An Age-Structured Model for Pneumococcal Infection with Vaccination

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Abstract

Pneumococcal diseases, or infections caused by *Streptococcus pneumoniae*, are a major cause of morbidity and mortality worldwide, primarily affecting the young and the old. The development of an effective vaccine against these infections, especially the younger ages, has not been successful despite the licensing of the pneumococcal conjugate vaccine (PCV7). The design of vaccines that induce immunity via distinct mechanisms provide an opportunity for the use of mathematical models in the evaluation of their impact at the population level. We present an age-structured epidemiological model of pneumococcal disease dynamics and explore of the role of vaccination. The model is re-formulated as a system of ordinary differential equations that aggregates individuals into relevant age groups. The goals of this work are twofold: (1) to explore the effects of targeting nasopharyngeal colonization and/or infection via vaccination in younger age groups, and (2) to demonstrate the utility of this framework as a public health tool to theoretically study the impact of a vaccine strategy before implementation.

1 Introduction

Infections caused by *Streptococcus pneumoniae*, or pneumococcal infections cause substantial morbidity and mortality worldwide. Invasive pneumococ-

cal diseases (IPDs), including pneumonia, bacteremia, and meningitis, primarily affect the young and elderly. Most affected are children in developing countries, with annual estimates of 1 million deaths due to pneumococcal pneumonia alone ([23]). In developed countries, the disease burden is largely carried by elderly adults and young children, with older children and healthy adults virtually unaffected in the absence of other predisposing risk factors. In Australia in 2001, there were 459 cases of IPDs in adults over the age of 65, and 613 in children under the age of four [6]. Transient nasopharyngeal colonization, which is a common occurence for all individuals, always precedes infection. This colonization occurs through casual contacts and is responsible for the horizontal transmission of pneumococcal infections. However, the prevalence of asymptomatic colonization does not reflect the same trend as that of the infections. Carriage rates, which are typically around 30% in children, decrease to between 10-15% in adults and only increase slightly in older adults (over 65) [1, 14, 15]. These observed differences cannot be readily explained simply by differences in transmission and infection rates, as nearly all relevant processes in the dynamics are nonlinear and depend strongly on age. Thus we study these processes within an age-structured framework that incorporates the impact of vaccination.

The current polysaccharide vaccine (PPV23) prevents infection only in the elderly [20] and has no impact on the colonization of immunized individuals [2], while the more recently licensed protein conjugate vaccine (PCV7) is thought to reduce colonization of the seven vaccine-included serotypes [5, 7, 13]. However, accompanying this effect is typically the increased colonization prevalence of other, possibly more invasive, serotypes. Therefore, the protection a vaccine may provide against colonization should be closely monitored, as there may be opportunities for serious infections resulting from the colonization of competing bacteria. The PCV7 induces a strong protective immune response in children against infection [3], but is costly and requires multiple doses, and is therefore likely not a feasible solution for less developed regions. Pneumococcal vaccination development is an active research area, with the goal of providing a solution that achieves as many of the following objectives as possible: protection against all serotypes, affordability, temperature-stability, a single dose immunization schedule, etc. But whether to focus on the inhibition of colonization or infection is not a simple question, and it is likely that there will be differences in immunogenic mechanisms that are effective in different age groups. Thus, there is a need to understand how these immunogenic influence disease dynamics, and thereby vaccine development, in an age-structured population.

We introduce a mathematical model describing pneumococcal infection

dynamics in an age-structured population. We incorporate a general vaccination by the age-dependent function $\phi(a)$ allowing for the consideration of any vaccine strategy involving pneumococcal vaccines, which are possibly immunogenic via distinct mechanisms. The model is reformulated as a system of ordinary differential equations of the infection dynamics of age groups, an approach that lends itself well to computations. We discuss the effects of vaccinating a population, focusing on the immunization of younger age groups, against colonization or infection, or a combination of both. Further, we exhibit the strengths of this approach as a public health simulation tool enabling officials to quantify the effects of specific vaccine strategies in a population before their implementation.

2 Continuous age-structured model

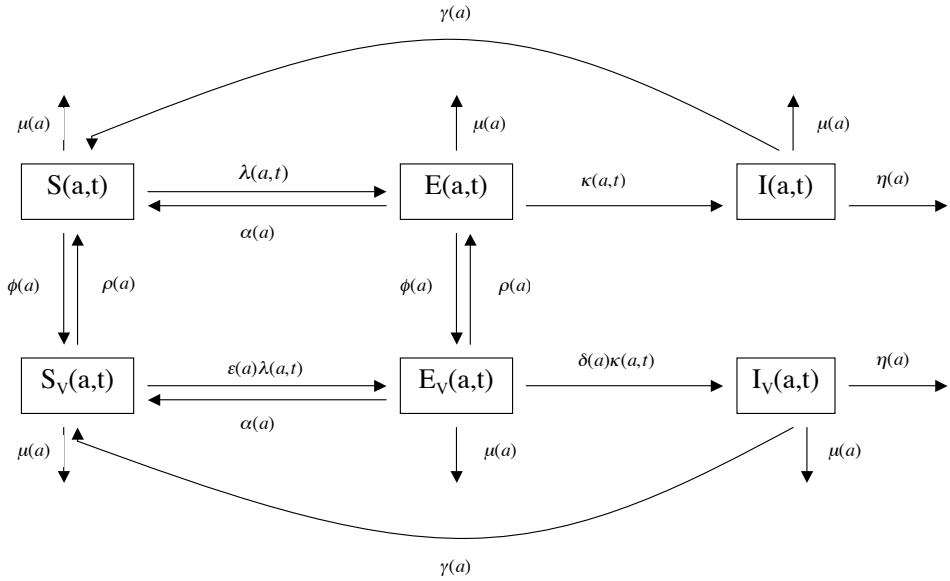

Figure 1: Pneumococcal infection dynamics with vaccination as a function of age.

We formulate a model in which $n(a,t)$ (in units of "number per age") denotes the density of individuals of age a ($a \in [0,\infty)$). These individuals are classified by their infection state at time t. Individuals are susceptible to pneumococcal infection $S(a,t)$, asymptomatically colonized by *S. pneumoniae*, represented by the class $E(a,t)$, or infected $I(a,t)$. Both susceptible

$S(a,t)$ and asymptomatically colonized individuals $E(a,t)$ are effectively vaccinated at the age-dependent vaccination rate $\phi(a)$, that is, they move to states $S_V(a,t)$ and $E_V(a,t)$, respectively. Vaccination is not always completely protective, even against vaccine-included serotypes, thus there are also infected vaccinated individuals $I_V(a,t)$.

Transmission of *S. pneumoniae* occurs through respiratory droplets, and therefore the colonization process occurs as a result of an *effective contact* between a susceptible (or vaccinated susceptible) of age a at time t and any colonized or infected individual of age a' at time t, reflected in the effective contact rate $c(a,a')$. We note here that we have not assumed a specific form for the effective contact rate, although a common one would be that of proportionate mixing in which individuals are assumed to mix proportional to their age-dependent activity levels and densities.

The selected colonization rate $\lambda(a,t)$ for this investigation is given by

$$\lambda(a,t) = \frac{\int_0^\infty c(a,a')\left[E(a',t) + E_V(a',t) + I(a',t) + I_V(a',t)\right] da'}{\int_0^\infty N(a',t) da'} \qquad (1)$$

where $N(a,t)$ is the total number of individuals of age a at time t and $\lambda(a,t)$ has units of $\frac{1}{\text{time}}$. Typically, this colonization is only transient and hence we assume that individuals clear the bacteria at per capita rate $\alpha(a)$. Children take a longer time in reversing this colonization than adults, thereby motivating an age-dependent rate. Current estimates of the prevalence of colonized individuals of all ages range between 10-70%, depending on factors such as age, crowding, health care, etc. The possibility that a vaccine may be able to reduce the rate of colonization is incorporated via the function $\epsilon(a)$ taking values in the range $(0,1]$ where $\epsilon(a)$ is the age-dependent protection from colonization induced by vaccination.

Individuals unable to clear *S. pneumoniae* from the nasopharyngeal region progress to an infected state at the age-specific per capita rate $\kappa(a,t)$. In more developed countries, this primarily occurs in infants less than 2 years of age, adults over the age of 65 and less often in children between the ages of 2 and 5. Infection is common in children due to both a lack of exposure to similar serotypes (and hence a lack of protective antibodies), and/or due to a developing immune system (an inability to respond to certain antigens). With insufficient nutrition this development is delayed. Older children in developing countries experience higher infection rates than their counterparts in developed nations. In the elderly, infection occurs as a result of various failing arms of a deteriorating humoral immune response. Seasonal fluctuations in pneumococcal infections have been observed, and

are incorporated here in the infection rate $\kappa(a,t)$. It is worth noting that the colonization prevalence is not strongly associated with seasonality. In fact it is only shown to vary longitudinally in regions that experience drastic temperature changes. In all studies the authors found that an increase in pneumococcal infections correlates well with increases in other seasonal infections. Thus we consider the season to effectively decrease an individual's ability to reverse a colonization event. Therefore, the colonization or transmission rate $\lambda(a,t)$ does not incorporate this effect. Therefore, we model the seasonal infection rate by

$$\kappa(a,t) = \kappa_0(a)\left(1 + \kappa_1 \cos[\omega(t-\tau)]\right), \tag{2}$$

where κ_1 scales for the magnitude of the fluctuation, ω is the seasonal frequency, and τ shifts the peak of the trigonometric function to coincide with the annual peak of the infections, i.e., a phase shift. With this form the seasonal effects are proportional to the age-dependent mean infection rate, i.e., seasonality in individuals of ages who have higher mean rates of infection is stronger (an assumption supported by the data shown in Figure 1 in [18]).

Vaccination schedules are typically prescribed for certain ages, incorporated in the model by an age-dependent vaccination rate $\phi(a)$. The vaccines differ in the age groups for which they are suitable and the number of doses that are recommended. These aspects of the program considered determine the form of $\phi(a)$. The length of protection from immunization is also age-dependent and not all individuals complete multi-dose regimes. We take these factors into account when prescribing a form to $\rho(a)$, the rate at which individuals of age a revert to their corresponding unvaccinated class S or E. The protective effects of vaccines also change depending on the age of individuals to whom they are administered. These effects are reflected in the rates $\delta(a)$ and $\epsilon(a)$ (the vaccine efficacies are then $1-\delta(a)$ and $1-\epsilon(a)$.

Natural age-specific death occurs out of each compartment at the per-capita rate $\mu(a)$.The age-specific fatality due to pneumococcal disease is represented by the rate $\eta(a)$. Per capita case fatalities are significant in infected individuals of age 65 and increase with age. The outcome of IPD in children largely depends on their ability to clear the infection and on the availability/effectiveness of antibiotics - a defense that can be complicated by resistance. Therefore, the outcome of infection, and hence case fatality, depends on nutrition, geographic location, comorbidities, and age - e.g., infants are less able to mount a significant immune response and respond to antibiotics than toddlers.

We assume that all individuals are born susceptible and unvaccinated,

so the boundary conditions for the model are $E(0,t) = I(0,t) = S_V(0,t) = E_V(0,t) = I_V(0,t) = 0$ and $S(0,t) = \int_0^\infty f(a')n(a',t)da'$ where $f(a')$ is the age-specific per capita fertility rate.

The model equations are given by the following boundary value problem:

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right) S(a,t) = -\lambda(a,t)S(a,t) + \alpha(a)E(a,t) + \gamma(a)I(a,t) \tag{3}$$
$$+ \rho(a)S_V(a,t) - (\phi(a) + \mu(a))S(a,t),$$
$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right) E(a,t) = \lambda(a,t)S(a,t) + \rho(a)E_V(a,t) \tag{4}$$
$$- (\alpha(a) + \kappa(a,t) + \phi(a) + \mu(a))E(a,t),$$
$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right) S_V(a,t) = -\epsilon(a)\lambda(a,t)S_V(a,t) + \alpha(a)E_V(a,t) \tag{5}$$
$$+ \gamma(a)I_V(a,t) + \phi(a)S(a,t)$$
$$- (\rho(a) + \mu(a))S_V(a,t),$$
$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right) E_V(a,t) = \epsilon(a)\lambda(a,t)S_V(a,t) + \phi(a)E(a,t) \tag{6}$$
$$- (\alpha(a) + \delta(a)\kappa(a,t) + \rho(a) + \mu(a))E_V(a,t),$$
$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right) I(a,t) = \kappa(a,t)E(a,t) - (\gamma(a) + \eta(a) + \mu(a))I(a,t), \tag{7}$$
$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right) I_V(a,t) = \delta(a)\kappa(a,t)E_V(a,t), \tag{8}$$
$$- (\gamma(a) + \eta(a) + \mu(a))I_V(a,t),$$
$$S(0,t) = \int_0^\infty f(a')N(a',t)da',$$
$$E(0,t) = S_V(0,t) = E_V(0,t) = I(0,t) = I_V(0,t) = 0.$$

3 Derivation of discrete age model

We take an approach (outlined in [9] and applied in [10] and [11]) where system (3) – (8) is approximated by a system of ordinary differential equations. Model (3) – (8) makes it unnecessarily difficult to explore the impact of vaccination. In order to focus on the impact of age-classes we introduce a model that easily aggregates the age-groups of significance. We consider m age classes, where the ith class corresponds to the interval $[a_{i-1}, a_i]$ and $0 = a_0 < ... < a_m = \infty$. The age classes need not be of the same length;

that is, $a_i - a_{i-1}$ is not necessarily equal to $a_j - a_{j-1}$ for $i, j \in [1, ..., m]$. We define

$$X_i(t) = \int_{a_{i-1}}^{a_i} X(a,t)da$$

where $X_i = S_i, E_i, I_i, S_{Vi}, E_{Vi}, I_{Vi}, N_i$ represent the number of individuals in each ith age interval. In order to clarify our derivation, we look first at the demographic model given by

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right) N(a,t) = -\mu(a)N(a,t) \tag{9}$$
$$N(0,t) = \int_0^\infty f(a')N(a',t)da',$$

in which fatalities due to infection have been neglected. The solution of (9) via the method of characteristics yields the typical renewal equation

$$N(t) = \int_0^t f(a)p(a)N(t-a)da + \int_t^\infty f(a)\frac{p(a)}{p(a-t)}u_0(a-t)da, \tag{10}$$

with the second term depending only on the initial density $u(a,0) = u_0(a)$ and the probability of a newborn surviving to age a given by $p(a) = e^{-\int_0^a \mu(\sigma)d\sigma}$. If one looks for solutions of the form $N(t) = e^{qt}$ and lets $t \to \infty$, one arrives at the characteristic equation

$$\int_0^\infty f(a)e^{-\int_0^a \mu(\sigma)d\sigma}e^{-qa}da = 1. \tag{11}$$

Under suitable conditions on $f(a)$, there is a unique real q that solves this characteristic equation for the exponential rate of growth for the population. The statement that the population has reached a stable age distribution means that the solution is $N(a,t) = e^{qt}A(a)$, a common assumption [12]. If we define P_i to be the size of the ith age class at time 0, then under the assumption that $N(a,t) = e^{qt}A(a)$ we have that

$$N_i(t) = \int_{a_{i-1}}^{a_i} N(a,t)da = e^{qt}\int_{a_{i-1}}^{a_i} A(a)da = e^{qt}P_i \tag{12}$$

and

$$A(0) = \sum_{i=1}^{m} f_i P_i$$

where f_i are the coefficients of the approximated fecundity function $f(a) = \sum_{i=1}^{m} f_i \chi_{[}a_{i-1}, a_i]$ and χ is the characteristic function of the set $[a_{i-1} - a_i]$. Note that the births at time t are then given by $N(t) = \sum_{i=1}^{m} f_i N_i(t) = \sum_{i=1}^{m} e^{qt} f_i P_i$.

We use the above definitions to derive an ODE model from integrating the equations in system (3) – (8) over the interval $[a_{i-1}, a_i]$ with respect to a. The integration of Equation (9), and our previous definition give

$$\int_{a_{i-1}}^{a_i} \frac{\partial}{\partial t} N(a,t)da + \int_{a_{i-1}}^{a_i} \frac{\partial}{\partial a} N(a,t)da = -\int_{a_{i-1}}^{a_i} \mu(a)N(a,t)da$$
$$\frac{dN_i}{dt} + N(a_i,t) - N(a_{i-1},t) = -\mu_i N_i(t).$$

Making use of the solution $N(a,t) = e^{qt}A(a)$, we see that

$$\begin{aligned}\frac{dN_i}{dt} &= -e^{qt}A(a_i) + e^{qt}A(a_{i-1}) - \mu_i N_i \\ &= e^{qt}P_{i-1}\frac{A(a_{i-1})}{P_{i-1}} - e^{qt}P_i\frac{A(a_i)}{P_i} - \mu_i N_i.\end{aligned}$$

Now substituting $N_i = e^{qt}P_i$ (equation (12)) and defining $b_i = \frac{A(a_i)}{P_i}$ (which, under reasonable assumptions outlined in [9], is approximately given by $b_i \approx \frac{1}{a_i - a_{i-1}}$), we arrive at the following system, derived from first principles, for N_i:

$$\frac{dN_i}{dt} = b_{i-1}N_{i-1} - b_i N_i - \mu_i N_i \qquad \text{for } i = 2, ..., m-1,$$

and

$$\frac{dN_1}{dt} = \sum_{j=1}^{m} f_j N_j - b_1 N_1 - \mu_1 N_1$$
$$\frac{dN_m}{dt} = b_{m-1}N_{m-1} - \mu_m N_m.$$

Following the same approach we arrived at the following epidemiological model with variable length age classes:

For $i = 1$:

$$\frac{dS_1}{dt} = \sum_{j=1}^{m} f_j P_j - \lambda_1(t) S_1 + \alpha_1 E_1 + \gamma_1 I_1 + \rho_1 S_{V1} \tag{13}$$
$$- (\phi_1 + \mu_1 + b_1) S_1$$

$$\frac{dE_1}{dt} = \lambda_1(t) S_1 + \rho_1 E_{V1} - (\alpha_1 + \kappa_1(t) + \phi_1 + \mu_1 + b_1) E_1 \tag{14}$$

$$\frac{dS_{V1}}{dt} = -\epsilon_1 \lambda_1(t) S_{V1} + \alpha_1 E_{V1} + \gamma_1 I_{V1} + \phi_1 S_1 - (\rho_1 + \mu_1 + b_1) S_{V1} \tag{15}$$

$$\frac{dE_{V1}}{dt} = \epsilon_1 \lambda_1(t) S_{V1} + \phi_1 E_1 - (\alpha_1 + \delta_1 \kappa_1(t) + \rho_1 + \mu_1 + b_1) E_{V1} \tag{16}$$

$$\frac{dI_1}{dt} = \kappa_1(t) E_1 - (\gamma_1 + \eta_1 + \mu_1 + b_1) I_1 \tag{17}$$

$$\frac{dI_{V1}}{dt} = \delta_1 \kappa_1(t) E_{V1} - (\gamma_1 + \eta_1 + \mu_1 + b_1) I_{V1}, \tag{18}$$

$i = 2, .., m - 1$:

$$\frac{dS_i}{dt} = -\lambda_i(t) S_i + \alpha_i E_i + \gamma_i I_i + \rho_i S_{Vi} \tag{19}$$
$$- (\phi_i + \mu_i + b_i) S_i + b_{i-1} S_{i-1} \tag{20}$$

$$\frac{dE_i}{dt} = \lambda_i(t) S_i + \rho_i E_{Vi} - (\alpha_i + \kappa_i(t) + \phi_i + \mu_i + b_i) E_i + b_{i-1} E_{i-1} \tag{21}$$

$$\frac{dS_{Vi}}{dt} = -\epsilon_i \lambda_i(t) S_{Vi} + \alpha_i E_{Vi} + \gamma_i I_{Vi} + \phi_i S_i \tag{22}$$
$$- (\rho_i + \mu_i + b_i) S_{Vi} + b_{i-1} S_{Vi-1}$$

$$\frac{dE_{Vi}}{dt} = \epsilon_i \lambda_i(t) S_{Vi} + \phi_i E_i \tag{23}$$
$$- (\alpha_i + \delta_i \kappa_i(t) + \rho_i + \mu_i + b_i) E_{Vi} + b_{i-1} E_{Vi-1}$$

$$\frac{dI_i}{dt} = \kappa_i(t) E_i - (\gamma_i + \eta_i + \mu_i + b_i) I_i + b_{i-1} I_{i-1} \tag{24}$$

$$\frac{dI_{Vi}}{dt} = \delta_i \kappa_i(t) E_{Vi} - (\gamma_i + \eta_i + \mu_i + b_i) I_{Vi} + b_{i-1} I_{Vi-1}, \tag{25}$$

$i = m$:

$$\frac{dS_m}{dt} = -\lambda_m(t)S_m + \alpha_m E_m + \gamma_m I_m + \rho_m S_{Vm} \tag{26}$$

$$- (\phi_m + \mu_m)S_m + b_{m-1}S_{m-1} \tag{27}$$

$$\frac{dE_m}{dt} = \lambda_m(t)S_m + \rho_m E_{Vm} \tag{28}$$

$$- (\alpha_m + \kappa_m(t) + \phi_m + \mu_m)E_m + b_{m-1}E_{m-1}$$

$$\frac{dS_{Vm}}{dt} = -\epsilon_m\lambda_m(t)S_{Vm} + \alpha_m E_{Vm} + \gamma_m I_{Vm} + \phi_m S_m \tag{29}$$

$$- (\rho_m + \mu_m)S_{Vm} + b_{m-1}S_{Vm-1}$$

$$\frac{dE_{Vm}}{dt} = \epsilon_m\lambda_m(t)S_{Vm} + \phi_m E_m \tag{30}$$

$$- (\alpha_m + \delta_m\kappa_m(t) + \rho_m + \mu_m)E_{Vm} + b_{m-1}E_{Vm-1}$$

$$\frac{dI_m}{dt} = \kappa_m(t)E_m - (\gamma_m + \eta_m + \mu_m)I_m + b_{m-1}I_{m-1} \tag{31}$$

$$\frac{dI_{Vm}}{dt} = \delta_m\kappa_m(t)E_{Vm} - (\gamma_m + \eta_m + \mu_m)I_{Vm} + b_{m-1}I_{Vm-1}. \tag{32}$$

All age-dependent rates are approximated by step functions with at most $m-1$ discontinuities. The effective contact rates are given by

$$\lambda_i(t) = \frac{c_{i,i'}\left[E_{i'} + E_{Vi'} + I_{i'} + I_{Vi'}\right]}{\sum_{i=1}^{m} N_i}, \tag{33}$$

The rate $\rho(a)$ incorporates the effect of not all individuals receiving all recommended doses, as well as the loss of protection induced by the vaccine. This is not the naturally acquired immunity resulting from repeated exposure to pneumococci over one's lifetime, as this is incorporated in the infection and colonization rates implicitly. If the retention of individuals into a vaccine program is represented by the rate $1 - r_i$, the length of the vaccine protection for a particular age group is p_i, and the length of time since the individuals have received their last dose l_i, then a suitable form for ρ_i is given by

$$\rho_i = \begin{cases} (1 - r_i)\left(\frac{1}{p_i - l_i}\right) & \text{for } p_i > l_i \\ 0 & \text{for } p_i \leq l_i. \end{cases} \tag{34}$$

The vaccination rate $\phi(a)$ is determined entirely by the first dose of a recommended regimen since the retention of individuals in a given regime is

taken into account by $\rho(a)$.

4 Determination of parameters

We consider 14 age classes, with finer discretizations in the younger and older age ranges since it is likely not reasonable to take a constant parameter values in the most affected age groups if the age ranges are taken too large. That is, within these ranges, the infection processes may be occurring at significantly different rates. We discuss in [22] a method to determine an appropriate discretization based on a model comparison statistic in the context of potentially available surveillance data. Here we have used data and observed trends from various sources to determine a reasonable discretization. The age classes are: (0,2 months], (2,4 months], (4,6 months], (6,24 months], (2,5 years], (5,10 years], (10,15 years], (15,50], (50,65], (65,70], (70,75], (75,80], (80,85], and (85, ∞), and are identified throughout the paper as groups numbered 1 through 14. Note that the lengths of the age ranges vary, as the dynamics of the infections are quite different among the youngest and eldest age ranges, which are most affected. In contrast, it is reasonable to consider ages 15-50 for example as exhibiting similar behavior with respect to pneumococcal diseases.

Many model parameters are readily available in census reports and the scientific literature for most populations, and some sources are suggested in Table 1. Here we discuss the information typically available for these parameters and use reasonable estimates for our computations.

Fertility and natural mortality rates are typically provided via recorded figures in census reports. Demographic rates and age distributions vary drastically when comparing more and less developed countries. The estimates of age-specific infections and reports of colonization prevalence that are used in this study, are specifically relevant to more developed countries. Therefore, the demographic rates (along with other reasonable epidemiological parameters) shown in Table 2 are consistent with a population in a developed country, producing an essentially constant population with a stable age distribution. Later, we investigate the effect of an increased fertility rate, such that the population is exponentially growing and a higher proportion of the population are in the younger age classes.

There are many parameters, however, that are not readily available in literature, such as effective contact rates and mean infection rates. It is worthwhile to note that these rates, along with the number of individuals in each epidemiological stage, determine the age-specific force of infection and therefore, the horizontal spread of infection. The estimation of these rates from surveillance data is discussed in [22]. However, reports of age-specific infections are available via the Australian NNDS website [6]. These,

Table 1: Available parameters for discrete age-structured model with 14 age classes, along with sources where parameter values may typically be found, shown in the top portion of the table. The values shown for parameters denoted by a * have not been fixed according to any particular source.

$f(a)$	Demographic/census reports*
$\mu(a)$	Demographic/census reports*
$\eta(a)$	[16], [17],[18]
$\alpha(a)$	[4]

Table 2: Typically known parameter values for the structured model with 14 age classes used in simulations. Parameter values are not specific to any given population, but are reasonable for a developed country.

f_1 0	f_2 0	f_3 0	f_4 0	f_5 0	f_6 0	f_7 0
f_8 0.002	f_9 0	f_{10} 0	f_{11} 0	f_{12} 0	f_{13} 0	f_{14} 0
μ_1 $3.889e^{-4}$	μ_2 $3.889e^{-4}$	μ_3 $3.889e^{-4}$	μ_4 $3.889e^{-4}$	μ_5 $1.112e^{-5}$	μ_6 $1.112e^{-5}$	μ_7 $1.112e^{-5}$
μ_8 $1.3e^{-5}$	μ_9 $4e^{-4}$	μ_{10} 0.0075	μ_{11} 0.0075	μ_{12} 0.0075	μ_{13} 0.0075	μ_{14} 0.0075
α_1 $\frac{1}{8}$	α_2 $\frac{1}{6}$	α_3 $\frac{1}{3}$	α_4 1	α_5 1	α_6 $\frac{4.5}{3}$	α_7 $\frac{4.5}{3}$
α_8 $\frac{4.5}{3}$	α_9 $\frac{4.5}{3}$	α_{10} $\frac{4.5}{3}$	α_{11} $\frac{4.5}{3}$	α_{12} $\frac{4.5}{3}$	α_{13} $\frac{4.5}{3}$	α_{14} $\frac{4.5}{3}$
η_1 0.8	η_2 0.6	η_3 0.4	η_4 0.2	η_5 0.01	η_6 0.02	η_7 0.05
η_8 0.09	η_9 0.1	η_{10} 0.12	η_{11} 0.2	η_{12} 0.35	η_{13} 0.4	η_{14} 0.4

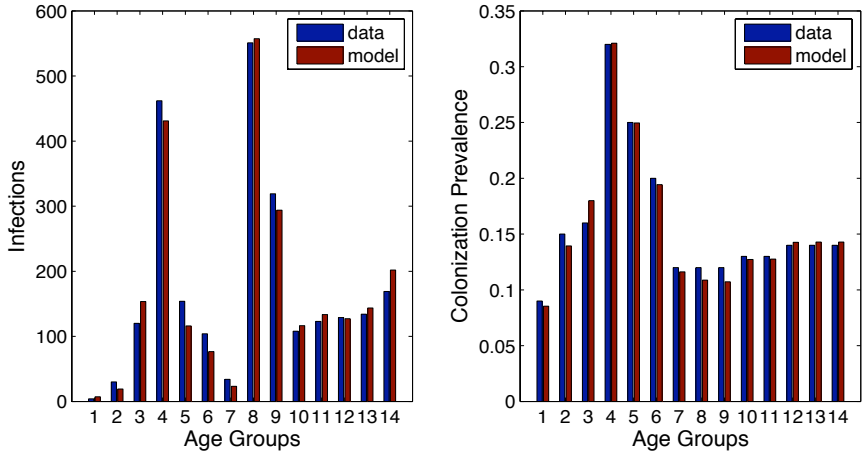

Figure 2: Model calculations of age-specific infections during one year and colonization prevalence profiles compared to infection data from the Australian NNDS [6], and colonization estimates reasonable for developed countries.

together with reasonable estimates of colonization prevalences gathered from various sources (such as [14], [15], [1]), allow us to estimate reasonable values for the mean infection rates and constant age-specific force of infection, as given in Table 3. Calculating the annual infections for each age group and the colonization prevalence from the steady state solution of the model, we observe agreement between the compiled 'data' and the model with the chosen parameters (Figure 2).

It is reasonable to take the force of infection as constant if the infections are endemic and there is no vaccine being administered. This approach is outlined in [9], which is a slightly modified version of the more general approach taken in [19] and [8]. In this case, the vaccination of elderly risk groups is unchanged before and after the childhood vaccination program considered is implemented, and therefore the force of infection is unaffected. A contact matrix, based on the assumption of proportionate mixing (in which individuals mix according to their activity levels), can then be calculated following the procedure described in [9]. The lack of clear estimates for recovery rates in the literature, along with our previous efforts in the unstructured ODE model [21] which has shown that the value of this rate does not affect the values of the other unknown rates, suggests that it is reasonable to fix the recovery rates at 1 $\frac{1}{\text{month}}$ for all age classes.

Table 3: Parameter values that are typically unknown for the 14-age class structured model that were used in simulations. These values give good agreement with observed data, shown in Figure 2.

λ_1	λ_2	λ_3	λ_4	λ_5	λ_6	λ_7
0.07	0.072	0.08	0.13	0.33	0.24	0.13
λ_8	λ_9	λ_{10}	λ_{11}	λ_{12}	λ_{13}	λ_{14}
0.183	0.1802	0.2193	0.2193	0.25	0.25	0.25
κ_1	κ_2	κ_3	κ_4	κ_5	κ_6	κ_7
$2e^{-4}$	$3.2e^{-4}$	$2e^{-3}$	$3.5e^{-4}$	$6e^{-5}$	$3e^{-5}$	$1.5e^{-5}$
κ_8	κ_9	κ_{10}	κ_{11}	κ_{12}	κ_{13}	κ_{14}
$4.8e^{-5}$	$6.3e^{-5}$	$1.1e^{-4}$	$2e^{-4}$	$2e^{-4}$	$2.8e^{-4}$	$3e^{-4}$

Vaccine efficacy studies, which are done before licensing of a vaccine and certainly before widespread implementation, most often report the expected protection provided to risk groups. Usually some measure of the duration of protection is also reported. Once a fraction of the population has been given the vaccine, the protection induced typically differs slightly from that reported in studies. Therefore, when studying the vaccine impact theoretically, ranges containing these reported values should be used. Before implementation, the effect of various vaccination rates on morbidity or whatever end point is of interest, should be studied. After implementation, the actual vaccination rates obtained are usually available via public health departments.

Since we are considering the effects of childhood vaccination in this study, we include but do not specifically study the vaccination of older risk groups by the polysaccharide vaccine (PPV23). The conjugate vaccine (PCV7) is recommended for children at the ages of 2, 4, and 6 months for a 3-dose regimen in the US and Australia. In this formulation, ϕ_2 reflects the fraction of children effectively given their first dose, and the retention of children in the vaccine program is incorporated into the rates ρ_3 and ρ_4. Studies of nasopharyngeal carriage do not consistently support a significant *overall* reduction upon immunization by the conjugate vaccine. However, to illustrate the impact of both aspects of protection, we include this effect by taking $\epsilon_i < 1$ in the younger age classes. This is to study the potential effect of other vaccines in development which could significantly reduce colonization in children, affecting the overall infection dynamics in the population. So the parameters we refer to as a 'standard' childhood vaccine program (shown

Table 4: Vaccine parameters used to represent a 'standard' childhood immunization program, and also the vaccination of older risk groups by PPV23. Variations from these parameters in the younger age groups will be used to explore the effects of different vaccination strategies. Efficacy parameters for the younger age classes are specified in each numerical solution shown in Sections 5 and 6.

ϕ_1	ϕ_2	ϕ_3	ϕ_4	ϕ_5	ϕ_6	ϕ_7
0	0.9	0	0	0	0	0
ϕ_8	ϕ_9	ϕ_{10}	ϕ_{11}	ϕ_{12}	ϕ_{13}	ϕ_{14}
0	0.001	0.03	0.03	0.03	0.03	0.03
ρ_1	ρ_2	ρ_3	ρ_4	ρ_5	ρ_6	ρ_7
0	0	0.05	0.05*0.25	1/30	0	0
ρ_8	ρ_9	ρ_{10}	ρ_{11}	ρ_{12}	ρ_{13}	ρ_{14}
0	0.01583	0.015	0.015	0.015	0.015	0.015
δ_8	δ_9	δ_{10}	δ_{11}	δ_{12}	δ_{13}	δ_{14}
1	0.8	0.6	0.6	0.6	0.6	0.6
ϵ_8	ϵ_9	ϵ_{10}	ϵ_{11}	ϵ_{12}	ϵ_{13}	ϵ_{14}
1	1	1	1	1	1	1

in Table 4) represent widespread distribution of a childhood vaccine in addition to the current adult vaccination in more developed countries. The parameters specifying the efficacies of the childhood vaccines are specified as various strategies are discussed below.

5 Effects of Vaccination

We implemented childhood vaccination in simulation studies with the model given by Equations (13) - (32) to discuss the impact of vaccines targeting infections, asymptomatic colonization, or both of these stages. We explore the effects on the age structure of the infections in a population in addition to the overall reductions in morbidity. Specifically, we examined a) the prevalence of infections and colonization as a function of age after steady state has been reached, b) the changes in the overall prevalence of both infected and colonized individuals with time, and c) the average ages of infected and colonized individuals as a function of time to describe the epidemiological picture.

Results of simulations for the immunization of children with a vaccine

targeting against infections only is considered in Figure 3. To represent such a vaccine, the parameter values $\epsilon_i = 1$ for $i = 1, ..., 5$ and $\delta_i = 0.1$ for $i = 1, ..., 5$ were chosen. The top panels of Figure 3 depict comparisons of the age-specific colonization prevalences and infections before vaccination is applied and five years afterward. Such a vaccine as considered here only has a noticeable effect on the number of infections in the age groups of those directly vaccinated, as is also seen in the bottom of Figure 3, which shows the prevalence of infections and colonization changing with time as the vaccine is administered. This is to be expected since infections are not spread through casual contacts with infected individuals, and horizontal spread of pneumococci occurs primarily through contacts with colonized individuals. Infections contribute to this horizontal spread minimally due to their relatively small prevalence in comparison with the colonization prevalence. While protection against infection is desirable in an individual, such vaccines impact only directly vaccinated groups. Therefore, these vaccines will have only limited impact in a population.

In contrast, should a childhood vaccine protect only against the colonization stage, the individual is not protected against infection in the event of being colonized. However, the potential for protecting a population is greater, as is evident in Figure 4. Vaccine efficacy parameters for this program are $\epsilon_i = 0.1, \delta_i = 1$ for $i = 1, ..., 5$. A reduction in colonization prevalence following implementation of this vaccine is shown to result in a corresponding reduction in infections (Figure 4, top panels). Further, a marked decrease in infections (and colonized individuals) can be seen in age groups that are not directly immunized by the vaccine considered. Interestingly, the greatest impact on the overall age-structure of the infections is in the infection stage, as demonstrated in the bottom panels of Figure 4 . This supports vaccines targeting colonization as having a significant impact on the dynamics of infections within a population. A direct comparison between these two different strategies can be seen in Figure 5. Although both vaccines have the same 'efficacy' (90% in vaccinated classes), the impact of that which targets colonization is greater in the population as a whole, resulting in less infections in nearly every age class.

More realistically, a vaccine may be able to protect against both, although not as effectively as was considered in the two previous scenarios. Figure 6 depicts a comparison of the impact of a less effective combination vaccine - one which protects against both stages - and the vaccine which strongly protects against colonization only. The combination vaccine protects much less efficiently against both stages as considered previously with parameter values $\epsilon_i = 0.5$ and $\delta_i = 0.3$ for $i = 1, ..., 5$. The less effective

combination vaccine can potentially achieve reductions in morbidity that are comparable to the more effective single vaccine as can be seen in Figure 6. It is important to note that such effects cannot be achieved without protecting against the colonization stage, which most significantly impacts the horizontal spread of the infections.

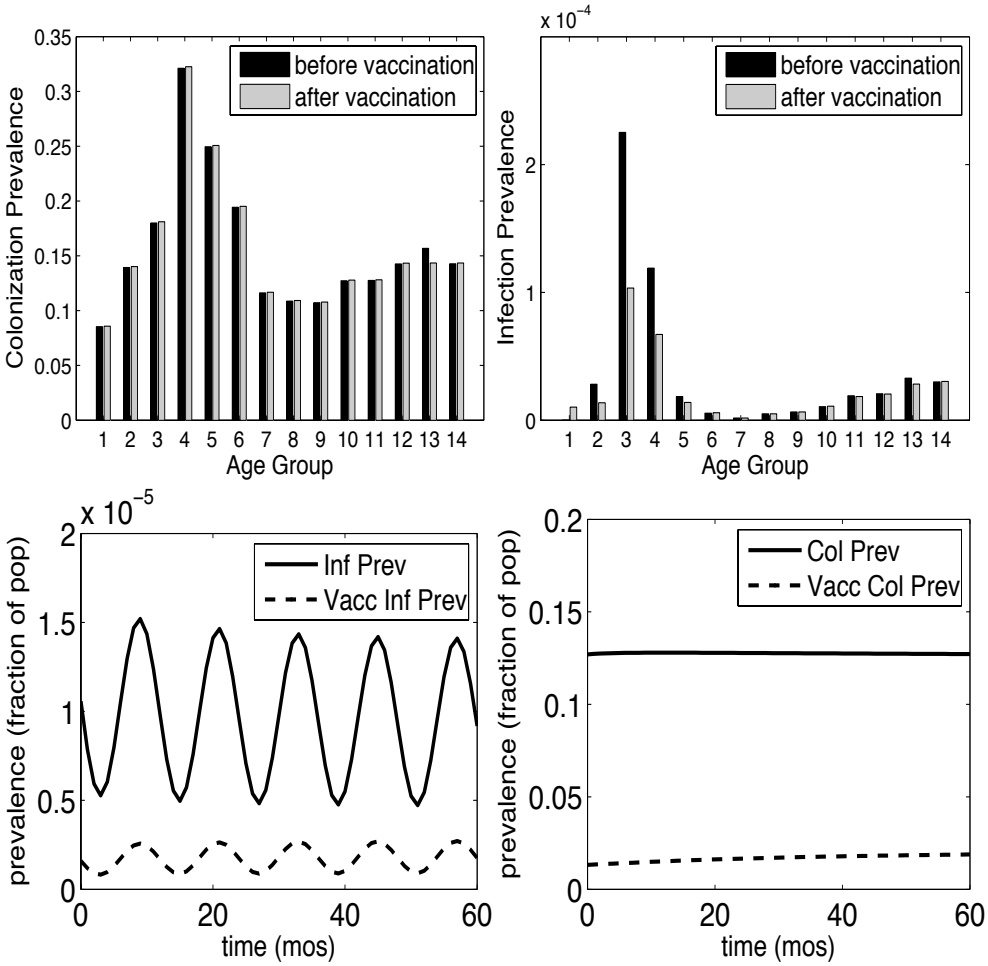

Figure 3: Infection and colonization prevalences before and after a vaccine is implemented which targets the infection stage only (top panels). Infection and colonization prevalences as vaccination (targeting infections only) is applied (bottom panels).

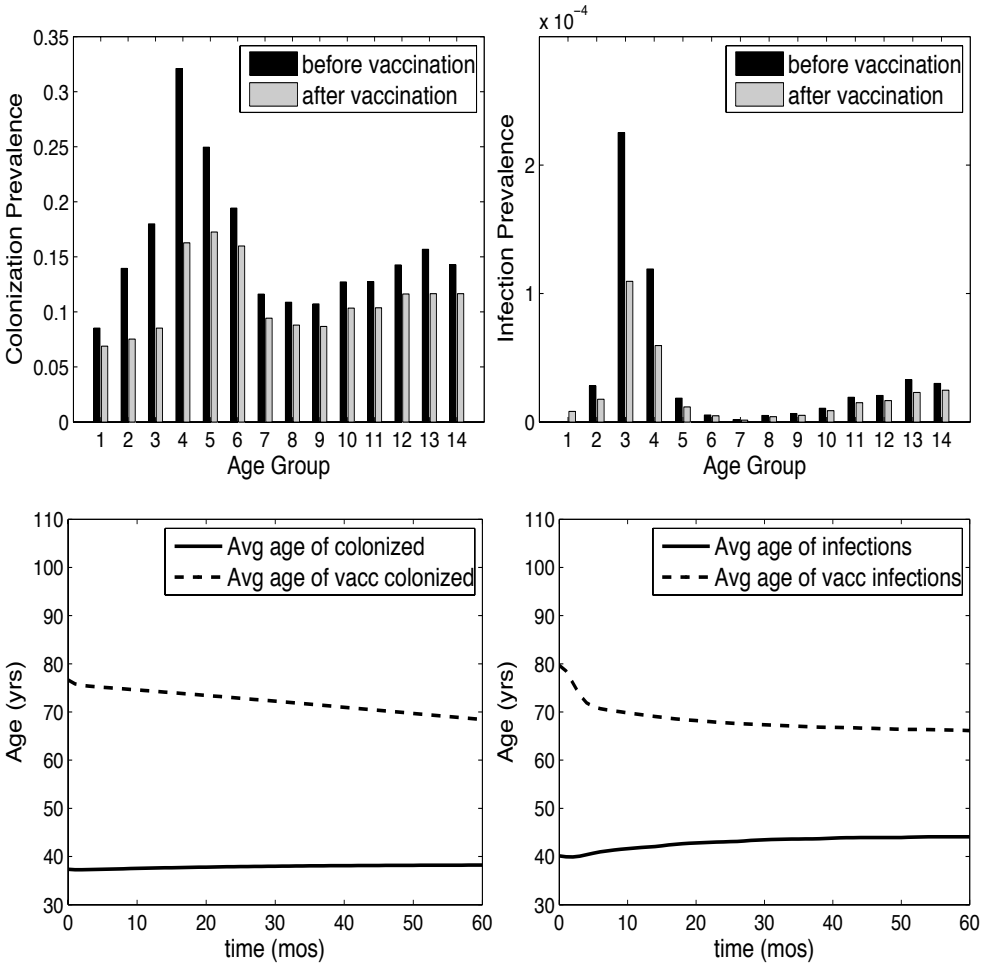

Figure 4: Infection and colonization prevalences before and after a vaccine is implemented which targets the colonization stage only (top panels). The average ages of colonization and infection as vaccination (targeting colonization only) is applied (bottom panels).

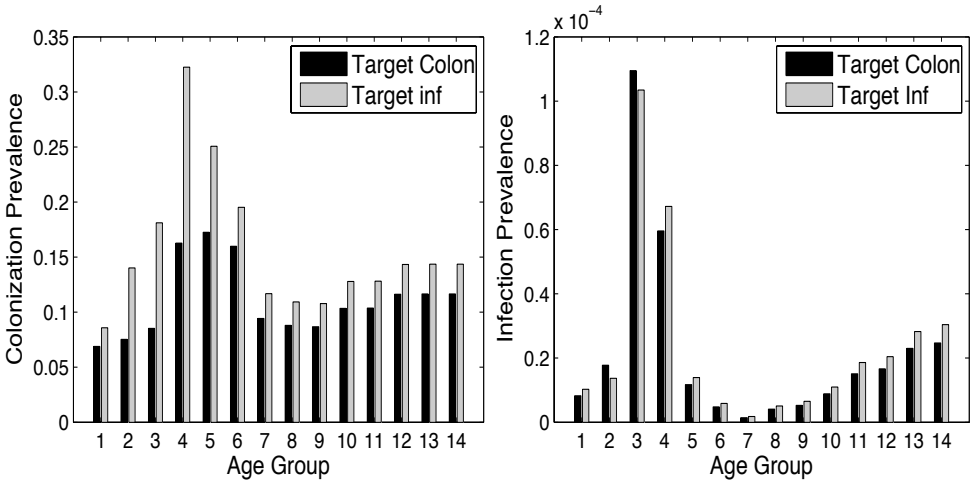

Figure 5: A comparison of the overall impact of vaccines targeting only infections and only colonization.

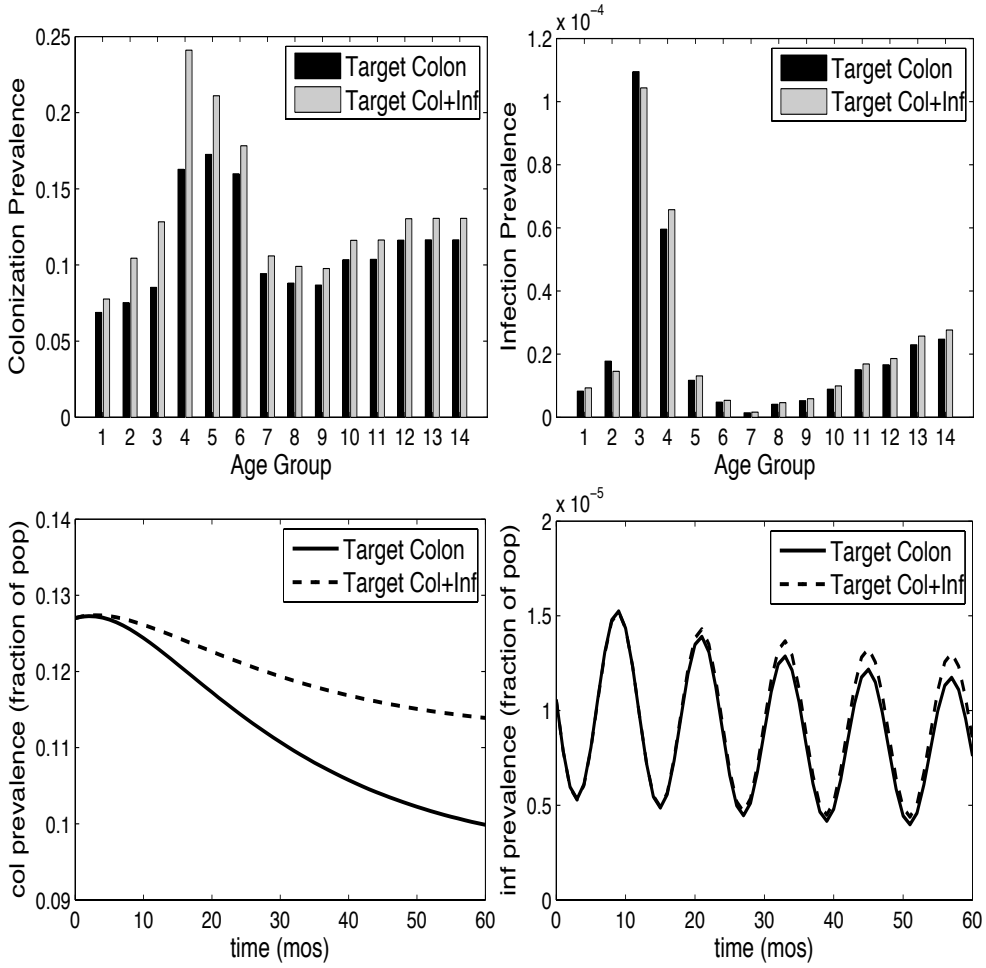

Figure 6: A comparison of the overall impact of vaccines targeting only colonization and both infection and colonization.

6 Vaccine Strategies

We demonstrate the ways in which this model combined with the computational approach used here can aid in the design of vaccine strategies. Namely, we highlight that factors in an immunization program such as target groups and the number of doses recommended, which are readily determined by public officials, can be manipulated easily in this framework. The effects of hypothetical programs may then be quantified in terms of overall disease burden and fatality as well as any possible changes in the age groups affected. We also demonstrate that the results are sensitive to the knowledge of the population studied, as changing the demographics drastically changes the effect that a given immunization program may have on disease dynamics.

If the duration of protection is increased, by decreasing ρ for age classes 5 and 6, we see a distinctive reduction in these age classes - specifically when compared with the prevalences under the standard vaccination program (Figure 7). We can also see the impact of this reduction in other age classes, an effect which is likely due to the reduction of nasopharyngeal carriage in these groups. Similarly, if the duration of protection is decreased, or ρ is increased, the increase in infections and colonization in other age groups can be primarily attributed to the increase in carriage in the younger age groups. This kind of study can be used to study the potential benefits of prescribing an additional dose in a vaccine program, provided that it is known how the older age groups respond to the vaccine.

The current vaccination rate may be unrealistically high for some populations, and the increase in prevalence as a result of lesser vaccination rates are shown in Figure 8. It should be noted that the overall incidence rates are never decreased enough to suggest that eradication is a possibility, and that the reduction of infections is the best outcome in this parameter regime. The average ages of infected and colonized individuals (not shown) manifested a similar but inverse relationship, such that as less children were vaccinated the average ages decreased. Thus, a higher infection age appears to be indicative of a lower prevalence, and not a change in risk groups.

If the fertility rates are doubled, indicating a growing population size as well as a changed age structure of the population, the 'standard' vaccine appears to be ineffective. The prevalences before and after vaccination are either of comparable magnitude for each age class or increase, with the exception of groups 3 and 4 (Figure 9). The average ages of infected and colonized individuals also decrease, indicating that children are being afflicted at a greater rate than they can be effectively protected through vaccination. This suggests that the demographic information of the population in ques-

tion is imperative when designing a vaccine program, especially since the standard parameters used here represent a program that is more effective than any vaccine(s) currently available.

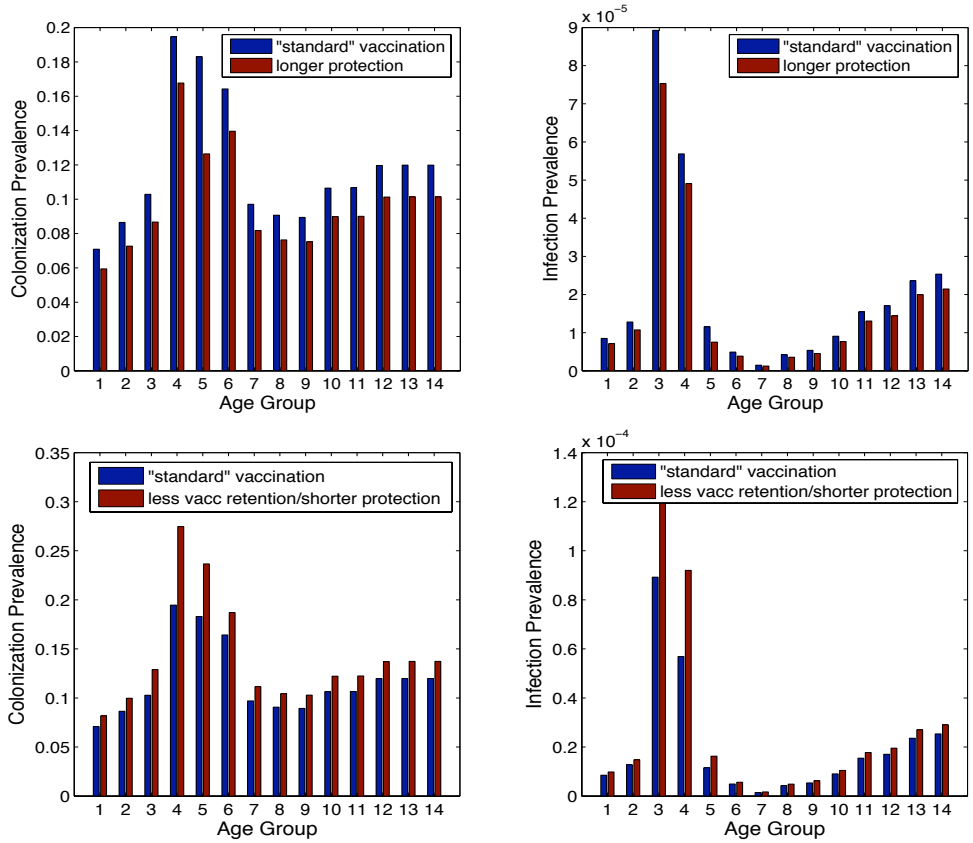

Figure 7: Infection and colonization prevalences when childhood vaccination is implemented according to the parameters in Table 4, as compared to a vaccine with a longer duration of protection (lower ρ) (shown in the top panel), or as compared to a vaccine with a shorter duration of protection (higher ρ) (bottom panel). A lower ρ could also indicate decreased retention in multi-dose immunization programs.

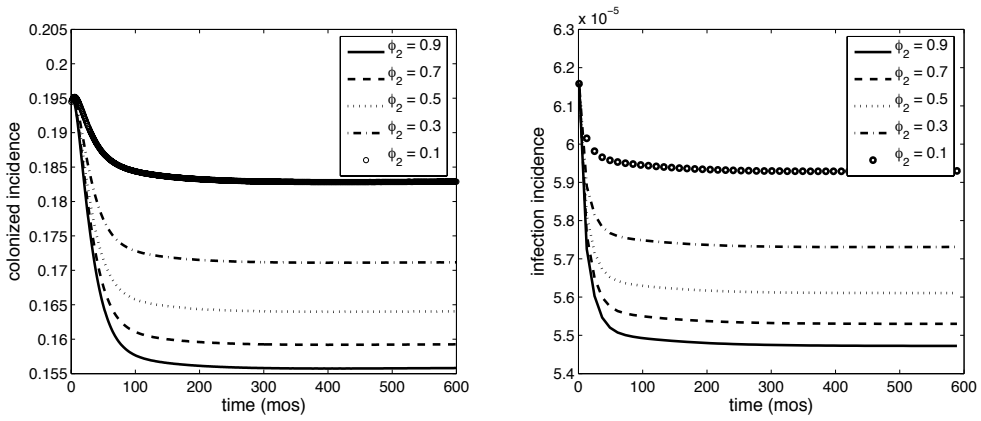

Figure 8: Colonization and infection incidences as a function of time for fixed vaccination rates ϕ.

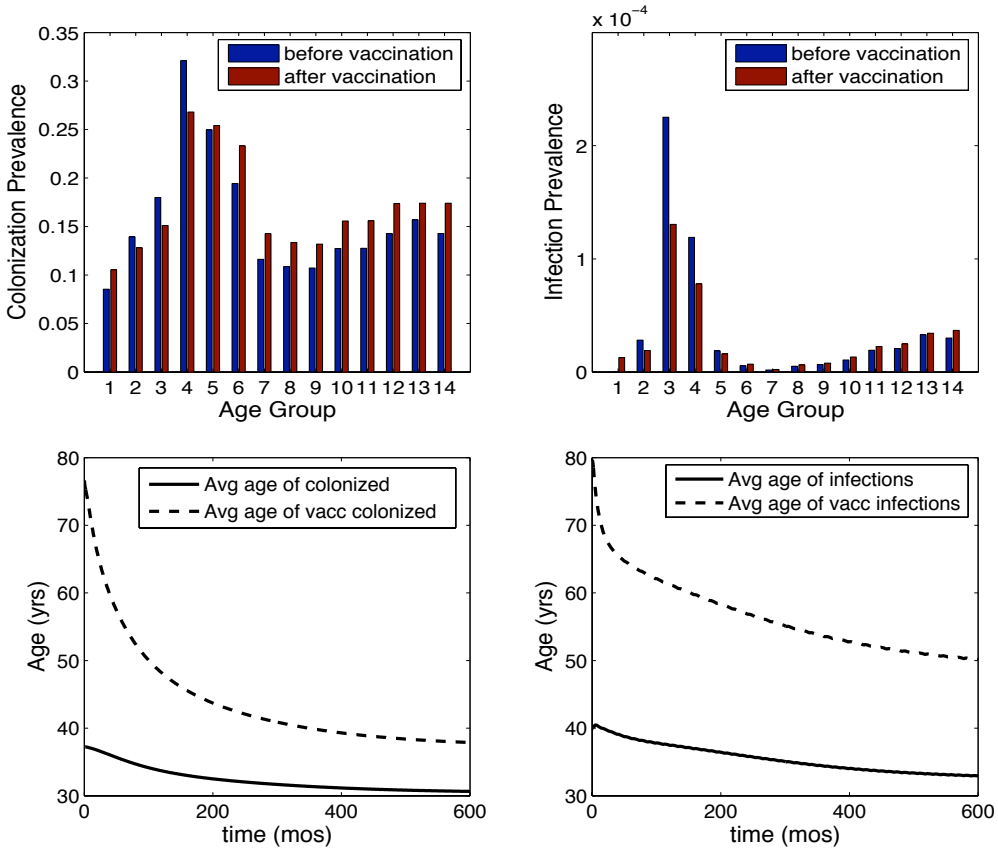

Figure 9: The age-specific infection and colonization prevalences before and after standard vaccination if the fertility rates are doubled (top panel). The bottom panels contain the average ages of infected and colonized individuals as the vaccine program is implemented in an exponentially growing population.

7 Summary and concluding remarks

We have formulated an age-structured epidemiological model that facilitates the aggregation of key age groups. Making use of realistic estimates for infection and colonization prevalences, we have estimated the force of infection for each class, and estimated a contact matrix, allowing for the numerical evaluation of a childhood vaccine strategy. The parameters here are not specific to any particular population, but are generally representative of more developed countries such as the US and Australia.

As vaccines are being developed to protect against pneumococcal infections, it is important to understand the impact of targeting against both epidemiological stages that play a role in the dynamics of these infections. We have shown that targeting colonization has the greatest potential for population-wide impact. Although a protective effect in the colonization stage has potentially substantial benefits to the overall picture of morbidity and mortality in pneumococcal infections, it is also thought that decreasing the colonization induces a selective pressure for pneumococci to become more invasive. While this may not be necessarily the case, widely inhibiting the colonization of vaccine-included serotypes provides an opportunity for non-included serotypes, which could cause serious infection. This could potentially reduce the protection against infection, rendering the vaccine less effective depending on the balance of these two effects. After widespread immunization of children by PCV7 in Australia (as discussed in [21]), initial mathematical modeling studies suggest the protective effect of the vaccine appears to be waning in the years following the initial implementation (provided no substantial change in coverage occurred). However, with the information in the data available the reason for this cannot be concluded, but the results clearly suggest the need for further examination. An additional concern may be that the reduction of colonization in younger children may result in the delayed development of adaptive immunity to *S. pneumoniae*, the effects of which are unclear, but have the potential to change the age-structure of the infections. These concerns warrant further investigations as vaccine development progresses.

The modeling framework used here can be used as a public health tool to investigate aspects of vaccination such as the duration of protection, retention in multi-dose programs, and changes in vaccination coverage obtained. Simulations show that increased length of vaccine protection significantly impacts the prevalence of the infections in children, and noticeably also that in adults. Should the response of older children to the proposed vaccines be known, this type of study could be used to quantify the benefit of

expanding the groups for which the vaccine is recommended, or potentially prescribing an additional dose as part of a given strategy. The variations in vaccine coverage that were explored implied different levels of morbidity, but not a significant change in behavior, that is, the infections (and colonization) reached an endemic state each time. Thus, any vaccine that is comparably effective as that represented by the 'standard' set of parameters will only have a limited impact. This type of study can be used to theoretically quantify the impact of any prevention initiatives for any infectious disease.

Finally, an increase in fertility was shown to have a tremendous effect on the landscape of pneumococcal infections, as children are colonized and infected either at the same or greater extent than they are effectively protected by vaccination. The lack of reduction of colonization and infection prevalences in children are mirrored in the older age groups, who are affected by their younger counterparts comparable to prevaccine scenarios. This suggests that demographic information of the vaccinated population is crucial, as erroneous information on the structure of the population could lead to prescribing ineffective vaccine strategies.

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