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Indirect protection obtained by *Haemophilus influenzae* type b vaccination: analysis in a structured population model

T. LEINO[1*], T. TAKALA[2], K. AURANEN[1,3], P. H. MÄKELÄ[1] AND A. K. TAKALA[1,4]

[1] *National Public Health Institute, Helsinki, Finland*
[2] *Helsinki University of Technology, Espoo, Finland*
[3] *Rolf Nevanlinna Institute, University of Helsinki, Finland*
[4] *Orion Corporation, Orion Pharma, Espoo, Finland*

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SUMMARY

We used a structured population model to study factors determining the magnitude of indirect protection in *Haemophilus influenzae* type b (Hib) vaccination. On a simulation platform mimicking the population of Finland, a Hib transmission and immunity model, including cross-reactive bacterial encounters, was formulated. Utilizing different vaccination coverages and vaccine types we could study how fast the incidence of Hib disease declined due to direct and indirect vaccination effects. With the Finnish vaccination schedule we could reproduce the observed disappearance of Hib cases. Our results show that an indirect effect was already significant with a relatively low vaccine coverage, even with a vaccine only partly reducing carriage acquisition. This suggests that the vaccination schedule and vaccine to be used should be chosen to result, in addition to immunological memory, in high antibody concentrations, sufficient to reduce carriage, the latter being the main factor behind successful elimination of transmission and disease.

INTRODUCTION

The conjugated *Haemophilus influenzae* type b (Hib) vaccines have proved efficient in reducing the incidence of invasive Hib disease among the vaccinated and, in some populations, also among the unvaccinated [1]. The effect in the unvaccinated is a consequence of herd immunity: conjugate vaccines reduce nasopharyngeal Hib carriage in the vaccinated [2–4] and thus limit transmission from them to those unvaccinated. However, there has been variance in the extent of such indirect protection. Despite a high vaccination coverage in The Netherlands, the incidence of disease among the unvaccinated did not decline in the way seen in the United Kingdom or Finland [5]. Moreover, in Alaska Hib disease re-emerged among newborns even though 97% of infants old enough to be vaccinated received the vaccine, indicating very weak or non-existing herd effects [6].

Bacteria with surface structures similar to Hib antigens (e.g. *Escherichia coli* K100) are capable of inducing antibodies towards Hib bacteria [7, 8]. Exposure to these bacteria is assumed to contribute to the development of immunity against invasive Hib disease [9, 10]. Using a mathematical model to compare data on invasive disease in the United Kingdom and Finland we have previously argued that the rate of cross-reactive contacts varies between populations and that different exposure to such bacteria can partly explain the geographical variation in Hib epidemiology [11]. It has also been suggested that cross-reactive bacteria play a role in

* Author for correspondence: Dr T. Leino, National Public Health Institute, Mannerheimintie 166, FIN 00300 Helsinki, Finland.

the post-vaccination era by securing persistence of Hib antibody concentrations [10, 12]. One remaining question is what effect exposure to these bacteria has on the rate of Hib elimination in populations.

Haemophilus influenzae together with other encapsulated bacteria (*Neisseria meningitidis* and *Streptococcus pneumoniae*) are not particularly contagious but require close contact for transmission. The spread of these microbes thus occurs mainly in families, day-care institutions or military garrisons [13, 14]. The risk of an individual to encounter these bacteria is associated with their prevalence in the population, but even more so, in the small groups an individual belongs to. Thus, when studying transmission and changes in transmission due to direct and indirect vaccination effects, the constitution and distribution of different small groups in the population have to be taken into account.

We built an individual-based stochastic simulation model to study Hib transmission and disease [15]. The model was calibrated to produce the observed age-specific prevalence of Hib carriage and incidence of invasive disease in Finland before the onset of Hib conjugate vaccination. Immunity against disease was assumed to be the result of encounters with both Hib and cross-reactive bacteria. In this paper, we used the simulation model to study some of the main factors behind a successful intervention with Hib conjugate vaccines: (1) the direct and indirect vaccination effects on disease and on carriage depending on the vaccine used and (2) the magnitude of indirect protection achieved depending on the vaccination coverage.

METHODS

Population model

A population comparable to the Finnish one was divided into contact sites. Attending these sites depended on age: day care for toddlers up to 3 years old, day care for children from 4 to 6 years, school from 7 to 16 years, and a family (sizes 1–10) until 20 years old. After 20 years individuals started to pair up to produce new families. The distribution of necessary parameters such as birth and death rates, rate of marrying, attending day-care centres, distribution of sizes of families and day-care units followed the official demographic statistics of Finland for the year 1995. To stabilize the simulation, a population of size 100 000 was simulated for 10 years, then followed by 10 years of simulation with ongoing vaccination. In this article, the results were collected as averages from 10 separate simulations. The model is explained in more detail in ref. [15].

Modelling Hib transmission

Hib is mainly transmitted in contact sites. For each individual, the simulation monitored all contacts in these sites and the proportion of Hib carriers among them. Mixing within the sites was assumed homogenous. In addition, all individuals received a small, constant background intensity of exposure from the whole population of which the simulation represents only a fraction. Heterogeneity in susceptibility to carriage was required when adjusting the model to account for the age-specific carriage prevalence: adults (>22 years) had a 50% lower risk of becoming carriers after exposure to Hib when compared to children (<17 years). We assumed the duration of carriage to follow an exponential distribution with mean duration of 4 months [16].

Modelling Hib immunity

Immunity against invasive Hib disease is produced actively in response to Hib and cross-reactive bacterial encounters. Due to age-specificity in the ability to generate protective concentration of antibodies ($>0{\cdot}15\,\mu$g/ml), only children >1 year old gain protective immunity as a response to such contacts [11]. Furthermore, distribution of times of being immune after such encounters also depends on age. Approximately 60% of newborns have inherited immunity of maternal origin, which wanes over time, and practically all children are susceptible to disease by the age of 9 months. No immunity against carriage was gained via preceding carriage, the model for Hib carriage in a pre-vaccination era was, thus, a so-called S–I–S (Susceptible–Infectious–Susceptible) model.

To quantify the role of cross-reactive bacteria in Hib immunity we used results from a previous study comparing invasive disease in the United Kingdom and Finland [11]. It suggested that among young children in Finland <30% of all exposures that led to Hib antibody production were due to Hib. This corresponds to a constant rate of $\sim 0{\cdot}5$ cross-reactive bacterial encounters per individual per year, which was used in the present study.

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Table. *Proportions of children below 5 years of age protected*

Year	Proportion vaccinated (%)	Effectively protected against disease (%)	Proportion vaccinated and ⩾12 months old (%)	Proportion protected against carriage (%)
1986	3	38	0	0
1987	12	48	7	7
1988	30	58	22	15
1989	62	82	52	36
1990	84	100	74	54
1991	90	100	80	57
1992	90	100	80	53

After the start of vaccination the proportion of vaccinated by the end of each year were calculated according to the actual vaccination schedule (first column). The proportion actually protected against disease (second column) is higher and contains both vaccinated children and children who have acquired natural protection by exposure to Hib or cross reactivity. Only children who were vaccinated and over 12 months old could be protected against carriage (third column). In the last column fewer children are protected against carriage as waning of vaccine immunity is taken into account.

Vaccination effect in the model

Hib vaccination may reduce Hib disease in two ways: it may reduce acquisition of Hib carriage and, even when unsuccessful in preventing transmission, it may prevent the progression of carriage to invasive disease. Based on animal studies, it has been suggested that concentrations of the magnitude of 10 μg/ml in serum would reduce carriage acquisition [17]. These results are supported by empirical human data [18].

Vaccine types and coverage

According to empirical data on antibody concentrations after national vaccination schedules [19, 20], three types of vaccines were modelled. They all had 100% efficacy against disease, but the effect on carriage varied: 100%, 50% and no effect on carriage for those vaccinated. Effect was assumed to be all-or-nothing, i.e. for the scenario of 50% protection against carriage, half of the children were assumed to acquire full protection, while 50% were left without any protection against carriage. We also tested the effect of the coverage on the incidence of disease: coverages of 80 and 40% were taken as representing industrialized and developing countries respectively.

Vaccination performed in Finland

To study the role of indirect effects in the actual vaccination intervention carried out in Finland we collected information about the vaccination schedule, vaccination coverage, duration of immunity produced by vaccination and the observed disappearance of disease.

In the first conjugate vaccine efficacy trial, approximately half of the Finnish birth cohort during the study period of October 1985 to August 1987, i.e. 58000 children, were vaccinated in infancy with three doses of the Hib conjugate PRP-D, followed by a booster dose during the second year of life [21]. The other (control) half of the birth cohort was vaccinated with the same vaccine but only once, at age 24 months. Immediately after this trial a comparison study between two different Hib conjugate vaccines (PRP-D and HbOC) was started, with the aim of recruiting the whole birth cohort of children from the period September 1987 to August 1989 [22]. The coverage of this effort, consisting of two doses in infancy and a booster dose during the second year of life, was 94%. Thereafter, all Finnish children received the Hib conjugate vaccine (PRP-T) with the latter schedule, and the coverage surveys performed have shown coverage from 94 to 99%.

For the simulation we assumed, based on the actual serological data [19], that each child who has received Hib vaccine by age 4 months is protected from disease, while protection against carriage only develops in the second year of life (⩾12 months). We calculated, for each year after the start of vaccination, the proportion of children <5 years who were vaccinated and thus protected from disease (Table,

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first column) or from carriage (Table, third column). The proportion of children actually protected against disease during each year is higher as, in addition to vaccination, exposure to Hib or cross-reactive bacteria results in protective immunity (Table, second column). Waning of immunity against carriage was approximated from the observed antibody concentrations as follows: all vaccinated children were protected against carriage at age 12 months, 50% of them remained protected 1 year later, and still 20% of them were protected 5 years later [19]. The proportion actually protected against carriage (Table, fourth column) is thus smaller than estimated directly from the proportion vaccinated (see Table, third column).

In addition to a nationally ongoing recording of invasive Hib disease cases, an intensified surveillance was carried out in Finland during 1985–1986 [23]. At that time the size of the birth cohort was ~60000, and during one year, there were 197 cases of invasive Hib infections in children aged 0–15 years. The surveillance continued throughout the vaccination trials and thereafter [23]. In 2 years after the introduction of vaccination, the incidence had fallen by 50%, to 95 cases per year and in 4 years the disease was practically eliminated (Fig. 2).

RESULTS

The incidence of disease with vaccines differing in their effect on carriage

In the simulations we examined the use of three types of vaccines, each with an assumed 100% efficacy against disease, but differing in their ability to reduce carriage. With 100% coverage (Fig. 1*a*), the type of vaccine did not matter: all three tested vaccines led to elimination of invasive disease among children <5 years. With an 80% coverage (Fig. 1*b*) the results differed only marginally: a vaccine reducing carriage by 50% resulted in only 5% more disease after 4 years than a vaccine blocking acquisition of carriage completely, and both vaccines practically eliminated the disease in 10 years. Even 40% coverage with a vaccine blocking carriage led to a 75% reduction in disease in 4 years and practically eliminated the disease in 10 years (Fig. 1*c*). A vaccine with any effect on carriage limits the disease burden better than a vaccine without such an effect. For example, 40% coverage with a vaccine reducing acquisition of carriage by half, led to the same result in 10 years as

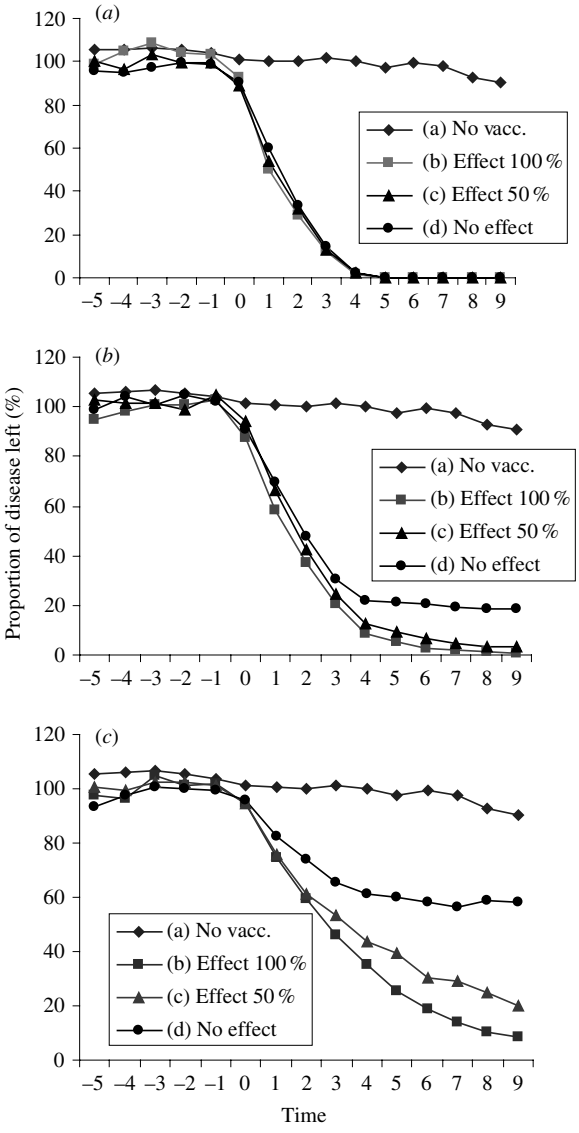

Fig. 1. Incidence of invasive Hib disease before and after the onset of Hib conjugate vaccination, based on 10 simulations each of 100000 individuals. The pre-vaccination level is marked as 100%. Four lines are presented in each panel corresponding to the effect the vaccine has on coverage: (a) no vaccination at all; (b) 100% effect on carriage; (c) 50% effect on carriage; (d) no effect on carriage. The three panels illustrate (*a*) 100%, (*b*) 80%, (*c*) 40% vaccination coverage.

80% coverage with a vaccine with no effect on carriage (Fig. 1*b*, *c*), and thereafter the vaccine affecting carriage would be even better.

Indirect effects

We note that the difference between curves pertaining to 'no vaccination' and 'vaccine with no effect on carriage' is due to the direct vaccine effect on disease. Differences between the curves 'vaccine with no effect

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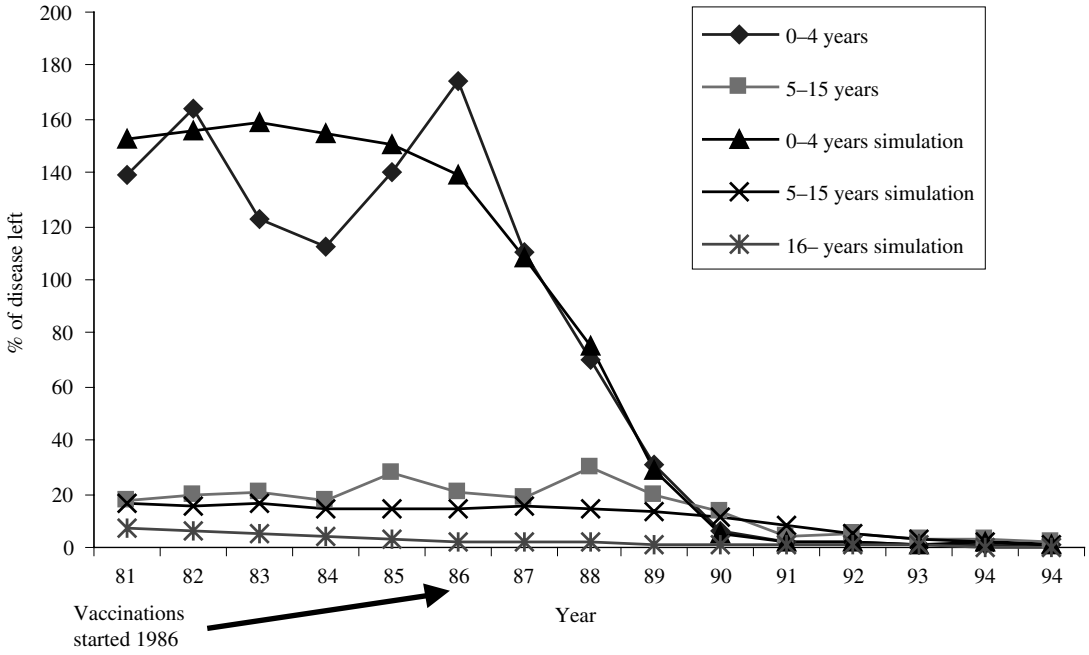

Fig. 2. Observed and simulated numbers of invasive Hib disease in Finland before and after the onset of Hib conjugate vaccination in 1986 (black arrow), shown in two age groups: 0–4 and 5–15 years. Also the simulated number of cases in a cohort >15 years old is shown, based on 10 simulations each of 100 000 individuals. The numbers of simulated cases were scaled up to the size of the Finnish population (approximately 5 million individuals).

on carriage' and, say, the curve with 50% reduction in acquisition of carriage are solely due to indirect protection. When the coverage was high and the vaccine very effective (100%) against disease, indirect effect was hard to document. This is explained by the early occurrence of the disease, predominantly among infants and toddlers. The direct effect of the vaccine given during infancy 'overrides' the indirect protection, which therefore cannot be observed. However, if the coverage was not optimal, say 80%, there is clearly an added value in using a vaccine that reduces carriage acquisition.

It is worth noting that already a 50% effect on carriage was adequate to drastically limit transmission even with a low coverage (Fig. 1*b*, *c*). Moreover, as the 50% reduction of carriage was modelled as an all-or-nothing effect (see Methods section), the vaccine-induced reduction of carriage in the extreme situation (40% coverage, 50% efficacy towards carriage) would only be 20%, sufficient, however, to cause a clear indirect effect (Fig. 1*c*).

Observed disappearance of invasive Hib disease in Finland

By running the model using the actual vaccination timetable used in Finland, the observed disappearance of invasive Hib disease could be reproduced (Fig. 2). The incidence of disease decreased synchronously in the vaccinated cohorts both in the observed data and in the simulated situation. The peak in 1986 in the number of observed cases of invasive Hib disease in children <5 years old is probably due to the intensified surveillance at the time. Cases also disappeared in children in the 5–15 years age group, partly because of indirect protection, and partly as vaccinated cohorts grew older and started to enter this age group 5 years after the start of vaccination.

The underlying prevalence of Hib carriage among children <5 years declined following vaccination as seen in the carriage profile produced by the simulation model (Fig. 3). The carriage prevalence in this age cohort fell by one third by the end of 1988 when 23% of the age cohort had gained protection against carriage directly by vaccination (Fig. 3, Table) suggesting a slight indirect effect due to reduced transmission. Striking indirect protection, however, is seen among children aged 5–15 years during years 0–5, i.e. before any of vaccinated children had entered this cohort. By that time, solely by indirect protection, Hib carriage in this older cohort had been reduced by 40% (Fig. 3).

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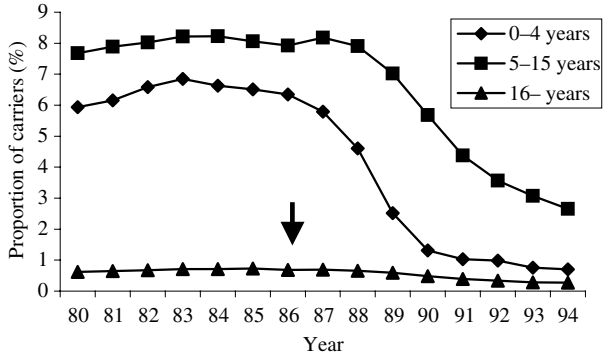

Fig. 3. Prevalence of Hib carriage in Finland in three age groups (0–4, 5–15 and >15 years) produced by the simulation model. Large-scale vaccination with Hib conjugate vaccine were started at the beginning of 1986 (black arrow).

DISCUSSION

It is difficult to forecast the magnitude and clinical significance of indirect protection if the vaccine only moderately reduces the risk of carriage acquisition. Furthermore, the coverage of vaccination and, especially for infections requiring close contact for transmission, the contact structure of the population affects the resulting indirect effects. The rate of disease reduction also depends on the age distribution of cases: when young children account for the majority of cases, infant vaccination quickly reduces disease incidence with a vaccine efficacious against disease. In this study we examined the magnitude of the indirect effect produced with vaccines having varying effects on carriage, combined with different vaccination coverages in a structured simulation model.

According to our results even a fairly small effect on carriage results in a considerable reduction in the incidence of invasive Hib disease. In one or two decades after the start of such a vaccination programme the disease will be eliminated. This suggests that the epidemiology of Hib is fragile and easily disturbed in case carriage, and thus transmission, is affected. Unlike the case with other paediatric diseases such as measles, Hib disease did not shift to older age groups even when vaccination reduced Hib carriage and thus the chances of Hib contact during the first years of life. The reason for this lack of shift in age of contracting Hib disease when transmission is limited is due to the continuous development of immunity by the exposure to cross-reactive bacteria, included in our model.

One reason behind the broad range of indirect effects observed in populations with high vaccination coverage could be the different vaccines used. The immune response of infants to the different conjugate Hib vaccines varies [24–26]. In fact, in Alaska the major explanation for the resurgence of the disease seemed to be a lack of herd immunity due to a particular vaccine (PRP-OMP) known to cause poor secondary responses at consecutive doses and thus lower antibody concentrations than other Hib conjugate vaccines [24]. The actual concentration of antibodies is important: even though all vaccines give protection against *invasive disease*, protection against *carriage* seems to be related to the capability of the vaccine to induce sufficiently high antibody concentrations [17, 18, 27].

Further, the vaccination schedule can affect the success in achieving a notable herd effect. In areas where invasive disease occurs at an early age the protection already obtained after the first dose is of major importance. The relevance of a booster dose, especially in these areas, has been under debate [5, 28–30]. There has also been interest in reducing the number of doses or in using fractional doses due to the high cost of conjugate vaccines [18, 31]. However, the booster dose at the second year of life markedly increases serum antibody concentrations [19], probably also extending the duration of immunity against Hib carriage. Unsatisfactory indirect protection due to the lack of a booster dose during the second year of life could well be one of the reasons behind the recently observed rising incidence of invasive Hib diseases in the United Kingdom [32].

The minimum vaccination coverage needed to achieve a significant reduction in transmission by indirect effect depends on the frequency of contacts close enough to allow transmission and on the effect the vaccine has on carriage acquisition for such contacts. Reduction of disease would, therefore, be more demanding in areas with heavy transmission due to crowding, for example. Knowledge about the dynamics of transmission, especially within families, has been argued as being crucial for successful elimination of Hib disease by vaccination [33]. In this work we used a population simulation model structured in terms of contact sites. The structure as well as the demography can be broadly taken as representative for industrialized countries. For conclusions concerning developing countries the population in the model should be restructured.

As well as the contact pattern and demography, the invasive Hib disease pattern used in the model was also based on data from Finland. If invasive

disease occurs at a much younger age it may seem irrelevant whether the protective effect against carriage, obtainable only after the booster dose, is gained or not. However, although disease in certain countries occurs very early in life, carriage continues past 1 year of age [1, 34]. A 50% effect of vaccination on carriage with 80% vaccination coverage among the cohort of children between 1 and 2 years, would lead to satisfactory coverage (~40%) among the total cohort of children <2 years causing significant indirect protection. In fact, even when vaccination coverage is high a reduction of transmission would be useful, as not all vaccinated individuals acquire protective direct immunity from vaccine, and there will always be younger infants who are unvaccinated.

According to the initial assumptions, the duration of protection against disease and carriage was practically permanent. This was based on analyses of duration of Hib immunity demonstrating that antibody levels are sustained through intermittent stimuli by exposure to Hib or cross-reactive bacteria. However, this continuous process may not lead to sustained antibody concentrations high enough (>10 μg/ml) to prevent further carriage acquisition. To account for this, in the scenario reconstructing the situation in Finland, the duration of protection against carriage was approximated from actually measured antibody concentrations (Table, third column; Fig. 2).

Coen et al. assumed the conjugate Hib vaccine to (at least partially) protect from both carriage and invasive disease [35]. Two mechanisms of carriage reduction were modelled: prevention of acquisition or shorter duration of carriage. Their conclusion was that if no effect was assumed on the duration of carriage the vaccine has to be very effective in preventing acquisitions in order to explain the observed drastic decline in the incidence of Hib disease. However, the rate of waning immunity was assumed to be equal for both immunity to disease and to carriage. Our theoretical simulations, not allowing waning of immunity, showed a clear indirect effect already with a limited effect on carriage acquisition (20% reduction) and are not very far from the results of Coen et al. Some diversity is due to the differences in contact structure: transmission in our model occurs via families, school classes and day-care units, while in their model Hib is spread in a more diffuse, homogenous manner, the latter being more difficult to disturb. Moreover, a stochastic approach allows us more confidence in working with situations approaching elimination of disease than the deterministic approach used in the modelling by Coen et al.

CONCLUSION

Understanding the reasons for the observed differences in indirect protection produced by vaccination programmes could facilitate decisions in countries considering Hib vaccination. In this work we have studied what characteristics in the Hib vaccination process lead to indirect protection. By using a structured model we were able to estimate the magnitude of indirect protection produced by vaccines affecting carriage, and thus transmission, at a varying intensity. Indirect effect was already significant at relatively low vaccine coverage, even with a vaccine having only a moderate effect on carriage.

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