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Modelling transmission, immunity and disease of *Haemophilus influenzae* type b in a structured population

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SUMMARY

An individual-based stochastic simulation model was constructed to study the epidemiology of *Haemophilus influenzae* type b (Hib) transmission, immunity and invasive disease. Embedded in a demographic model, the transmission model of Hib carriage employs the most important social mixing patterns with three types of contact sites (family, day-care group, and school class). The model includes immunity against invasive Hib disease, initiated and boosted by Hib carriage and cross-reactive bacterial encounters. The model reproduces the observed age patterns in Hib carriage and disease in Finland before large-scale use of the Hib conjugate vaccines. The model was used to investigate characteristics of Hib transmission. The analysis emphasizes transmission between children and adults in families while pointing out the importance of pre-school and school-aged children in maintaining Hib circulation. Carriage in these age groups is thus identified as being essential to target for sustained effects of interventions by vaccination.

INTRODUCTION

Transmission of *Haemophilus influenzae* type b (Hib) occurs through asymptomatic carriers. Most episodes of Hib carriage pass without clinical symptoms, and only in rare cases does carriage proceed to invasive disease (e.g. meningitis or epiglottitis). Therefore, transmission of asymptomatic nasopharyngeal carriage lies in the focus of investigation of Hib epidemiology. Transmission in turn is influenced by the recurrent nature of carriage acquisition and the typical clustering of Hib carriage in family and day-care settings [1–6].

Clustering of Hib follows from the notion that close contacts between individuals are required for Hib to be transmitted effectively. Therefore, it is useful to employ direct information about appropriate social mixing groups providing such contacts in the analysis of epidemiological data. For example, the typical age pattern in prevalence of Hib carriage, the initial increase from birth until school-age and the subsequent gradual decrease to a low level in adulthood, can be assumed to reflect the intensity and nature of contacts in families, day-care centres and schools. Quantification of the number of individuals susceptible to infection and characterization of the nature and frequency of their contacts are of utmost importance when producing predictions of the impact of vaccine interventions [7, 8].

Mathematical simulation models of transmission are valuable tools to describe and analyse the epidemiology of an infection and its relation to disease. Coen et al. applied an age-structured deterministic

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compartmental model to investigate the pre- and post-vaccination epidemiology of Hib, using data from England and Wales [9, 10]. According to their analysis, individuals of all ages may acquire Hib carriage while transmission is characterized by within-age-group mixing, i.e. individuals tend to transmit carriage to other individuals of approximately the same age. Based on the relatively low force of infection of Hib carriage, they also inferred that other, cross-reactive bacterial encounters, in addition to Hib, are needed to induce and maintain immunity against invasive Hib disease.

In this paper, we introduce a stochastic individual-based model of Hib transmission, immunity and disease. Different contact sites are defined to represent typical sites of Hib transmission: family, day-care group and school class. These contact sites are realized in a demographic model of a population in an industrialized country (Finland). On top of the demographic model we add the transmission model of Hib carriage, with site-specific contact rates. The dynamics of transmission follows the SIS (susceptible–infectious–susceptible) model [11–13]. Age dependence in transmission results from age dependence of attending different contact sites and from the demographic processes of the population. Finally, the model includes acquired immunity against Hib disease, stimulated and boosted by recurrent episodes of Hib carriage or encounters with cross-reactive bacteria. Invasive Hib disease is modelled as a rare outcome in non-immune individuals at the onset of Hib carriage.

Individual-based transmission models in structured communities have previously been used to study, e.g. prevention of influenza epidemics [14, 15] and spread of smallpox [16], but not to investigate Hib epidemiology. Contrary to earlier, compartmental Hib models [9, 10], the current individual-based approach allows us to easily parametrize the complex social structure ('who meets with whom'). Such a structure realistically captures patterns of transmission of a pathogen like Hib for which children serve to provide pathways of infection between families. The model also allows us to base the relation between infection and disease on explicit individual-specific histories of immunity and its stimulation. In addition, a stochastic approach provides a natural way to address questions of eliminating Hib carriage and disease.

This is the first of two articles modelling Hib epidemiology before and after large-scale vaccinations respectively. It introduces the population model as well as the models of Hib transmission and immunity, with the specific aim of studying how well a model based on contact sites, rather than on an explicit age structure, can explain the intensity of Hib transmission and the typical age-dependent pattern of Hib carriage. The model is also used to analyse contact site and age-specific infection rates and the transmission potential of Hib. This is important for understanding observed current trends in morbidity due to Hib during large-scale vaccinations with the conjugate vaccines in many countries. The second article [34] will apply this model as a platform to analyse interventions with the Hib conjugate vaccines.

MATERIALS AND METHODS

Definitions

Carriage and susceptibility

The term infectious carrier (I_C) is used for individuals with nasopharyngeal Hib colonization (carriage). Individuals not carrying Hib are susceptible (S) to carriage. The SI_CS (susceptible–infectious carrier–susceptible) model [12] is applied to model the transmission of Hib.

Contact sites

It is assumed that carriage is transmitted from person to person in three different contact sites: family, day-care group, and school class. A contact between two individuals signifies the presence of both in the same contact site. Contacts can be overlapping: school-aged children attend both school and family, and a fraction of younger children attend day-care groups and family. Some people are single and do not attend any contact site. The rate of potentially infectious contacts means the rate at which a carrier transmits Hib to individuals in his/her contact sites, given that they are all susceptible.

Immunity

In this article, immunity is only considered against disease. Individuals with an antibody concentration above $0{\cdot}15\,\mu$g/ml are considered immune, as has been suggested by several studies [17–20]. Immunity develops in an age-specific manner in response to carriage of Hib or cross-reacting bacteria. The latter term is used for other bacteria stimulating or boosting immunity in excess of the observed Hib carriage.

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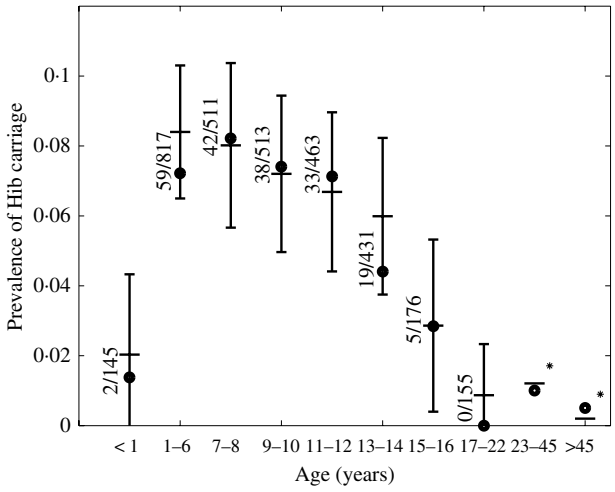

Fig. 1. Age-specific prevalence of Hib carriage. The circles show the observed mean prevalence of carriage in 10 age groups in Finland in 1974–1976; the observed proportions are indicated with numbers. Simulated results from our model are shown for comparison: the predicted mean prevalences are indicated by horizontal lines and the vertical intervals show the 95% predictive intervals of the proportion of carriers in samples that have sizes corresponding to the observed sample sizes. * The values in the two oldest age groups are based on refs [5] and [6] (see text).

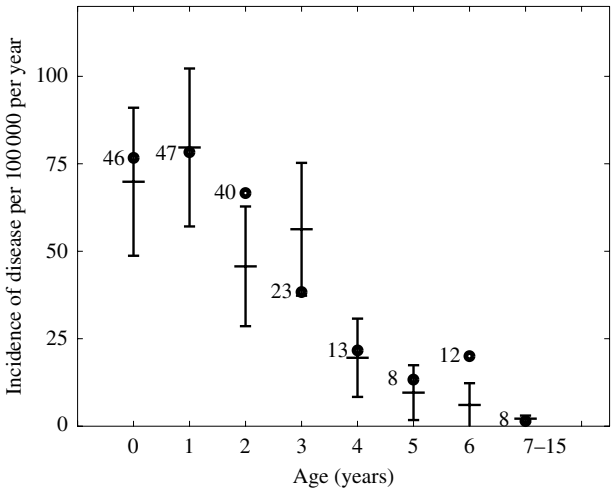

Fig. 2. Incidence of invasive Hib disease among children <16 years old in Finland in 1985–1986. Incidences are shown in 1-year age groups below 7 years and in one group for the rest (7–15 years). The circles show the observed incidences, and the numbers indicate cases of invasive disease in each age category (size of the respective age categories approximately 60 000 children, except 540 000 in the oldest category). Simulated results are indicated by horizontal lines for the predicted mean incidences, and by vertical intervals for the 95% predictive intervals of the mean incidences in samples that have sizes corresponding to the observed sample sizes.

Disease

Non-immune susceptible individuals (antibody concentration $<0{\cdot}15\ \mu$g/ml) may acquire invasive disease when being infected, i.e. at the onset of carriage.

Calibration data

In this section, we summarize datasets on Hib carriage and disease that were used to estimate model parameters (calibration) and to assess its performance.

Hib carriage

Figure 1 presents age-specific data on Hib carriage in Finland during 1974–1976, collected from 3211 children and adolescents up to 22 years of age [18, 21]. The prevalence was low in newborns, increased up to 8% at school age and declined thereafter to almost zero in adults. Limited data in the general adult population were available, and prevalences lower than those based on studies on families with young children were assumed [5, 6]. Specifically, we assumed 1% carriage in age group 23–45 years (the typical age range for parents of young children) and 0·5% in age group >45 years.

Hib disease

Figure 2 shows the age-specific incidence of Hib disease in children <16 years of age in Finland in 1985–1986, before the large-scale use of Hib conjugate vaccines [22]. A retrospective review of laboratory data indicated that 98% of the diagnostic findings had been notified. During one year of intensified surveillance, 197 cases accumulated, corresponding to a cumulative risk of contracting Hib disease during childhood of 330/100 000. There was notable variance in the incidence of Hib disease with age. The incidence was highest among children aged 6–11 months (approximately 130/100 000 per year) and declined thereafter to a fraction among children >5 years old (approximately 5/100 000 per year). Just above 5% of all invasive Hib disease in Finland occurred in adults [23, 24].

Carriage in families and day-care centres

Limited data were available on clustering of carriage in contact sites. The proportion of families of size 4–5 with young children (<7 years of age) and with at least one Hib carrier has been estimated to be approximately 10% [6]. Conditional upon there being at least one carrier in such families, the magnitude of

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the prevalence of carriage in young children has been approximately 50%. In adults the corresponding conditional prevalence has been in the range of 10–20%. The overall prevalence of Hib carriage in day-care groups has varied between 10 and 20%. [4–6, 25, 26].

Population model

The contact sites (families, day-care centre, school) were realized in a demographic simulation model whose population mimicks that of Finland in the mid-1990s. Detailed statistics from Finland were available for the construction and calibration of the population model [27]. These included data on, for example birth and death rates, rates of marriage and divorce, attendance at day-care centres and size of day-care groups.

In the model, each individual has one of five possible states: (1) child; (2) single adult; (3) spouse without children; (4) spouse with children; or (5) single parent. Each individual moves out of his/her parents' household and settles in a single-adult household at age 20 years. Single (or single-parent) women marry at an age-dependent rate. The expected age of the husband equals the age of the marrying woman. Each married woman gives birth at a rate that depends on her age and on the number of children in her family. Single women do not give birth in the model. Of the newborns, 51·5% are male. If parents divorce, their children live with the mother in 85% of the cases. The life expectancy is 77 and 84 years for men and women respectively. Half of the households are single-adult families, 20% are households with 2 adults only, and 30% households with children (the average number of children is 1·8).

A fraction of children (44%) attend day-care centres from 6 months to 7 years of age. Depending on the type of day care, the group size is 3–6 (family day care, 65% of day-care attendees) or 6–13 (day-care centre, 35% of day-care attendees) for children between 1 and 3 years. For children between 4 and 7 years, the respective group sizes are 3–6 or 13–23. All children attend school between ages 7 and 16 years. The typical size of a school class is 20–30, but the effective size of school classes (number of classmates relevant to transmission) was set at approximately 10 in the model.

The model of Hib transmission, immunity and disease

Figure 3 describes the dynamics of Hib infection (carriage) by using two states: non-carrier

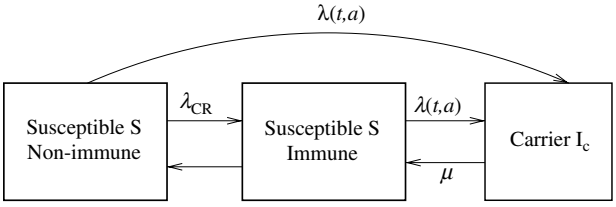

Fig. 3. The model of Hib carriage and immunity. Susceptible individuals acquire carriage at rate $\lambda(t, a)$ [see eqn (1)]. Carriage is cleared with rate μ and the individual turns susceptible again but is immune against disease (susceptible/immune). If Hib carriage or a cross-reactive encounter do not boost immunity, the individual returns eventually to be susceptible/non-immune (see text). Children <2 years old may return directly to susceptible/non-immune. Boosting of immunity in susceptible individuals occurs through cross-reactive encounters with rate λ_{CR}. For simplicity, the figure omits boosting of immunity in Hib carriers by cross-reactive encounters. Disease may emerge in non-immune susceptibles at the onset of Hib carriage.

or 'susceptible' (S) and 'infectious carrier' (I_C). The model of Hib carriage thus follows the SI_CS dynamics. Additionally, susceptibles and carriers may be immune against invasive disease. Immunity is stimulated and boosted by Hib carriage or encounters with cross-reactive bacteria. At the onset of carriage, non-immune individuals may contract invasive disease. The sections below describe how the model was constructed for Hib carriage, immunity and disease.

Susceptible → carrier

For an individual, the numbers of individuals in his/her family, day-care group and school class at time t are denoted by $N_f(t)$, $N_d(t)$, and $N_s(t)$ respectively. The numbers of carriers in these contact sites are $I_f(t)$, $I_d(t)$ and $I_s(t)$ respectively. The *per capita* rate, force of infection, at which a susceptible individual of age a acquires Hib carriage at time t is defined as

$$\lambda(t,a)=\beta(a)\left[c_f\frac{I_f(t)}{N_f(t)-1}+c_d\frac{I_d(t)}{N_d(t)-1}+c_s\frac{I_s(t)}{N_s(t)-1}+\kappa\right], \quad (1)$$

where c_f, c_d and c_s denote contact rates specific to family, day-care group and school class respectively. The age-dependent relative susceptibility is given by $\beta(a)$. Contacts are assumed to be distributed equally over all members of each contact place, i.e. the force of infection depends linearly on the proportion of infectives in a contact site. Rate κ is the external force of infection from outside of the simulated population. Not all terms apply for each individual; for example,

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adults only have the family contribution, and singles only the external force of infection, κ. The day-care rate is different for children aged between 1 and 3 years (c_{d1}) than for children aged between 4 and 6 years (c_{d2}).

In summary, individuals mix homogeneously and are equally infectious within each contact place (see [28]), but susceptibility varies with age. Age-dependent contact rates are not considered explicitly, but age-dependent transmission is conveyed by the age dependence in attending different contact sites and by the demography of the population.

Carrier → susceptible

We assume that duration of Hib carriage follows an exponential distribution with a mean duration of 4 months [6].

Non-immune → immune

The model for development and duration of immunity against Hib disease has been reported by Auranen et al. and Leino et al. [29–31]. Immunity against Hib disease is induced by previous Hib carriage and by encounters with cross-reactive bacteria. We assume that cross-reactive bacterial encounters occur at the rate $\lambda_{CR}=0{\cdot}5$ per individual per year (see [31]), independent of Hib dynamics. Each Hib carriage or cross-reactive encounter may raise a response in the antibody concentration of the individual. Up to 80% of children <1 year old remain non-immune. As the ability of the child to produce antibodies develops with age, a larger proportion of older children acquires immunity to disease after Hib carriage or a across-reactive bacterial encounter. After 2 years of age, almost everyone is capable of producing responses above $0{\cdot}15\,\mu$g/ml.

Immune → non-immune

Duration of immunity is modelled as the time until the antibody level drops below the cut-off value. As the ability to produce antibodies develops with age, subsequent duration of immunity increases. For children <2 years old, antibody respones are low and immunity is short-lived. After 2 years of age, the resulting immunity is clearly longer, with the estimated proportion of immunes being almost 50% after 5 years of the previous stimulus. We assume that the duration of immunity is the same after cross-reactive bacterial encounters as it is after Hib carriage.

Newborn infants may be initially protected by maternal antibodies. The duration of maternal immunity is shorter than immunity developed after bacterial encounters. Approximately 60% of newborns are immune at birth. At age 4 months, 90% of infants have become non-immune, and at age 9 months virtually everyone is non-immune.

Progression to disease

The probability of developing invasive disease at the onset of carriage was assumed to be constant (π) for all non-immune individuals. In the model, there is no difference in infectiousness between asymptomatic carriers and cases of Hib disease nor are cases isolated from the community. Although this may not reflect reality, it hardly influences the transmission dynamics since the prevalence of invasive disease is negligible compared to that of asymptomatic carriage.

Implementation and simulation

The population model was initialized to reflect the population statistics in Finland in 1995. Also Hib carriage and immunity against disease were initially assigned to individuals to reflect the empirical age-dependent data.

The model was run in 1-day steps for Hib transmission, and in 1-week steps for the population dynamics. For each individual, the force of infection was calculated from the numbers of carriers in the relevant contact sites, as in eqn (1). A susceptible individual contracted carriage during a 1-day step with a probability proportional to the force of infection. For each newly infected individual, a duration of carriage was drawn from the exponential distribution with a mean of 4 months. Encounters with cross-reactive bacteria were sampled with a constant intensity (λ_{CR}). After Hib carriage or encounter with cross-reactive bacteria, a random duration of immunity was sampled from the appropriate age-dependent distribution. When carriage started in a non-immune individual, Hib disease was contracted with probability π.

To mitigate features that were not easy to initialize, the model was always run-in for 10 years before collecting data from simulations. This run-in period allowed the transmission and immunity models to attain a relatively stationary phase. The model was tested with different population sizes from 10 000 to 100 000; within this range, the mean results remained essentially the same. Most results in this article were calculated as Monte Carlo averages from 1000 simulations in a population of 10 000 individuals.

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Table 1. *Model parameters. The list includes model parameters from external sources* [*duration of carriage, rate of cross-reactive* (*CR*) *encounters*] *and parameters calibrated to epidemiological data using the simulation model. The distribution of the duration of immunity against disease has no closed form* (*see* [*29, 30*])

Parameter	Notation	Value	Source
Rate of clearing carriage	μ	3·0/year	[6]
Mean duration of carriage	$1/\mu$	4 months	
Rate of CR encounters	λ_{CR}	0·50/year/person	[31]
Relative susceptibility	$\beta(a)$		*
0–16 yr		1·0	
17–22 yr		0·7	
>22 yr		0·5	
Contact rates			*
Family	c_f	1·10 μ	
Day care	c_{d1}, c_{d2}	1·10 μ, 1·31 μ	
School	c_s	0·63 μ	
External Hib infection rate	κ	0·0009 μ	
Probability of disease progression	π	7·5/1000	*

* Parameters estimated to fit epidemiological data by using the simulation model.

Calibration of model parameters

Empirical data on Hib carriage were used to find values for contact rates (c_f, c_{d1}, c_{d2}, c_s) and the relative susceptibility $\beta(a)$. Initial estimates of these parameters were first found from an approximation of the stationary state of the stochastic model and from data on the age-specific prevalence of Hib carriage in the 10 age groups of Figure 1. The initial estimates were then refined by Monte Carlo optimization, using a sum of squared deviances between the model predictions and the observed prevalences of Hib carriage in the 10 age groups. In the latter stage, susceptibility $\beta(a)$ was considered to be stepwise constant: adults (age >22 years) had a 50% lower susceptibility than children (age <17 years) (Table 1). Finally, given the other parameters, the probability of disease progression (π) was estimated by minimizing the difference between the model predictions and the observed incidence of invasive disease. The external force of infection (κ) was set at approximately 0·0026 *per capita* per year which corresponds to an average of 26 annual infections acquired from outside the simulated population of 10 000 individuals. Table 1 summarizes all the parameters and their values.

RESULTS

The simulation model was able to reproduce the empirical observations on carriage and disease relatively well. Figure 1 compares the model predictions and the observed mean prevalences in 10 age groups. The observed values lie within the 95% intervals predicted by the model in all age groups.

Figure 2 compares the predicted mean incidence of disease with the actual incidence in children <16 years old, as observed during the intensified surveillance. The predicted cumulative risk of disease during childhood (until 16 years) was 312/100 000 (*vs.* observed 330/100 000). The predicted fraction of all Hib disease that occurs in individuals ⩾16 years was 5·0% (*vs.* observed approximately 5%). The model could thus adequately describe the age distribution and magnitude of the incidence of Hib disease.

We inspected the model to illustrate the key features of Hib transmission. Most importantly, the implied age structure of the model, the transmission potential of Hib, the force of infection, and the relative role of different contact sites as sources of Hib infection were investigated. In the following, single individuals are omitted as they do not participate in Hib transmission in the model.

Age structure

The implied age structure of the transmission model was determined by factoring the rate of potentially infectious contacts according to the age groups of the carrier (donor) and the recipients. The rate of potentially infectious contacts is the rate at which a carrier infects the pool of individuals in his/her contact site(s), given that they were all susceptible

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Table 2. *Age structure of transmission within families*

Age group (years)	1	1–3	4–6	7–16	17–22	23–45	>45	Total rate/μ
<1	0	**15**	10	13	5	**56**	1	0·69
1–3	5	9	14	**17**	2	**51**	1	0·71
4–6	3	13	9	**26**	2	**43**	3	0·75
7–16	1	5	8	**34**	6	**33**	11	0·74
17–22	2	3	3	**25**	12	**28**	26	0·68
23–45	5	14	13	**31**	6	**25**	5	0·82
>45	0	0	1	**12**	6	6	**75**	0·60

The entries on each row represent proportions (%) of potentially infectious contacts by a carrier with family members in different age groups [see eqn (A 2) in the Appendix]. The total rate of potentially infectious contacts within families is given in the last column, relative to the rate, μ, of clearing carriage.
The two most important classes of recipients for each age group of the donor are indicated in bold.

(i.e. recipients). This quantity takes into account the number of recipients in the contact sites of a carrier and can be summed up from the contributions given by eqn (1). Table 2 presents the simulated results as a mixing matrix constrained to within-family contacts. The entries in the matrix give the average proportions of potentially infectious contacts with other family members. For details, see the Appendix.

Instead of a clear within-age-group mixing, individuals of all ages tend to infect school-aged and adult family members. Newborn infants tend to infect siblings a few years older. Apparently, the resulting matrix reflects the family structure of 'who lives with whom'. It should also be noted that, as a consequence of the model assumptions, the total rate of potentially infectious contacts with other family members is quite similar for carriers of all age groups.

Corresponding matrices were determined for day-care centres and school (Table 3). The result reflects our assumptions that in day care all individuals spread infection independent of age whereas in school transmission only occurs among classmates of the same age. Table 4 presents the overall mixing matrix with contributions from families, day care and school all summed together (see the Appendix). The inclusion of age-group-specific sites results in clearer within-age-group (diagonal) contacts in children not yet school-aged than in families. There is also a notable age pattern in the total rate of infectious contacts, with the highest rate occurring in school-aged children.

Table 3. *Age structure of transmission within day care (0–6 years) and school (7–16 years)*

Age group (years)	1	1–3	4–6	7–9	10–12	13–16	Total rate/μ
<1	27	73	0	0	0	0	0·28
1–3	13	58	29	0	0	0	0·52
4–6	0	26	74	0	0	0	0·56
7–9	0	0	0	91	9	0	0·63
10–12	0	0	0	11	76	13	0·63
13–16	0	0	0	0	15	85	0·32

The entries on each row represent proportions (%) of potentially infectious contacts by a carrier with individuals in day care in different age groups (see the Appendix). The total rate of potentially infectious contacts is given in the last column, relative to the rate, μ, of clearing carriage.

Table 4. *Age structure of overall transmission*

Age group (years)	1	1–3	4–6	7–16	17–22	22–45	>45	Total rate/μ
<1	3	**23**	9	11	4	**48**	1	0·79
1–3	6	**22**	17	13	2	**39**	1	0·93
4–6	2	15	**26**	20	2	**32**	2	1·00
7–16	1	3	5	**60**	3	**20**	7	1·24
17–22	2	3	3	**25**	12	**28**	26	0·68
23–45	5	14	13	**31**	6	**25**	5	0·82
>45	0	0	1	**12**	6	6	**75**	0·60
Average								0·81

The entries on each row are proportions (%) of potentially infectious contacts by a carrier with individuals in different age groups (see the Appendix). The total rate of potentially infectious contacts is given by the last column, relative to the rate, μ, of clearing carriage. These values take into account the fact that only a fraction of children attend day care.
The two most important age groups of recipients of each donor age group are indicated in bold.
The average rate of potentially infectious contacts is calculated from the last column of the table weighted according to the sizes of the age groups (see the Appendix).

Transmission potential

For Hib to remain endemic in a population, the rate of potentially infectious contacts must on average exceed that of clearing carriage [32]. The last column of Table 4 shows that this is true only in children aged between 4 and 16 years. An average rate of infectious contacts can be calculated by weighting the the age-group specific rates with the respective class sizes

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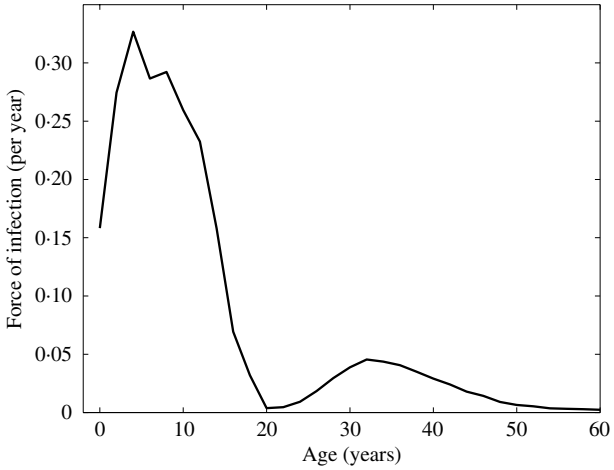

Fig. 4. Force of infection. The *per capita* rate per year at which a susceptible individual acquires Hib carriage, shown for individuals <60 years old. The rate is based on the simulation model, age-specific data on prevalence of Hib carriage, and the assumed mean duration of carriage of 4 months.

(see the Appendix). This calculation yields the average rate of 0·81 μ, corresponding to an average of 0·81 secondary infections for a carrier in a completely susceptible population. Restricting this calculation to children <16 years old, the average number of secondary infections for a carrier is 1·04, emphasizing the role of pre-school and school-aged children in maintaining Hib circulation.

Force of infection

The force of infection [*per capita* rate of carriage acquisition, eqn (1)] on a susceptible depends on the numbers of carriers in the contact sites. Figure 4 shows the endemic force of infection as determined by simulation. It starts at approximately 0·15 per year in children <1 year old and increases up to 0·3 per year in young school-aged children. Thereafter it declines until an increase again in the age range of parents of young children.

The relative force of infection (force of infection in day care divided by force of infection in family) was 0·9 in children <1 year old. Among older children attending day care, the force of infection in day care dominated; the relative force of infection was 1·9 and 2·5 in children 1–3 and 4–6 years of age respectively. Thus, day care was often the source of infection for day-care attendees. In school-aged children, the relative force of infection (family *vs.* school) was 1·2.

Clustering of carriage

In the simulated population, the proportion of families with carriage was 6%. Conditional upon there being at least one carrier in the family, the prevalence of Hib carriage was approximately 37%. Likewise, there was carriage in 55% of day-care groups, and conditional upon there being at least one carrier, the prevalence was 27% among day-care attendees. Although not perfectly matching, these values are in reasonably good agreement with values reported in the literature.

DISCUSSION

We constructed an individual-based stochastic simulation model to gain insight into the pre-vaccination epidemiology of Hib. In our approach, the transmission model of asymptomatic Hib carriage followed the SI_CS dynamics (susceptible–infectious carrier–susceptible), embedded in a demographic model describing Finland in the mid-1990s. A contact structure was modelled through individuals attending different contact sites (family, day-care centre, school). Immunity against invasive disease was stimulated by the total rate of acquisition of Hib carriage and cross-reactive bacterial encounters. The immunity model has been an underlying framework for several studies in Hib epidemiology [6, 29–31].

The prevalence of Hib carriage typically exhibits a clear age-dependent pattern (Fig. 1). In each type of contact site, children were assumed to be equally susceptible and equally infectious. When calibrating the model to epidemiological data, the age dependency of carriage in children was thus assigned to site-specific contact rates. By contrast, a decline in susceptibility with age was required in adults (>16 years). With the resulting social mixing pattern for Hib transmission, the observed age-specific Hib carriage could be reproduced. Moreover, the typical clustering of Hib carriage in families and day care could be obtained.

Accordingly, the estimated force of infection mirrors the contact sites of the individual (Fig. 4). At age 20 years, when individuals leave their family and become single, the force of infection declines to nearly zero. Among adults of child-bearing age (23–45 years), the force of infection increases again. This is a direct consequence of the model structure with a considerable number of adults being exposed to carriage in children. Correspondingly, in the same age

group a peak in invasive disease has been reported in a population-based study [24]. This is well in accordance with our modelling results.

The rate of cross-reactive bacterial encounters defines the age pattern of invasive disease, with the peak incidence occurring earlier the larger the rate of cross-reactive boosting [31]. In the present study, we applied a rate of external boosting of approximately 0·5 encounters per individual per year. This is almost twice as large as the force of infection of Hib carriage, even in the age groups of most prevalent carriage, and more than 10 times larger than that in the adult population (Fig. 4). The estimated probability per carriage to develop invasive disease was less than one in a hundred (7·5/1000) which is well in agreement with a previously obtained value (approximately 5/1000) [31]. Taking these Hib and cross-reactive assumptions into the model, the invasive Hib disease pattern in Finland could be reproduced (Fig. 2). When a smaller rate of cross-reactive bacterial encounters was tested, the age distribution of invasive disease shifted towards older age groups and the predicted overall risk during childhood to contract invasive disease increased.

Information on 'who meets whom' is crucial for learning about the pathways of transmission. In previous models of Hib transmission homogeneous mixing has been assumed within and between age-specific strata [9, 10]. This, however, may not be a realistic assumption for human social behaviour. We assumed homogeneous mixing only within the contact sites. The background force of infection, κ, was introduced to compensate for weaker, occasional contacts. The demographic structure of our model admits Hib to be transmitted as a percolation of carriage through a net of inter-connected families. The net consists of strong 'close-range' interact ions (contacts) between individuals, instead of weak contacts between large strata. Although our model is undoubtedly simplified, we assume this model to be more appropriate for Hib.

The age pattern of Hib transmission is clearly apparent from Table 4. Transmission among children of the same age is notable. In addition, parents are important donors and recipients of Hib infection. In general, the mixing structure is more scattered than that used in previous Hib models [10]. Apparently, this results from contacts between individuals of different ages in the population: day-care attendees and school-aged children meet children of the same age at day-care centres and school respectively. In addition, the model straightforwardly employs the information of 'who lives with whom' within families.

A small number (R_0) of secondary infections for a carrier is typical of an infection without immunity against re-infection [13]. We determined R_0 empirically by simulation. The value 0·83 is clearly smaller than the previously estimated value of 1·03 [10] and, in fact, would not seem to permit Hib to persist endemically [32]. However, according to our analysis, children aged between 4 and 16 years are the core group of Hib transmission, as quantified by the prevalence of carriage and by the rates of potentially infectious contacts (Table 4). The average number of secondary infections was 1·04 in this age range. These results imply that pre-school and school-aged children were essential in maintaining Hib circulation before large-scale vaccination with the Hib conjugate vaccines began in Finland. It should be noted that, because of immature immunity, the bulk (80%) of invasive disease in Finnish children occurred before 4 years of age.

In conclusion, the small number of secondary infections for a single carrier implies that even moderate interventions of Hib carriage by vaccination may have notable consequences on transmission. However, the pattern of transmission supports the view that for obtaining sustained indirect protection (herd immunity) in the population, the effect of vaccination on carriage should carry over to older children [33]. This requires a long-lasting direct vaccine effect on carriage. In case this is not achieved adequately, residual disease may emerge in non-vaccinated individuals.

In a complementary paper [34], the simulation model will be used to assess in detail the effects of large-scale immunization with the Hib conjugate vaccines on Hib carriage and disease, considering varying coverages of vaccination and different degrees of the vaccine effect on carriage.

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APPENDIX

In the following, singles are omitted as they do not participate in the transmission of Hib carriage in the

model. Specifically, every individual has at least one family contact.

Age structure

Let $\delta_k^{(i)}$ be an indicator with value 1 if individual i is in age group k and 0 otherwise. Based on eqn (1), the average rate of potentially infectious contacts exerted on family members of age group j (recipients) by an individual of age group k (donor) is

$$m_{jk}^f = \frac{\beta_j c_f \sum_i q_j^{f(i)} \delta_k^{(i)}}{\sum_i \delta_k^{(i)}}, \quad \text{(A 1)}$$

where β_j is the relative susceptibility in age group j and $q_j^{f(i)}$ is the proportion of family members of individual i that are in age group j. The proportion of potentially infectious contacts of an individual of age group k with family members of age group j is given by

$$\gamma_{jk}^f = \frac{m_{jk}^f}{\sum_j m_{jk}^f}. \quad \text{(A 2)}$$

Table 2 presents values of γ_{jk}^f, determined by simulation of the demographic model.

Expressions similar to (A 1) hold for an individual attending a day-care centre (m_{jk}^d) or school (m_{jk}^s). Values for j and k are taken as zero for age groups k (donor) or j (recipient) that do not attend the contact place. Table 3 presents the corresponding proportional values γ_{jk}^d and γ_{jk}^s for age groups with day-care or school contacts.

The total average rate of potentially infectious contacts from an individual of age k is $m_k = \sum_j m_{jk}^f + 0{\cdot}44 \sum_j m_{jk}^d + \sum_j m_{jk}^s$. As only a fraction (0·44) of children are in day care, the day-care contribution is multiplied by 0·44. The last column in Table 4 reports values of m_k in the simulated population, relative to the rate μ of clearing carriage. Table 4 also presents the proportions of the total average rate exerted into different recipient age groups.

Transmission potential

The expected number of secondary infections by one carrier in a completely susceptible population (R_0) is calculated as the ratio of the rate of potentially infectious contacts to the rate of clearing carriage. In the complete population, the appropriate rate of potentially infectious contacts is the weighted average of rates m_k over the age (group) distribution.

Force of infection

In the endemic state, the force of infection on a susceptible depends on the distribution of carriers in the population. The average force of infection exerted on a susceptible family member of age group j is given by

$$\lambda_j^f = \frac{\beta_j c_f \sum_i q^{fc(i)} \tilde{\delta}_j^{(i)}}{\sum_i \tilde{\delta}_j^{(i)}}, \quad \text{(A 3)}$$

where $\tilde{\delta}_j^{(i)}$ is an indicator function for individual i being susceptible and of age j, and $q^{fc(i)}$ is the proportion of carriers of all family members of individual i. The total force of infection in age group j can again be calculated by summing up the contributions from families, day care and school. The force of infection was determined at year 10 after the start of simulation.

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