Dynamic Models of Meningococcal Carriage, Disease, and the Impact of Serogroup C Conjugate Vaccination

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Much interest has surrounded the use of conjugate vaccines in recent years, with the development of vaccines against disease caused by *Haemophilus influenzae* type b, *Neisseria meningitidis*, and *Streptococcus pneumoniae*. These vaccines offer the potential for safe and effective disease control, but some questions remain, particularly regarding the duration and mechanisms of protection and the longer-term impact of vaccination on carriage. In this paper, the authors use data on immunization with serogroup C meningococcal conjugate vaccines in England and Wales to develop and apply a mathematical model to investigate the direct and indirect (herd immunity) effects of a conjugate vaccine program. A realistic, age-structured, dynamic model was developed and parameterized and was fitted to epidemiologic data from England and Wales. The effects of a range of vaccine strategies, including hypothetical scenarios, were investigated. The basic reproduction number was estimated to be 1.36. Catch-up vaccination targeting teenagers generated substantial herd immunity and was important in controlling disease rapidly. The results were sensitive to changes in the assumptions regarding the method of vaccine action, particularly duration of protection and efficacy of vaccination against carriage acquisition. This model can be used to help predict the potential impact of vaccine strategies both in the United Kingdom and elsewhere.

Abbreviation: MCC, meningococcal serogroup C conjugate.

Conjugate vaccine technology has been successfully applied to childhood vaccines against *Haemophilus influenzae* type b disease and more recently against serogroup C meningococcal disease and pneumococcal disease, offering excellent prospects for disease control. The United Kingdom was the first country to introduce the meningococcal serogroup C conjugate (MCC) vaccine at the end of 1999. The MCC immunization program has had a considerable public health impact; the vaccine provides high levels of direct protection in the short term (1, 2) and reduces the prevalence of serogroup C carriage, resulting in herd immunity (3, 4). While these effects can be directly observed for the program adopted in the United Kingdom, other methods must be used to predict longer-term trends or to explore the effects of alternative vaccination programs in the United Kingdom or elsewhere. To fully account for the herd immunity effects of vaccination, a transmission-dynamic model must be used (5, 6). Here, we use pre- and postvaccination data from England and Wales to develop, parameterize, and apply a mathematical model to explore the impact of different MCC vaccination strategies. Many of the issues raised here may also be relevant to other conjugate vaccine programs.

Asymptomatic carriage of *Neisseria meningitidis* is common, and, as with *H. influenzae* type b and *Streptococcus pneumoniae*, invasive disease is a rare outcome of infection. Carriers thus play a key role in transmission. The population prevalence of meningococcal carriage is about 10 percent,
although it is highly age specific, with a low prevalence in young children that rises to a peak of about 25 percent in teenagers (7). Repeated episodes of meningococcal carriage (8, 9) and carriage of the closely related, nonpathogenic Neisseria lactamica (7) are thought to be important in generating natural immunity against disease.

The MCC vaccine contains the serogroup C polysaccharide only and so cannot be expected to provide any protection against carriage or disease caused by other serogroups. Serogroup C carriage is rare compared with other meningococcal serogroups and _N. lactamica_ (3, 10). Even though the prevalence of serogroup C carriage was reduced by 66 percent in teenagers (in whom meningococcal carriage is most prevalent) following the introduction of MCC vaccination (3), this reduction represents a small change in overall meningococcal carriage. Serogroup C infection is not a major factor (because of its low prevalence) in generating immunity to disease for either serogroup C or other serogroups, so very few extra susceptibles will be generated as a result of vaccinating against serogroup C. Therefore, it is unlikely that the dynamics of carriage of other meningococcal serogroups or _N. lactamica_ will be affected; the dynamic model described here looks only at the effect of vaccination on serogroup C-specific carriage and disease and assumes that the force of infection with other meningococcal serogroups and _N. lactamica_ will not differ following MCC vaccination.

The MCC vaccines have been shown to provide high levels of protection in the short term, and, for children vaccinated after the age of 5 months, effectiveness remains high at least 4 years after immunization (11). However, protection wanes to low levels only 1 year after scheduled vaccination of routinely vaccinated infants (11), despite the demonstration of immunologic memory (12). This problem raises important questions about both the use of the current vaccine schedule in the United Kingdom and the role of immunologic memory in long-term protection. The number of cases of serogroup C disease in infants remains low despite the declining efficacy, probably because of high levels of herd immunity, but it is not clear how long these herd effects will be sustained. The duration of direct protection in older children is also unclear at present.

One of the advantages of mathematical models is that different assumptions and scenarios can be tested. In addition, future changes to the vaccine schedule can be modeled, offering policy makers another tool with which to inform their decisions.

**MATERIALS AND METHODS**

**Population**

The population is stratified into 75 one-year age cohorts. Births are equal to deaths, and there is no migration. At the end of each year, individuals in age class _i_ move into age class _i + 1_, newly born individuals are introduced into age class 0, and all individuals in age class 74 die (mortality is assumed to be zero up to this point), as in the realistic age-structured models of Schenzle (13).

**Model structure**

In the model, individuals in age class _i_ can exist in one of nine mutually exclusive compartments (figure 1; in an unvaccinated population, only the three central compartments of the model are applicable). (Refer to appendix 1 for model equations.) Individuals may be susceptible to infection (S if unvaccinated, _V_ if vaccinated), a carrier of serogroup C meningococci (C_CV_), or a carrier of another meningococcal serogroup or _N. lactamica_ (OIV). We assume for simplicity that coinfection with more than one serogroup or with _N. lactamica_ does not occur. The presence of other meningococcal serogroups and _N. lactamica_ in the model serves to reduce the proportion of susceptibles in the population.

Susceptible individuals become infected according to the age-specific forces of infection, which are constant over time for infections other than serogroup C (λ_C). For serogroup C (λ_C(t)), the force of infection varies according to the number of serogroup C carriers in the population. Individuals recover naturally from carriage at rates _r_C_ and _r_O_. Meningococcal disease is shown explicitly in the model structure (figure 1) because transmission occurs via carriers and disease incidence at age _i_ is a function of the number of individuals becoming infected with serogroup C at age _i_ (θ_i).

In the model, vaccination is implemented as a discrete event at a specified point in time ( _t_ = _t_v_ for catch-up vaccination, _t_ = _t_r_ for routine vaccination) and age (according to the vaccine schedule implemented). At this point, individuals are transferred into the equivalent vaccinated compartments according to the effective coverage proportion _ψ(t)_ (table 1). Primary vaccine failures remain in the unvaccinated compartments. Those who respond are assumed to have complete protection against serogroup C disease and some degree of protection (γ) against acquiring serogroup C carriage. Secondary vaccine failure can occur through waning immunity (at rate _w_r_ for routine vaccination, _w_v_ for catch-up vaccination), leaving vaccinated individuals at the same risk as unvaccinated individuals of serogroup C carriage and disease. A proportion of serogroup C carriers, _m_ , may spontaneously recover and be transferred into the vaccinated noncarrier compartment upon vaccination. Vaccinated serogroup C carriers may also experience a higher recovery rate than unvaccinated carriers, according to a factor _z_ , and may be less infectious than unvaccinated C carriers, according to the proportion _δ_. The duration of protection against carriage is assumed to be the same as the duration of protection against disease, although, unlike disease, the degree of protection against carriage is not 100 percent.

**Parameterization**

**Forces of infection.** For other serogroups _O_, the age-specific forces of infection were fixed at equilibrium values from the best-fitting susceptible-infected-susceptible model of carriage and disease described in a corresponding paper (14). The age-specific equilibrium carriage prevalences for _C_ and _O_ from the same source (14) were used as the initial
conditions for the model. The force of infection for serogroup C was age and time dependent ($\lambda_{C_i}(t)$), varying as a function of the number of vaccinated and unvaccinated serogroup C carriers in each age class $j$ and the rate of effective contacts between individuals in age class $i$ and those in age class $j$, as follows:

$$\lambda_{C_i}(t) = \sum_j b_{ij} (C_j(t) + \delta CV_j(t)).$$

Mixing patterns appropriate for meningococcal disease are described in appendix 2. The effects of changing the mixing assumptions were explored in a sensitivity analysis.

**Reproduction numbers.** The basic reproduction number ($R_0$) is defined as the average number of secondary infections that would be produced in a completely susceptible population by a typical infectious individual (15) and, as such, measures the inherent transmissibility of an infection. The calculation of $R_0$ for a given set of mixing assumptions is described in appendix 3 (16). The effective reproduction number, $R(t)$, defined as the number of secondary infections produced by a typical infectious individual at time $t$, was also estimated after vaccination was introduced (appendix 3).

The **risk of disease given infection**, $\theta_i$. The risk of serogroup C disease given infection was estimated by fitting a model to both age-specific carriage and disease data, as described previously (14).

**Recovery rates.** On the basis of published data, the average duration of carriage was assumed to be 9 months for meningococcal disease (17) and 4 months for *N. lactamica* (9). Because the model combines all infections other than serogroup C, the recovery rate for “other” infections in the model was age dependent according to the proportion of meningococcal versus *N. lactamica* carriers. To our knowledge, there have been no recent studies of the duration of serogroup C carriage, but it has been hypothesized that the hypervirulent strains that have prevailed recently have a short duration of carriage. To account for this possibility, duration of serogroup C carriage was varied between 1 and 9 months in a sensitivity analysis, and the model predictions were compared with the observed data from England and Wales by using a least-squares approach.

Vaccinated individuals were assumed to recover from serogroup C carriage at the same rate as unvaccinated individuals ($r = 1$). The reduction in the prevalence of serogroup C carriage in vaccinated compared with unvaccinated individuals was therefore assumed to be due to a reduced acquisition rate.

**Vaccine-associated parameters.** The effective coverage by age, $\psi_i$, was estimated from the observed data from England and Wales (12; table 1). The efficacy of vaccination against carriage acquisition, $\gamma$, was estimated to be 67 percent (3), with a range of 0–90 percent considered. Direct protection from vaccination varied according to age at vaccination. For children vaccinated at 2, 3, and 4 months of age, protection was assumed to last for 15 months on average (11); for children vaccinated at 12 months of age, protection was assumed to last an average of 5 years; and for children vaccinated at older ages, the vaccine was...
TABLE 1. Effective vaccination coverage, by age, used in all simulations based on estimated coverage for the England and Wales routine program and campaigns (Trotter et al. (2))

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Routine vs. catch-up vaccination</th>
<th>Estimated coverage</th>
<th>Estimated efficacy</th>
<th>Effective coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Routine</td>
<td>0.89</td>
<td>0.85</td>
<td>0.76</td>
</tr>
<tr>
<td>1</td>
<td>Catch-up 1</td>
<td>0.84</td>
<td>0.84</td>
<td>0.70</td>
</tr>
<tr>
<td>2</td>
<td>Catch-up 1</td>
<td>0.76</td>
<td>0.84</td>
<td>0.63</td>
</tr>
<tr>
<td>3</td>
<td>Catch-up 1</td>
<td>0.76</td>
<td>0.99</td>
<td>0.75</td>
</tr>
<tr>
<td>4</td>
<td>Catch-up 1</td>
<td>0.76</td>
<td>0.99</td>
<td>0.75</td>
</tr>
<tr>
<td>5</td>
<td>Catch-up 1</td>
<td>0.81</td>
<td>1.00</td>
<td>0.81</td>
</tr>
<tr>
<td>6</td>
<td>Catch-up 1</td>
<td>0.87</td>
<td>1.00</td>
<td>0.87</td>
</tr>
<tr>
<td>7</td>
<td>Catch-up 1</td>
<td>0.87</td>
<td>1.00</td>
<td>0.87</td>
</tr>
<tr>
<td>8</td>
<td>Catch-up 1</td>
<td>0.88</td>
<td>0.92</td>
<td>0.80</td>
</tr>
<tr>
<td>9</td>
<td>Catch-up 1</td>
<td>0.89</td>
<td>0.92</td>
<td>0.81</td>
</tr>
<tr>
<td>10</td>
<td>Catch-up 1</td>
<td>0.88</td>
<td>0.92</td>
<td>0.81</td>
</tr>
<tr>
<td>11</td>
<td>Catch-up 1</td>
<td>0.88</td>
<td>0.95</td>
<td>0.83</td>
</tr>
<tr>
<td>12</td>
<td>Catch-up 1</td>
<td>0.87</td>
<td>0.95</td>
<td>0.83</td>
</tr>
<tr>
<td>13</td>
<td>Catch-up 1</td>
<td>0.86</td>
<td>0.95</td>
<td>0.81</td>
</tr>
<tr>
<td>14</td>
<td>Catch-up 1</td>
<td>0.83</td>
<td>0.95</td>
<td>0.79</td>
</tr>
<tr>
<td>15</td>
<td>Catch-up 1</td>
<td>0.84</td>
<td>0.95</td>
<td>0.79</td>
</tr>
<tr>
<td>16</td>
<td>Catch-up 1</td>
<td>0.70</td>
<td>0.92</td>
<td>0.65</td>
</tr>
<tr>
<td>17</td>
<td>Catch-up 1</td>
<td>0.60</td>
<td>0.92</td>
<td>0.56</td>
</tr>
<tr>
<td>18–24</td>
<td>Catch-up 2</td>
<td>0.43</td>
<td>0.92</td>
<td>0.40</td>
</tr>
</tbody>
</table>

* The same coverage was assumed as for those aged 16–17 years not participating in full-time education.

TABLE 2. Vaccine strategies simulated by using the transmission dynamic model

<table>
<thead>
<tr>
<th>Strategies</th>
<th>Age at routine vaccination</th>
<th>Age group targeted for catch-up vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introductory strategies*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strategy 1</td>
<td>2, 3, 4 months</td>
<td>None</td>
</tr>
<tr>
<td>Strategy 2</td>
<td>12 months</td>
<td>None</td>
</tr>
<tr>
<td>Strategy 3</td>
<td>2, 3, 4 months</td>
<td>&lt;18 years</td>
</tr>
<tr>
<td>Strategy 4</td>
<td>2, 3, 4 months</td>
<td>&lt;25 years</td>
</tr>
<tr>
<td>Strategy 5</td>
<td>12 months</td>
<td>&lt;18 years</td>
</tr>
<tr>
<td>Strategy 6</td>
<td>12 months and 12 years</td>
<td>None</td>
</tr>
</tbody>
</table>

Future strategies† | Change to the United Kingdom vaccination schedule |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Strategy 7</td>
<td>Add a booster dose at 12 years of age, 12 years after the start of the campaign.</td>
</tr>
<tr>
<td>Strategy 8</td>
<td>Switch from a 2-, 3-, and 4-month routine schedule to one dose at 12 months, 5 or 10 years after the start of the campaign.</td>
</tr>
<tr>
<td>Strategy 9</td>
<td>Switch from a 2-, 3-, and 4-month routine schedule to one dose at 12 months and one dose at 12 years, 5 or 10 years after the start of the campaign.</td>
</tr>
</tbody>
</table>

* When different strategies were compared, the catch-up campaign was implemented in month 3 for all age groups because it was not necessary to model the phased implementation.

† Given that routine infant vaccination has commenced and the phased catch-up campaign has been implemented.
**RESULTS**

Model validation

We compared the number of cases of serogroup C meningococcal disease predicted by the phased introduction model with the number of observed cases in England and Wales, varying the duration of carriage and mixing patterns (table 3). Proportional mixing did not fit well because the number of predicted cases declined too quickly compared with the observed cases. A 3-month duration of serogroup C carriage, as shown in figure 2, resulted in the best fit, so this duration was used in the base-case model. The model provides a good description of the pattern of cases through age and time. It predicts that the prevalence of serogroup C carriage in individuals aged 15–17 years is 71 percent lower 1 year after vaccination, which is close to that observed in a large carriage study (point estimate = 66 percent, 95 percent confidence interval: 28 percent, 85 percent) (3). It was also very clear from this exercise that there must be some indirect effect of vaccination for the model to reproduce the results observed. Because of remaining uncertainty, sensitivity analyses for key parameter values and model assumptions are reported.

**Reproduction numbers**

$R_0$ for serogroup C meningococcal infection was estimated to be 1.36, with a range of 1.2–1.36 according to the mixing patterns assumed (table 4). These estimates of $R_0$ are low (as would be expected for a susceptible-infected-susceptible infection with a low prevalence of carriage), implying that control by vaccination should be achievable if immunity is long lived (critical immunization thresholds of 17–26 percent). In the first year of the campaign, it was estimated that 17.5 percent of the population was effectively vaccinated. In the second year, the rate increased to 21.3 percent and is predicted to rise each year because of the routine infant immunization program (without taking waning into account). In addition to vaccine-induced immunity, approximately 12.7 percent of the population will be carriers of strains other than serogroup C, reducing the proportion of susceptibles in the population still further and enhancing the ability to control disease through vaccination.

The expected values of $R(t)$ were estimated for each year following introduction of vaccination by using the model based on the United Kingdom schedule and phased catch-up campaign (figure 3). The longer the duration of protection from vaccination, the longer that $R(t)$ is estimated to stay below 1. When $R(t)$ is approaching 1, it may be necessary to introduce a booster dose of vaccine to increase population immunity and reduce $R(t)$ to below 1, although the prevalence of carriage and incidence of disease may still be low at this point.

**Introductory vaccination strategies 1–6**

Strategy 1 (routine vaccination at 2, 3, and 4 months) has the least impact on disease incidence (figure 4); the duration of protection is short, and there is little herd immunity because serogroup C carriage is so rare in young children. Strategy 2 (routine vaccination at age 12 months) is more effective because of the longer duration of protection, but the indirect effects are still small. By comparison, disease is rapidly controlled under strategies 3 and 4, where individuals younger than age 18 years and younger than age 25 years, respectively, are targeted in a catch-up campaign in addition to routine vaccination at age 2, 3, and 4 months (figure 4). Targeting such a wide age range for catch-up vaccination has a large effect on the transmission dynamics of serogroup C meningococci. Extending vaccination to those less than age 25 years (strategy 4) is estimated to have prevented 30 additional cases compared with strategy 3, reducing disease incidence by a further 8 percent.

Routine vaccination at 12 months of age with a catch-up (strategy 5) was equivalent in terms of total cases averted compared with strategy 3, where infants were vaccinated at 2, 3, and 4 months of age. Over the 24-year time window,
245 cases occurred in infants less than age 1 year under strategy 5 compared with 144 cases under strategy 3. However, more cases were prevented at older ages with strategy 5.

The impact of strategy 6, which uses a routine dose at age 12 years in addition to routine vaccination, is much slower than those strategies that use a catch-up campaign because a large number of children remain susceptible to disease during the 11 years it takes for all at-risk age groups to be targeted. However, this strategy is likely to be more effective in the long term than strategies with a one-off campaign.

**Sensitivity analysis**

Higher efficacy against carriage acquisition and longer duration of protection both improve the impact of all programs compared with the base case (table 5). If proportional mixing is assumed, the impact of all programs is greater than if mixing is assumed to be assortative because carriage is reduced across a wider age range.

**Future vaccine strategies**

Introducing a routine booster dose into the phased United Kingdom model in year 12 (strategy 7) was estimated to prevent only 10 additional cases in years 12–24 compared with the base case (table 6). A booster dose is more effective if the duration of vaccine protection is less than 10 years; otherwise, disease incidence is too low for the booster to have much impact (figure 5).

**FIGURE 2.** Comparison of the observed number of cases of laboratory-confirmed serogroup C disease reported to the Meningococcal Reference Unit of England and Wales with those predicted by the base-case model, by age group and year.
The benefits of strategy 8 (switching from the 2-, 3-, and 4-month schedule to one dose at age 12 months) are clear in terms of resources, because infants receive only one vaccine dose rather than three. In addition, the duration of protection is longer in children vaccinated at 12 months of age than in those vaccinated in infancy. The key question here is whether this switch leads to an increase in the number of potentially preventable cases in children less than 1 year of age. If herd immunity is sufficient, then infants will be indirectly protected. Under base-case conditions, the number of cases in children less than 1 year of age is reduced or stays the same if the switch is made 5 or 10 years after vaccine introduction, respectively. Changing after 5 years is predicted to prevent an additional 29 cases overall (table 6). Strategy 9, which in the long term reduces the total number of doses each child receives from three to two, also results in additional cases being averted. For all of the future strategies, the changes appear to have a relatively small impact because the number of cases has declined to low levels and little ongoing serogroup C transmission is predicted.

If we assume that the vaccine protects against carriage acquisition for only 2 years but protects against disease for a total of 10 years, then the number of cases begins to increase again 10 years after the introduction of vaccination. Therefore, under these conditions, future changes, especially adding a booster dose, will be more effective.

**DISCUSSION**

These models provide useful insights into the potential effects of different MCC vaccination programs on a population level. The estimated basic reproduction number of about 1.36 indicates the effort required to control serogroup C transmission, although achieving the elimination threshold will depend on the degree and duration of protection conferred by vaccination. Monitoring the effective reproduction number may help to inform future vaccination strategies (20). If $R(t)$ approaches 1, introducing a booster dose in teenagers may be necessary to directly protect children in whom routine infant vaccination has waned. In this scenario, teenagers would be most vulnerable to disease, and targeting this age group for a booster dose would also have the advantage of boosting herd immunity.

The model that predicted the “best fit” compared with the observed cases was one in which the duration of serogroup C carriage was an average of 3 months. This estimate supports the hypothesis that serogroup C strains have a higher recovery rate and move quickly through populations while maintaining a low prevalence.

**FIGURE 3.** Effective reproduction number (average number of secondary infections per carrier) for serogroup C meningococci estimated after the introduction of the meningococcal serogroup C vaccine program in England and Wales, by average duration of vaccine protection in those vaccinated in the campaign. All other parameter values are assumed to be at their base-case level.

**FIGURE 4.** Predicted number of annual cases of meningococcal serogroup C disease in England and Wales under vaccination strategies 1–6 (refer to table 2 for more information on these strategies).

**TABLE 4.** Basic reproduction number for serogroup C meningococci, according to the mixing assumptions and duration of carriage

<table>
<thead>
<tr>
<th>Epsilon $\epsilon^*$</th>
<th>Preferential mixing within $\pm 1$ year of age</th>
<th>Preferential mixing within $\pm 2$ years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R_0 \dagger$</td>
<td>$p_C \dagger$ (%)</td>
</tr>
<tr>
<td>0</td>
<td>1.20</td>
<td>16.7</td>
</tr>
<tr>
<td>0.5</td>
<td>1.21</td>
<td>17.4</td>
</tr>
<tr>
<td>0.8</td>
<td>1.23</td>
<td>18.7</td>
</tr>
<tr>
<td>0.9</td>
<td>1.26</td>
<td>20.6</td>
</tr>
<tr>
<td>0.95</td>
<td>1.30</td>
<td>23.1</td>
</tr>
<tr>
<td>0.98</td>
<td>1.36</td>
<td>26.5</td>
</tr>
<tr>
<td>Proportional mixing</td>
<td>1.31</td>
<td>23.9</td>
</tr>
</tbody>
</table>

* Determines the degree of within-age-band mixing ($\epsilon = 1$ = all mixing within age band).
† $R_0$, basic reproduction number; $p_C$, minimum immunization coverage required to eliminate transmission of the infection.
From the analysis of different vaccine strategies, it is clear that a routine infant vaccination program without a catch-up component is the least effective, because children are protected for only a short period of time and herd effects are minimal. Teenagers, in whom carriage prevalence is highest, must be targeted to maximize herd immunity. The large catch-up campaign reduces the prevalence of carriage to such an extent that it takes many years to recover. Even if the vaccine provides only short-term protection against carriage acquisition (with longer-term protection against disease only), the initial impact on carriage still has long-term effects. The future vaccine strategies considered under these conditions have little impact on the number of cases of disease because disease incidence and serogroup C transmission are predicted to have declined to low levels by the time the changes are made. This finding has important implications for the cost-effectiveness of MCC vaccination; reducing the number of doses, for example, by switching to one dose at 12 months of age, does not appear to increase the number of cases even in those less than 1 year of age.

### TABLE 5. Sensitivity analysis: impact of alternative parameter values on the total cases of serogroup C disease (all ages) predicted in years 1–24 following the introduction of meningococcal serogroup C vaccination under strategies 1–6* in England and Wales

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Strategy 1</th>
<th>Strategy 2</th>
<th>Strategy 3</th>
<th>Strategy 4†</th>
<th>Strategy 5</th>
<th>Strategy 6‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td>18,700</td>
<td>15,300</td>
<td>1,200</td>
<td>800</td>
<td>1,200</td>
<td>4,100</td>
</tr>
<tr>
<td>Duration of protection after catch-up vaccination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 years</td>
<td>N/A§</td>
<td>N/A</td>
<td>1,100</td>
<td>800</td>
<td>1,100</td>
<td>3,900</td>
</tr>
<tr>
<td>5 years</td>
<td>N/A</td>
<td>N/A</td>
<td>1,600</td>
<td>1,200</td>
<td>1,500</td>
<td>4,500</td>
</tr>
<tr>
<td>Duration of protection after routine vaccination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>Base case</td>
<td>N/A</td>
<td>Base case</td>
<td>Base case</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>2 years</td>
<td>17,800</td>
<td>18,400</td>
<td>1,100</td>
<td>800</td>
<td>1,200</td>
<td>4,300</td>
</tr>
<tr>
<td>5 years</td>
<td>N/A</td>
<td>Base case</td>
<td>N/A</td>
<td>Base case</td>
<td>Base case</td>
<td>Base case</td>
</tr>
<tr>
<td>10 years</td>
<td>N/A</td>
<td>12,300</td>
<td>N/A</td>
<td>N/A</td>
<td>1,100</td>
<td>4,000</td>
</tr>
<tr>
<td>Efficacy against carriage acquisition, $\gamma$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>0</td>
<td>19,600</td>
<td>18,500</td>
<td>17,000</td>
<td>16,800</td>
<td>16,100</td>
<td>15,300</td>
</tr>
<tr>
<td>0.3</td>
<td>19,200</td>
<td>16,900</td>
<td>2,300</td>
<td>1,900</td>
<td>2,300</td>
<td>5,200</td>
</tr>
<tr>
<td>0.9</td>
<td>18,400</td>
<td>14,500</td>
<td>1,000</td>
<td>700</td>
<td>1,000</td>
<td>3,800</td>
</tr>
<tr>
<td>Mixing assumptions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\gamma = 0.5$, preferential mixing ±1 year</td>
<td>18,600</td>
<td>14,400</td>
<td>1,000</td>
<td>800</td>
<td>1,000</td>
<td>3,900</td>
</tr>
<tr>
<td>$\gamma = 0.98$, preferential mixing ±2 years</td>
<td>18,600</td>
<td>15,200</td>
<td>1,300</td>
<td>1,000</td>
<td>1,000</td>
<td>4,000</td>
</tr>
<tr>
<td>Proportional</td>
<td>17,200</td>
<td>14,800</td>
<td>600</td>
<td>400</td>
<td>600</td>
<td>3,400</td>
</tr>
</tbody>
</table>

* If no vaccination program is implemented, 22,300 cases were predicted among those of all ages in years 1–24.
† The United Kingdom strategy was most similar to this strategy (although the campaign was initially aimed at just those less than 18 years of age (i.e., strategy 3)).
‡ In strategy 6, duration of protection after catch-up vaccination refers to the duration of protection following routine vaccination of teenagers.
§ N/A, not applicable.

### TABLE 6. Impact of future vaccination strategies under base-case conditions

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Change in no. of total cases compared with the base case</th>
<th>Change in no. of total cases in children aged &lt;1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strategy 7</td>
<td>–10</td>
<td>–1</td>
</tr>
<tr>
<td>Strategy 8, switch after 5 years</td>
<td>–29</td>
<td>–4</td>
</tr>
<tr>
<td>Strategy 8, switch after 10 years</td>
<td>–4</td>
<td>0</td>
</tr>
<tr>
<td>Strategy 9, switch after 5 years</td>
<td>–47</td>
<td>–5</td>
</tr>
<tr>
<td>Strategy 9, switch after 10 years</td>
<td>–16</td>
<td>–1</td>
</tr>
</tbody>
</table>
the true mixing patterns are unknown, and simplifying assumptions must be made. Nevertheless, by fitting the model to pre- and postimmunization data from the United Kingdom, parameter estimates (such as the length of carriage and mixing patterns) could be refined.

Currently, meningococcal conjugate vaccines against only serogroup C are in widespread use. However, serogroup A conjugate vaccines for use in the African meningitis belt (21) and quadrivalent A, C, Y, and W-135 conjugate vaccines are being developed. The experience with MCC vaccines clearly has important implications, particularly for the vaccines for the Africa project, where opportunities to immunize may be limited and vaccine strategies must aim to maximize the impact on disease in a timely and cost-effective manner. Given the importance of herd immunity demonstrated here, this task must involve targeting the age groups in whom carriage is most prevalent. In addition, development of other vaccines aimed at preventing serogroup B disease is progressing (22–25). These vaccines are unlikely to have significant efficacy against carriage acquisition (23). Without herd immunity resulting from a reduction in carriage, the medium-term impact of these vaccines is likely to be limited. Future meningococcal vaccines that offer protection against more commonly carried serogroups may have a much greater impact on the population biology of N. meningitidis and N. lactamica. Estimating the impact of such vaccines will require complex models, informed by data on serologic responses to carriage and cross-protection between strains.

Although the United Kingdom experience has been emphasized here, these models can be adapted to investigate MCC vaccine strategies in other settings. We modeled the accelerated infant immunization schedule used in the United Kingdom, but many other countries prefer to spread out immunizations over a longer period of time and/or offer a booster in the second year of life. Routine immunization at 2, 4, and 6 months of age, for example, may leave infants unprotected for longer, but, as shown with the 12-month routine schedule modeled here, these infants may be indirectly protected if herd immunity from a catch-up campaign is sufficient. The experience with H. influenzae type b vaccines (26) shows that the postvaccine era may be far from straightforward.

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Conflict of interest: none declared.

REFERENCES


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APPENDIX 1

Dynamic Model Structure in Equations

\[
\frac{dS_i(t)}{dt} = r_C C_i(t) + r_O O_i(t) - S_i(t) (\lambda_C(t) + \lambda_O)
\]
\[
+ w_s S_i(t) + w_v S_V(t)
\]
\[
\frac{dC_i(t)}{dt} = \lambda_C(t) S_i(t) - r_C C_i(t) + w_r C_R(t) + w_v C_V(t)
\]
\[
\frac{dO_i(t)}{dt} = \lambda_O S_i(t) - r_O O_i(t) + w_r O_R(t) + w_v O_V(t)
\]
\[
\frac{dR_i(t)}{dt} = \lambda_C(t) S_i(t) - r_C C_R(t) - S_R(t)
\]
\[
\times [(1 - \gamma) \lambda_C(t) + \lambda_O] - w_r S_R(t)
\]
\[
\frac{dCR_i(t)}{dt} = (1 - \gamma) \lambda_C(t) S_R(t) - z_r CR_R(t) - w_r C_R(t)
\]
\[
\frac{dOR_i(t)}{dt} = \lambda_O S_R(t) - r_O O_R(t) - w_r O_R(t)
\]
\[
\frac{dSV_i(t)}{dt} = z_r CV_i(t) + r_O O_V(t) - S_V(t)
\]
\[
\times [(1 - \gamma) \lambda_C(t) + \lambda_O] - w_r S_V(t)
\]
\[
\frac{dCV_i(t)}{dt} = (1 - \gamma) \lambda_C(t) S_V(t) - z_r CV_V(t) - w_r C_V(t)
\]
\[
\frac{dOV_i(t)}{dt} = \lambda_O S_V(t) - r_O O_V(t) - w_r O_V(t)
\]

The model population is stratified into 75 cohorts (0, 1, ... 74) corresponding to each year of age. At the end of each year, individuals in age class i move into age class i + 1, newly born individuals are introduced into age class 0, and all individuals in age class 74 die (mortality is assumed to be zero up to this point) (13).

The recovery rate for infection \( K \) is \( r_K \), so is the relative recovery rate for vaccinated serogroup C carriers, \( \gamma \) is the vaccine efficacy against carriage acquisition, and \( \lambda_{KI} \) is the age-specific force of infection for infection \( K \).

The initial conditions for the model are based on the endemic equilibrium (14). The age-specific forces of infection for other serogroups are fixed over time at equilibrium values. The force of infection for serogroup C is age and time dependent, as described in the text and in appendix 2.

At time \( t = t_e \), a catch-up campaign is implemented, whereby

\[
SV_i = SV_i + \psi V_i S_i
\]
\[
S_i = S_i - \psi V_i S_i
\]

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\[
CV_i = CV_i + (1 - m)\psi V_i C_i \\
C_i = C_i - (1 - m)\psi V_i C_i \\
OV_i = OV_i + \psi V_i O_i \\
O_i = O_i - \psi V_i O_i
\]

At time \( t = t_r \), routine immunization is implemented, whereby

\[
SR_i = SR_i + \psi R_i S_i \\
S_i = S_i - \psi R_i S_i \\
CR_i = CR_i + (1 - m)\psi R_i C_i \\
C_i = C_i - (1 - m)\psi R_i C_i \\
OR_i = OR_i + \psi R_i O_i \\
O_i = O_i - \psi R_i O_i
\]

where \( \psi V_i(t) \) and \( \psi V_i(t) \) are the effective vaccine coverage for routine and catch-up vaccination, respectively, and \( m \) is the proportion of serogroup C carriers that recover upon vaccination.

**APPENDIX 2**

**Mixing Patterns**

The simplest assumption of random mixing is not reasonable for meningococcal disease because the force of infection is age dependent. Edmunds (unpublished observations) demonstrated a strong correlation in the ages of index and secondary invasive meningococcal disease cases identified in clusters between 1995 and 1998. The age of about 80 percent of the secondary meningococcal cases was within 2 years of that of the index case, and 57 percent had an age difference of less than 1 year. Although it is likely that the observed cases in clusters represent chains of transmission rather than direct transmission from index case to secondary case, this indicates that transmission and mixing is assortative by age. The mixing pattern described below reflects this. The contribution of the narrow age band in which preferential mixing occurs is described by a parameter \( \varepsilon \):

\[
\lambda_{CI}(t) = \beta_i \left( \varepsilon \left( \sum_{i=1}^{74} (C_i(t) + \delta CV_i(t)) \right) 
+ (1 - \varepsilon) \left( \sum_{i=0}^{74} (C_i(t) + \delta CV_i(t)) \right) \right),
\]

where \( \beta_i \) is the probability of an effective contact for an individual of age \( i \) and \( \varepsilon \) represents the degree to which mixing is homogeneous versus heterogeneous. That is, if \( \varepsilon \) is 0, then all contact is assumed to occur randomly by age; if \( \varepsilon \) is 1, then contact is assumed to occur between only those individuals of the same age or \( \pm 1 \) year of age. An alternative mixing assumption used \( \pm 2 \) years of age. The formula was modified for the age groups at either end of the distribution, so only two age groups contributed rather than three: for age 0, those aged 0 and 1 years were included; for age 74 years, those aged 73 and 74 years contributed. A similar adjustment was made for the \( \pm 2 \)-year age model.

Age-specific betas \( (\beta_i) \) were estimated for different values of \( \varepsilon \) by using the defined mixing structure and the equilibrium values of \( \lambda_{CI} \) and the prevalence of serogroup C carriage estimated previously (14). In the base case, a 1-year age band and \( \varepsilon = 0.98 \) were chosen because it resulted in a similar proportion of infections within this age band (59 percent), as observed in the disease data (57 percent). Because of the uncertainty about the true mixing patterns, the effects of different values of \( \varepsilon \) and the effect of taking \( \pm 2 \) years rather than \( \pm 1 \) year were investigated in the sensitivity analysis. An alternative proportional mixing pattern was also considered.

**APPENDIX 3**

**Estimating Reproduction Numbers**

The basic reproduction number \( (R_0) \) is defined as the average number of secondary infections that would be produced in a completely susceptible population by a typical infectious individual (15, 16, 27). The critical immunization threshold, \( p_c \), is the minimum immunization coverage required to eliminate endemic transmission of the infection (if vaccination induces permanent and complete immunity to infection) and can be calculated by using the relation \( p_c = 1 - 1/R_0 \) (15).

Mathematically, \( R_0 \) is defined as the largest eigenvalue of the next-generation matrix \( (G) \) (16). Each element of the next-generation matrix \( G \) is composed as follows: \( g_{ij} = dS_i q_{ij} \). Hence, \( g_{ij} \) is equal to the number of secondary infections in group \( i \) produced by an infective in group \( j \), where \( d \) is the average duration of infectiousness, \( S_i \) is the number of susceptibles in the \( i \)th age class, and \( q_{ij} \) is the transmission rate between age classes \( i \) and \( j \). To calculate \( R_0 \) (the reproduction number in a totally susceptible population), the proportion of susceptibles in each age class is set to be 1. The matrix contains the values of the transmission rates between ages \( i \) and \( j \), which, in this model, is dependent on age, \( \varepsilon \), and \( \beta \). The next-generation matrix \( G \) in the base case, where mixing is preferential within a \( \pm 1 \)-year age band and everyone is susceptible, can be estimated as follows:

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The effective reproduction number, $R(t)$, allows for population immunity and depends on the age-specific proportion susceptible and the age-specific $R_0$. After the introduction of vaccination, the change in $R(t)$ can be approximated as the change in carriage prevalence over a 3-month time period (the average serial interval):

$$G = \left( \begin{array}{cccc}
\varepsilon \beta_0 S_0 d & \varepsilon \beta_1 S_1 d & (1-\varepsilon) \beta_0 S_0 d & (1-\varepsilon) \beta_1 S_1 d & (1-\varepsilon) \beta_0 S_0 d & \ldots \\
\varepsilon \beta_1 S_1 d & \varepsilon \beta_2 S_2 d & \varepsilon \beta_1 S_1 d & (1-\varepsilon) \beta_2 S_2 d & (1-\varepsilon) \beta_1 S_1 d & \ldots \\
(1-\varepsilon) \beta_2 S_2 d & \varepsilon \beta_3 S_3 d & \varepsilon \beta_2 S_2 d & \varepsilon \beta_3 S_3 d & \varepsilon \beta_2 S_2 d & \ldots \\
(1-\varepsilon) \beta_3 S_3 d & (1-\varepsilon) \beta_3 S_3 d & \varepsilon \beta_3 S_3 d & \varepsilon \beta_3 S_3 d & \varepsilon \beta_3 S_3 d & \ldots \\
(1-\varepsilon) \beta_4 S_4 d & (1-\varepsilon) \beta_4 S_4 d & (1-\varepsilon) \beta_4 S_4 d & \varepsilon \beta_4 S_4 d & \varepsilon \beta_4 S_4 d & \ldots \\
\ldots & \ldots & \ldots & \ldots & \ldots & \ldots 
\end{array} \right) .$$

The effective reproduction number, $R(t)$, allows for population immunity and depends on the age-specific proportion susceptible and the age-specific $R_0$. After the introduction of vaccination, the change in $R(t)$ can be approximated as the change in carriage prevalence over a 3-month time period (the average serial interval):

$$R(t) \approx \frac{\sum_i C_i(t+3 \text{ months})}{\sum_i C_i(t)} .$$

Given the inherent 12-month periodicities in the model (i.e., individuals changing age bands), a smoother result is obtained if the formula is adjusted as follows:

$$R(t) \approx \left( \frac{\sum_i C_i(t+12 \text{ months})}{\sum_i C_i(t)} \right)^{0.25} .$$