The meningococcus, *Neisseria meningitidis*, shows a dichotomy between a ‘silent’ process (carriage in the upper respiratory tract [MC]) and an overt disease process (invasive disease [MD]). This phenomenon is also seen with other bacterial pathogens like *Haemophilus influenzae* type b (Hib), 2 *Streptococcus pneumoniae* 3,4 and *Bordetella pertussis*. 5 As early as 1945 Aycock and Mueller 6 observed that, although MD incidence varied by season, prevalence of MC did not; the implication being that carriage could not be the sole risk factor for MD. Post-war studies from the US and Belgium confirm that MC continues to lack a seasonal component.7,8

Invasive disease is mainly reported passively through laboratory reporting and notification systems that are liable to underascertainment. 9 In contrast, active swabbing of the nasopharynx must be undertaken to identify MC. Swabbing is expensive, time consuming and poorly standardized between studies. In one survey concordance of two consecutive swab results was 93%.10 although sensitivity of a single swab in detecting MC has been estimated at 50%. 11 Despite these uncertainties, data sets of acceptable quality of MC prevalence exist for both *N. meningitidis* and the related asymptomatic infection *N. lactamica*. Neisseria lactamica bacteria share the nasopharyngeal colonisation site with meningococci though they are not associated with invasive disease. Prevalence of *N. lactamica* carriage (LC) peaks around the latter half of the second year of life, at a time when MD incidence starts to decline, and when MC prevalence is lowest.7 The possibility that LC has an inhibitory effect on MC and MD has received some attention since the bacterium was characterized in 1969.7,10,12 In a longitudinal study, 23 of 35 (66%) *N. lactamica* carriers had fourfold or greater rises in serum IgG antibody to meningococci of serogroups A, B and C, compared with 5% of controls (P < 0.001).7 This finding suggests an
induction of immunological protection closely associated with LC, despite the fact that N. lactamica strains do not possess a polysaccharide capsule.

Bacterial infections can be analysed within a framework where the primary unit of variance is the state of the host, namely susceptible, infected or immune. In this analysis we used data sets of carriage and disease to explore a number of models of meningococcal infection, with particular reference to the potential for LC to affect MC and MD. The models make the explicit distinction between the common asymptomatic (MC and LC) and the rare symptomatic (MD) infection. We did not attempt to incorporate meningococcal strain variations that reflect the complex genetic and antigenic structure of these bacteria.

Materials and Methods

The data

Duration of carriage was estimated by means of an exponential decay model of carriage fitted to a data set of MC in a cohort of 158 Belgian schoolchildren, who were followed up monthly between March 1975 and May 1976. All children initially carried the meningococcus. As no equivalent follow-up data set was available for LC, the mean duration of LC was taken as 3.5 months from the studies of Gold et al. and Blakebrough et al. We also derived estimates from the age-stratified prevalence data.

Age-related data sets of colonization and disease were used to fit and test models. For the estimation of the force of infection as a function of age, \( \lambda(a) \) (the rate of acquisition of carriage), we used a combined data set for MC and LC (Figure 1a and b). One data set was obtained from Gloucestershire, UK, and the other from Danbury, Connecticut, USA. The two data sets were merged for a number of reasons. Firstly, both studies documented both MC and LC simultaneously, ideal for the testing of models of the interaction between the two infections. Secondly, similar swabbing and microbiological techniques were used. The confidence intervals for the two data sets overlapped, suggesting that they did not differ significantly, despite the fact that they were generated in different decades and different continents. The two communities sampled have similar demographic histories and are classed together as ‘Established Market Economies’. Furthermore the UK and US have similar epidemiological patterns of MD. The combined data set provided a higher statistical power for the purposes of fitting models.

We used an age-structured data set of the incidence of MD in England and Wales published by Jones and Mallard (Figure 1c). The data set was characterized by a major peak at age 7 months and a minor one at age 20 years. As the raw data were no longer available (DM Jones, personal communication), the average number of cases per age group per year was calculated from the published rates and from the total number of MD isolates received at the Public Health Laboratory Service (PHLS) Meningococcal Reference Unit between 1984 and 1991. We added two additional data points corresponding to the 20–24 and 25–90-year-old age groups; these were provided by Dr M Ramsay, of the PHLS Communicable Disease Surveillance Centre, Colindale, UK.

Fitting the asymptomatic carriage data sets

Age-structured deterministic models of MC, MD and LC were tested against observed epidemiological patterns. The same general model of asymptomatic carriage was used to fit the MC and LC data sets. This is illustrated schematically by a flow diagram in Figure 2a where boxes represent categories of infection and the arrows represent the flow of individuals between them. In the model, hosts are born in the susceptible class (S), such that at birth \( S(a = 0) \) equals the total population birth cohort. The simplest possible models were the Susceptible-Carriage-Resistant (SCR), Susceptible-Carriage-Susceptible (SCS), and SCR-SCS models. The set of equations used for these models is

\[
\frac{dS(a)}{da} = C(a)\cdot r_1 \cdot (1 - z) - S(a)\cdot \lambda(a) \\
\frac{dC(a)}{da} = S(a)\cdot \lambda(a) - C(a)\cdot r_1 \\
\frac{dR(a)}{da} = C(a)\cdot r_1 \cdot z
\]

with boundary conditions \( S(0) = 1, C(0) = 0, \) and \( R(0) = 0. \) All state variables, \( S(a), C(a), \) and \( R(a) \) are proportions of the total population in age class \( a. \) Individuals in the susceptible class (S) move into the asymptomatic carrier class (C) at an age-dependent rate, known as the force of infection, \( \lambda(a) \), which may be age dependent. Carriage is then lost at a rate \( r_1. \) The model is SCS when \( z = 0, \) SCR when \( z = 1 \) and SCR-SCS when \( z \) has a value intermediate between 0 and 1.

First the LC and MC model forms were fitted to the LC and MC data sets respectively. To test the hypothesis of the inhibitory effect of LC on MC the best-fitting LC model was used to fit the MC data set, as part of a joint MC-LC model.

Fitting the MD data set

A study of US military recruits has shown that protective immunity could be triggered by MC. Such protection was generally demonstrated to be strain-specific, and occasionally cross-protective. The same study suggested that similar trends may occur among 2–13-year-old children. It would seem reasonable to suggest that this process of sensitization via experience of nasopharyngeal colonization is the mechanism of natural immunization which occurs especially throughout childhood. The chief objection to such a hypothesis is its expectation that all children who have not experienced MC should develop systemic disease upon exposure to the meningococcus. As a solution to the paradox, Goldsneider et al. suggested that only a proportion of carriage acquisitions, let us call it \( \zeta \), occurred in susceptible individuals that acquired strain of great enough pathogenicity as to trigger invasive disease. The model of the disease process presented in this paper makes use of the same principle, except that the constant proportion \( \zeta \) is replaced by the age-dependent rate \( \Phi(a) \). This is equivalent to the proportion of carriers of age \( a \) that succumb to meningococcal disease per year. The disease data set was fitted using the best-fitting MC-LC model (Figure 2b), with the addition of disease categories. Four families of functions were used to estimate this rate, all of which are of the form

\[
\Phi(a) = MAX[\Phi(a)_1, \Phi(a)_2]
\]
Figure 1 Model fits to the data sets of asymptomatic carriage (MC and LC) and MD. (a) The LC data set; (b) the MC-LC-protection model fitted to the MD data set, and (c) the MD data set.
Mode of Neisseria Infection

Model fitting techniques and 95% confidence limits

The goodness of fit of the models was maximized by minimizing the binomial deviance of the model from the data by maximum likelihood using standard techniques. The binomial deviance, \( L \), is given by the expression,

\[
L = 2 \sum_{a=1}^{N} \left[ R_a \cdot \ln \left( \frac{R_a}{q_a \cdot N_a} \right) + (N_a - R_a) \cdot \ln \left( \frac{N_a - R_a}{N_a \cdot (1 - q_a)} \right) \right]
\]

which is asymptotically distributed as \( \chi^2_{m-v} \) with \( m-v \) degrees of freedom, where \( m \) is the number of observations (age classes) and \( v \) is the number of parameters being fitted. For example, when the data set under consideration was MC, then \( q_a \) was the expected prevalence generated by the model at age \( a \), \( N_a \) was the observed number of people sampled within the age class with mean age \( a \), and \( R_a \) was the number of carriers found in that age class. Thus a high \( P \)-value indicates a high probability that, had the model been true, the deviance between data and model (\( p_a \)) arose by chance. The 95% confidence limits for the parameter estimates were calculated as the range of parameter values that resulted in a binomial deviance, \( L \), equivalent to the lowest \( L + \chi^2(v,a) \), where \( v \) (the degrees of freedom) is the number of fitted parameters and \( a \) equals 0.05, the threshold significance probability.

Results

Duration of carriage

Analysis of the data on a cohort of 158 carriers in Belgian schoolchildren revealed an average rate of loss of \( N. meningitidis \) carriage of 0.904 per person per year, resulting in an estimate of average duration of carriage of 13.3 months. The estimate of mean duration of LC from the age-stratified prevalence data was 3.4 months for the SCS model (95% CI: 2.7–4.4 months), and 3.9 months for the SCS-SCR model (95% CI: 2.9–5.9 months).

Asymptomatic carriage and the infectious process

Neisseria lactamica carriage (LC)

Both the SCS and SCS-SCR models fitted the data sets adequately (Figure 1a). The SCS model fitted the data best assuming a variant of the functional form suggested by Farrington, in comparison with a range of alternative functions including the polynomial functions used by Grenfell & Anderson (Figure 3a). The form of the function was,

\[
\lambda L(a) = \left[ (a/(a - \gamma)) \cdot e^{(-a/\beta)} + \gamma \right] \cdot [(1 + \varepsilon) \cdot e^{(-a/\alpha)}]
\]

The resulting estimated age-dependence in the rate of acquisition (force of infection) of LC is shown in Figure 3a. The 'Farrington' function describes the force of infection, \( \lambda L(a) \), rising initially, reaching a peak, and thereafter declining to a plateau. This is the first term in square brackets, where \( \alpha \) is the initial rate of increase, \( \beta + \gamma \) is the age of the peak (= 2.4 years), and \( \gamma \) is the plateau (= 0.095 per susceptible per year). The second term in the square brackets is a correction that allows the functional form to decline further in the older ages. The SCS-SCR model fitted the LC data (Figure 3a) with the simple 'Farrington' function, as the correction term was not needed.

The single-hump decay model,

\[
\Phi(a) = a_1 + a_2 \cdot \exp(-a/a_3)
\]

the complex-hump decay model 1,

\[
\Phi(a) = a_1 \cdot \exp(-a/a_2)
\]

\[
\Phi(a) = a_1 + a_2 \cdot \exp(-a/a_3)
\]

the complex-hump decay model 2,

\[
\Phi(a) = a_1 \cdot \exp(-a/a_2)
\]

\[
\Phi(a) = a_1 + a_2 \cdot \exp(-a/a_3)
\]

and the double-hump decay model,

\[
\Phi(a) = a_1 + a_2 \cdot \exp(-a/a_3)
\]

\[
\Phi(a) = a_1 + a_2 \cdot \exp(-a/a_3)
\]

\[
\Phi(a) = a_1 + a_2 \cdot \exp(-a/a_3)
\]
The form of the function is depicted in Figure 3a. The SCR-SCS model predicts that a proportion 0.13 (= z) of LC acquisitions trigger immunity to re-acquisition, implying that by age 50 years 15% of the human population would remain susceptible to LC acquisition and that complete immunity is not attained by any age class. The peak age for the force of infection was estimated as 2.7 years. The SCS model was used for the remaining analyses because of the simplicity of the model form.

**Neisseria meningitidis carriage (MC)**

No simple compartmental model (SCR, SCS-SCR, SCS) fitted the MC data set adequately. The SCR model fitted worst (deviance, \(L = 1366.53\)). The other models fitted increasingly better in the order: SCS-SCR (\(L = 92.35\)), and SCS (\(L = 20.21\)). A non-parametric model was used to investigate the form of the age-dependence in the force of infection, \(\lambda M(a)\). This analysis established that the low prevalence of carriage in the early years

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**Figure 3** Estimated functional forms and parameter estimates (95% confidence intervals in brackets) for the rates of acquisition (forces of infection) of LC and MC (a), and for the per-carrier incidence of MD (b). a) The force of infection of LC (\(L\)): 1) SCR-SCS model: \(\alpha = 0.642 (0.393, 0.897), \beta = 2.480 (1.707, 3.330), \gamma = 0.235 (0.133, 0.317), z = 0.125 (0.0626, 0.172), rL = 3.10 (2.04, 4.13), \chi^2_9 = 6.8, p = 0.66. 2) SCS model: \(\alpha = 0.441 (0.332, 0.549), \beta = 2.288 (1.736, 2.880), \gamma = 0.095 (0.0720, 0.1184), \epsilon = 0.779 (0.588, 0.971), k = 0.0252 (0.01897, 0.03148), rL = 3.576 (2.744, 4.460), \chi^2_9 = 6.3, p = 0.61. 3) The force of infection of MC (\(M\)): model depicted in Figure 3c: \(\alpha = 0.024 (0.0202, 0.0270), \beta = 20.59 (17.92, 23.52), \gamma = 0.0035 (0.00299, 0.00400), \delta = 0.391 (0.332, 0.448), h = 19.26 (16.42, 22.03), \sigma = 3.884 (3.333, 4.430), \delta = 0.215 (0.183, 0.247), \chi^2_4 = 3.2, p = 0.52. b) The per-carrier yearly risk of MD, \(\phi (a)\): three lines are represented: the middle line represents the maximum likelihood estimate and the outer lines are those estimated using the upper and lower confidence limits for the parameter estimates. Notice that the outer lines are >95% confidence intervals because the 95% confidence limit for one parameter may not necessarily coincide with the limit for another parameter.22 Parameters: \(a_1 = 3.332 (2.834, 3.812), a_2 = 0.194 (0.178, 0.214), b_1 = 0.0190 (0.0167, 0.0215), b_2 = 2.048 (1.759, 2.334), \gamma_1 = 0.00117 (0.00104, 0.00134), \gamma_2 = 7.824 (6.653, 8.555), \gamma_3 = 5.62 \times 10^{-3} (4.97 \times 10^{-3}, 6.29 \times 10^{-3})\)
of life is too low to be explained by the SCS model with the assumed duration of carriage of 13 months. The only model that could fit the MC data was one where MC acquisition is inhibited during the second year of life. The ‘temporary immunity’ model fitted the data accurately (Figures 1b, and 2c; \( L = 3.24; P = 0.52 \)), and was consistent with inhibition of MC by LC for a mean period 1/\( \delta \) = 4.65 years (95% CI : 4.06 to 5.46) after the loss of LC. Hosts are born susceptible (S) and either acquire LC or MC with forces of infection \( \Lambda L(a) \) and \( \Lambda M(a) \), respectively. The model assumes the possibility for mixed infections to occur (MLC), although these are expected to be rare. Individuals in the LC class progress to the SL class that are susceptible to LC acquisition but temporarily immune to the acquisition of MC. The latter then flow back to the class susceptible to MC acquisition (S) at a rate \( \delta \). The ‘Farrington’ function was again successful in the estimation of the functional form of the force of infection, \( \Lambda M(a) \), except for a range of ages whereas a Gaussian function had to be used to account for the observed peak of carriage prevalence in the 18–22 year age range. Omission of the Gaussian function led to the failure of the fitting process. The functional form used was,

\[
\Lambda M(a) = \text{MAX} \{ \Lambda(a)_{\text{Farrington}}, \Lambda(a)_{\text{Gaussian}} \}
\]

\[
\Lambda(a)_{\text{Farrington}} = \alpha - (a - \lambda) \cdot e^{-(a/\beta)} + \lambda
\]

\[
\Lambda(a)_{\text{Gaussian}} = \epsilon \cdot \exp \left( -\frac{(a - \eta)^2}{2 \cdot \pi \cdot \sigma^2} \right)
\]

The fitted form is displayed in Figure 3a. The parameters for the ‘Farrington’ function have been introduced above. The Gaussian function was a description of the normal distribution where parameter \( \epsilon \) is a scale parameter representing the maximum size of the peak, \( \eta \) is the age at which the peak in \( \lambda(a)_{\text{Gaussian}} \) occurs, and \( \sigma \) is the standard deviation of the peak.

**Modelling the meningococcal disease process**

The complex-hump decay model 2 fitted the MD data set better than any other (\( L = 20.24 \); \( df = 26; P = 0.78 \); Figures 1b and 3b). The model that fitted the MD data set suggests that infants have the greatest per-carrier rates of illness (7–12% of MC carriers per year). The model predicts this rate to fall with age after the first 6 months of life. In particular it predicts a 10-fold decline in carriage after a serogroup A epidemic in The Gambia to some extent encompassing different epidemic and endemic patterns,32 but it would be necessary to have an improved understanding of the pattern of nasopharyngeal carriage for each of the ET-complexes associated with the various observed epidemiological patterns.

Analysis of the age-related data set of MC and LC revealed that asymptomatic colonization is unlikely to stimulate acquired immunity to the acquisition of other yet-to-be encountered strains of meningococci, favouring the SCS models over the SCR-SCS models, for any age group (\( P < 0.001 \); Figure 1b). Nevertheless, given that, once acquired, MC and LC have limited durations, there must be a form of immunity. This SCS pattern could be consistent with strain- or variant-specific immunity where there are many individual variants, and where there is little or no cross-protection, against carriage, between variants. The existence of natural immunity to meningococcal carriage has never been established, although Hassan-King et al.33 ascribed a decline in carriage after a serogroup A epidemic in The Gambia to some form of herd immunity independent of the immunization programme. We estimate an average duration of 13 months for MC after the colonization event, which is broadly consistent
with previous estimates obtained by other means. By the 1930s it was understood that the duration of meningococcal carriage was highly variable, with a median duration of 10 months.\textsuperscript{34} Other studies have provided estimates that ranged from 9.6 to 14.5 months.\textsuperscript{35,36} The limited information on LC duration, together with our independent estimate, suggests that this infection is more short lived than MC. The fitted LC model is consistent with little or no immunity to re-acquisition.

The theory of inhibition of acquisition of MC by LC with delayed effects ($\delta > 0$) was supported by this analysis and was consistent with a number of studies of the immunogenic properties of \textit{N. lactamica}. One study in particular demonstrated that asymptomatic carriage of \textit{N. lactamica} resulted in fourfold or greater rises in titres of antibody to capsulated strains of \textit{N. meningitidis}, significantly more frequently than in controls.\textsuperscript{37} Since \textit{N. lactamica} organisms do not possess a polysaccharide capsule, the cross-reactions observed must have been due to the presence of other non-capsular antigens. \textit{Neisseria lactamica} and \textit{N. meningitidis} are known to share lipoooligosaccharide (LOS) epitopes.\textsuperscript{38} \textit{Neisseria lactamica} strains also share at least one class of OMP (class 3) with \textit{N. meningitidis}, with some degree of homology in the sequence of amino acid residues that are responsible for the interaction with serum antibodies.\textsuperscript{39} Suker et al.\textsuperscript{40} showed 65% sequence identity for the genes encoding the class 3 OMP of \textit{N. meningitidis} and \textit{N. lactamica}. It is therefore possible that \textit{N. meningitidis} and \textit{N. lactamica} bacteria interfere with each other via cross-reactions with the immune system of the host. Olsen et al.\textsuperscript{41} showed that a high prevalence of LC was associated with a low incidence of MD in households in the Faeroe Islands (OR = 0.19; 95% CI: 0.08–0.47). Our analysis suggests that this could have been due to inhibition of MC, as well as by a more direct inhibition of the invasive disease process. Griffiss et al.\textsuperscript{42} even suggested the widespread use of intentional colonization with \textit{N. lactamica} strains to control MD.

The estimated forces of infection (acquisition rates per susceptible in the population) for \textit{N. lactamica} ($\lambda L$) and \textit{N. meningitidis} ($\lambda M$) are consistent with those calculated directly from a range of studies.\textsuperscript{7,41} In particular Gold et al.\textsuperscript{7} calculated an initial value for $\lambda L$ of 0.24 in infants declining to 0.12 in 6–8-year-olds, whereas they observed an initial rise for $\lambda M$ from 0.02 in infants to 0.03 in 6–8-year-old children. These were very close to our maximum-likelihood estimates (Figure 1a and b). The fitted model suggested that there might have been two overlapping trends influencing $\lambda M$. We estimated a long-term and shallow rise for $\lambda M$ from 0 at birth and peaking at 21.5 years of age. Superimposed on this was a sharp rise of $\lambda M$ to a peak of 0.385 per susceptible, per year, at 19.75 ± 4.0 years of age. What causes such dramatic changes? The force of infection may be affected by two independent processes: immunity to colonization (possibly caused by LC), and behavioural characteristics that result in some age groups at greater risk of acquisition than others. In our models, the peak of acquisition (force of infection) of MC in late teenagers could account for the second peak of MD observed in this age group.

The meningococcal carriage and disease data sets are consistent with short-lived maternal immunity against MD.\textsuperscript{38,43} The peak incidence of MD in the 6–7 month age group is consistent with a balance between the opposing effects of a falling rate of MD per carrier ($\phi(a)$) and a rising rate of acquisition of carriage ($\lambda M(a)$) (compare functional forms in Figure 3a and b). The estimated exponential decay model for $\phi(a)$ is similar to the age-dependent decline of disease risk per carrier measured by Kaiser et al.\textsuperscript{44} among close contacts of index cases in a civilian population of Florida, US, in the midst of an MD epidemic. Age specific rates of illness, $\phi(a)$, in part reflect the pattern of acquisition of natural immunity to MD. Goldschneider et al.\textsuperscript{45} reviewed factors contributing to the development of natural immunity to MD. They showed that serum bactericidal antibodies confer protective immunity and concluded that one of the most significant immunogenic stimuli must be the acquisition of asymptomatic carriage of meningococci in the nasopharynx. The first episode of carriage was suspected to act as a stimulus causing either disease or acquisition of natural immunity. This was confirmed in two follow-up studies of US military recruits in which the acquisition of MC led within a period of 10 days either to MD or to the development of protective serum antibodies.\textsuperscript{40,42} We did not explicitly consider this mechanism in our model of MD because the models we used do not consider the time delay between acquisition and onset of disease within individuals. However, our model is implicitly consistent with this finding because disease may occur in long-term carriers who acquire pathogenic strains.

The pattern of acquired immunity to MD is made complicated by the antigenic structure of the meningococcal population. When compared with asymptomatic carrier isolates, most isolates from MD cases represent limited sets or ‘complexes’ of genotypes. It would seem that specific bacterial genotypes are more likely than others to overcome the defences of the host. The population of pathogenic genotypes would be a dynamic one, with a constant influx of novel genotypes supplanting previously existing ones.\textsuperscript{45} Non-conjugated polysaccharide meningococcal vaccines against serogroups A, C, Y, and W-135 are available and are used mainly for protection of close contacts and for prevention of disease in wider populations during local outbreaks.\textsuperscript{46} Improved meningococcal vaccines are under development. If conjugated meningococcal polysaccharide vaccines reduce carriage, as seen with Hib vaccines,\textsuperscript{47,48} the inclusion of adults in a meningococcal vaccine programme could reduce rates of MD in unvaccinated populations. The impact of new vaccines on disease rates in vaccinated and unvaccinated populations could usefully be explored with mathematical models such as those developed here. If future vaccines should share common antigens with \textit{N. lactamica} and thereby lead to reduced prevalence of LC, the success of the immunization programme may be impaired. Mathematical models could be used to simulate the effect of such programmes.

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