Understanding the impact of Hib conjugate vaccine on transmission, immunity and disease in the United Kingdom

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SUMMARY

A rise in invasive *Haemophilus influenzae* type b (Hib) infections occurred 8 years after vaccine introduction in the United Kingdom. Aspects of Hib vaccine delivery unique to the United Kingdom have been implicated. The authors developed a fully age-structured deterministic susceptible–infected–resistant–susceptible mathematical model, expressed as a set of partial differential equations, to better understand the causes of declining vaccine effectiveness. We also investigated the consequences of the vaccine's impact on reducing Hib transmission for maintenance of immunity. Our findings emphasized the importance of maintaining high post-immunization antibody titres among age groups at greatest risk of invasive infections. In keeping with UK population-based estimates, low direct efficacy of immunological memory against disease was found, cautioning against over-reliance on evidence of priming alone as a correlate of population protection. The contribution of herd immunity to disease control was reinforced. Possible intervention strategies will be explored in subsequent work.

INTRODUCTION

Haemophilus influenzae type b (Hib) conjugate vaccine was introduced into the United Kingdom's immunization schedule in October 1992. An initial 1-year 'catch-up' programme offered children up to 4 years a single dose of vaccine [1]. Infants were immunized at 2, 3 and 4 months of age without a 'booster' dose [2]. Resultant relatively low post-immunization antibody concentrations were further reduced by the use of a less immunogenic Hib conjugate vaccine combined with diphtheria, tetanus and acellular pertussis (DTaP-Hib) in 2000 and 2001 [3]. Despite an initial marked reduction in cases, resurgence of infections was noted 8 years after vaccine introduction [4], necessitating a national catch-up immunization campaign [5].

The United Kingdom's initial experience of high vaccine effectiveness despite low Hib antibody concentrations inspired confidence in the protective efficacy of immunological memory [2]. Memory immune responses are evidenced by the rapid production of high avidity antibodies on re-exposure to antigenic challenge. Direct protection following the UK infant primary course proved lower than anticipated, however, being only 61% over the first 2 years, and 27% thereafter [6], possibly masked by the catch-up

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(a) Unvaccinated proportion

(b) Vaccinated proportion
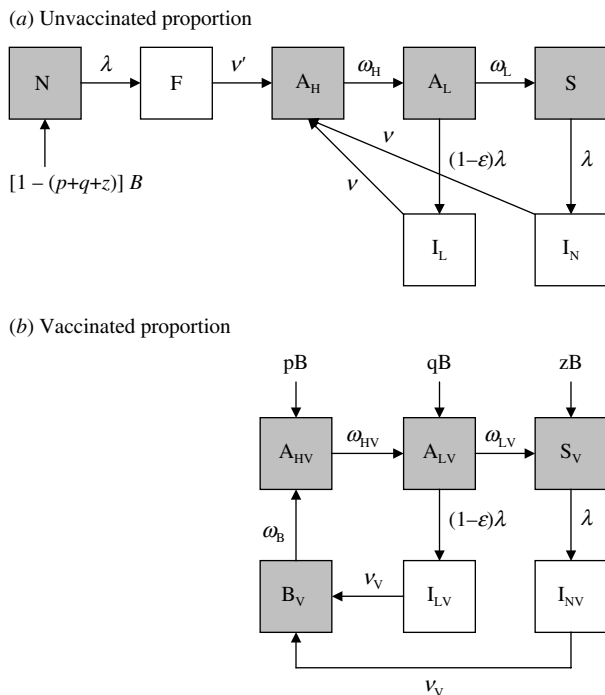
Fig. 1. Age-structured model. (*a*) Unvaccinated proportion. Mutually exclusive compartments represent the different epidemiological status of individuals in the population in relation to the infection. Arrows describe flows between these compartments. Individuals are born immunologically naive (N), until they acquire their first Hib infection (F). Following clearance of colonization, individuals seroconvert and move to the high antibody (A_H) compartment. This state denotes a period of absolute resistance to re-acquisition of infection. Over time, immunity wanes and individuals move into the low antibody (A_L) category. Here the presence of low-level measurable immunity provides incomplete protection against infection. With the waning of antibody from low to undetectable levels, individuals are once again fully susceptible to acquisition (S). Infections acquired in the presence of low (I_L) or no detectable (I_N) circulating antibody are assumed to have a reduced likelihood of progressing to invasive disease compared with the first infection (F). With clearance of carriage from either the I_L or I_N state, immunity is stimulated to the protective (A_H) level and the cycle of waning immunity, re-infection and stimulation of immunity begins again. (*b*) Vaccinated proportion. Immediately following primary vaccination, individuals enter the model with high (A_{HV}), low (A_{LV}) or undetectable (S_V) antibody levels. This bypassing of the immunologically naive (N) state removes the risk of progression to invasive disease associated with the first ever infection (F) which is experienced by the unvaccinated group. The proportion in each immune category at the outset depends on the immunogenicity of vaccines in use at any given time. The degree of protection against acquisition in these three states is assumed to be identical to that experienced by unvaccinated individuals with high (A_H), low (A_L) or undetectable (S) immunity. As before, infections may arise in the face of low or unmeasurable antibody, in

campaign originally employed [6, 7]. The demonstration of increased risk of vaccine failure in recipients of DTaP-Hib vaccine confirmed the need for higher antibody concentrations to protect against Hib disease [3].

Hib conjugate vaccines also provide indirect protection [2] by delaying carriage acquisition in infants [8, 9], resulting in a decline in colonization prevalence with widespread use [10–12]. However, episodes of carriage are temporally associated with development of natural immunity [13, 14], believed to be the reason for the observed decline in serious Hib infections with age [15–17]. It is therefore possible that lower Hib carriage prevalence may have negative consequences for maintenance of population immunity.

Mathematical models provide a useful framework within which to explore general principles regarding transmission of infectious agents and the likely impact of immunization [18]. We developed a model to better understand interacting factors contributing to the rise in serious Hib infections observed in the United Kingdom. It was structured to allow examination of key assumptions about the degree and duration of natural and vaccine induced protection against carriage and invasive disease, and incorporated critical aspects of vaccine implementation. We further sought to assess the impact of a vaccine known to block Hib transmission on maintenance of immunity. Of particular interest was the way in which these effects were influenced by assumptions regarding social mixing.

METHODS

Model structure

We developed an age-structured deterministic susceptible–infected–resistant–susceptible model with modifications, expressed as a set of partial differential equations (PDEs) [Appendix 1 (available online),

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this instance denoted as I_{LV} and I_{NV} respectively. The same risks of progression to invasive disease are assumed as from the I_L and I_N conditions. Following recovery from infection, immunity is boosted to a higher level than would be seen in an unvaccinated population (B_V). From here, antibodies wane to the post-immunization level (A_{HV}), with this additional step making the duration of protection following an episode of natural exposure longer in individuals who have been vaccinated. With waning of immunity, the cycle of re-acquisition and boosting of antibody levels can recur.

Fig. 1]. To avoid consideration of maternal immunity, subjects entered the model aged 6 months, progressing through until the age of 20·5 years. Initial conditions reflected the population distribution of individuals susceptible to, infected with, or resistant to Hib in the pre-vaccine era.

From immunization introduction, a fraction of each new birth cohort entered the vaccinated proportion. 'Catch-up' immunization was simulated by transfer of the relevant subjects in the target birth cohorts to the vaccinated high antibody-resistant compartment. Children infected at the time of immunization were transferred to the corresponding low or no antibody immunized infected compartment (i.e. $I_L \rightarrow I_{LV}$, $I_N \rightarrow I_{NV}$) as conjugate vaccination does not clear established carriage [9].

Vaccine-induced immunity was assumed similar to natural immunity with two important distinctions. Hib vaccine was highly immunogenic in infants aged <2 years, in whom natural exposure provoked a negligible immune response. Further, infants primed by immunization manifested lifelong 'booster' antibody responses on re-exposure to Hib.

All infections in the model were episodes of oropharyngeal carriage. Invasive disease cases, rare by comparison, were not explicitly described but were calculated as a proportion of colonization events.

Data sources

Hib carriage

The largest population-based study of Hib carriage prior to widespread vaccination involved 1110 children aged 0–16 years attending outpatient clinics in the United States (Fig. 2) [19]. The only similar UK-based study included children up to 72 months, and employed less sensitive microbiological methods [20]. The larger dataset was therefore used.

Model outputs describing the impact of immunization on colonization rates among pre-school-aged children were compared with a series of cross-sectional carriage studies conducted in British nurseries between 1992 and 2002 [12].

Hib seroepidemiology

The seroepidemiological data used to parameterize and validate the model were taken from a study of changing population immunity to Hib, using excess diagnostic serum donated by English hospitals in 1990–1991, 1994, 1997 and 2000 [7].
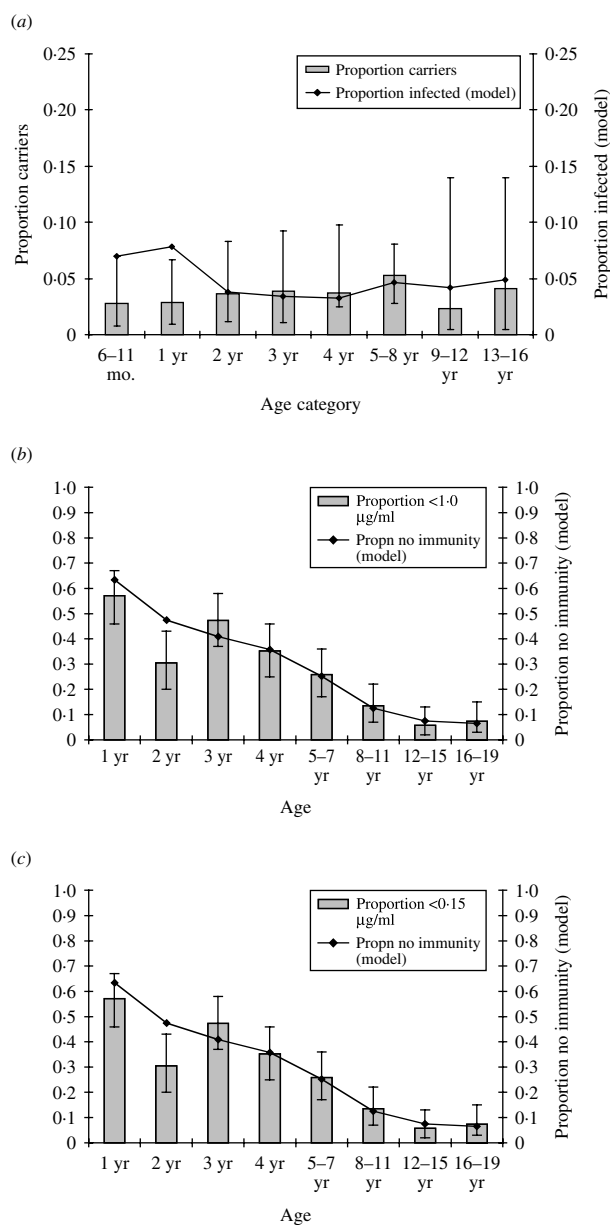
Fig. 2. Best fit of the ODE model used for parameter estimation to: (*a*) Hib carriage prevalence in the United States by age, 1976 (error bars represent 95% confidence intervals of population estimates). (*b*) Hib antibody titres <1·0 μg/ml in English children by age, 1990–1991 (error bars represent 95% confidence intervals of population estimates). (*c*) Hib antibody titres <0·15 μg/ml in English children by age, 1990–1991 (error bars represent 95% confidence intervals of population estimates).

Hib disease

Hib cases were identified by the Health Protection Agency (HPA) through laboratory reports to the *Haemophilus* Reference Unit (HRU) and Communicable Disease Surveillance Centre [4]. The strain had

to be cultured from a normally sterile site, unless the diagnosis was epiglottitis. For organisms sent to the HRU serotype was confirmed by polymerase chain reaction.

Vaccine coverage

The proportion of children receiving three primary Hib doses by 12 months in the United Kingdom between 1992 and 2002 was taken from Cover of Vaccination Evaluated Rapidly data (http://www.hpa.org.uk/cdr/archive04/immunisation04.htm). Quarterly uptake estimates for the 1992–1993 catch-up campaign came from a North Thames study [1].

Model parameterization

The Table summarizes the parameters estimated, and gives the final values used in the model. Their derivation is described below.

Susceptible→Infected

Individuals with antibody titres below the assay detection limit ($<0.15\,\mu$g/ml) were deemed fully susceptible to the force of infection (N, S, S_V). Levels of antibody between 0·15 and 1·0 μg/ml (A_L, A_{LV}) provided incomplete protection against acquisition, represented by the parameter ε, which was subjected to sensitivity analysis. Titres $\geqslant 1.0\,\mu$g/ml conferred complete resistance.

Justification for these assumptions came from animal challenge experiments [21, 22] and human studies describing delayed acquisition of Hib in the months following immunization [8, 9]. While the antibody threshold necessary for protection against colonization remains undefined, the value of 5·0 μg/ml suggested by one study [23] was too high to explain herd immunity in the United Kingdom [2, 24]. Hib vaccine trials report immunogenicity in relation to purported correlates of long (1·0 μg/ml) and short-term (0·15 μg/ml) protection against invasive disease [17]. Use of these values to define cut-offs between high (A_H, A_{HV}), low (A_L, A_{LV}) and undetectable (S, S_V) antibody compartments was therefore convenient, and consistent with the UK population experience.

Four age groups were defined: 0·5–1·99 years (home or nursery), 2–4·99 years (nursery or play group), 5–10·99 years (primary school) and 11–20·5 years (secondary or tertiary educational institution). The force of infection (λ) for each of the groups was calculated in Excel using a log-likelihood method to fit observed pre-vaccination carriage and sero-epidemiology profiles to outputs of an ordinary differential equation (ODE) model (Appendix 2, online) representing the equilibrium, pre-vaccination age distribution of the PDE model.

The importance of between-group mixing was encapsulated by further defining λ as follows, where $C(a, a')$ determines the influence of infectious people of age group a' in contributing to new infections in age group a, and $\beta(a)$ denotes the age-dependent susceptibility to acquisition of individuals in age group a.

$$\lambda(a, t) = \int_{0\cdot 5}^{20\cdot 5} C(a, a')\beta(a)[Y(a', t)\mathrm{d}a'],$$

and

$$Y(a', t)\mathrm{d}a' = [F(a', t)\mathrm{d}a' + I_L(a', t)\mathrm{d}a' + I_N(a', t)\mathrm{d}a' \\ + I_{LV}(a', t)\mathrm{d}a' + I_{NV}(a', t)\mathrm{d}a'].$$

This effective contact parameter $C\beta$ is a two-dimensional step function that can be represented by a matrix of constants. Values of $\beta(a)$ were calculated according to the method of Anderson & May [25] using the equilibrium distribution of the number of infections by age. Results comprised the elements of a 'Who Acquires Infection From Whom' (WAIFW) matrix under different assumptions of the relative values of $C(a, a')$ (Appendix 3, online). The WAIFW matrix was then used to calculate the force of infection at all subsequent time steps based on the number of carriers by age at each preceding time step:

$$\begin{bmatrix} \lambda_1 \\ \lambda_2 \\ \lambda_3 \\ \lambda_4 \end{bmatrix} = \begin{bmatrix} C_{11}\beta_1 & C_{12}\beta_1 & C_{13}\beta_1 & C_{14}\beta_1 \\ C_{21}\beta_2 & C_{22}\beta_2 & C_{23}\beta_2 & C_{24}\beta_2 \\ C_{31}\beta_3 & C_{32}\beta_3 & C_{33}\beta_3 & C_{34}\beta_3 \\ C_{41}\beta_4 & C_{42}\beta_4 & C_{43}\beta_4 & C_{44}\beta_4 \end{bmatrix} \times \begin{bmatrix} Y_1 \\ Y_2 \\ Y_3 \\ Y_4 \end{bmatrix}$$

Infected→Resistant

Average carriage duration of 2·4 months was noted in toddlers in a nursery in the United States observed over one year [26]. This figure was consistent with data from studies of babies in private homes [9] and institutions [27] and was assumed independent of age and vaccination status.

Resistant→Susceptible

A temporal relationship between Hib carriage and rising antibody titres has been demonstrated [13].

Table. *Summary of parameter values*

Model parameter	Mean value	Mean duration in group
Demographic parameters		
Births per quarter, B	6250	
Population size, N	500 000	
Proportions vaccinated, p, q, z	0–1 where $p+q+z \leqslant 1$	
Routine infant immunization	$p=0.83$, $q=0.07$, $z=0.02$	
Poorly immunogenic vaccine	$p=0.63$, $q=0.19$, $z=0.10$	
Biological parameters		
Duration of carriage for first infection		
ν'	5	2·4 months
Duration of carriage for subsequent infections		
ν (unvaccinated)	5	2·4 months
ν_V (vaccinated)	5	2·4 months
Duration of immunity		
Unvaccinated		
ω_{H1} (0·5–1·99 years)	6·36	0·16 years
ω_{H2} (2–4·99 years)	0·67	1·50 years
ω_{H3} (5–10·99 years)	0·46	2·18 years
ω_{H4} (11–20·5 years)	0·51	1·96 years
ω_L (all ages)	0·12	8·06 years
Vaccinated		
ω_{HV1} (0·5–0·99 years)	0·80	1·25 years
ω_{HV2} (1–1·49 years)	0·56	1·79 years
ω_{HV3} (1·5–1·99 years)	0·48	2·08 years
ω_{HV4} (2–20·5 years)	0·43	2·33 years
ω_{LV} (all ages)	0·20	5·0 years
Duration of immunity following re-exposure to Hib in vaccinated individuals		
ω_{B1} (0·5–0·99 years)	0·43	2·33 years
ω_{B2} (1–1·49 years)	0·57	1·75 years
ω_{B3} (1·5–1·99 years)	0·69	1·45 years
ω_{B4} (2–20·5 years)	0·95	1·05 years
Relative protection against acquisition from low antibody state		
ε	0·25	
Force of infection, λ		
λ_1 (0·5–1·99 years)	0·47	
λ_2 (2–4·99 years)	0·24	
λ_3 (5–10·99 years)	0·47	
λ_4 (11–20·5 years)	0·72	
Rate of progression to invasive disease, δ		
δ_1 (0·5–0·99 years)	0·0118	
δ_2 (1·0–1·99 years)	0·0044	
δ_3 (2·0–2·99 years)	0·0044	
δ_4 (3·0–3·99 years)	0·0039	
δ_5 (4·0–4·99 years)	0·0021	
δ_6 (5·0–20·5 years)	0·00009	
Protection against progression against invasive disease afforded by low levels of measurable antibody, θ		
θ	0·36	
Protection against progression against invasive disease afforded by previous natural or vaccine exposure to Hib in the absence of measurable antibody, μ		
μ	0·36	

Age-dependent maturation of immune responsiveness to the Hib capsular polysaccharide poly-ribosyl-ribitol-phosphate (PRP) mirrors that observed following exposure to the whole organism [28] justifying its use as a proxy marker [29], with an age-independent rate of antibody decay [30]. From these data, sensible estimates of the age-dependent duration of protection ($1/\omega_H(a)$) were made. Given the uniform waning rate, and the fixed thresholds defining boundaries between compartments, time spent in the low antibody (A_L) category ($1/\omega_L$) was independent of age. These initial estimates of $\omega_H(a)$ and ω_L were optimized to fit population data using the same ODE model used to calculate the force of infection (Appendix 2, online).

Parameters describing resistance due to UK primary course conjugate vaccination ($\omega_{HV}(a)$, ω_{LV}) were estimated from clinical trials data [2, 24]. A series of trials conducted in US toddlers reported age-dependent antibody responses and persistence following a single dose of Hib-CRM$_{197}$ conjugate (HbOC) [31, 32], the vaccine predominantly used in the catch-up campaign. The estimated duration of low-level antibody persistence after immunization ($1/\omega_{LV}$) was later subjected to sensitivity analysis.

The concept of the boost response was key to considering long-term implications of immunization. Rising antibody titres following Hib colonization are an order of magnitude greater in children immunized with conjugate vaccines in infancy [33]. The response to PRP boosting following receipt of an infant primary course was used as a proxy of natural exposure [29]. Based on the similarity of recorded boost responses in children 1, 4 and 10 years following primary immunization [34–36], a uniform peak post-boost titre of 100 μg/ml was assumed.

Vaccine 'take'

Changing vaccine immunogenicity was represented by the proportions of individuals achieving high ($\geqslant 1\cdot 0$ μg/ml), low ($0\cdot 15$–$1\cdot 0$ μg/ml) and undetectable ($< 0\cdot 15$ μg/ml) post-immunization antibody titres (p, q and z). Given 92% immunization coverage, values for p, q and z following Hib combined with diphtheria, tetanus and whole cell pertussis (DTwP-Hib) [2, 24] were 0·83, 0·07 and 0·02 respectively. Following administration of three doses of DTaP-Hib to one third of all infants in the 2000–2001 birth cohorts, corresponding values of these parameters were 0·63, 0·19 and 0·10 [37].

HbOC, used for catch-up immunization, was highly immunogenic in children aged 12 months and older, with 98–99% achieving post vaccination Hib antibody titres >1·0 μg/ml [31, 32].

Progression to disease

The quasi-steady-state approximations used to calculate numbers of Hib cases were defined according to a series of equations (Appendix 4, online), which describe the age-dependent risk of invasive disease ($\delta(a)$). The efficacy of low levels of detectable antibody (θ) and immunological memory (μ) at preventing progression to bacterial invasion were subjected to sensitivity analysis.

Implementation and simulation

The method of characteristics was used to find numerical solutions to the PDEs (Appendix 1, online). These were reduced to a series of ODEs along the characteristic lines $t = a +$ constant, within 80 sequential 3-month age cohorts. The equations were solved by fourth-order Runge–Kutta integration using Model Maker Version 4 software (Cherwell Scientific, UK). The force of infection for each age category was integrated and updated at each time step.

RESULTS

Degree and duration of natural immunity and vaccine-induced protection against carriage (ε) and invasive disease (θ, μ)

Given 100% protection of the high antibody state against colonization, the best fit to observed data was achieved assuming 25% protection of low titre antibody against carriage acquisition. The corresponding level of invasive disease risk reduction attributable to low or unmeasurable immunity in those with prior Hib exposure was 35%.

The age-dependent distribution of invasive Hib infections could not be solely attributed either to the absence of circulating anti PRP antibodies, or a heightened risk of bacterial invasion linked to the 'first ever' Hib infection (F). Our model achieved an excellent fit to sequential cross-sectional English data describing Hib infections and immunity (Fig. 3). In order to then reproduce the observed disease epidemiology (Fig. 4), strong age dependence of the likelihood of progression to invasive disease ($\delta(a)$) had to be assumed.

Effects of changing vaccine use over time (p, q, z)

The catch-up immunization programme used in the United Kingdom over the first year of vaccine introduction caused rapid interruption of Hib transmission, resulting in marked transient effects. The time between peaks was relatively short, and the natural tendency of the system was a series of declining oscillations resolving to a new stable equilibrium within 25 years (Fig. 5).

An important consequence of the use of poorly immunogenic vaccines in 2000–2001 was an expansion of the susceptible infant pool, which amplified the second transient peak in infections (Fig. 5). More importantly, it 'exposed' the intrinsically higher risk of progression to invasive disease noted in younger children, leading to an associated increase in observed Hib disease (Fig. 4).

Impact of interrupting Hib transmission on maintenance of population immunity

A reduction in Hib circulation had a negative impact on maintenance of specific antibodies. The model reproduced the decline in the proportion of English children with high Hib antibody titres, and the rise in those with unmeasurable levels, noted in serosurveys from the late 1990s (Fig. 3).

Effect of social mixing assumptions on carriage and disease

Initial disease control was not achievable under homogeneous mixing assumptions. WAIFW matrices associated with best fit to population data assumed strongly assortative (within age group) mixing (Appendix 3, online). In contrast, for children aged <2 years, household mixing with an older sibling was the most potent source of infection. Infants thus colonized were further instrumental in re-infecting their older siblings.

DISCUSSION

How do natural and vaccine-induced immunity protect against Hib infections?

The model explored the contribution of high- and low-titre antibody and immunological memory to direct and indirect protection against Hib disease. Based on observation of delayed carriage acquisition over the first year of life following primary immunization [8, 9], relatively low titres [38] of antibody ($\geqslant 1{\cdot}0\,\mu$g/ml) were deemed sufficient to prevent colonization. With waning of indirect protection induced by catch-up immunization, true effectiveness of the infant primary vaccine schedule was unmasked, resulting in resurgence in infections. Direct efficacy estimates derived from the model compared favourably with those calculated from invasive disease incidence in the UK population using the screening method [6], which were considerably less than those assumed elsewhere [38]. Our results cautioned against over-reliance on immunological memory as a predictor of population protection [39, 40].

The alternative conclusion was that the main effect of vaccination was to delay the age at first colonization with Hib until the intrinsic risk of invasive infection was reduced. Consistent with this viewpoint, among Alaskan populations with a high incidence of early onset Hib disease, a change of vaccine formulation in the mid 1990s resulting in lower post-primary antibody titres was associated with an increase in invasive disease [41]. Rhesus monkey models of Hib infection confirm a heightened risk of meningitis secondary to bacteraemia in the first few months of life [42]. Such exquisite susceptibility of infants aged <2 years to bacterial invasion has previously been attributed to the inability of this age group to respond to polysaccharide antigens [15–17]. With others, we observed an age-related risk in excess of this marker of immunological immaturity [43]. Rather than focusing on maintenance of herd immunity [38], which is likely to fluctuate, ensuring direct protection by maintaining high antibody titres throughout the period of greatest disease risk may be the most effective immunization strategy.

How much of the observed epidemiology in the United Kingdom could be attributed to the way in which Hib vaccines were used?

The United Kingdom's use of a primary immunization series without a booster left infants with relatively low antibody titres through the vulnerable second year of life [2]. This strategy seemed effective while herd immunity was strong [44]. It was unfortunate that waning of this effect [45] was superimposed on the use of less immunogenic vaccines for the primary course during 2000 and 2001 [3], further exposing infants to risk of acquisition of Hib at a vulnerable age.
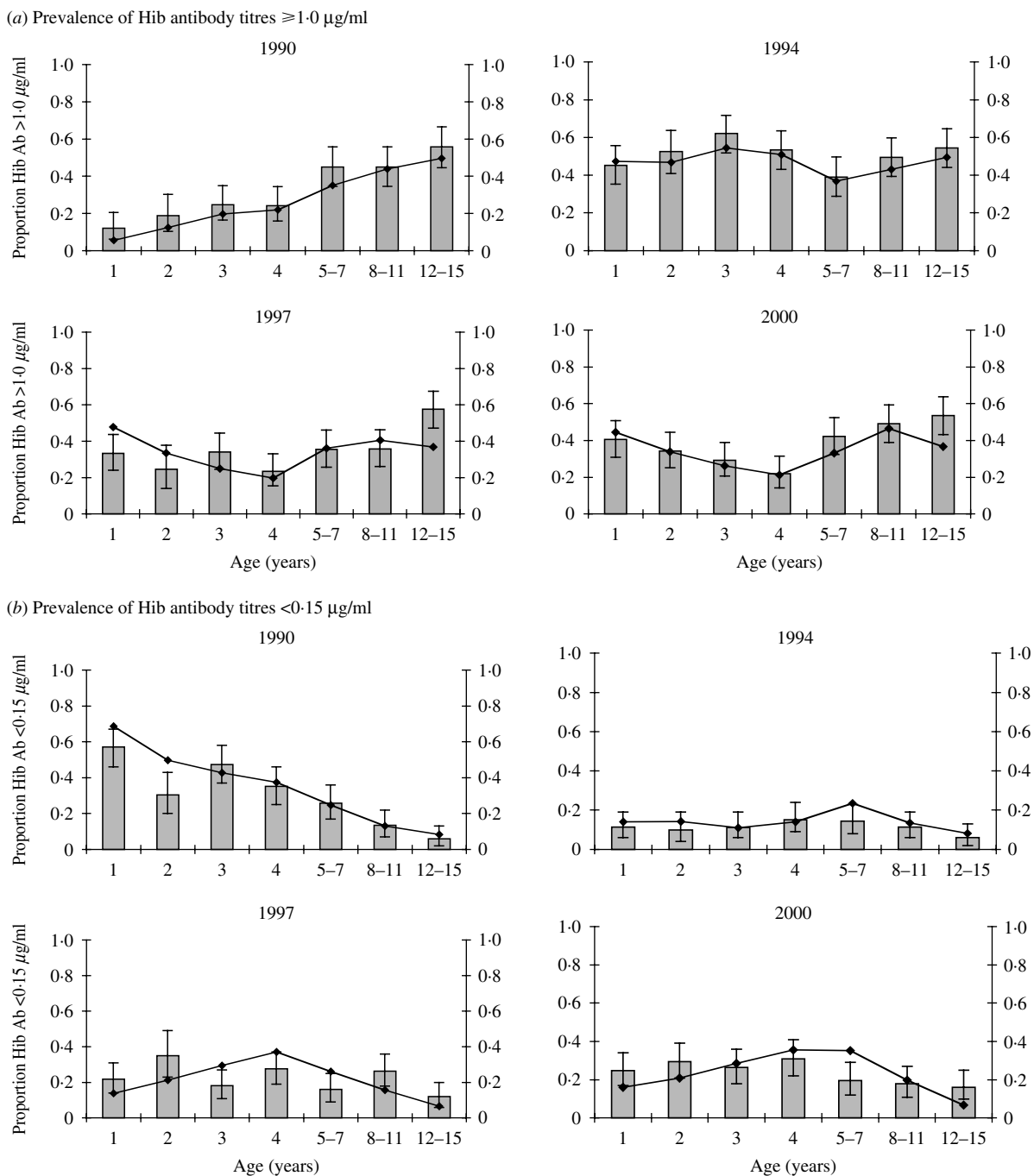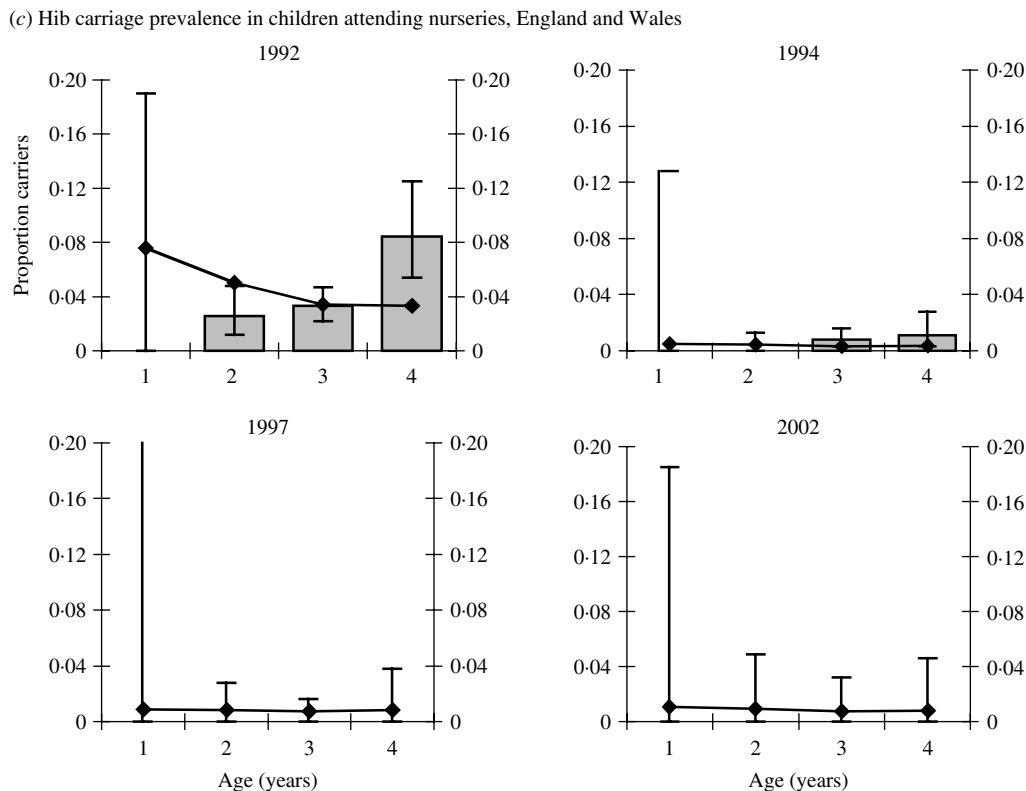
(a) Prevalence of Hib antibody titres ⩾1·0 µg/ml

(b) Prevalence of Hib antibody titres <0·15 µg/ml

Fig. 3. For legend see facing page.

How important is Hib transmission for maintenance of vaccine-induced immunity?

The model's assumptions regarding the pre-vaccination force of infection and the impact of immunization on transmission resulted in an immunity profile in the population that was an excellent fit to observed UK data [7]. A decline in antibody titres within 2 years of Hib vaccine introduction has subsequently been described in English adults, suggesting that recurrent Hib colonization is necessary for maintenance of immunity in all age groups [45]. On these grounds, we feel that the relatively high [43, 46, 47] forces of infection estimated in the model were justified.

(*c*) Hib carriage prevalence in children attending nurseries, England and Wales

Fig. 3. PDE model fit to English data following vaccine introduction in October 1992 at 2, 3 and 4 months (error bars represent 95% confidence intervals of observed data). (*a*) Prevalence of Hib antibody titres $\geqslant 1 \cdot 0 \ \mu$g/ml. (*b*) Prevalence of Hib antibody titres $< 0 \cdot 15 \ \mu$g/ml. (*c*) Hib carriage prevalence in children attending nurseries, England and Wales. ■, Observed; −◆−, model.

Who acquires Hib infections from whom in the population?

Consistent with previous studies, within-age group mixing was necessary to explain observed patterns of Hib transmission [43, 47], and the impact of vaccination on disease control. This was consistent with the need for prolonged close contact to acquire Hib infections in families [13], day-care centres [26] and orphanages [27]. In addition, our final mixing matrix incorporated the importance of older siblings as introducers of infection to households, with subsequent risks for pre-school-aged children, consistent with ecological studies from the 1950s [48]. Without this added assumption, invasive disease in infants would be eradicated with ease.

Our model structure was novel in incorporating the notion of the boost response following conjugate immunization. The average duration of vaccine protection in the model was intimately related to the ongoing force of infection. This was in contrast to other models of conjugate vaccination that specify

vaccine efficacy for a fixed period [49]. In this way, we were able to gain unique insights into medium- and long-term effects of immunization.

Another assumption that differed from previously published Hib models was the deliberate exclusion of boosting exposures to cross-reactive organisms. It has been observed that carriage of a range of encapsulated organisms may result in production of antibodies cross-reactive to PRP [50, 51]. One model has attributed 90% of natural immunizing contacts in British infants to such antigens [46]. Further, it has been speculated that ongoing colonization with these organisms would be sufficient to naturally boost immunity to Hib following a reduction in Hib circulation [38, 47, 52]. While antibodies stimulated by cross-reactive bacteria bind to PRP, Hib vaccination or natural infection results in the production of PRP-specific antibodies that do not necessarily bind cross-reactive antigens [53]. It is thus unclear whether cross-reactive bacterial exposures would boost vaccine-induced immunity. The rapid decline in Hib titres seen among English adults following vaccine
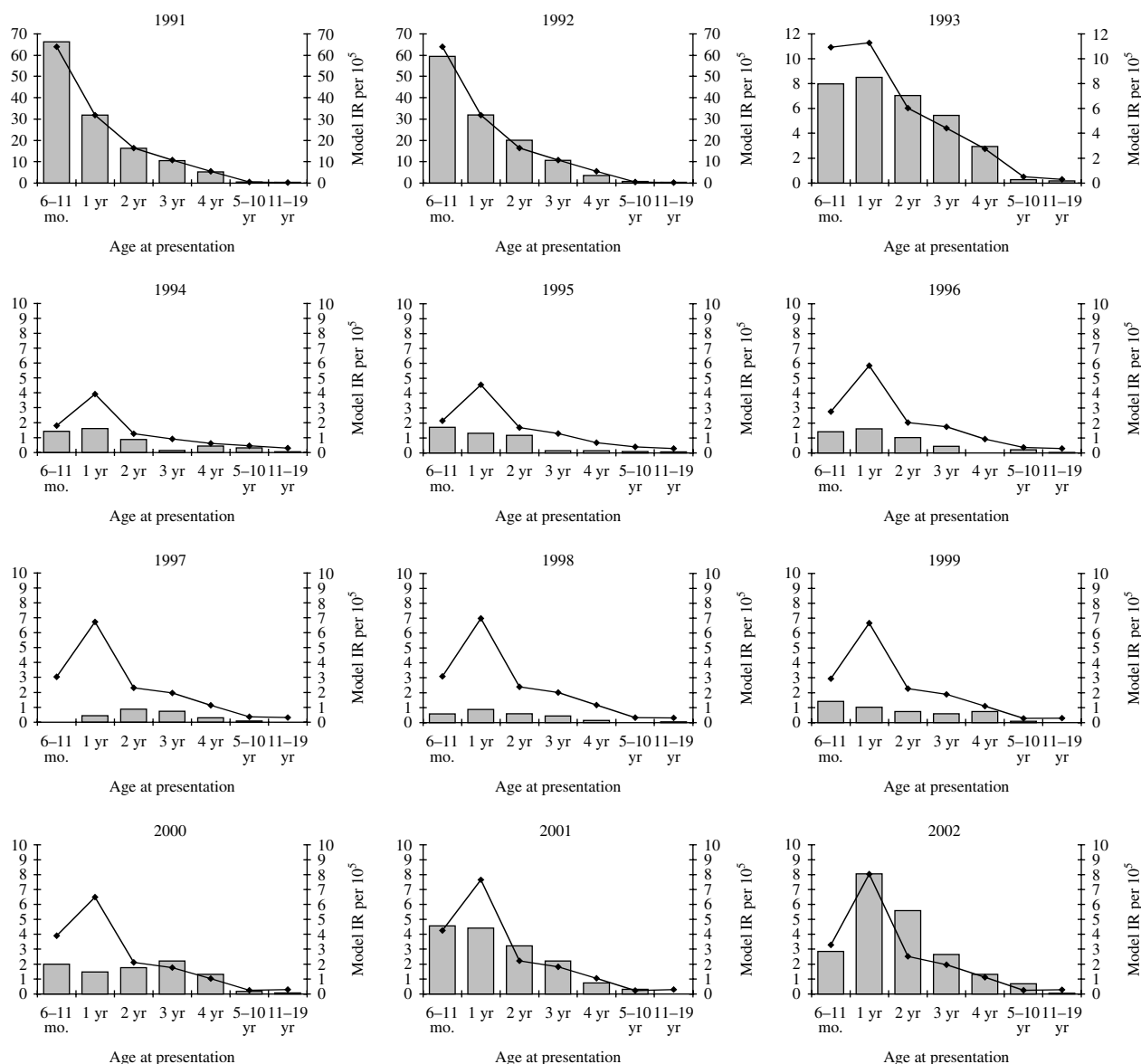
Fig. 4. Observed (□) and model (–◆–) predicted invasive Hib incidence by age and year, 1991–2002.

introduction further suggests that exposures to organisms other than Hib play a negligible role in boosting immunity to PRP [45].

The model had the limitation of being highly parameterized to allow exploration of epidemiological questions of interest. Parameters were, however, based on a large number of data points. Outputs describing the impact of immunization were validated against 10 years' invasive disease incidence data, three serosurvey collections and three cross-sectional carriage studies. Simulating initial excellent disease control followed by late recurrence of disease could only be achieved for a narrow range of assumptions, increasing confidence in the model's theoretical conclusions.

While rapid shifts in Hib disease in temporal concordance with observed UK data were well reproduced, we were unable to exactly replicate the incidence. This was expected, given the inherent limitations of models to fully capture the complexity of population effects. Predicted rates of invasive Hib infection in 1- to 2-year-olds were higher than observed levels in the late 1990s. Non-homogeneous reseeding of infections within small groups of immunized children may have resulted in a slower rise in disease incidence than was observed in the simulation. The importance of such 'patchy' transmission effects has been noted in the breakdown in correlation between measles outbreaks in large cities in England
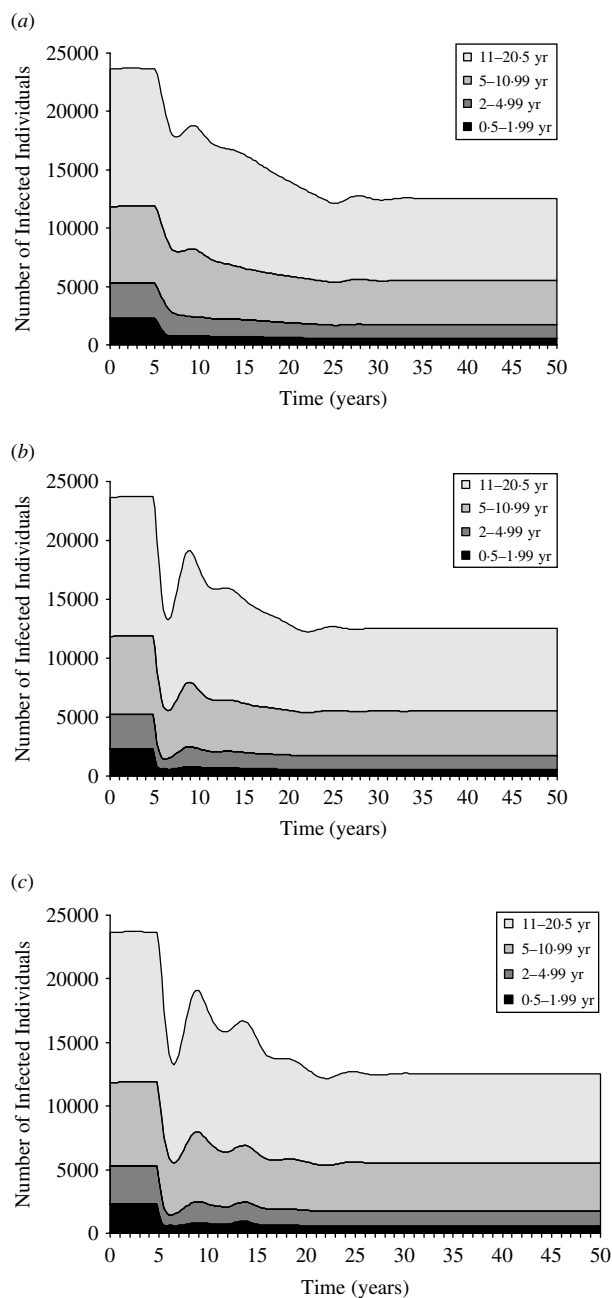
Fig. 5. Effects of vaccine scheduling and immunogenicity on all infections in the population by age group and time (vaccine introduction at $t = 5$ years). (*a*) Introduction of infant immunization alone. (*b*) Vaccine introduction accompanied by catch-up campaign. (*c*) Initial catch-up campaign, use of poorly immunogenic vaccine in years $t = 12$ and $t = 13$ (corresponding to 2000 and 2001).

data upon which to parameterize their force of infection. Adult Hib disease rates in Britain returned to pre-vaccination levels in 2002, in close temporal association with the rise in paediatric incidence [45]. Hib carriage prevalence is high among parents of Hib carriers [33] and cases [13, 55], who may represent the primary household infection [56].

Our model has informed understanding of declining Hib vaccine effectiveness in Britain, cautioning against over-reliance on immunological memory as a strategy for control of invasive bacterial disease. Alternatively, emphasis has been placed on maintenance of high post-immunization antibody titres among at-risk age groups. Recent experience with the meningococcal serogroup C conjugate vaccine in the United Kingdom has similarly highlighted the relationship between waning antibody titres and declining vaccine efficacy [57]. In subsequent work, we will use the model to address the likely impact of a range of interventions on disease rates. Meanwhile, the importance of ongoing surveillance of vaccine-preventable disease in order to identify unanticipated effects of immunization programmes is reinforced.

ACKNOWLEDGEMENTS

NOTE

Supplementary information accompanies this paper on the Journal's website (http://journals.cambridge.org).

DECLARATION OF INTEREST

None.

following vaccine introduction [54]. The later rise in disease cases in this age group did not fully achieve the height of the observed incidence in 2002. This may in part have been due to the absence of adults in the model, because of insufficient pre-vaccination

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