
The influence of competition and vaccination on the coexistence of two pneumococcal serotypes

Y. ZHANG^{1*}, K. AURANEN^{2,3} AND M. EICHNER¹

¹ Department of Medical Biometry, University of Tuebingen, Tuebingen, Germany

² National Public Health Institute (KTL), Helsinki, Finland

³ Rolf Nevanlinna Institute, University of Helsinki, Helsinki, Finland

(Accepted 22 June 2004)

SUMMARY

Streptococcus pneumoniae (pneumococcus) is one of the most important bacterial pathogens and a leading cause of mucosal infections (e.g. otitis media) and various forms of serious diseases (e.g. pneumonia, meningitis, bacteraemia) in developing and developed countries. Based on the polysaccharide capsule, there are at least 90 different pneumococcal serotypes, which may compete with each other to colonize the nasopharynx. Newly developed protein–polysaccharide conjugated vaccines have been shown to provide protection against disease caused by the serotypes included in the vaccine, and also against colonization (carriage). It is feared that yet uncommon, but nonetheless pathogenic serotypes which have been suppressed by competition, may become more prevalent in carriage and disease after large-scale use of conjugate vaccines. In this paper, we use transmission models of pneumococcal carriage to study how competition and vaccination influence the coexistence of two serotypes. According to our results, direct (physical) competition between two pneumococcal serotypes only influences colonization if the duration of naturally acquired immunity is short. By contrast, indirect (antibody-mediated) competition is of influence only if naturally acquired immunity is long lasting. Vaccination reduces the prevalence of the target serotype – an effect that is enforced by the presence of directly competing bacteria. The emergence of a non-target serotype after vaccination is only observed if bacteria compete directly. These results emphasize the importance of studying whether bacteria compete directly or indirectly and for how long people are protected in order to assess the long-term effects of sero-competition.

INTRODUCTION

Streptococcus pneumoniae are among the most important bacterial pathogens worldwide, causing infections that range from mild mucosal infections (e.g. otitis media) to serious invasive disease (e.g. meningitis and bacteraemia). While the usually asymptomatic carrier

state (colonization) is a prerequisite for pneumococcal disease, it is also essential for pneumococcal transmission. There are at least 90 different serotypes of pneumococci that may differ in their ability to colonize hosts, their duration of carriage and their virulence [1, 2]. Colonized hosts are typically reported to carry a single serotype, but simultaneous carriage of different pneumococcal serotypes sometimes occurs [2, 3]. The current detection methods of simultaneous carriage may be sub-optimal [4]. Bacteria of different pneumococcal serotypes may compete with each other to

* Address for correspondence: Y. Zhang, Department of Medical Biometry, Westbahnhofstr. 55, 72070 Tuebingen, Germany.
(Email: yidi.zhang@uni-tuebingen.de)

colonize the human host. Such competition can be either direct (physical) or indirect (through cross-reacting immunity). Competition determines the joint ecology of pneumococcal serotypes in the human host population.

Multivalent pneumococcal vaccines have been available since 1977 and are effective in preventing serious pneumococcal diseases among adults caused by serotypes included in the vaccine [5, 6]. In contrast to these polysaccharide vaccines, the newly developed protein–polysaccharide conjugated vaccines are, furthermore, effective in preventing disease in children under 2 years of age [7]. Moreover, many studies have shown that the conjugate vaccines reduce carriage of serotypes included in the vaccine and, concomitantly, an increase in carriage of non-vaccine types has been observed [8, 9]. If the non-vaccine serotypes are inherently of low pathogenicity, such serotype replacement in carriage cannot increase the incidence of pneumococcal disease. However, if there are non-vaccine serotypes that have been suppressed by competition of the vaccine types, but are nonetheless pathogenic, the incidence of pneumococcal disease may not decline in the long run.

In this paper, we develop deterministic transmission models to study how competition and vaccination influence the coexistence of two pneumococcal serotypes in a population. Previously, the potential for serotype replacement has been studied for two or more directly competing serotypes [10]. Here, we consider both direct and indirect competition and distinguish different modes of competition within both alternatives. The implications of the results with regard to large-scale use of pneumococcal vaccines are discussed.

MODEL DESCRIPTION

We developed two SIRS models to examine the influence of competition and vaccination on the equilibrium prevalence of coexisting pneumococcal serotypes. The models are defined as deterministic differential equation systems (for details see Appendix). The two models correspond to two different mechanisms of competition between the serotypes (see below). The structures of the models are schematically depicted in Figure 1 (direct competition) and Figure 2 (indirect competition) and the epidemiological stages are explained in Table 1.

In both models, individuals are born susceptible (S), become colonized (C) and finally develop temporary

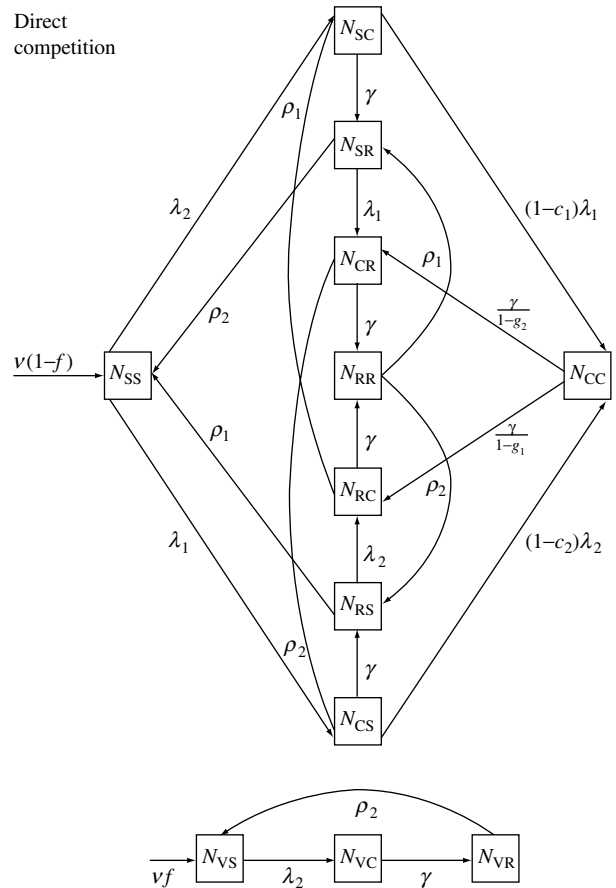


Fig. 1. Schematic representation of the model with direct competition. Boxes denote epidemiological stages of individuals, arrows denote transitions from one stage to another. Individuals are born susceptible (N_{SS}) unless vaccinated (N_{VS}), become colonized (subscript C), develop immunity (subscript R) and finally lose their immunity and become susceptible again (cf. Table 1). Transition rates and competition parameters are explained in Tables 2 and 3.

immunity (R). After some time, they lose their immunity and become susceptible again (S–I–R–S). Newborn individuals enter the population at a constant rate ν and the death rate is μ . To simplify matters, we defined a constant population size where the birth rate is equal to the death rate. Susceptible individuals (stage N_{SS}) become colonized with serotype 1 (stage N_{CS}) or serotype 2 (stage N_{SC}) at rates λ_1 and λ_2 respectively. The contact rates λ_1 and λ_2 can be calculated from the basic reproduction numbers [$R_{01} = \beta_1 / (\gamma + \mu) = 2.2$ and $R_{02} = \beta_2 / (\gamma + \mu) = 1.8$ respectively] [10]. Colonized individuals either become super-colonized with the other serotype (stage N_{CC}) or recover from colonization and become immune (stages N_{RS} and N_{SR}) at the same rate γ , respectively. We used a carriage duration of 30 days [11]. Immune individuals

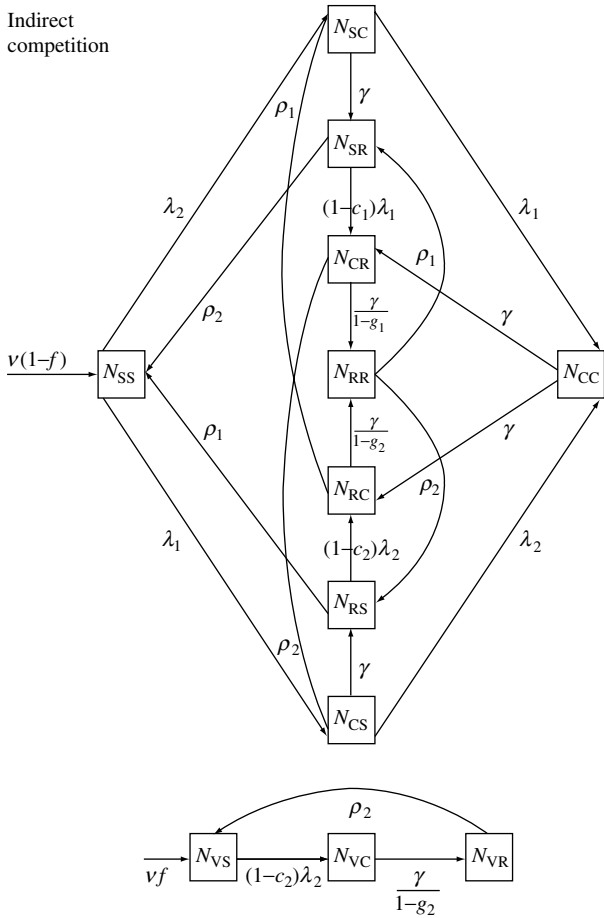


Fig. 2. Schematic representation of the model with indirect competition. Boxes denote epidemiological stages of individuals, arrows denote transitions from one stage to another. Individuals are born susceptible (N_{SS}) unless vaccinated (N_{VS}), become colonized (subscript C), develop immunity (subscript R) and finally lose their immunity and become susceptible again (Table 1). Transition rates and competition parameters are explained in Tables 2 and 3.

either become susceptible again at rates ρ_1 and ρ_2 respectively, or are colonized with the other serotype (stages N_{RC} and N_{CR}) which leads to immunity against both serotypes (N_{RR}).

Our model considers vaccination with a completely protective vaccine against serotype 1 (target serotype): a fraction, f , of all newborns enters the class of vaccinated but uncolonized individuals (stage N_{VS}), whereas the remaining fraction $1-f$ is added to the class of unvaccinated susceptible individuals (stage N_{SS}). Vaccinated individuals cannot be colonized with the vaccine serotype, but may be colonized with the other serotype (stage N_{VC}), after which they become immune (stage N_{VR}) and finally lose their immunity and become susceptible again (stage N_{VS}).

Table 1. *Epidemiological stages*

Stage	Serotype 1	Serotype 2
N_{SS}	Susceptible	Susceptible
N_{SC}	Susceptible	Colonized
N_{SR}	Susceptible	Temporarily immune
N_{CS}	Colonized	Susceptible
N_{CC}	Colonized	Colonized
N_{CR}	Colonized	Temporarily immune
N_{RS}	Temporarily immune	Susceptible
N_{RC}	Temporarily immune	Colonized
N_{RR}	Temporarily immune	Temporarily immune
N_{VS}	Immune (vaccinated)	Susceptible
N_{VC}	Immune (vaccinated)	Colonized
N_{VR}	Immune (vaccinated)	Temporarily immune

Competition between the two serotypes can be direct or indirect. In the model with direct competition (Fig. 1), bacteria of both serotypes only compete with each other if they are present in the same host at the same time. The first possibility to incorporate such direct competition is to assume that individuals who are already colonized with one serotype are partially protected against colonization with the other serotype: the rates of a second colonization are reduced by a factor $1-c_1$ or $1-c_2$ respectively. The second possibility assumes that hosts who carry both serotypes (N_{CC}) clear colonization quicker (with rates $\gamma/1-g_1$ and $\gamma/1-g_2$ respectively). In the third possibility, the infectiousness of super-infected individuals is reduced by factors $1-b_1$ and $1-b_2$ respectively. Thereby the contribution of the super-colonized to the force of infection (λ_1 and λ_2) is reduced (see Appendix).

In the model with indirect competition (Fig. 2), competition is not caused by the physical presence of the bacteria, but by the presence of cross-reacting antibodies. In this case vaccination (against the target serotype) is assumed to give similar protection against the non-target serotype as natural infection with the target serotype. Again, we consider three different modes of competition: (i) hosts who already are immune against one serotype may be partially immune against colonization with the other serotype (competition parameters c_1 and c_2), (ii) they may clear colonization together with the other serotype faster (competition parameters g_1 and g_2) or (iii) they may produce a reduced force of infection (competition parameters b_1 and b_2 , see Appendix).

Unless stated otherwise, we used the parameter values given in Table 2. The differential equations were solved numerically using programs written in Turbo Pascal.

Table 2. Standard set of model parameter values which are used throughout this paper unless stated otherwise; the life expectancy $1/\mu$ is set to 75 years [for calculation of the force of infection (λ_1 and λ_2) see Appendix]

Parameter	Serotype 1	Serotype 2
Contact rate (per day)	$\beta_1=0.073$	$\beta_2=0.050$
Duration of carriage (days)	$1/\gamma=30$	$1/\gamma=30$
Duration of immunity (days)	$1/\rho_1$ and $1/\rho_2$ vary	
Vaccinated fraction	$f=0$	

Table 3. Competition parameters. Only one set of competition parameters is used at a time, whereby the other parameters are set to zero (for parameter values see figures and text)

Symbol	Competition parameter
c_1, c_2	Parameter regulating the susceptibility
b_1, b_2	Parameter regulating the force of infection
g_1, g_2	Parameter regulating the duration of carriage

RESULTS

Direct competition

The effects of the three different modes of direct competition on the equilibrium prevalence are compared in Figure 3. All modes of competition show the same qualitative behaviour. We, therefore, only discuss the effect of competition on susceptibility to super-colonization (parameters c_1 and c_2) and neglect the other modes of competition.

Figure 4(a–c) shows how the prevalence of two directly competing serotypes changes under increasing competition. Figure 4a depicts a situation where there is practically no immunity against either of the two serotypes. For the chosen parameter values, both serotypes can only coexist if competition is moderate. In Figure 4(b, c), the duration of immunity is set to 1 and 5 months respectively. The existence of immunity considerably reduces the equilibrium prevalences of the two serotypes. As a consequence, colonized people come into contact less frequently with bacteria of the competing strain and the effect of direct competition diminishes. Even for immune durations of only 5 months, the effect of direct competition becomes negligible (Fig. 4c).

In Figure 5(a–c), we examine the effect of vaccination on the equilibrium prevalence of the

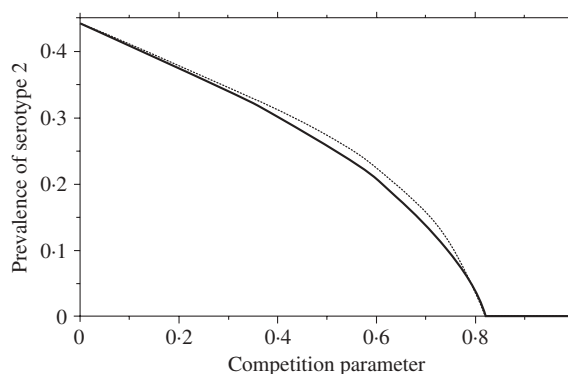


Fig. 3. Influence of direct competition with serotype 1 on the equilibrium prevalence of serotype 2. We compare three different modes of competition. For each curve, only one pair of competition parameters is used, whereby the other two pairs are set to zero. (1) parameters c_1 and c_2 (—) determine to what extent the susceptibility of an individual is reduced if he or she is already colonized by one serotype, (2) parameters b_1 and b_2 (---) determine to what extent the duration of carriage is reduced in individuals who are colonized with both serotypes (the line coincides with the solid line for $c_1=c_2$), (3) parameters g_1 and g_2 (·····) determine to what extent the force of infection, exerted by individuals who are colonized with both pathogens, is reduced (for details, see Appendix). Unvaccinated population; parameter values as given in Table 2.

non-target and target serotype (serotype 1). We consider the case without immunity (Fig. 5a) and compare weak competition ($c_1=c_2=0.2$, Fig. 5a) with moderate competition ($c_1=c_2=0.5$, Fig. 5b) and strong competition ($c_1=c_2=0.9$, Fig. 5c). Vaccination reduces the prevalence of the target serotype (solid lines) and, thereby, also influences the prevalence of the non-target serotype (dashed lines). This indirect effect is profound if the non-target serotype was strongly suppressed before vaccination (Fig. 5b, c). In extreme cases, vaccination can even enable the persistence of non-target serotypes which were completely out-competed while the target serotype was still abundant (Fig. 5c). Competition also reduces the critical vaccination coverage which is needed to eliminate the target serotype (Fig. 5a–c). There is a larger reduction in critical vaccination coverage when the inhibition by the non-target serotype is stronger.

Indirect competition

If bacteria compete indirectly via cross-reacting antibodies, we can again compare the three modes of competition described above. Similar to the model with direct competition, all modes of indirect competition show the same qualitative behaviour (results

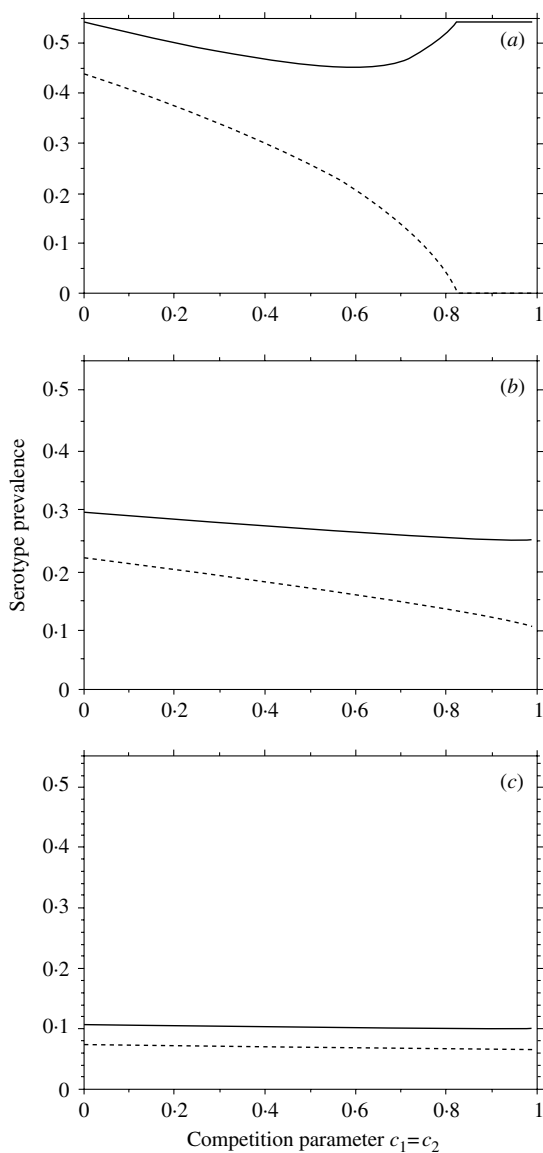


Fig. 4. Influence of *direct* serotype competition on the equilibrium prevalence of two serotypes. The mean duration of immunity is (a) 0 months, (b) 1 month, (c) 5 months respectively, for both serotypes. The competition parameters c_1 and c_2 determine to which extent the susceptibility of an individual is reduced if he or she is already colonized by one serotype (all other competition parameters are set to zero). Unvaccinated population; parameter values as given in Table 2. —, Serotype 1; - - - - -, serotype 2.

not shown), so that we will only use competition parameters c_1 and c_2 in the following and neglect the other modes of competition.

Figure 6(a, c) illustrates how the prevalences of two indirectly competing serotypes change under increasing competition. Figure 6a shows a situation where immunity against one of the two serotypes lasts for only 1 month whereas in Figure 6(b, c), the duration

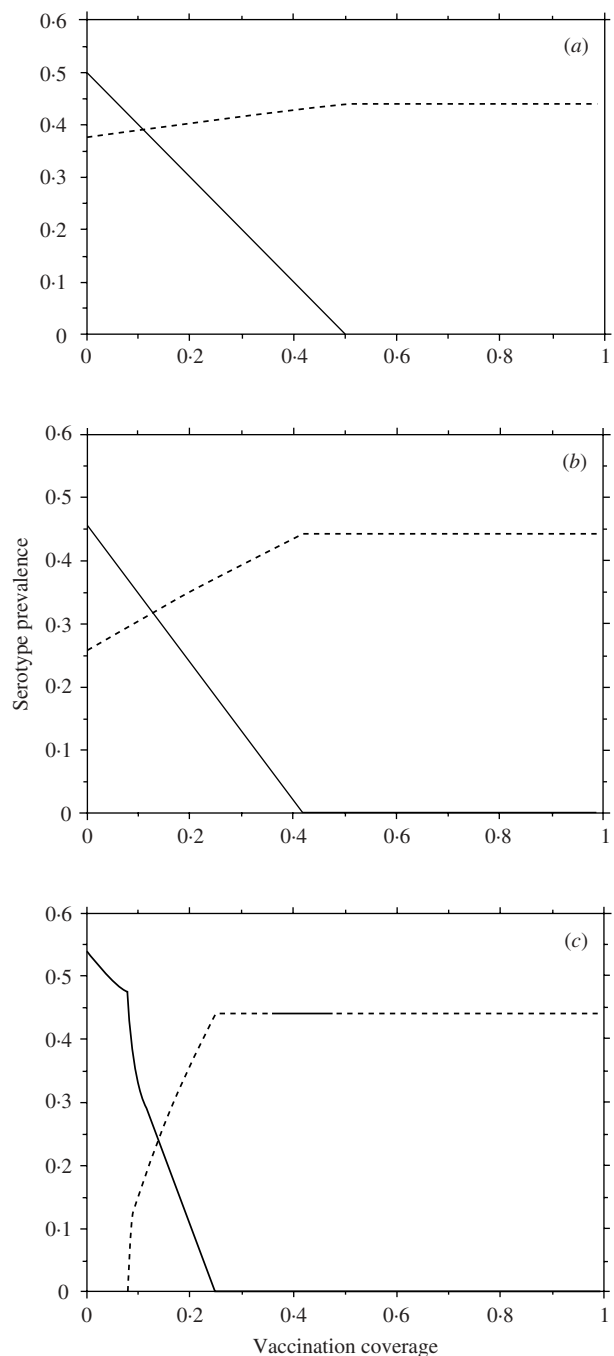


Fig. 5. Effect of vaccination on the equilibrium prevalence of target (serotype 1) and non-target serotype. The two serotypes compete *directly*. We set competition parameters $c_1 = c_2$ to 0.2 in (a), to 0.5 in (b) and to 0.9 in (c); all other competition parameters are set to zero. The duration of immunity is set to zero for both serotypes; other parameter values as given in Table 2. —, Serotype 1; - - - - -, serotype 2.

of immunity is set at 5 and 100 months respectively. With increasing duration of immunity, bacteria of any one serotype are more likely to encounter hosts who are already immune against the other serotype

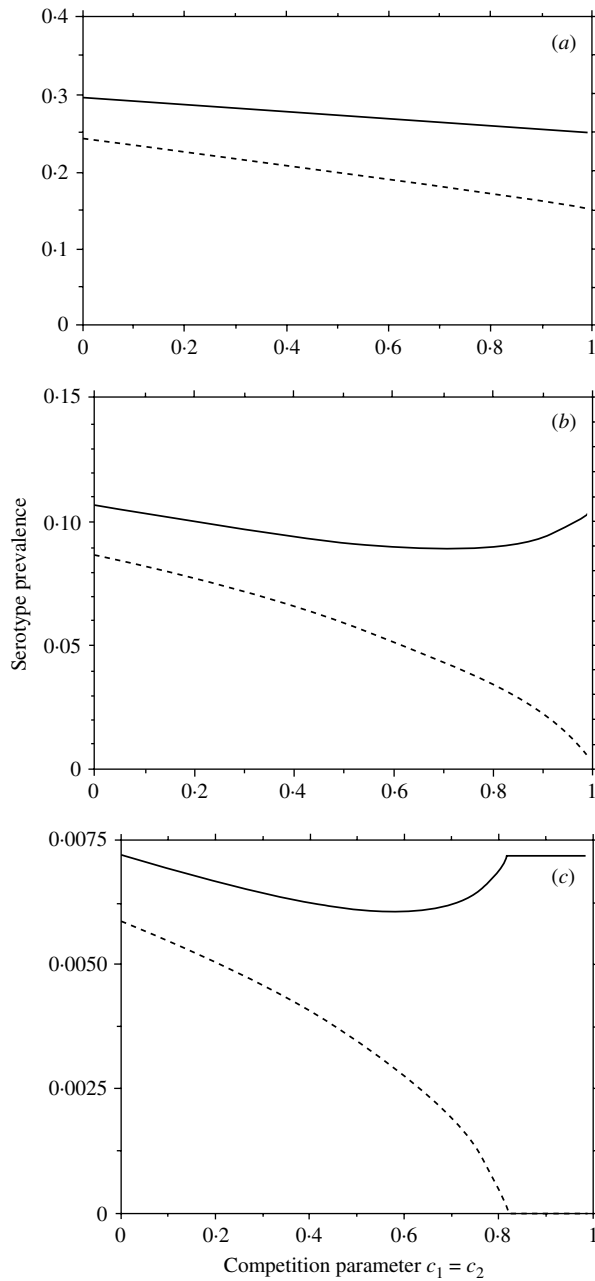


Fig. 6. Influence of *indirect* serotype competition on the equilibrium prevalence of two serotypes. Duration of immunity is (a) 1 month, (b) 5 months, (c) 100 months respectively, for both serotypes. The competition parameters c_1 and c_2 determine to what degree the susceptibility of an individual is reduced if he or she is already colonized by one serotype (all other competition parameters are set to zero). Unvaccinated population; parameter values as given in Table 2. —, Serotype 1; ----, serotype 2.

and, thus, the effect of indirect competition increases. For long-lasting immunity, both serotypes can only coexist if competition is weak (Fig. 6c).

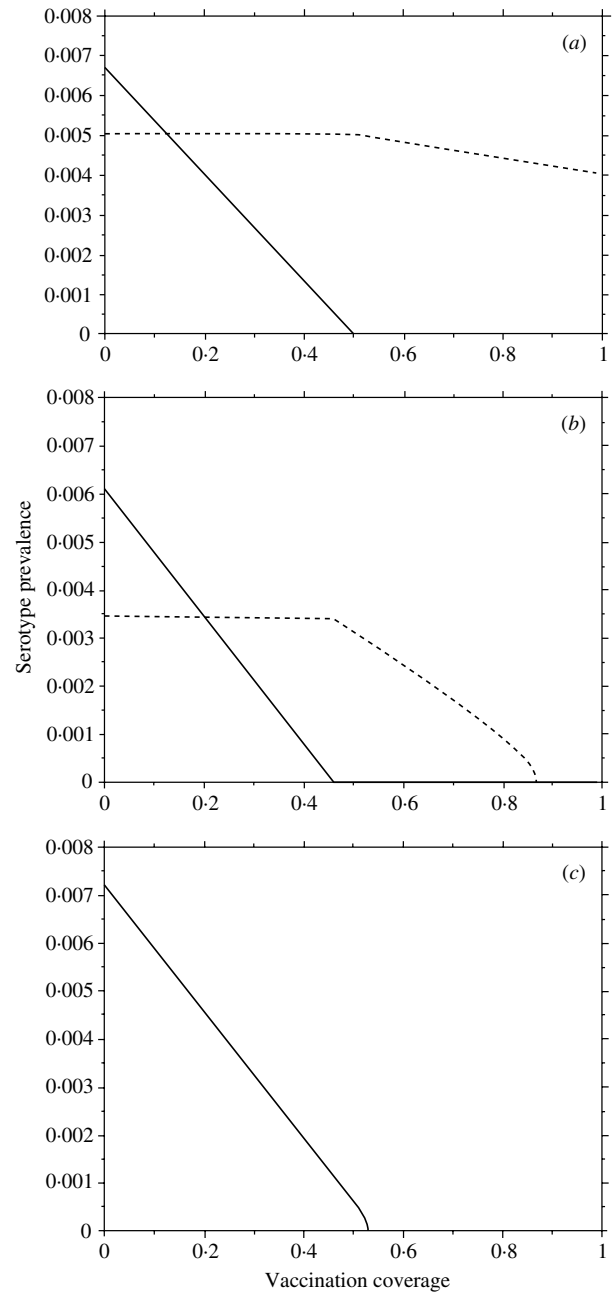


Fig. 7. Effect of vaccination on the equilibrium prevalence of target (serotype 1) and non-target serotype. Bacteria of the two serotypes compete *indirectly*. We set competition parameters $c_1 = c_2$ to 0.2 in (a), to 0.5 in (b) and to 0.9 in (c); all other competition parameters are set to zero. The duration of immunity is set to 100 months for both serotypes; other parameter values as given in Table 2.

In Figure 7(a-c), we examine the effect of vaccination on the equilibrium prevalence of the non-target and target serotype (serotype 1). Vaccination reduces the prevalence of the target serotype (solid lines), but also reduces the prevalence of the non-target serotype (dashed lines). Thus serotype

replacement cannot occur under indirect competition. In Figure 7a, we assume that natural immunity is practically permanent (100 months). In this case, the fraction of people who are immune against the target serotype remains constant until this serotype persists (this effect has frequently been reported for models of the SIR type; cf. [12]). Only if the vaccination coverage exceeds 50% does the fraction of immune individuals increase, and so does the pressure on the non-target serotype. In another extreme case, where natural immunity is very short and immunity is caused by vaccination, even a low vaccination coverage impairs the equilibrium prevalence of the non-target serotype.

DISCUSSION

We have analysed transmission dynamic models of bacteria to study how competition and vaccination influence the coexistence of two serotypes. We have specifically addressed the question of how duration of immunity against carriage affects the potential for vaccination to induce replacement of the vaccine serotype by the non-vaccine serotype. In general, such replacement means that the non-vaccine serotype benefits from reduced competition by the vaccine serotype. Two different types of competition were considered: direct (physical) and indirect (antibody-mediated). In the model with direct competition, a monovalent vaccine with perfect protection was assumed. In the model of indirect competition, vaccine-induced protection against the non-target type was assumed to be similar to immunity following carriage of the target type.

Keeping all other parameters unchanged, duration of natural immunity strongly influences the equilibrium prevalence of the two serotypes: the longer the duration of immunity, the lower the equilibrium is for both serotypes. If the duration of immunity is long, and the prevalence accordingly low, bacteria of the two types will rarely meet in the same host and the potential influence of direct competition is minimal (Fig. 4c).

In contrast, under similar circumstances indirect competition can be very influential (Fig. 6c). Moreover, under indirect competition vaccination reduces the prevalence of both serotypes (Fig. 7a–c) and no replacement would occur. This result obviously depends on the assumption that vaccination has an impact on both serotypes under indirect competition, i.e. when immunity against carriage is mediated by antibodies.

If immunity is short-lived with corresponding high prevalence, indirect competition cannot be influential (Fig. 6a) whereas direct competition can (Fig. 4a). Moreover, vaccination under direct competition can lead to serotype replacement (Fig. 5a–c). This has previously been noted by Lipsitch [10]. It has also been observed from several models [12] that competition between serotypes reinforces the effect of a serotype-specific vaccine so that the target type can be eliminated with a lower coverage than without competition. This phenomenon occurs under both direct and indirect competition. In the case of direct competition the critical coverage of vaccination will be strongly reduced with increased competition (up to 50% from weak to strong competition) whereas the effect is minimal by indirect competition. Under strong indirect competition the critical vaccination coverage slightly increases.

Three alternative modes of competition were considered in which the vaccine can effect either the susceptibility to colonization, infectiousness of the colonized, or duration of colonization. All three modes of competition have practically the same effect on the equilibrium prevalence of the serotypes, under both direct and indirect competition. This implies that it may not be important to distinguish between such modes of effect, at least in the case where competition acts with similar strength on both serotypes (we assumed $c_1 = c_2$ in our model).

Lipsitch [10] used models of transmission dynamics to study competition between two or more serotypes and concluded that serotype-specific vaccines will increase the prevalence of serotypes not included in the vaccine that compete with the vaccine serotypes. These (SIS) models neglected the possibility of natural immunity and thus only considered direct competition between the serotypes. The data presented in Figures 5 and 6a correspond to the model of Lipsitch [10].

We considered the coexistence of only two serotypes. If more than two serotypes are coexisting, the competition effect is similar as in the two serotypes model. If there is no vaccination, the prevalence of all serotypes will be reduced with increasing competition, some weak serotypes may be out-competed, as only stronger serotypes can persist under strong competition. Just as in the two serotypes models, serotype replacement can occur after vaccination by direct competition. In the extreme case, an increase in prevalence of one or more serotypes may be greater than the decrease of the prevalence of the target serotype [10]. If vaccine-mediated antibodies cross-react with

non-target serotypes, their prevalence will be reduced with increasing vaccination coverage.

Serotype replacement in pneumococcal carriage does not necessarily imply concomitant increase in pneumococcal disease. The extent of the latter will depend on intrinsic differences in pathogenicity across the serotypes. If the non-vaccine types are of lower pathogenicity than the vaccine serotypes, replacement would only serve to enhance the effectiveness of vaccination in reducing disease. In contrast, if non-vaccine types are similar to vaccine types in their ability to cause disease, long-term effectiveness of vaccination could be questioned. It is believed that the extent of heterogeneity among the serotypes is different for different disease manifestations. In particular, it has been suggested that the potential for true replacement in pneumococcal otitis media is more likely than that in invasive pneumococcal disease [13].

Our studies confirm that serotype replacement in pneumococcal carriage can occur under direct competition between serotypes. For the case of antibody-mediated competition we observed that vaccination reduces both the prevalence of target and non-target serotype so that vaccination may also help to eliminate other pneumococcal types. In order to assess the long-term effects of sero-competition, it is, therefore, important to study whether bacteria compete directly or indirectly and for how long individuals are protected after colonization.

ACKNOWLEDGEMENTS

This work is part of the project Pnc Euro which was financed by the European Commission (Contract no. QL4-CT-2000-00640) within the framework of Quality of Life and Management of Living Resources Programme (1998–2002).

APPENDIX

Model with direct competition

$$dN_{SS}/dt = v(1-f) + \rho_1 N_{RS} + \rho_2 N_{SR} - (\lambda_1 + \lambda_2 + \mu) N_{SS}$$

$$dN_{CS}/dt = \lambda_1 N_{SS} + \rho_2 N_{CR} - [\gamma + (1-c_2)\lambda_2 + \mu] N_{CS}$$

$$dN_{SC}/dt = \lambda_2 N_{SS} + \rho_1 N_{RC} - [\gamma + (1-c_1)\lambda_1 + \mu] N_{SC}$$

$$dN_{CC}/dt = (1-c_1)\lambda_1 N_{SC} + (1-c_2)\lambda_2 N_{CS} - \left(\frac{\gamma}{1-g_2} + \frac{\gamma}{1-g_1} + \mu\right) N_{CC}$$

$$dN_{RS}/dt = \gamma N_{CS} + \rho_2 N_{RR} - (\lambda_2 + \rho_1 + \mu) N_{RS}$$

$$dN_{SR}/dt = \gamma N_{SC} + \rho_1 N_{RR} - (\lambda_1 + \rho_2 + \mu) N_{SR}$$

$$dN_{RC}/dt = \lambda_2 N_{RS} + \frac{\gamma}{1-g_1} N_{CC} - (\gamma + \rho_1 + \mu) N_{RC}$$

$$dN_{CR}/dt = \lambda_1 N_{SR} + \frac{\gamma}{1-g_2} N_{CC} - (\gamma + \rho_2 + \mu) N_{CR}$$

$$dN_{RR}/dt = \gamma N_{CR} + \gamma N_{RC} - (\rho_1 + \rho_2 + \mu) N_{RR}$$

$$dN_{VS}/dt = vf + \rho_2 N_{VR} - (\lambda_2 + \mu) N_{VS}$$

$$dN_{VC}/dt = \lambda_2 N_{VS} - (\gamma + \mu) N_{VC}$$

$$dN_{VR}/dt = \gamma N_{VC} - (\rho_2 + \mu) N_{VR}$$

$$\lambda_1 = \beta_1 [N_{CS} + (1-b_1)N_{CC} + N_{CR}]$$

$$\lambda_2 = \beta_2 [N_{SC} + (1-b_2)N_{CC} + N_{RC} + N_{VC}]$$

Model with indirect competition

$$dN_{SS}/dt = v(1-f) + \rho_1 N_{RS} + \rho_2 N_{SR} - (\lambda_1 + \lambda_2 + \mu) N_{SS}$$

$$dN_{CS}/dt = \lambda_1 N_{SS} + \rho_2 N_{CR} - (\gamma + \lambda_2 + \mu) N_{CS}$$

$$dN_{SC}/dt = \lambda_2 N_{SS} + \rho_1 N_{RC} - (\gamma + \lambda_1 + \mu) N_{SC}$$

$$dN_{CC}/dt = \lambda_1 N_{SC} + \lambda_2 N_{CS} - (2\gamma + \mu) N_{CC}$$

$$dN_{RS}/dt = \gamma N_{CS} + \rho_2 N_{RR} - [(1-c_2)\lambda_2 + \rho_1 + \mu] N_{RS}$$

$$dN_{SR}/dt = \gamma N_{SC} + \rho_1 N_{RR} - [(1-c_1)\lambda_1 + \rho_2 + \mu] N_{SR}$$

$$dN_{RC}/dt = (1-c_2)\lambda_2 N_{RS} + \gamma N_{CC} - \left(\frac{\gamma}{1-g_2} + \rho_1 + \mu\right) N_{RC}$$

$$dN_{CR}/dt = (1-c_1)\lambda_1 N_{SR} + \gamma N_{CC} - \left(\frac{\gamma}{1-g_1} + \rho_2 + \mu\right) N_{CR}$$

$$dN_{RR}/dt = \frac{\gamma}{1-g_1} N_{CR} + \frac{\gamma}{1-g_2} N_{RC} - (\rho_1 + \rho_2 + \mu) N_{RR}$$

$$dN_{VS}/dt = vf + \rho_2 N_{VR} - [(1-c_2)\lambda_2 + \mu] N_{VS}$$

$$dN_{VC}/dt = (1-c_2)\lambda_2 N_{VS} - \left(\frac{\gamma}{1-g_2} + \mu\right) N_{VC}$$

$$dN_{VR}/dt = \frac{\gamma}{1-g_2} N_{VC} - (\rho_2 + \mu) N_{VR}$$

$$\lambda_1 = \beta_1 [N_{CS} + N_{CC} + (1-b_1)N_{CR}]$$

$$\lambda_2 = \beta_2 [N_{SC} + N_{CC} + (1-b_2)(N_{RC} + N_{VC})]$$

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