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The Hib immunization programme in the Oxford region: an analysis of the impact of vaccine administration on the incidence of disease

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SUMMARY

In May 1991 an immunization programme against *Haemophilus influenzae* type b (Hib) infection began within the Oxford region. We validate a deterministic mathematical model of Hib by comparison with the incidence of disease in the Oxford region, 1985–97. The comparison of model results with observed outcome allows an exploration of some of the poorly understood properties of the immunization programme. Model results and observed incidence are consistent with a vaccine that blocks the acquisition of carriage. Similarly, the data suggest that factors other than experience of Hib carriage are likely to have generated acquired immunity to Hib disease prior to the introduction of vaccination. Hence it is unlikely that waning of vaccine-derived protection will result in a resurgence of disease. The inclusion in the immunization schedule of a booster dose, as used in other countries, would have provided very little extra benefit.

INTRODUCTION

The invasion of human tissue by *H. influenzae* bacteria can result in a variety of clinical conditions ranging from otitis media to pneumonia and meningitis. A proportion of these bacteria possess a polysaccharide capsule, and on the basis of this capsular antigen they can be classified into six serotypes, a to f [1]. Although all serotypes are capable of causing disease, *H. influenzae* type b (Hib) was responsible for more than 90% of invasive disease [2–4]. In May 1991 an experimental trial was set up in the Oxford region. Approximately half the infant population, 27860 infants, were vaccinated with the Hib conjugate vaccine PRP-T, in which polyribosylribitol phosphate (PRP) is conjugated to tetanus toxoid [5]. In October 1992 a mass immunization programme was begun in the United Kingdom, using an 'accelerated immunization schedule' in which 3 doses of PRP-T were administered at 2, 3, and 4 months of age [6]. In addition, a 'catch-up' programme was introduced for the first year, where children 12–48 months of age received a single dose of HbOC, a conjugate vaccine in which PRP is conjugated to a non-toxic mutant of diphtheria toxoid [7]. The decision to introduce conjugate Hib vaccines was based upon vaccine trials that demonstrated a reduced incidence of disease in vaccine recipients [8, 9]. Since then, the widespread use of vaccine has caused dramatic declines in Hib disease incidence [10–13]. However, the optimal vaccination strategy remains unclear, partly because of a limited understanding of the epidemiology of Hib. For example, the UK immunization programme differs from that used in other countries, such as the United States, by the omission of the 'booster dose' at roughly 1 year after the 3 doses of primary immunization [14]. It was reasoned that, if the protection

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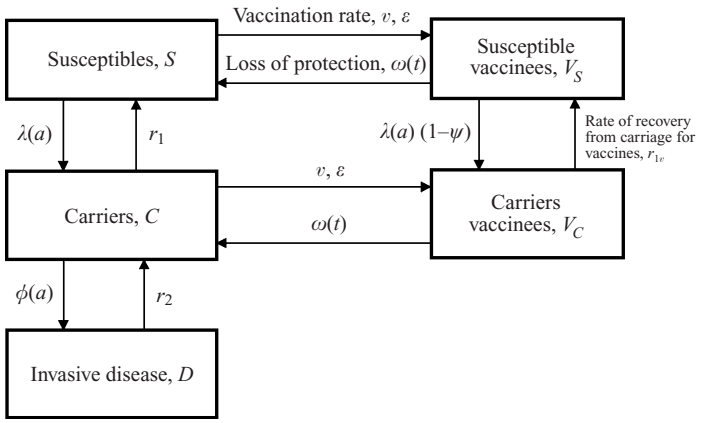

Fig. 1. A schematic representation of the model of Hib (see text for details).

induced by primary immunization did not wane with time, the booster dose would be unnecessary. There is believed to be a threshold concentration of antibodies for protection against Hib disease, estimated at 0·15 μg/ml [15], derived from studies of disease in the unvaccinated population [16]. This figure continues to be used in the interpretation of data on serum antibody concentrations in the vaccinated population. There is evidence that in infants serum antibody levels wane with time post-vaccination, often below 0·15 μg/ml [6, 17]. However, waning antibody levels following conjugate vaccination may be irrelevant to protection against disease as these rely on qualitatively different aspects of the immune system [18]: their ability to induce memory B-cells means that the absolute serum concentration of Hib antibody may be less relevant.

The introduction of Hib vaccination has so far been an unqualified success. To learn the lessons for future vaccination programmes some of the reasons for that success deserve exploration. To that end we have developed a mathematical model describing the epidemiology of Hib carriage and invasive disease which includes vaccination. We validate the model by comparing predictions with the observed incidence of invasive disease available for the Oxford region, 1985–97.

MATERIALS AND METHODS

The population of the Oxford region

Taking 1988 as the mid-year the population of the Oxford region was estimated at 2518000, of whom 171800 were less than 5 years of age (Office of Population Censuses and Surveys). The birth rate and age dependent *per capita* mortality rates were fitted in order to generate the age structure of the population. Data on the incidence of invasive disease caused by Hib were collected by the Haemophilus Reference Laboratory at the Oxford Public Health Laboratory [19, unpublished data]. The data comprise numbers of cases that occur every year in children 0–10 years of age, the age group reported to experience the great majority of all Hib invasive disease in the UK [4]. Between 1985 and 1990 a yearly average of 63 cases was observed, and thereafter there were 39 cases (1991), 53 cases (1992), 9 cases (1993) and 1 or 0 cases until 1998 [19].

The model

A mathematical model describing asymptomatic carriage and Hib disease, based on a review of data on the prevalence of carriage and the incidence of disease by age has previously been described [4, 20]. The impact of immunization was investigated by adding the following factors to the model: age specific vaccination rates, the waning of protective efficacy and vaccine-induced protection against asymptomatic carriage. This extended model is illustrated schematically in Figure 1. Our earlier analysis indicated that incomplete naturally acquired immunity to carriage is likely and therefore the model is in the form of a 'susceptible-infected-susceptible' (SIS) model as detailed in Coen [20]. In the model asymptomatic carriers are assumed to be infectious. At birth everyone ($X(0, t)$) is assumed susceptible to the acquisition and establishment of carriage, after which there is an age dependent incidence of carriage, the force of infection, $\lambda(a)$. Asymptomatic carriers, $C(a, t)$, experience disease, $D(a, t)$, at an age dependent rate $\phi(a)$, which is high at birth but declines rapidly

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thereafter [20]. Vaccination is represented by the addition of the two vaccinee classes. Both susceptibles and carriers may have been vaccinated ($V_s(a,t)$ and $V_c(a,t)$ respectively). Our assumptions on vaccine efficacy are related to a general model of vaccination described by McLean and Blower [21], and explicitly represent various possible mechanisms of vaccine failure. Infants are vaccinated at a time-dependent rate $v(a)$. A proportion of such vaccinations, ϵ, known as the 'take', lead to immediate protection from disease. If the vaccines fail to provide protection from carriage (rather than disease), there will be no protection from acquisition of carriage ($\psi = 0$) and the rates of recovery from carriage will be the same in vaccinee and normal carriers ($r_1 = r_{1v}$). If, however, the vaccine also protects from carriage, then two mutually inclusive possibilities arise: 1, the acquisition of Hib carriage by susceptible vaccinees ($V_s(a,t)$) might be reduced ($\psi > 0$); 2, vaccinees might recover more quickly from the carrier state ($r_{1v} > r_1$). Finally, the vaccine has a protective efficacy against disease that may wane at a time dependent rate $\omega(t)$.

The model is represented by the following set of partial differential equations:

$$\frac{\delta S(a,t)}{da}+\frac{\delta S(a,t)}{dt} = r_1 C+\omega(t) V_S - (\lambda(a)+\mu(a)+v(a)\epsilon) S$$

$$\frac{\delta C(a,t)}{da}+\frac{\delta C(a,t)}{dt} = \lambda(a) S+\omega(t) V_C+r_2 D - (r_1+\mu(a)+\phi(a)+v(a)\epsilon) C$$

$$\frac{\delta D(a,t)}{da}+\frac{\delta D(a,t)}{dt} = \phi(a) C-(r_2+\mu(a)) D$$

$$\frac{\delta V_S(a,t)}{da}+\frac{\delta V_S(a,t)}{dt} = v(a)\epsilon S+r_{1v} V_C-(\omega(t) +\{\lambda(a)(1-\psi)\}+\mu(a)) V_S$$

$$\frac{\delta V_C(a,t)}{da}+\frac{\delta V_C(a,t)}{dt} = (\lambda(a)(1-\psi)) V_S+v(a)\epsilon C - (r_{1v}+\omega(t)+\mu(a)) V_C.$$

The risk of acquiring infection depends on the rate at which susceptibles interact with Hib carriers across all ages, such that

$$\lambda(a) = \int_0^\infty \beta(a,a')\frac{Y(a')}{N(a')}da'.$$

For simplicity age is divided into groups such that $\lambda(a) \equiv \lambda(i)$

$$\lambda(i) = \sum_{j=1}^{5} \beta(i,j)\frac{Y_j}{N_j},$$

where $\beta(i,j)$ is a transmission coefficient that depends on the age of the 'donor' (j) and on that of the 'recipient' (i), and N(a') is the number of persons in age class a'. We divide the population into five age classes $i = 1, 2, \ldots, 5$ (aged 0–1, 2–5, 6–14, 15–24 and 25–90 years). $\beta(i,j)$ is a matrix of 25 transmission coefficients called the 'Who Acquires Infection (carriage) From Whom' (WAIFW) matrix. The values of $\lambda(i)$ can be derived from studies of the prevalence of carriage and the values Y_j follow on from these, but this leaves 25 unknowns in five equations. We follow the method of Anderson and May [22] who derive values of $\beta(i,j)$ by constraining the matrix to contain only five values. A range of matrix constraints were employed.

Vaccination rates

In 1993, during the Hib vaccination programme, vaccine coverage was studied in the North East Thames region [23]. Children were followed for 1 year to determine the proportion receiving vaccine. An estimate of the proportion who have received vaccine is complicated by the age schedule for vaccination, i.e. some children receive vaccine between ages that cover less than a year while vaccination efforts lasted for a year. Thus, the proportion, p, who have received vaccine after a year is:

$$p = 1-\exp(-v\alpha),$$

where v is the instantaneous rate at which children receive vaccine measured in units per year, and α is the age period over which they are actually vaccinated. The following proportions of vaccination coverage (p) generated the vaccination rates (v) used in model simulations: 90% of 2–4 months old infants born in 1991, although only half the population was targeted [19], 92 and 93% of 2–4 months old infants born in 1992 and from 1993 onwards respectively [24]. For the catch-up programme, carried out in 1992–3, we used coverage proportions published by O'Brien [23]: 87, 77 and 34% of 1-, 2- and 3-year-old children respectively. A booster dose, if it were to be included, would probably be given at the same time as the Measles–Mumps–Rubella (MMR) vaccine. Therefore we assumed that it would have the same coverage (91%) as that published for MMR [25].

Waning vaccine protective efficacy

National surveillance for clinical vaccine failures has been in place since routine immunization began in

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1992 and allows conclusions to be drawn about waning vaccine protection [26]. Data on vaccine failures were used in combination with a study of antibody concentrations in vaccinated Oxford children of different ages (17, P. Heath, unpublished data). An exponential decay model is used for the loss of protection:

$$\rho(t) = \rho(0)\,\epsilon, \exp\left(-\int_0^t \omega(t')\,\delta t'\right)$$

where $\rho(t)$ is the proportion of age a individuals protected for time t in the population (i.e. the proportion in categories $V_S(a,t)$ and $V_C(a,t)$), $\rho(0)$ is the proportion of individuals initially inoculated at time 0, ϵ is the 'take' of the vaccine, and $\omega(t)$ is the time-dependent rate at which individuals lose the protection. The parameter $\omega(t)$ was considered to be a variable dependent on time post-immunization, which allows for the possibility of waning protective efficacy. The functional form and estimates of the 'take' (ϵ) and waning $\omega(t)$ were estimated using maximum likelihood methods experimental data [17]. In estimating the failure rate we assumed that no change in the incidence of carriage had occurred. As we shall see this is unlikely to be correct. Therefore, the estimates of the rate of loss of vaccine derived protection from disease are very much a lower bound. Dropping the age dependency we used the vaccine failure data to fit $\rho(t)$ by maximum likelihood, in order to estimate the post-immunization time dependence of the rate of protection loss of protection, $\omega(t)$, as a linear or exponential function. It is throughout assumed that loss of vaccine-induced protection leads to susceptibility to acquisition of both disease and carriage.

In fitting the model to the data set, we used a maximum likelihood deviance function which assumes binomial errors. (The deviance function approximates the χ^2 distribution with $n-v$ degrees of freedom, where n is the number of observations and v is the number of parameters being fitted.) When fitting the model to a data set, a high p value is indicative of a high probability that if the model were true chance was accountable for the discrepancies between data and model expectations [27].

Protection from carriage

The possibility that the vaccines protect against carriage is of interest because it would prevent the spread of the Hib organism leading to direct benefits of protection from disease for the vaccine recipients. Whereas unconjugated PRP vaccine does not confer protection against Hib carriage, evidence for such protection has accumulated for a range of conjugate vaccines [28–31]. One study suggests that PRP-T conjugate vaccine administration in 7–19-month-old infants is associated with the appearance of significant levels of IgG antibody in saliva [32]. Kauppi and colleagues [33] had previously shown the ability of salivary IgG antibodies to clear carriage in infant rats. Barbour and colleagues [29] found an inverse relationship between the Hib colony count grade and the serum anti-PRP IgG concentration, and Barbour and colleagues [30] subsequently demonstrated that infants vaccinated with PRP-T vaccine, as well as their mothers and siblings, have a low relative risk of acquiring Hib carriage (RR = 0·505; 95% CI: 0·468, 0·544). Nevertheless, the mechanism that leads to protection is not fully understood. The vaccine can have two direct influences on carriage in vaccinees. On the one hand it can prevent susceptibles for acquiring the Hib organism, which was considered in the vaccination model as the proportion of acquisitions that failed to lead to colonization of the pharynx, ψ. On the other hand the vaccine can assist clearance of the organism ending the carrier state. This effect implies a higher rate of loss of carriage for effectively vaccined carriers, r_{1v}. As information from cohort studies of vaccination was unavailable, we explored the impact of reduced duration of carriage on the one hand (r_{1v}), and reduced acquisition of carriage on the other (ψ), by testing the fit of the model against the post-immunization time series data set.

Elimination

Because the mathematical model of Hib is a deterministic large population approximation it cannot predict extinction because the number of carriers never reaches exactly zero. To explore elimination we used a method described by Renshaw [34] that allows the calculation of the threshold number of carriers, n_0, estimated in the deterministic simulation for which there is probability q of extinction within the next time interval of width t [35, 36]. The expressions used are the following:

$$x = \frac{m - m\exp\left(-(b-m)\,t\right)}{b - m\exp\left(-(b-m)\,t\right)}$$

$$n_0 = \log_{10}(q-x).$$

Given parameters b (the per-carrier rate of 'production' of carriers) and m (the per-carrier rate of 'loss' of carriage), a q of 0·95 and a t of 1 year enable

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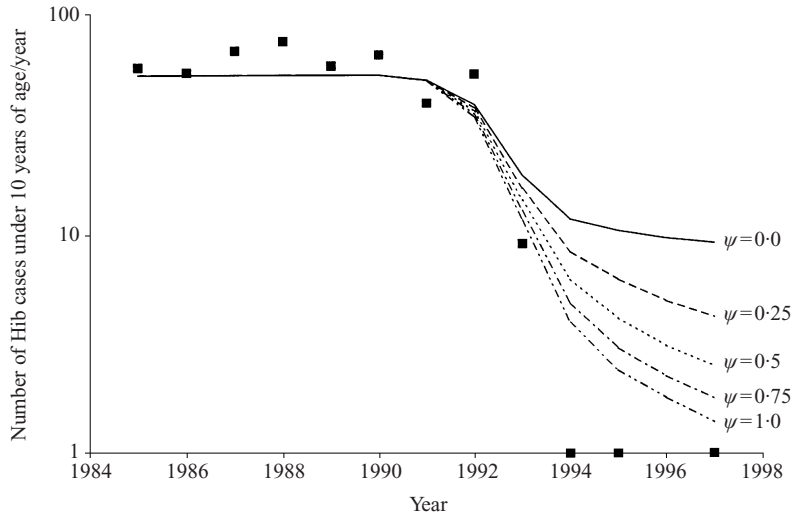

Fig. 2. Retrospective fit of the Hib model to the observed time series of Hib disease in the Oxford region. A range of assumptions on the degree of vaccine protection against acquisition of carriage (ψ) are compared against the data.

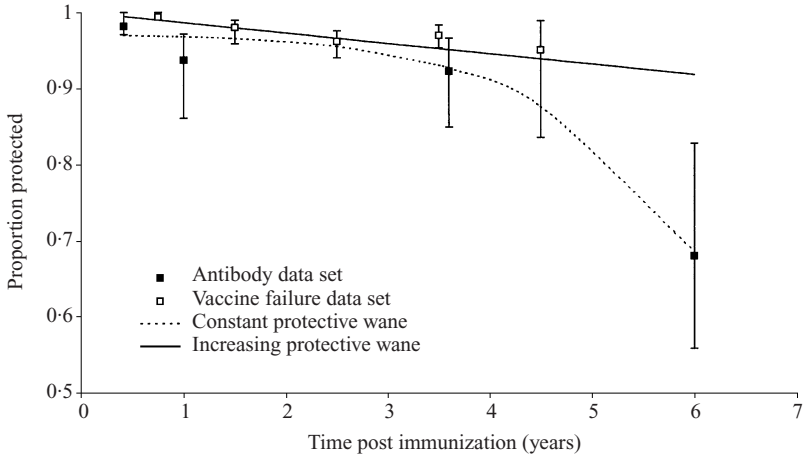

Fig. 3. Proportion of vaccinees protected from Hib invasive disease. Two data sets are displayed together with 95% confidence intervals, and fitted models. The data are a time series of vaccine failures (empty squares), and serum anti-PRP antibody concentrations (full squares). It was assumed that concentrations less than 0·15 μg/ml were not protective. The antibody study involved the follow-up of four cohorts of vaccinees: 107 up to 5 months, 95 up to 12 months, 153 up to 43·2 months and 59 up to 72 months post immunization. The vaccine failure data originate from a national surveillance study of Hib vaccine failures. The number of vaccine failures in each age group are compared with the number expected based on child-years exposure and age-specific attack rates in the pre-vaccine era [26] (14 at 5–11 months, 33 at 12–23 months, 24 at 24–35 months, 10 at 36–47 months and 3 at 48–59 months of age between 1992 and 1998). Models were fitted to the data sets using maximum likelihood techniques (continuous and broken lines).

us to estimate that the elimination of Hib carriage over the next year is possible with 95% certainty if the carrier population size falls below n_0. A q value of 0·95 will give extremely conservative estimates for time to extinction. The parameter b is the average rate of acquisition of new infections *per carrier*, over all age classes:

$$b = \beta\left(\frac{S}{C}\right)C = \beta S,$$

where β is the transmission coefficient of Hib, S is the number of susceptibles and C is the number of carriers in the population. The carrier 'removal' rate, m, is given by the expression:

$$m = m' + p_1 r_1 + p_2 r_{1v},$$

where m' represents the average mortality rate over all age classes, p_1 is the proportion of unvaccinated carriers, and p_2, the proportion of vaccinated carriers, is equal to $1-p_1$. Both b and m are dynamic as S, C

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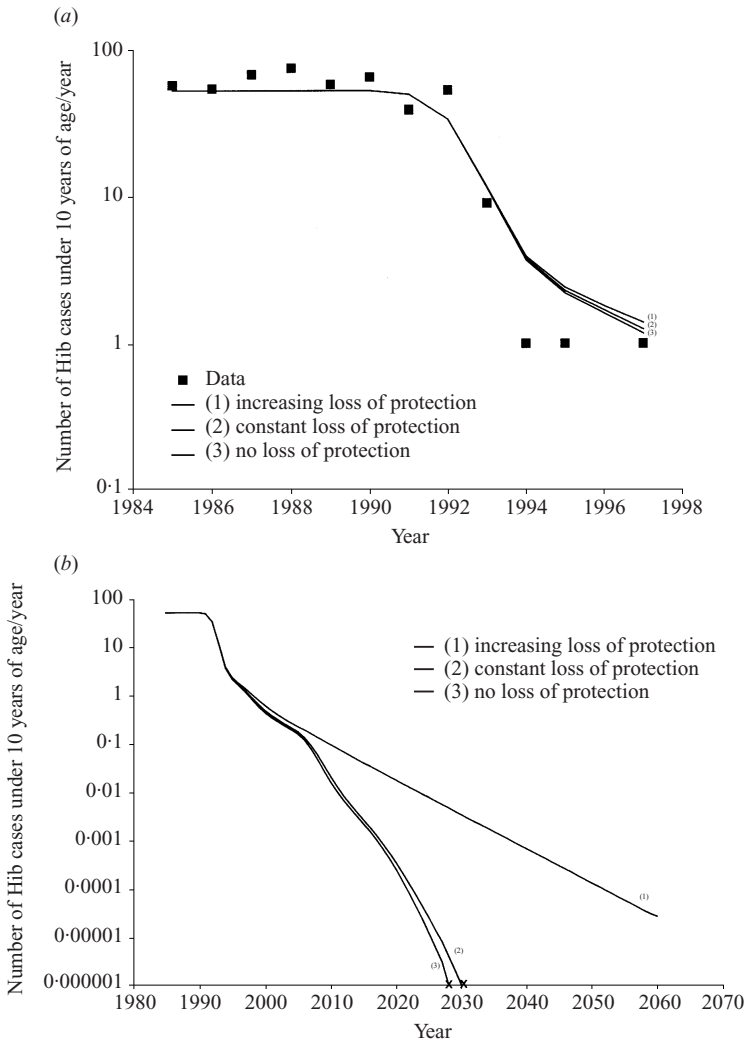

Fig. 4. Short (*a*) and long (*b*) term predictions of the Hib model (lines) concerning the trends of incidence of Hib disease pre and post-immunization in children younger than 10 years of age. Three models of waning protective efficacy of the vaccine against invasive Hib disease are compared and matched against a time series data set (filled squares). The data set was collected in the Oxford Region, 1985–95 from Booy and colleagues [19] and PHLS for the Oxford Region.

and p_1 vary during the immunization programme; therefore the elimination threshold n_0 changes as a function of the number of susceptibles, and the proportion in the vaccinee categories (p_2), which are parameters included in the model.

Reintroduction of Hib

The continuous movement of people into and out of the countries where Hib is endemic will allow for the reintroduction of the organism at a rate that is currently unquantifiable. Therefore, we represent the influence of travel using a constant force of infection λ_i that is unaffected by the immunization programme [36]. We used a range of four values: 0, 100th, 1000th and 10000th of the equilibrium force of infection estimated at 0·08 per susceptible per year on average across all age classes [20].

Hib carriage and immunity to Hib disease

Hib carriage is thought to play a significant role in priming the immune system against invasive Hib disease [20]. Nevertheless, micro-organisms that cross-react with Hib capsular polysaccharide may also contribute to levels of acquired immunity to Hib disease [37, 38]. If the immunization programme successfully reduces the number of Hib carriers in the population then a reduction in the acquisition rate of Hib carriage is expected, as well as a reduction of any associated acquired immunity. This effect may lead to an increase of the 'force of disease', $\phi(a)$ (the rate at

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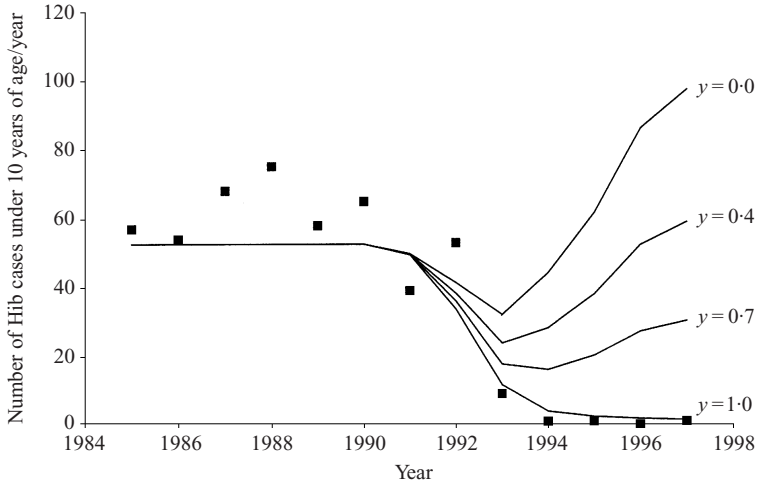

Fig. 5. Retrospective fit of the Hib model to the observed time series of Hib disease in the Oxford region. A number of assumptions concerning the role of factors other than experience of Hib carriage in generating immunity to disease (y) are compared against the data.

which carriers become diseased in our model), throughout all age classes.

In our earlier work [20] we derived an age specific rate at which carriers progress to disease which falls from a maximum at birth ($\phi(0) = \gamma + \alpha = 0{\cdot}151$) to a minimum, γ at a rate ($\beta = 1{\cdot}127$) per year of age:

$$\phi(a) = \gamma + \alpha \exp(-\beta a).$$

This rate is modified by the presence of vaccination. We assume that there are two extremes of influence of previous exposure to carriage. At one extreme, exposure to carriage has no influence on per-carrier susceptibility, $\phi(a)$, hence reduction of Hib carriage by vaccination does not lead to an increase in the overall incidence of Hib disease. At the other extreme, exposure to carriage is the only determinant of acquired protection from disease. This extreme hypothesis predicts that all protection from disease depends on exposure to carriage: in the absence of carriage there will be no decline in per-carrier susceptibility to disease, $\phi(a)$, with increasing age ($\phi_2(a) = \gamma + \alpha$). Between these extremes if we assume a fraction (y) of protection is caused by cross-reactive organisms then

$$\phi_2(a) = \gamma + \alpha(1-y) + \alpha y \exp(-\beta a).$$

Following vaccination the rate of progress to disease will depend upon the reduction in previous exposure to carriage. This can be measured as the ratio of carriage after vaccination to that before vaccination, δ:

$$\delta = \frac{1 - \exp\left(-\int_0^a \lambda'(t-a', a')\, da'\right)}{1 - \exp\left(-\int_0^a \lambda(a')\, da'\right)}.$$

where a is age, t is time post-immunization. $\lambda(a)$ is the force of infection before vaccination and $\lambda'(t-a, a)$ is the age and time dependent force of infection following vaccination. Thus, our revised rate of progress to disease following vaccination $\phi_v(a)$ is

$$\phi_v(a) = \phi_1(a) + (1-\delta)(\phi_2(a) - \phi_1(a)).$$

RESULTS

The observed incidence of Hib

The success of the Hib vaccination programme in the Oxford region was evaluated by the ascertainment of Hib disease cases among children younger than 10 years of age. The numbers of Hib invasive disease cases are compared with model predictions for a variety of assumptions to gain retrospective insights about the behaviour of the vaccine. It is not possible on the basis of our data to distinguish between a vaccine that prevents the acquisition of carriage and one that accelerates recovery from carriage. However, the data are only consistent with a very effective vaccine. For example, assuming that there is no change in the rate of loss of carriage in vaccinees, then only substantial protection from acquisition of carriage ($\psi \approx 1$) is consistent with the observed incidence of disease (Fig. 2).

A concern about the epidemiology of Hib is whether the protective effect of vaccination will fade. We can explore this directly through the analysis of vaccine failure data [24], which suggests that the protective efficacy of the conjugate Hib vaccine wanes with time, where the best fitting model is one of constant loss of vaccine protection ω_f equal to 0·0142 per vaccinee per

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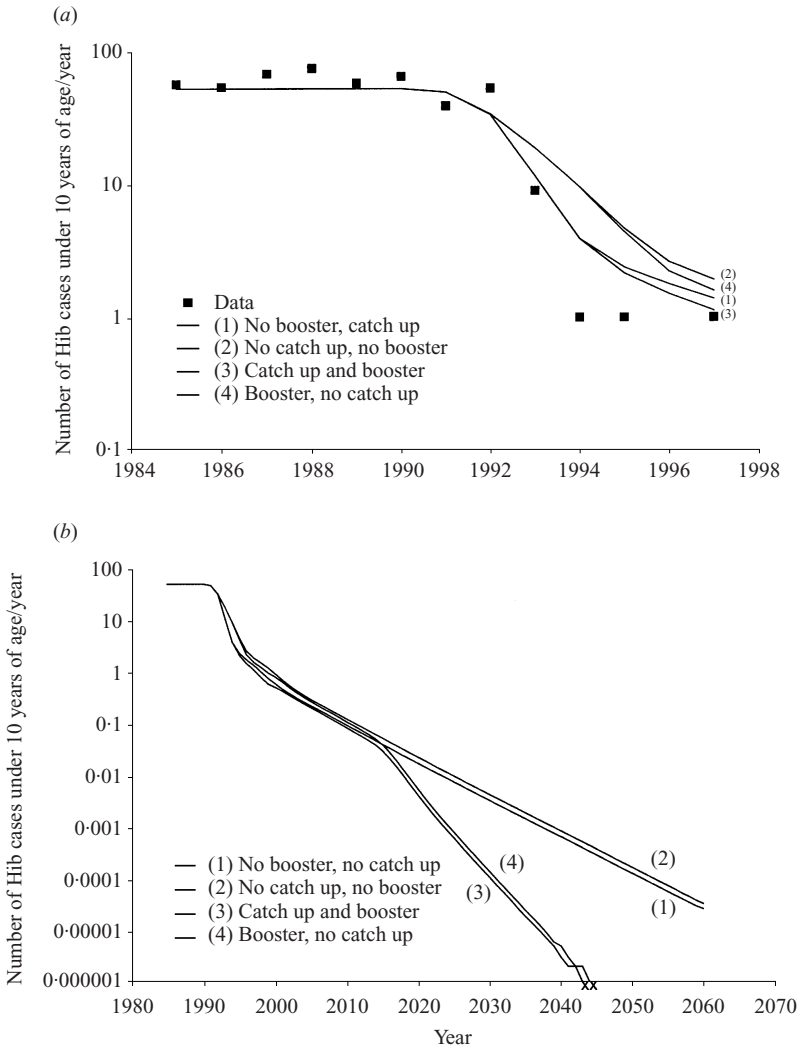

Fig. 6. (*a*) The short-term impact of four immunization programme strategies on the incidence of Hib disease in children younger than 10 years of age. No reintroduction of Hib carriage is assumed ($\lambda_i = 0$), and post-immunization pattern of acquired immunity to disease is assumed unaltered by changes in the experience of carriage ($y = 1$). (*b*) Long-term trends where the immunization programme is continued. Four scenarios are compared. The first one is the *status quo* situation where the strategy was to exclude the booster dose and include the catch-up programme. The second one is the omission of both booster dose and catch-up programme. The third one was the inclusion of both booster dose and catch-up programme. And the fourth one was the Hib immunization programme with the booster dose only.

year ($\chi^2 = 7{\cdot}26$; D.F. $= 4$; $p = 0{\cdot}12$: *P*-value greater than 0·05 is indicative of an adequate fit) (Fig. 3). Antibody data [17, P. Heath, unpublished data] shows a similar trend, except that it predicts an increased waning of protective efficacy 4–6 years from the vaccination event. This result depends on the observation of a cohort of 59 vaccinees for 6 years post-immunization, a relatively small sample size, which results in wide 95% confidence intervals. The best fitting model for antibody data was:

$$\omega(t) = \alpha \exp(\beta t),$$

where $\alpha = 0{\cdot}0264$ and $\beta = 0{\cdot}198$ ($\chi^2 = 8{\cdot}588$; D.F. $= 3$; $P = 0{\cdot}04$; Fig. 3). The vaccine failure data show a significantly lower reduction in protection throughout ($\chi^2 > 20{\cdot}0$; D.F. $= 1$, $P < 0{\cdot}001$). The fitted model is consistent with ϵ equal to unity, i.e. 100% seroconversion on injection of the vaccine. The accelerating decline at 6 years is only apparent in the antibody data, but vaccine failure data are currently unavailable for such a long follow up period.

Figure 4*a* illustrates the consequence of different assumptions about the loss of protection through time after vaccination. It is not possible, from the incidence

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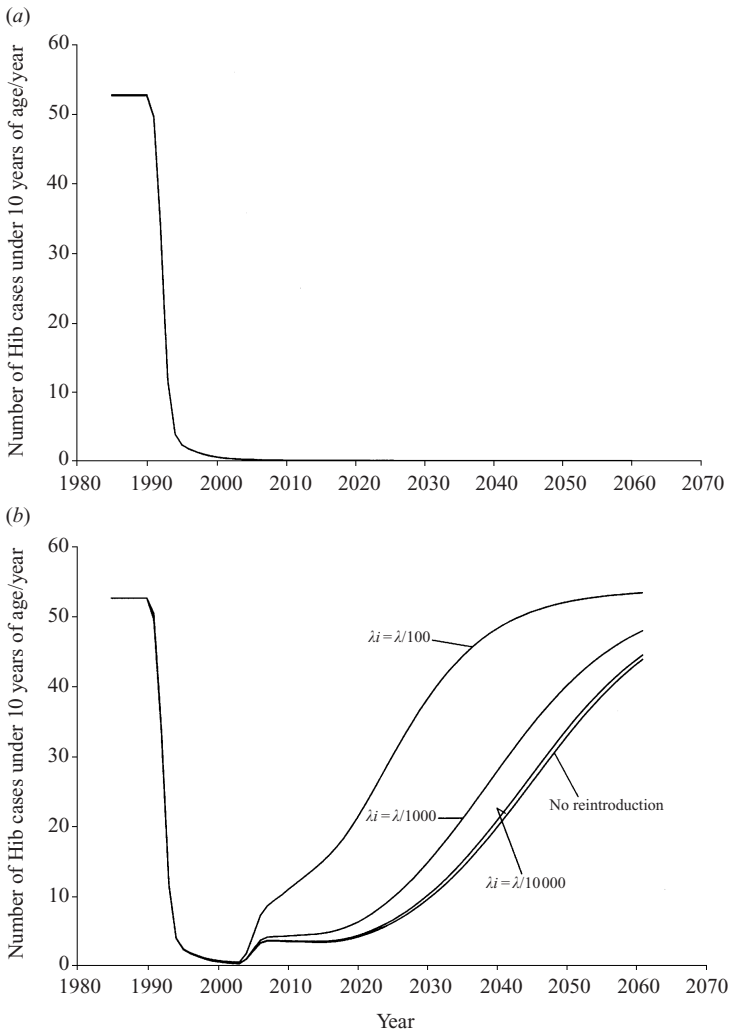

Fig. 7. Long-term trends predicted by the Hib model, with different assumptions for the relative importance of reintroduction of Hib carriage by travellers, (*a*) when the immunization programme is continued, and (*b*) where it is stopped in January 2003.

data, to discriminate between assumptions about fading protection, nor, projecting forward, does it make much difference (Fig. 4*b*). The model kept track of the time until elimination has a probability of 0·95 at the *next time step*. An increased rate of waning protection makes a great deal of difference on this time (from 2028 and 2030 to 2063), which may be an issue should eradication be pursued, but there is very little difference in disease incidence with low levels being maintained.

A perverse impact of vaccination increasing susceptibility to disease amongst those who no longer acquire wild infection-derived protection can be ruled out on the basis of disease incidence in Oxford. The only assumption that allows the model to generate the observed incidence is one where prior to vaccination carriage of Hib was not the main source of protection from disease (Fig. 5).

The vaccination policy

In the short term the addition of the catch-up programme resulted in a significant improvement in the control of Hib disease. The model suggests that the catch-up programme helped avoid approximately 17 Hib cases between 1993 and 1996 in the Oxford region alone (Fig. 6*a*, see no booster, catch-up), but that its omission would have had no significant long-term impact on the incidence of disease (Fig. 6*b*). The omission of a booster dose in the UK's vaccination programme clearly made no difference to the impact of the programme (Fig. 6*a*).

The exogenous reintroduction of infection

If the vaccination programme is maintained, then different assumptions about the rate of infectious carriage being reintroduced through contacts with

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(*a*) Matrix A

Age class (years)	0–1	2–5	6–14	15–24	25–90
0–1	β_2	β_1	β_1	β_1	β_1
2–5	β_1	β_3	β_1	β_1	β_1
6–14	β_1	β_1	β_3	β_1	β_1
15–24	β_1	β_1	β_1	β_4	β_1
25–90	β_1	β_1	β_1	β_1	β_5

(*b*) Matrix B

Age class (years)	0–1	2–5	6–14	15–24	25–90
0–1	β_2	β_1	β_1	β_2	β_1
2–5	β_1	β_3	β_1	β_1	β_1
6–14	β_1	β_1	β_3	β_1	β_1
15–24	β_1	β_1	β_1	β_4	β_1
25–90	β_1	β_1	β_1	β_1	β_5

(*c*) Matrix C

Age class (years)	0–1	2–5	6–14	15–24	25–90
0–1	β_2	β_1	β_1	β_2	β_1
2–5	β_1	β_3	β_1	β_1	β_1
6–14	β_1	β_1	β_3	β_1	β_1
15–24	β_2	β_1	β_1	β_4	β_1
25–90	β_1	β_1	β_1	β_1	β_5

(*d*) Matrix D

Age class (years)	0–1	2–5	6–14	15–24	25–90
0–1	β_2	β_1	β_1	β_1	β_1
2–5	β_1	β_3	β_1	β_1	β_1
6–14	β_1	β_1	β_3	β_1	β_1
15–24	β_2	β_1	β_1	β_4	β_1
25–90	β_1	β_1	β_1	β_1	β_5

(*e*) Matrix E

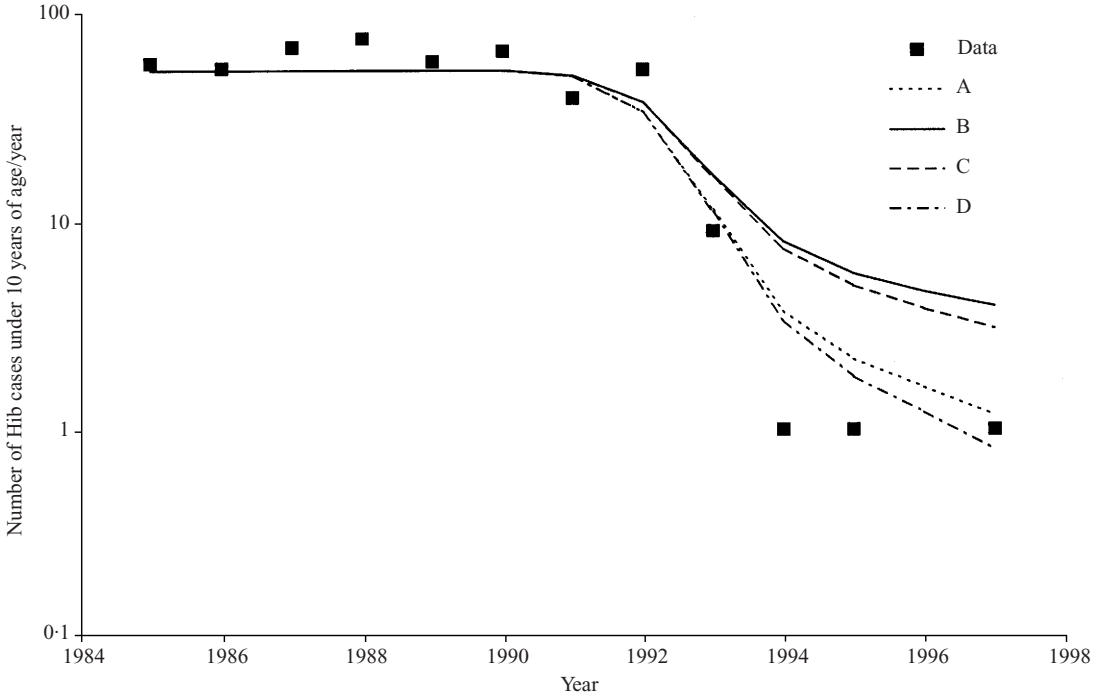

Fig. 8. Who Acquires Infection from Whom (WAIFW) matrices used in the Hib model simulations. Four matrices were most significant (see text for more details), whose estimates for the transmission coefficients are presented below. The units are numbers of yearly infectious events per susceptible in a totally infectious population. (*a*) Matrix A: $\beta_1 = 5{\cdot}739 \times 10^{-2}$, $\beta_2 = 2{\cdot}384$, $\beta_3 = 2{\cdot}436$, $\beta_4 = 2{\cdot}349$, $\beta_5 = 2{\cdot}085$. (*b*) Matrix B: $\beta_1 = 5{\cdot}795 \times 10^{-2}$, $\beta_2 = 0{\cdot}581$, $\beta_3 = 2{\cdot}436$, $\beta_4 = 2{\cdot}361$, $\beta_5 = 2{\cdot}085$. (*c*)

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other populations has very little impact on the incidence of disease (Fig. 7*a*). However, should vaccination be withdrawn there will be an inevitable resurgence of disease to pre-1990 levels. The importance of this effect depends upon the rate of reintroduction of cases (Fig. 7*b*).

Mixing matrices

It is possible on the basis of the observed incidence to gain some insight into the pattern of mixing that must exist for the transmission of Hib. Most conformations of WAIFW matrices produced β transmission coefficients with negative values. Four matrices were considered which might have relevance to Hib epidemiology, A–D (Fig. 8*a–d*). Matrix A assumes within age class mixing, matrix B assumes that infants acquire Hib organisms from the 15- to 25-year-old age class, and matrix C assumes that also the 15- to 25-year-old age class acquires Hib organisms from infants. Finally, matrix D assumes that the 15- to 25-year-old age class acquires Hib organisms from infants but not *vice versa*. The models that are most consistent with the observed series of Hib disease are those that assume mixing matrices A and D (Fig. 8*e*).

DISCUSSION

Widespread Hib immunization has been very successful in all the countries where it has been introduced. Furthermore, a number of studies carried out in Finland, the United States and the United Kingdom show that the Hib immunization programmes have led to significant reductions of Hib carriage [17]. The model predicts elimination of cases of Hib within the year 2000, which compares well with the observation that, in the Oxford region, no cases were observed in 1996 although one more case was detected in 1997. Without eradication (i.e. global elimination), a population where infection has been eliminated is still susceptible to its reintroduction. This is perhaps obvious, but it is worth illustrating the increase in disease when vaccination is withdrawn because the impetus for vaccination will fade as disease becomes a memory. It is vital that vaccination programmes are maintained or Hib disease will re-emerge (Fig. 7*b*).

The models where experience of nasopharyngeal acquisition of Hib carriage plays a role in acquired immunity to invasive disease provide poor fits to the time series data. Such models would predict post-immunization *increases* in the incidence of disease in the older age classes, which have not so far been observed (Fig. 5). This is consistent with our earlier observation that by age 10 years less than 40% of the population experienced Hib carriage despite the observation that by this age Hib disease is rare (1000-fold reduction in risk of disease by this age) [20].

The Hib model succeeded in predicting the time series of Hib invasive disease both before and after the immunization programme began. The discrepancies between model projection and observation could be within the stochastic realizations of the model, but could also reflect assumptions of the models. If the population of the Oxford region is heterogeneous with respect to acquisition rates of Hib carriage (forces of infection), model predictions could differ. For example, the force of infection for Hib could be greater in day care centres (DCCs) than in the general population. This is supported by a number of studies which show a higher prevalence of carriage in DCCs than in the general population, especially if the DCCs had experienced cases of Hib invasive disease [39, 40]. In one such study, where carriage in a group of 66 DCC children was followed-up for 1 year, it was estimated that forces of infection for toddlers (of 18–35 months of age) were in the range 0·25–1·55, and for older children (of 36 months–6 years of age) 0·105–0·9 [39]. These values are much higher than the estimate of 0·08 acquisitions per susceptible per year for the general population of these age classes [20]. In the first years of the immunization programme vaccinees were young children who were likely to be in day care, resulting in the highest concentration of immunization where most of the infectious contacts took place. Thus, the inclusion of a DCC compartment in the Hib model might lead to greater impacts of the immunization programme on the incidence of Hib disease.

The form of the WAIFW matrix had interesting

Matrix C: $\beta_1 = 5{\cdot}795 \times 10^{-2}$, $\beta_2 = 0{\cdot}581$, $\beta_3 = 2{\cdot}436$, $\beta_4 = 2{\cdot}198$, $\beta_5 = 2{\cdot}085$. (*d*) Matrix D: $\beta_1 = 5{\cdot}790 \times 10^{-2}$, $\beta_2 = 2{\cdot}383$, $\beta_3 = 2{\cdot}436$, $\beta_4 = 1{\cdot}675$, $\beta_5 = 2{\cdot}085$. (*e*) Impact of the four WAIFW matrix configurations A–D on the fit of the models to the time series data of yearly incidence of Hib disease in children younger than 10 years of age. The best fitting matrices are those that assume within age class mixing (A) and where 0–1 years old children also infect 15–24 year old adults (D). See text for details.

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effects on the predictive value of the model (Fig. 8*e*). The matrices most consistent with the observed time series of Hib disease were those that assumed within age group mixing (matrix A), or an additional risk of infection in 15- to 25-year-olds from contact with children younger than 2 years of age (matrix D). This suggests that the majority of carriage amongst children will be acquired from their own age group, and some may be spread to adults but not often from adults to children.

Cases of vaccine failure provide direct evidence of a loss of protection efficacy. There have been 85 such vaccine failures nationally in the first 6 years of the immunization programme, an analysis of which suggested that protection may wane over the first 4 years. Comparison of the time series of vaccine failures with the number of cases of Hib disease expected (based on pre-vaccination attack rates) provides us with a very insensitive but direct method for the estimation of protective efficacy of the vaccine. Unfortunately, antibody levels in serum provide less certainty over the protected status of the vaccinee. Nevertheless, assuming a protective threshold of 0·15 μg/ml, the antibody data set appears to reflect the vaccine failure data set (Fig. 3). Antibodies may provide a reasonable surrogate of protection following vaccination [18], but with a lower threshold than 0·15 μg/ml for conjugate vaccines because of the presence of immunologic memory. However, the impact of vaccine in reducing the prevalence of carriage is such that a loss of protection is of little epidemiological consequence except when considering eradication.

The different policy options available on the introduction of vaccination could be simulated and retrospectively evaluated. The presence of the catch-up programme did not affect the long-term success of the immunization programme (Fig. 6*b*) but, in the short term it resulted in a significant improvement in the control of Hib disease, with an average of 17 Hib cases in the Oxford region avoided. That it was not entirely overshadowed by the success of the primary immunization programme is noteworthy, particularly since lower coverage rates were probably achieved than in the primary immunization programme [23], and since it did not affect the ages of highest risk of disease. Nevertheless, the catch-up programme did target those ages with highest rates of carriage.

The success of the primary immunization programme lies in the low R_0 of the Hib infection [20], in the high vaccination coverage adopted, and in the protective efficacy of the vaccine against both disease and carriage. Therefore, where coverage for primary immunization programme is low, as in Ireland [41], for example, the catch-up programme may make a more significant impact on the control of Hib disease.

The proposed booster dose would not significantly improve control regardless of waning vaccine protection for two epidemiological reasons. First, the majority of disease occurs in the age group younger than that which would be targeted with a booster dose. Second, the very low reproductive number of Hib (1·03 assuming no acquired immunity, and 3·3 assuming acquired immunity to Hib carriage [20]) means that any addition on the fraction to the population protected will be of little importance compared to the effects of primary immunization.

In conclusion, the use of a mathematical model to analyse retrospectively the impact of the Hib immunization programme in the Oxford region has generated a number of insights that may be valuable in designing the introduction of vaccine into other populations as well as when considering the use of vaccinations to prevent other bacterial infections. We have illustrated the importance of continuing vaccination, while showing that the loss of protection is not important when the reproductive rate of infection is maintained below unity. This could probably be maintained by a vaccine that was only partially protective, but the initial rate of decline in disease incidence suggests that the conjugate vaccine was very successful in preventing carriage.

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