceptible to Hib disease (i.e. with Hib antibody concentration below 0·15 μg/ml) at age a when the latest Hib or CR encounter occurred at age u ($< a$).

Proportions $f(a; u)$ suppose knowledge of the time of the latest encounter with Hib or CR bacteria. Because this could not be observed directly, an expression was derived to determine the proportion of susceptibles that was independent of such information. Consequently, the proportion of susceptibles among children of age a can be presented as follows:

$$V(a) = \int_{0{\cdot}75}^{a} f(a; u) g_a(u) \mathrm{d}u, \quad a > 0{\cdot}75.$$

This is a weighted average of proportions $f(a; u)$, the weighting function $g_a(u)$ being the proportion (probability density) of children of age a whose latest immunizing Hib or CR encounter occurred at age u ($< a$). Function $g_a(u)$ can be expressed in terms of rate $\lambda(a)$:

$$g_a(u) = \lambda(u) \exp\left(-\int_{u}^{a} \lambda(w) \mathrm{d}w\right), \quad 0{\cdot}75 \leqslant u \leqslant a.$$

Due to the inability of infants to respond to polysaccharide antigens, acquired immunity is considered only from age 9 months (i.e. 0·75 years) on. Immunity before 9 months of age is determined by maternally derived antibodies as explained above. The age-dependent ability of a child to respond to Hib antigens as well as the rate of decline of antibodies after such responses were assumed to be similar in both populations.

Incidence of invasive Hib disease

As a rare outcome in a susceptible, an encounter with Hib develops into invasive disease. There is no clear evidence that the chance of any encounter with Hib progressing to disease would depend differentially on age, after a low antibody concentration has been accounted for. Because of this, and in lack of other information, the probability of a Hib contact (when susceptible) to progress into invasive disease was taken to be constant. It is denoted by π.

The rate of Hib-specific encounters is denoted by $\lambda_{\mathrm{Hib}}(a)$. The relative quantity, proportion of Hib in all immunizing contacts, is then $c = \lambda_{\mathrm{Hib}}(a)/\lambda(a)$. We assumed proportion c to be constant across age in the absence of data suggesting otherwise. The incidence rate of Hib disease per year per child can thus be written as $\mu(a) = \pi c V(a) \lambda(a)$, where the rate of Hib and CR encounters is inflated by the probabilities of being susceptible, $V(a)$, for the contact being with Hib, c, and of the contact with Hib progressing to disease, π.

Statistical analysis

The estimation of the model was based on a likelihood expressing the probability density of the observed data under different values of the model parameters. For a single child, the likelihood was comprised of a contribution from the observed age at Hib disease, if at all, and of the 'survival experience' of no invasive disease over the study period. Thus, the individual log-likelihood contribution from child i who contracted invasive Hib disease at age a_i was

$$\begin{aligned} \log L_i &= \log \mu(a_i) - \int_0^T \mu(w) \mathrm{d}w \\ &= \log(\pi c) + \log(V(a_i)\lambda(a_i)) \\ &\quad - (\pi c) \int_0^T [V(w)\lambda(w) \mathrm{d}w], \end{aligned}$$

where T was 11·4 years in Finland (the maximum age of paediatric cases) and 10·0 years in the UK. The log-likelihood for the complete data in a cohort of N_c individuals was obtained by summing up the individual contributions: $\log L = \Sigma_i L_i$ where i ran from 1 to N_c. In Finland, N_c was 60000, and in the UK where a 2-year follow-up data were available, N_c was 400000. Most children did not experience Hib disease during the study period up to age T, contributing only the latter parts of the above expressions.

Because parameters π and c appear in the likelihood only as a product, they cannot be estimated separately. Consequently, the estimable parameters in the model were the rate of infection of immunizing contacts, $\lambda(a)$, and the proportion of immunizing contacts on susceptibles that progress to invasive disease, given by the product πc. The rate was parameterized as a linear spline function with 5 knots within the interval [0, T]. The knots of the spline were allowed to assume

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random locations with stochastic spacing [42], and an autoregressive smoothing prior was imposed on the values of the spline at the knots. Markov chain Monte Carlo methods were used to calculate parameter estimates and model-based predictions in a Bayesian analysis [30].

In summary, the inferences in this work were based on age-specific data of invasive Hib disease as a source of information about the frequency of immunizing contacts. This approach resembles the estimation of forces of infection from notification data for many childhood diseases. Due to the recurrent nature of immunizing contacts, however, data on the age distribution of Hib disease had to be amended with knowledge about the age-specific duration of protective immunity. Consequently, the estimated rate of immunizing contacts is due to Hib and CR bacteria capable of inducing immunity to Hib disease.

Table 1. *Age-specific numbers of observed cases and incidences of invasive Hib disease in the UK and Finland*

	UK		Finland	
Age (years)	Number of cases	Incidence/ 100000/ year	Number of cases	Incidence/ 100000/ year
< 0·5	71	36	7	23
0·5–1	162	81	39	130
1–2	148	37	47	78
2–3	85	21	40	67
3–4	53	13	23	38
4–5	21	5·3	13	22
5–6	8	2·0	8	13
6–7	3	0·8	12	20
7–8	1		5	
8–9	1		2	
9–10	2		0	
10–11	0		0	
11–12	0		1	

RESULTS

The observed incidence of Hib disease in the UK and Finland

During the first 6 months of life the incidence of invasive Hib disease in the UK was 1·5 times of that in Finland (Table 1). Moreover, more than 40% of paediatric cases in the UK occurred during the first year in comparison of the mere 23% in Finland. Thereafter the order clearly changed. During the second year of life, the incidence in Finland was double that in the UK and the difference still increased with age: during the fifth year the incidence in Finland was four times higher than in the UK. In addition to the later occurrence of Hib disease in Finland, also the overall risk differed between the two populations: based on the observed numbers of cases and the cohort sizes, the overall risk of contracting invasive Hib disease during childhood was 330/100000 in Finland, and 140/100000 in the UK, i.e. more than double in Finland in comparison with the UK.

Duration of maternally derived immunity

Around 60% of new-borns had antibodies above the presumed protective level (0·15 μg/ml). Based on the logistic regression model the proportion of children whose maternally derived antibodies were above this level was 30% at the age of 2 months. At the age of 4 months, when the first dose of Hib conjugate vaccine is given in Finland according to the current vaccination schedule, 90% of infants were already susceptible and at the age of 9 months practically everyone.

Age-specific antibody responses to Hib and CR stimulus

Figure 1 presents the individual responses to Hib polysaccharide (Hib-PRP) vaccine in 464 children as well as the estimated geometric mean of the antibody concentration as a function of age. The model predicts no antibody responses above the presumed protective concentration (0·15 μg/ml) below 6 months of age. At around 9 months, half of the children respond with antibody concentrations above the protective level. After 2 years of age practically all children are able to respond accordingly.

Duration of acquired immunity

The duration of the acquired immunity was estimated from the age-specific antibody response (Fig. 1) and the subsequent rate of decline of Hib antibodies [29]. Figure 2 presents function $f(a; u)$, i.e. proportion of children with antibody concentrations above 0·15 μg/ml when the age (u) at the latest Hib or CR encounter varies from 0·75 to 2 years. At around 1

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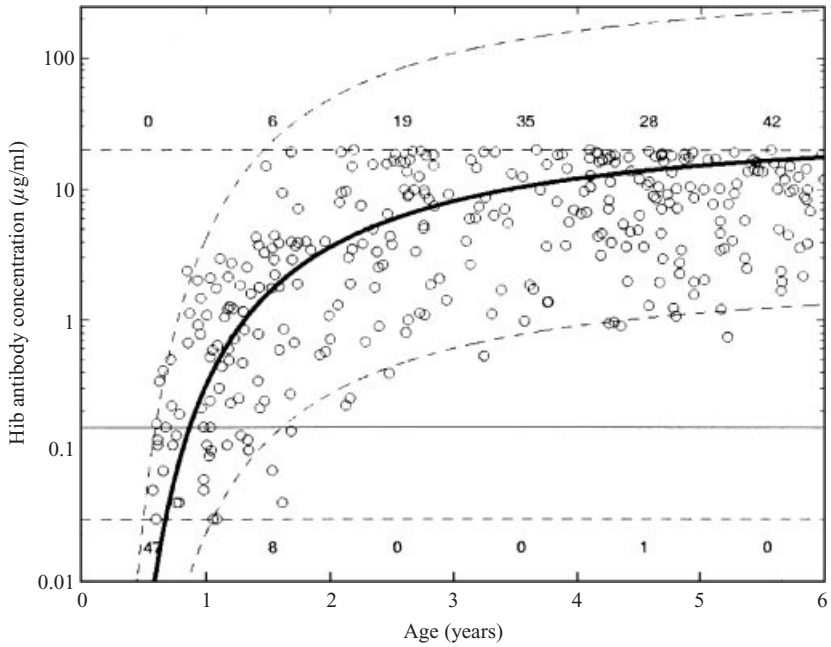

Fig. 1. Age-related antibody response to Hib. Observations from 464 children 3 weeks after vaccination to Hib polysaccharide vaccine (circle). The estimated predictive geometric mean response (solid curve) and the 95% predictive intervals for log-concentrations (dashed curves) are also shown. Only measurements between the detection limits log (20) and log (0·03), marked by horizontal dashed lines, are shown in the figure. The proportions of observations above/below the detection limits are indicated as percentages in the corresponding age classes (0–1 year, 1–2 years, etc.). These censored observations were accounted for in the analysis.

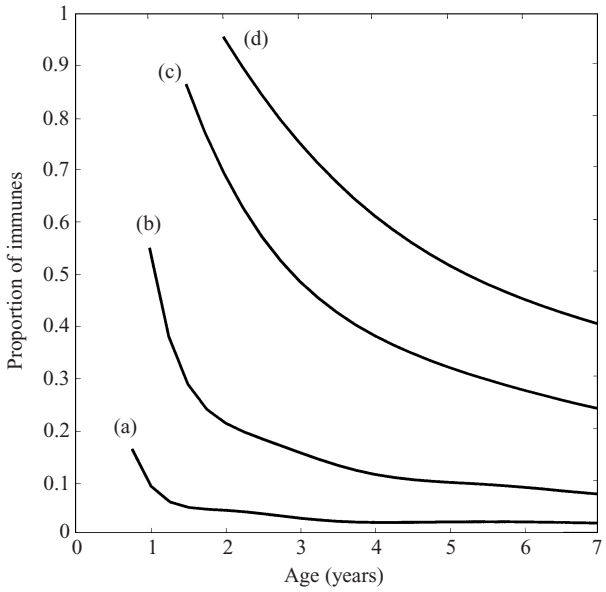

Fig. 2. Duration of acquired immunity. The curves present the proportion of children, $f(a; u)$, with antibody concentrations above 0·15 μg/ml when the latest Hib or CR encounter varies from (*a*) $u = 0{\cdot}75$ year; (*b*) $u = 1{\cdot}0$ year; (*c*) $u = 1{\cdot}5$ years; (*d*) $u = 2{\cdot}0$ years. The profiles after two years of age were similar to that at two years.

year of age, a fair number of children respond to Hib-PRP, but the antibody concentrations are still low and decline quickly, resulting in short-lasting effects in terms of predicted protection. Thus, 2 years after the response, less than 20% of the toddlers are above the presumed protective concentration. At the age of 2 years nearly all children are able to produce protective concentrations of antibodies and almost half of them are still immune at the age of 7 years (i.e. 5 years later), even without further immunizing contacts.

Rate of immunizing contacts (Hib and CR)

The estimated rate of immunizing contacts was higher in the UK than in Finland. In the UK, the initial rate of immunizing encounters was on average 0·6 per year, three times of that in Finland. After a sharp increase during the first year of life, the rates assumed rather stable behaviour until 3 years, being on average 1·2 and 0·7 per year in the UK and Finland, respectively. After 4 years of age, the estimated rates arose from very few observed cases, especially in the UK, and were very sensitive to the assumed prior information on the smoothness of the curves.

Proportion of immunes

Based on the estimated rates of immunizing contacts and the age-specific antibody response the proportions

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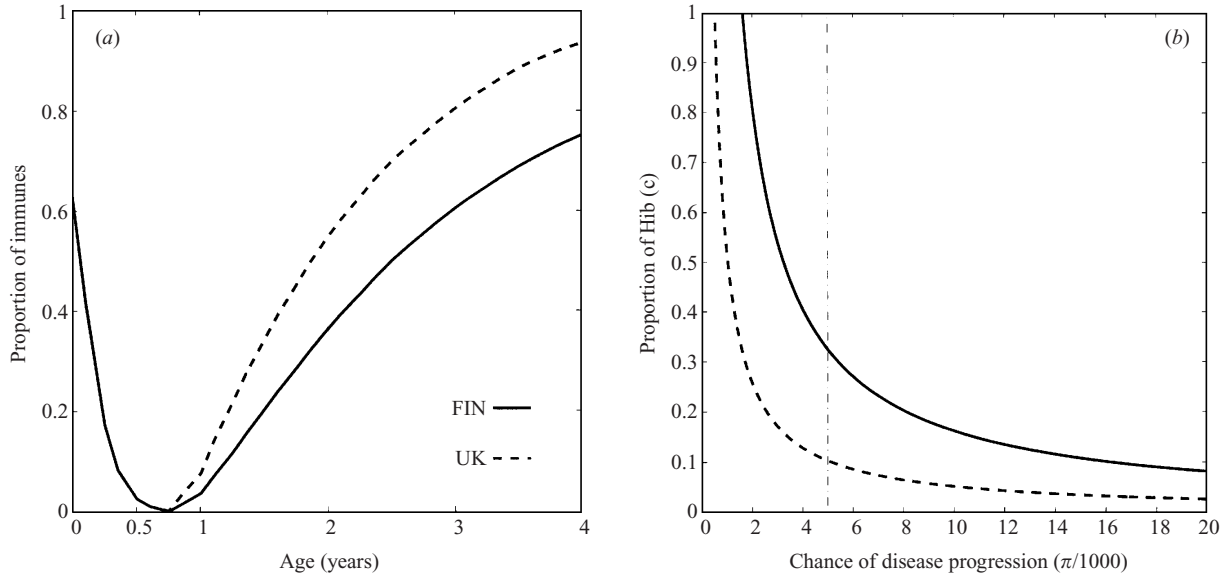

Fig. 3. (*a*) The estimated proportions of immune children by age in Finland (solid curve) and in the UK (dashed curve). (*b*) Chance of disease progression ($\pi/1000$) against proportion of Hib among all immunizing contacts in Finland (solid curve) and in the UK (dashed curve). The dot-dashed line indicates chance of disease progression of 5/1000, corresponding to proportion of Hib among immunizing contacts of 0·1 and 0·3 per year in the UK and Finland, respectively.

$V(a)$ of immunes in the two populations are presented in Figure 3a. The UK and Finnish curves are identical until 9 months of age as they are based on the same model of decay of passively obtained antibodies. Thereafter, due to the higher rate of immunizing contacts the children in the UK gained immunity faster: at 2 years of age less than 40% of Finnish children were immune, in the UK already 60%.

Proportion of contacts progressing to invasive disease

Among all immunizing contacts, only the proportion (c) entitled to Hib have the potential to progress to Hib disease. Unfortunately, it was not possible to estimate this proportion separately from parameter π, the chance of disease progression in a susceptible. However, we could assess the value of the product (πc), i.e. the proportion of immunizing contacts of susceptibles that progress to invasive disease. The estimates of this risk were 51 (90% credible interval 47–56) per 100000 in the UK and 162 (141–185) per 100000 in Finland. Apparently, the cumulative childhood risk of invasive disease (140 and 330 per 100000 in the two areas) are larger because they are based on each child contributing only one unit to the denominator (vs. several susceptible contacts during childhood).

Figure 3b illustrates possible combinations of chance π and proportion c that lead to the estimated value of their product. By fixing either one of the parameters the other can be read from the curve for each of the two populations. Furthermore, if the chance π of a Hib contact to progress to invasive disease in a susceptible can be assumed to be similar over populations, the proportion of Hib among immunizing contacts in Finland is roughly three times of that in the UK.

The relative quantities shown in Figure 3b allow us to examine further differences in Hib epidemiology between the two populations. Based on information of Hib carriage, the rate of Hib contacts among children 1–3 years old has been estimated to be roughly 0·1 per year per child in the UK [27]. According to the results presented above the rate of all immunizing contacts in the UK was in the order of 1 per year per child. Hence, the proportion (c) of Hib among all immunizing contacts would be approximately 10% in the UK, corresponding to a chance of disease progression of 5 per 1000 (see Fig. 3b). In Finland, assuming the same chance of disease progression, the proportion of Hib among all immunizing contacts would then be 30% (i.e. three times of that in the UK), giving the actual rate of Hib contacts of around 0·2/year in children 1–3 years old, double of that in the UK.

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DISCUSSION

Our results support earlier findings that cross-reactive bacteria may have a crucial role in natural Hib epidemiology [27, 28]. Furthermore, they suggest that population differences in the age-specificity and total childhood risk of invasive Hib disease may be partly attributable to varying frequencies of CR bacterial contacts. According to our model, a higher frequency of immunizing contacts in the UK resulted in earlier immunity against Hib disease in comparison to Finland. In the UK, practically all paediatric cases accrued before 5 years whereas in Finland 10% of the cases occurred still after 6 years of age. Combined with our conjecture that the rate of actual Hib contacts was lower in toddlers (1–3 years) in the UK, more frequent CR contacts suggest an explanation of the clearly smaller childhood risk of Hib disease.

Throughout the study, we used independently collected data from two separate populations in two different periods, i.e. the UK in 1990–2 and Finland in 1985–6. In the UK invasive Hib diseases were registered in the PHLS Regional Survey [31], enhanced by cross checking with routine laboratory reports to the PHLS Communicable Diseases Surveillance Centre (CDSC). The efficiencies of these two systems have been compared and the under-reporting evaluated in relation to each other [43]; no gold standard was available. A study, rather than a continuous survey, was set up in Finland to gather comprehensive baseline information of Hib epidemiology prior to a nation-wide conjugate vaccine trial [12]. Visiting the microbiological laboratories at the end of the pre-vaccination surveillance period further enhanced the reporting. The results presented here are prone to bias from heterogeneous under-reporting across age groups (which we consider unlikely in either of the data sets). By contrast, homogenous under-reporting would only affect the estimated risk (πc) of disease progression. In fact, if it happened mainly in the UK, it would diminish the difference in Hib proportions between the two countries. In any case, homogeneous missing of notifications would not deviate the estimates of the rates of immunizing contacts in the two populations [30].

We used a cut-off value of 0·15 μg/ml of present antibody concentration as indicating protective immunity. This concentration has been widely used in vaccine studies to compare different vaccines and vaccination schedules in their expected ability to protect vaccinees. In our model, the value of the protective concentration only affects the estimated duration of immunity to disease. To test the sensitivity of the results to duration of immunity, the rates were also calculated under the extreme case of permanent immunity to disease after the first contact with Hib or CR bacteria. In this analysis, the force of infection with Hib and CR exhibited the same overall pattern and remained at a relatively high level: in the UK the force of infection was around 60% in comparison to the transient immunity model, being still a magnitude higher of what has been estimated from Hib carriage data. In Finland the rate of infections would diminish to 0·4 per year (from 0·7) if immunity to disease was assumed permanent.

Assessments of the relative frequencies of Hib and CR contacts are obviously affected by the possible insensitivity of detection of Hib carriage. However, for only Hib to be responsible for the observed pattern of immunity, a major proportion of Hib carriage should have remained undetected.

The high proportion of bacteria other than Hib amongst immunizing contacts was rather unexpected. However, the results clearly illustrate that immunity against Hib disease arises effectively during the first years of life. Some mechanism of 'innate' immunity, improving with age, could contribute to more efficient protection against disease even without immunizing encounters. With the present modelling framework, such form of immunity would imply a decrease with age in the chance (π) of disease progression. In analogy to the permanent immunity model, the presence of such a mechanism can be expected to result in lower infection rates underlying the observed pattern of Hib disease. However, this age-specificity in the disease progression would fail to explain the observed difference between the populations.

Conjugate Hib vaccines have been successful both in protecting from invasive diseases and in reducing Hib carriage [44–48]. Although not uniformly, this reduction in carriage has contributed to herd immunity among the non-vaccinated [49–52]. There is evidence that immunity to disease is long lasting [53, 54]. However, whether the conjugate vaccine-induced memory together with continuous circulation of immunizing cross-reactive bacteria will sustain the effects on carriage in the long run remains a crucial epidemiological question [55–59]. This will eventually depend also on the possible effect of Hib conjugate vaccination in preventing carriage of CR bacteria.

The observation of an increase in Hib incidence in 2000 in the UK [http://www.phls.co.uk/

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publications/cdr.htm] is of concern and studies on antibody and carriage prevalences are planned. These new data may necessitate refinements to the model to explain the changing epidemiology of the infection. Such changes emphasise the importance of continued surveillance and of using such data to validate predictions from mathematical models.

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