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Penicillin-resistant pneumococcal meningitis: high antibiotic exposure impedes new vaccine protection

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SUMMARY

The frequency of meningitis due to penicillin-resistant *Streptococcus pneumoniae* (PRP) has increased in recent years, making treatment failure more likely. It is currently expected that pneumococcal conjugate vaccines might curb this trend. We investigated this issue using a mathematical model applied to the current prevalence of resistance and antibiotic exposure in the United States and in France. Our main finding was that the level of antibiotic exposure may limit the effect of the vaccine. In relatively low antibiotic exposure environments such as the United States, large-scale vaccination prevents a large part of PRP meningitis cases, whereas in high antibiotic-exposure environments such as France, vaccination alone does not lead to a substantial reduction in PRP meningitis incidence. Our results suggest that antibiotic exposure reduction will remain of primary importance for the control of PRP meningitis despite wide scale use of pneumococcal conjugate vaccines.

INTRODUCTION

Following the introduction of the *Haemophilus influenzae* type b conjugate vaccine and the subsequent reduction of *H. influenzae* meningitis, *Streptococcus pneumoniae* has become the leading cause of community-acquired bacterial meningitis in North America and in Europe. The annual incidence of pneumococcal meningitis is estimated at between 1 and 2 per 100 000 in industrialized countries, leading to approximately 3000 cases per year in the United States and 600 cases per year in France [1, 2].

The lethality of this infection is significantly higher than that of other bacterial meningitis; it is at least 10% in developed countries and 20–30% of patients are left with neurological sequelae or hearing loss [1]. A rapid increase in the incidence of infection with penicillin-resistant *S. pneumoniae* (PRP) has been reported worldwide [3–5]. Although most studies have not shown differences in the outcomes of meningitis caused by penicillin-resistant and susceptible pneumococci, failure of antibiotic treatment of meningitis has been observed with resistant bacteria and worse clinical outcomes are a possibility [6–9].

Vaccination against *S. pneumoniae* is a promising approach to controlling pneumococcal disease. New conjugate pneumococcal vaccines induce better immune responses in infants and young children than polysaccharide vaccines and protect against asymptomatic carriage of *S. pneumoniae* as well as against invasive disease. As most current PRP serotypes are included in the vaccine formulation, it has been suggested that conjugate vaccines may help reduce

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the burden of penicillin-resistant pneumococcal disease.

Several studies on 7- and 9-valent pneumococcal conjugate vaccines showed reductions in carriage of PRP among vaccinated children [10, 11]. Moreover, a recently published study has shown a significant decrease in the incidence of invasive pneumococcal disease in the United States since the start of vaccination of young children with a 7-valent conjugate vaccine in early 2000 [12]. However, recently presented data suggest that colonization with non-vaccine serotypes of *S. pneumoniae* is increasing in the United States, and that non-susceptible non-vaccine serogroups, such as serogroup 35, are emerging [13].

Pneumococcal conjugate vaccination is currently a major public health issue in most European countries. Despite encouraging results in the United States, many are concerned that the differences between the American and European serotype distributions may compromise vaccine efficacy in Europe [14, 15].

Antibiotic consumption rates vary up to fourfold among European countries [16, 17]. Both exposure to β-lactams and penicillin resistance of pneumococci are much lower in the United States than in southern European countries such as France or Spain [4, 18–20], the two biggest antibiotic consumers in the western world. This suggests that controlling penicillin-resistant pneumococcal disease might raise different issues in these European countries than in the United States.

Given that conjugate vaccines have only been used in the general population of a few countries and for a short time, it is too early to assess their long-term effects on *S. pneumoniae* colonization, invasive pneumococcal infections, or resistance selection from field data. Mathematical modelling provides an appropriate approach for studying the impact of these new vaccines. For instance, a model has been designed to investigate the phenomenon of serotype replacement, corresponding to an increase in carriage of non-vaccine serotypes [21].

In this study, we investigated the epidemiological changes that may result from the impact of large-scale conjugate vaccination on pneumococcal meningitis in both low and high antibiotic-exposure environments. More precisely, we simulated time changes in the incidence of pneumococcal meningitis and, among these infections, of penicillin-resistant cases, following the introduction of a conjugate vaccine in the United States and in France. We compared these changes to those obtained without vaccination and studied the impact of the vaccination coverage level.

The availability of a vaccine may change treatment patterns [22]. For instance, practitioners may prescribe antibiotics less often to vaccinated children, taking into account the reduced probability of their being infected by a pneumococcus. Hence, we also investigated the effect of combining conjugate vaccination with reductions of antibiotic exposure.

METHODS

Data

Initial and historical data in the United State were derived from the TRUST surveillance study in the United States between 1998 and 2002 [18] and on serotype-specific data on frequency of invasive pneumococcal disease according to age in the United States before and after the introduction of conjugate vaccination [12].

Initial and historical data in France was obtained from the 2001 annual report of the French Reference Centre for Pneumococci (NRC) [4]. The organization of the NRC has been described in detail elsewhere [23]. In short, 40–50 centres throughout France collect and send *S. pneumoniae* strains to the NRC. Each year approximately 2000 strains are typed and evaluated for susceptibility to various antibiotics.

We used these data to compute global minimum inhibitory concentration (MIC) distributions and colonization rates for vaccine-type (or non-vaccine-type) pneumococci in the population according to age by averaging the corresponding serotype-specific data over all serotypes included (or not included) in the vaccine weighted by the frequency of each serotype.

Model

This work builds on a model of selection for PRP in the community, which has been described in detail elsewhere [24]. Hosts enter the population at birth as non-carriers at a constant rate μ_N. In order to take into account the main epidemiological differences according to age, the population is structured into three age classes, namely young children (<2 years old), older children (2–15 years old) and adults ($\geqslant 15$ years). Ageing is modelled by transitions between age compartments, at a rate proportional to the age range of the compartments. A fraction, v, of children <2 years old is assumed to be vaccinated each year with a heptavalent conjugate vaccine, with vaccine protection lasting for an average time d_V. After loss of vaccine

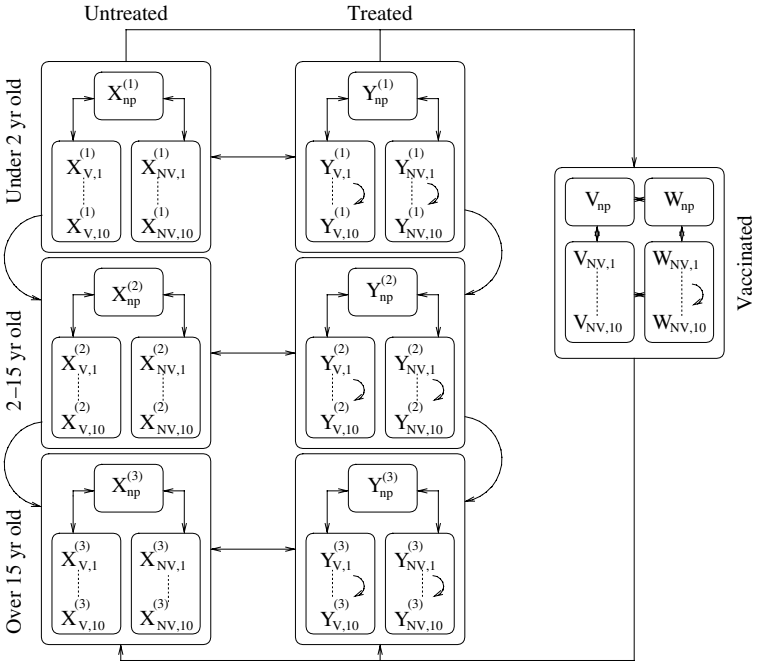

Fig. 1. Model structure. X_{np}, number of non-colonized individuals not exposed to antibiotics; Y_{np}, number of non-colonized individuals exposed to antibiotics; $X_{V,1}$, $X_{V,2}$, etc. (resp. $Y_{V,1}$, $Y_{V,2}$, etc.), numbers of unexposed (resp. exposed) individuals colonized by vaccine-type pneumococci with one of the 10 resistance levels (see text); $X_{NV,1}$, $X_{NV,2}$, etc., and $Y_{NV,1}$, $Y_{NV,2}$, etc., numbers of individuals colonized by non-vaccine-type pneumococci. The model is structured into three age classes. A portion of children <2 years old are vaccinated, in which case they can be untreated (V) or treated (W); vaccinated children can be colonized only with non-vaccine-type pneumococci.

immunity, vaccinated individuals return to unvaccinated compartments as adults.

Susceptible hosts may be colonized with *S. pneumoniae* either with one of the seven serotypes included in the heptavalent vaccine or not. Vaccinated hosts can only be colonized with the latter, and dual colonization is excluded. Colonization occurs following contact with hosts carrying vaccine-type or non vaccine-type bacteria; infectious contacts are more frequent between children than between adults, but do not depend on the type of bacteria involved. In the absence of antibiotic exposure, natural decolonization occurs after a time $1/\lambda$.

The resistance levels of all bacteria colonizing one host are represented by a single MIC, which takes one of 10 possible values: 0·06, 0·125, 0·25, 0·5, 1, 2, 4, 8, 16 and 32.

Hosts are deemed to be exposed to antibiotics independently of their carrier status, with a frequency α_1 for young children, α_2 for older children and α_3 for adults. In vaccinated hosts, this rate of antibiotic exposure is reduced to a value α_4. During antibiotic exposure, contacts with carriers are more liable to lead to colonization if the involved bacteria are resistant to antibiotics, and bacterial colonization is cleared with a probability $1-\sigma$. In hosts in whom colonization is not eliminated, bacteria with a mutation towards a higher resistance level may replace the original strains. Antibiotic exposure comes to an end after an average duration of $1/\gamma$. Finally, the mortality rate is μ_1 for young children, μ_2 for older children and μ_3 for adults. The model structure is depicted in Figure 1.

The values of model parameters for France and the United States are provided in the Table. Most parameter values were estimated from the literature [19, 20, 25]. Rates of infectious contacts were computed using our initial data by calibrating the model so that it reproduces the observed colonization rates in all age classes. Finally, we hypothesized a duration of vaccine immunity of $d_v = 13$ years, and a probability of non-decolonization following antibiotic exposure increasing with the resistance to penicillin of the involved bacteria (MIC m) by:

$$\sigma(m) = \frac{m^3}{0{\cdot}5 + m^3}.$$

We performed a sensitivity analysis using the Latin Hypercube sampling technique [26]. It showed that for predicting the incidence of PRP meningitis, the duration of carriage was the most critical parameter,

Table. *Values of model parameters in France and in the United States*

Parameter		Value (France)	Value (USA)
Birth rate	μ_N	0·013 yr^{-1}	0·014 yr^{-1}
Death rate in young children ($\leqslant$2 yr old)	μ_1	0·0058 yr^{-1}	0·0038 yr^{-1}
Death rate in older children (2–15 yr old)	μ_2	0·0024 yr^{-1}	0·0002 yr^{-1}
Death rate in adults (>15 yr old)	μ_3	0·0153 yr^{-1}	0·0106 yr^{-1}
Average duration of antibiotic exposure	$1/\gamma$	8 days	8 days
Duration of vaccine immunity	d_V	13 yr	13 yr
Frequency of antibiotic exposure in young children	α_1	1/30 wk	1/74 wk
Frequency of antibiotic exposure in older children	α_2	1/102 wk	1/250 wk
Frequency of antibiotic exposure in adults	α_3	1/208 wk	1/1027 wk
Frequency of antibiotic exposure in vaccinated children	α_4	1/30–60 wk*	1/74–148 wk*
Duration of pneumococcal carriage	$1/\lambda$	2·2 months	2·2 months
Infectious contact rate between young children	β_{11}	0·60 wk^{-1}	0·60 wk^{-1}
Infectious contact rate between older children	β_{22}	0·30 wk^{-1}	0·30 wk^{-1}
Infectious contact rate between adults	β_{33}	0·15 wk^{-1}	0·15 wk^{-1}
Infectious contact rate between young and older children	β_{12}	0·25 wk^{-1}	0·25 wk^{-1}
Infectious contact rate between young children and adults	β_{13}	0·25 wk^{-1}	0·25 wk^{-1}
Infectious contact rate between older children and adults	β_{23}	0·10 wk^{-1}	0·10 wk^{-1}

* Depending on the antibiotic exposure scenario, see text.

followed by the mean duration of antibiotic exposure (both were positively linked). This analysis also confirmed that a reasonably wide range of values for the duration of the vaccine immunity (from 5 to 30 years) had little effect on model outcomes.

Meningitis

Meningitis cases were presumed to represent a constant portion of the number of carriers, irrespective of *S. pneumoniae* serotype; in particular, the number of PRP meningitis cases was estimated from the number of carriers of penicillin-resistant pneumococci. Considering currently observed incidences of pneumococcal meningitis in young and older children ($\sim$13·0 and 1·0 cases/100 000 per annum) and adults ($\sim$0·8 cases/100 000 per annum), as well as pneumococcal colonization rates ($\sim$40% in children and 20% in adults), we computed the number of meningitis cases/100 000 per annum by multiplying the rate of colonization at a given time by a proportionality factor based on this data (for instance 0·8/0·2 = 4·0 for adults) [1].

Antibiotic exposure in a vaccinated population

We considered three scenarios regarding antibiotic exposure in children following the introduction of a conjugate vaccine:

Scenario A. Antibiotic exposure remained unchanged for all children. In this scenario, the antibiotic exposure of vaccinated children was the same as the antibiotic exposure of unvaccinated children: $\alpha_4 = \alpha_1 = 1/30$ weeks in France and 1/74 weeks in the United States.

Scenario B. Antibiotic exposure became less frequent for vaccinated children only. In this scenario, the antibiotic exposure of vaccinated children was half that of unvaccinated children: $\alpha_4 = \alpha_1/2 = 1/60$ weeks in France and 1/148 weeks in the United States.

Scenario C. Antibiotic exposure became less frequent for all children. In this scenario, the antibiotic exposure of all children was half that of unvaccinated children without vaccination: $\alpha_4 = \alpha_1 = 1/60$ weeks in France and 1/148 weeks in the United States.

RESULTS

In the United States, exposure to β-lactams as well as penicillin resistance are lower than in France [4, 18–20], while the incidence of meningitis is similar [1, 2]. In order to assess the impact of conjugate vaccines in these countries, we simulated pneumococcal meningitis incidence rates following the introduction of vaccination in the United States and in France. In the United States, we modelled starting vaccination in 2000, corresponding to the actual date of introduction of pneumococcal conjugate vaccines (Fig. 2*a*). In France, we modelled starting vaccination in 1997, as data regarding resistance was not available for the following years (Fig. 2*b*). Initial data regarding pneumococcal carriage, penicillin susceptibility and frequency of exposure to β-lactams corresponded

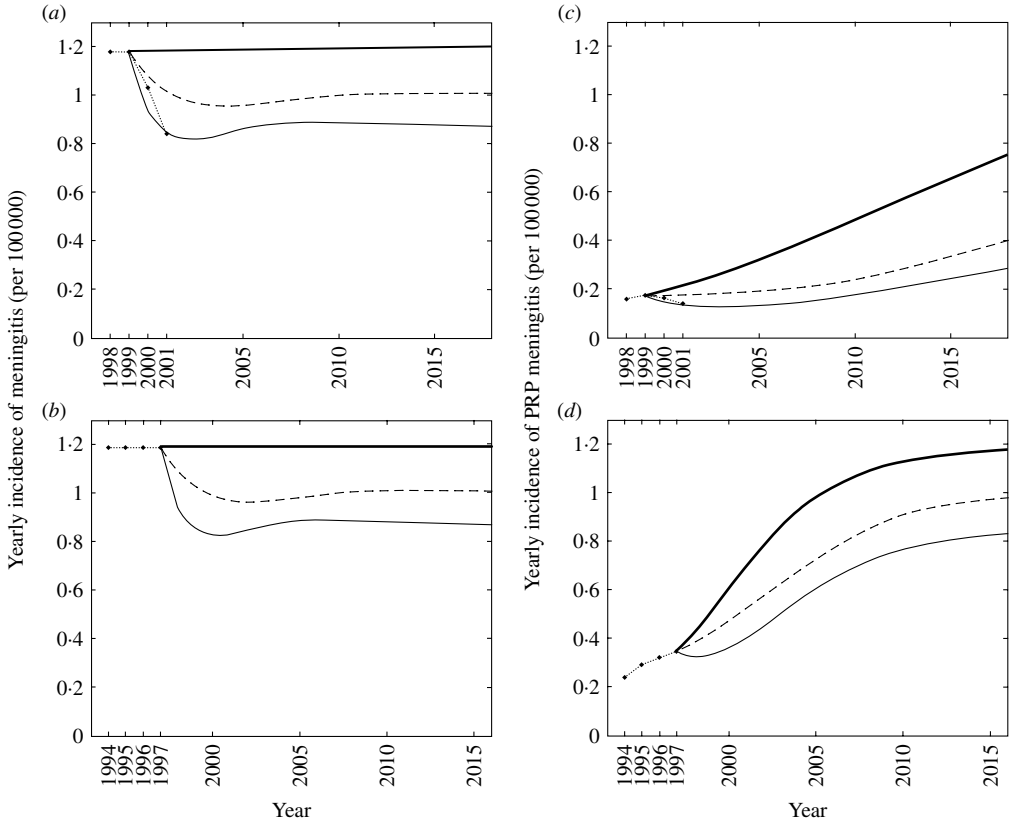

Fig. 2. Vaccination decreases meningitis incidence, but resistance selection may go on. Predicted yearly incidence of pneumococcal meningitis over 20 years without vaccination (bold lines) and with vaccination of children at a 30% (dashed lines) and a 100% (solid lines) coverage level. Panels (*a*) and (*b*) reflect all meningitis cases while panels (*c*) and (*d*) reflect penicillin-resistant cases only. The baseline situation and antibiotic exposure characteristics correspond to the United States (*a*, *c*) and France (*b*, *d*). Recent observed data (dotted lines) are plotted for the United States and France.

to the American situation in 2000 and the French situation in 1997. Model predictions were obtained under scenarios varying vaccination coverage from 0% (no vaccination) to 100%.

In a previous paper, we showed that the introduction of a conjugate vaccine led to the replacement in the colonized population of vaccine-type *S. pneumoniae* by non-vaccine-type *S. pneumoniae* [27]. The extent of this replacement was greatest when vaccine coverage was high. As a consequence, a sharp decrease in the overall incidence of meningitis was noted immediately after the beginning of vaccination, followed by a slow increase (Fig. 2*a*, *b*). Vaccination led to an increase in carriage of non vaccine-type *S. pneumoniae*, most of which are today still susceptible to penicillin. Therefore, using a conjugate vaccine led to a reduction in meningitis due to penicillin-resistant pneumococci (PRP; MIC $>1\,\mu$g/ml), the more so when the vaccination coverage was high. In the case of low antibiotic exposure, this reduction was maintained and increased over time (Fig. 2*c*). But in the case of high antibiotic exposure, resistance selection persisted for all serotypes, so that with time the incidence of PRP meningitis gradually increased again. After 20 years, it accounted for almost all meningitis cases, irrespective of vaccination coverage (Fig. 2*d*).

In the absence of vaccination, our model predicted a baseline incidence of *S. pneumoniae* meningitis of 17·8/100 000 people cumulated over the next 15 years. We computed the cumulated incidence of pneumococcal meningitis over 15 years after the start of vaccination and obtained the net gain in meningitis cases prevented by comparison to the baseline, according to vaccination coverage. We calculated this gain for the three antibiotic scenarios for antibiotic exposure described in the Methods section (scenarios A, B and C).

The gains associated with these three scenarios are shown according to vaccination coverage, in both the American and the French situations (Fig. 3*a*, *b*). As

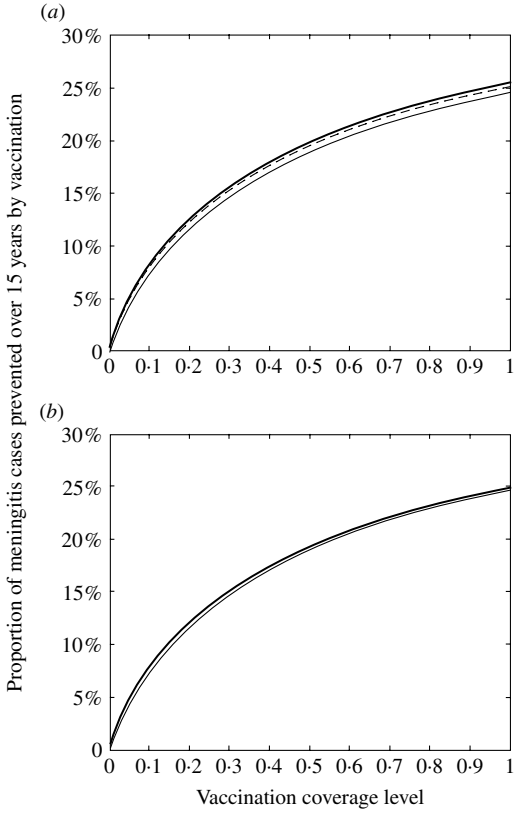

Fig. 3. Antibiotic exposure does not affect the overall percentage of meningitis prevented by vaccination. Proportion of cases of pneumococcal meningitis prevented over the next 15 years by conjugate vaccination relative to no vaccination, if antibiotic exposure remains unchanged following the introduction of vaccination (scenario A, bold line), the antibiotic exposure of vaccinated children is reduced by half (scenario B, dashed line) and the antibiotic exposure of all children, irrespective of their vaccinated status, is reduced by half (scenario C, solid line). The baseline situation for meningitis incidence and antibiotic exposure characteristics correspond to that of the United States before vaccine introduction (*a*) and France (*b*).

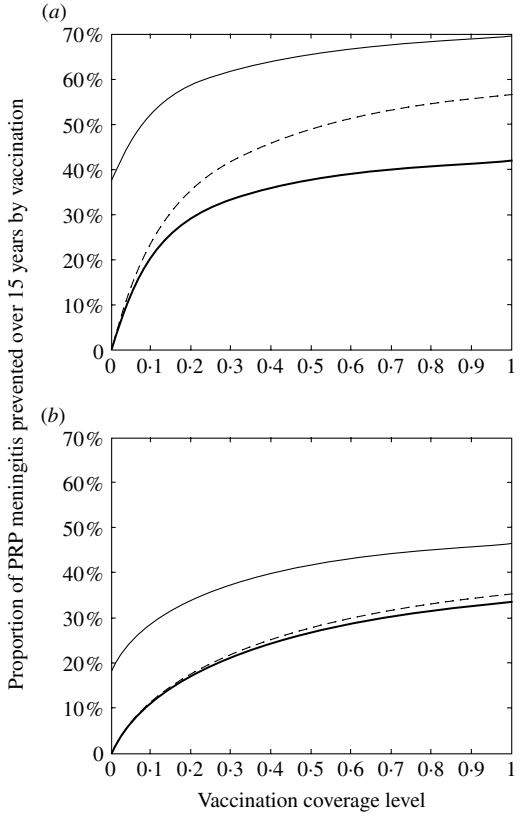

Fig. 4. More PRP meningitis is prevented by vaccination when antibiotic exposure is low or reduced. Proportion of cases of penicillin-resistant pneumococcal meningitis prevented over the next 15 years by conjugate vaccination relative to no vaccination, if antibiotic exposure remains unchanged following the introduction of vaccination (scenario A, bold line), the antibiotic exposure of vaccinated children is reduced by half (scenario B, dashed line), and the antibiotic exposure of all children, irrespective of their vaccinated status, is reduced by half (scenario C, solid line). The baseline situation for PRP meningitis incidence and antibiotic exposure characteristics correspond to that of (*a*) the United States before vaccine introduction and (*b*) France.

expected, the number of cases prevented increased with vaccination coverage. There was no substantial difference between the three antibiotic exposure scenarios in terms of reduction in cumulated meningitis cases. The largest gain, obtained for 100% vaccination coverage, represented $\sim$25% of the overall number of meningitis cases in both countries.

Because most non-vaccine serotypes are susceptible to penicillin, it is expected that vaccination may have an impact on resistance selection. Due to the current different situations in France and in the United States, our model predicts 5·5 cases of PRP meningitis for 100 000 people cumulated over the next 15 years in the United States and 12·7 cases in France in the absence of vaccination. We computed the difference in cumulated incidence over the next 15 years between this baseline and differing vaccination coverage levels, in order to quantify the gain in terms of cases of PRP meningitis prevented (Fig. 4*a*, *b*).

As previously, the gain associated with vaccination was greater when vaccination coverage was large; as expected, the greater the reduction in antibiotic exposure, the more PRP meningitis cases were prevented. In the American situation, vaccination combined with any of the three antibiotic exposure scenarios led to the prevention of at least 30% of PRP meningitis cases over 15 years, even for vaccination coverage levels as low as 20%. Without antibiotic

exposure reduction (scenario A), up to 42% of cases were prevented; a reduction in antibiotic exposure in vaccinated children (scenario B) improved vaccine efficacy, with up to 57% of cases prevented; and up to 70% of PRP meningitis cases were prevented when vaccination was combined with a reduction in antibiotic exposure for all children (scenario C) (Fig. 4*a*).

In the French situation, vaccination combined with no, or limited changes in antibiotic exposure (scenarios A and B) led to more limited gains in terms of PRP meningitis cases prevented, i.e. less than 25% for a vaccination coverage lower than 40%. In contrast with the American situation, reducing antibiotic exposure for vaccinated children did not improve vaccine efficacy. Only when vaccination was combined with a reduction in antibiotic exposure for all children did the overall number of PRP meningitis cases decrease by 25–45% over 15 years. This remained true for low vaccination rates, as the gain was ~35% of the number of PRP meningitis cases for a 20% vaccination rate (Fig. 4*b*). Compared with antibiotic reduction alone, the combination of this reduction and of vaccination allowed the prevention of up to an additional 25% of the overall number of PRP meningitis cases over 15 years (Fig. 4*b*).

DISCUSSION

Analysis of recent trends in penicillin and erythromycin single and dual resistance of *S. pneumoniae* in the United States [28] has shown that resistance is bound to increase in the near future. Although resistance is already more prevalent in France, further increases in resistance are likely [24]. Our results show that while PRP meningitis could follow the same trend, a substantial portion of these cases could be prevented by conjugate vaccines. However, those countries that would benefit the most from this effect of vaccines, i.e. countries with a high level of resistance, are less likely than others to observe it. Indeed, in countries where penicillin exposure is low, e.g. the United States, even low vaccine coverage leads to a substantial reduction in PRP meningitis, but additional public health interventions would be required to observe the same effect in countries where antibiotic exposure is high, e.g. France.

In the United States, a decline in the incidence of invasive pneumococcal disease has already been observed since the introduction of a pneumococcal conjugate vaccine in early 2000 [12]. Our predictions are consistent in magnitude with the observed data (Fig. 2*a*). As conjugate vaccination has not been introduced in France, no data are available for comparison in terms of the potential of the vaccine to limit resistance in high antibiotic-exposure environments. Model-predicted changes in the incidence of PRP meningitis in the absence of vaccination are consistent with the trends in resistance observed between 1994 and 1997 in France (Fig. 2*d*).

Evidence of serotype replacement has been found in several pneumococcal conjugate vaccine studies [29, 30], and it is a consistent prediction from mathematical models [31]. Moreover, very recent data from the United States show an increase in the proportion of non-vaccine *S. pneumoniae* over the period 2000–2003, as well as an increase in antibiotic resistance and the emergence of non-susceptible non-vaccine serogroups (35, NT), in agreement with our predictions [13].

We chose France and the United States as two typical countries regarding resistance of *S. pneumoniae*. The first represented countries with wide exposure to penicillin G and frequent resistance, such as Hong Kong, Singapore and Japan, as well as southern European countries such as Spain, Portugal, Belgium and Italy; the second represented countries with much reduced antibiotic consumption and resistance levels, such as the United Kingdom, Germany, Sweden, Denmark and Norway [32, 33]. Essentially the same results would have been obtained regarding the impact of vaccination using antibiotic exposure and resistance levels pertaining to other countries in these two groups.

Studies of vaccine efficacy have shown a reduction in carriage of serotypes cross-reactive with those included in the vaccine formulation [30]. This suggests that the vaccine might have a greater effect on pneumococcal meningitis incidence than is apparent in our results, and, since these cross-reactive serotypes are among the most resistant of non-vaccine-type *S. pneumoniae*, on PRP meningitis incidence [34]. However, adding most of these serotypes to the vaccine formulation did not change the long-term effects (results not shown).

Although our model did not take into account the possibility of dual colonization, simultaneous colonization with up to six different serotypes of *S. pneumoniae* has been observed in previous studies, with the consequence that serotype replacement under vaccination was favoured [29, 35]. Excluding the possibility of dual colonization was in favour of the vaccine efficacy.

The relationship between adaptation to colonization and virulence of individual serotypes is not yet fully understood [36]. The four most commonly isolated pneumococcal serotypes in children, which are also very likely to cause invasive disease, as well as frequently associated with reduced susceptibility to penicillin, are covered by the heptavalent vaccine. However, certain serotypes (e.g. 1 and 5), which are not in the vaccine, can play an important role in invasive disease, and in meningitis in particular, even though they are not frequent. An analysis including multiple serotypes and taking into account serotype fitness (for instance through differing durations of carriage) and invasiveness characteristics could help refine these predictions, and allow the evaluation of protocols for updating the vaccine formulation in terms of included serotypes.

In the model, vaccinated children were considered as belonging to the 2–15 years old age class in terms of age-specific carriage transmissibility and meningitis incidence. As pneumococcal meningitis incidence is highest in young children (aged <2 years), this assumption led to an underestimation of meningitis incidence in the model predictions. However, the main outcome of the model, i.e. the proportions of meningitis cases prevented by vaccination, was not affected.

Finally, there is evidence that the use of pneumococcal conjugate vaccines in itself may reduce antibiotic consumption, in particular through the prevention of upper and lower respiratory conditions usually considered to be of viral origin [22]. However, this reduction would only affect vaccinated children and may not prove sufficient to have an impact on PRP meningitis incidence in countries of high antibiotic exposure.

Our findings highlight the need for public health decisions on conjugate pneumococcal vaccines to take into account the antibiotic exposure of the target population. This is especially important in Europe, where antibiotic consumption rates may vary up to at least threefold, with southern countries such as France and Spain the biggest consumers in the western world [16]. In such high antibiotic-exposure environments, our analysis suggests that public health interventions combining vaccination with antibiotic exposure reduction will prevent a significant portion of PRP meningitis, whereas vaccination alone would be less efficient in the long term.

A more detailed description of the model equations used is available from the authors.

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