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A MATHEMATICAL MODEL FOR THE SPREAD OF 
STREPTOCOCCUS PNEUMONIAE WITH TRANSMISSION DUE 
TO SEQUENCE TYPE

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Abstract. This paper discusses a simple mathematical model to describe the spread of Streptococcus pneumoniae. We suppose that the transmission of the bacterium is determined by multi-locus sequence type. The model includes vaccination and is designed to examine what happens in a vaccinated population if MLSTs can exist as both vaccine and non-vaccine serotypes with capsular switching possible from the former to the latter.

We start off with a discussion of Streptococcus pneumoniae and a review of previous work. We propose a simple mathematical model with two sequence types and then perform an equilibrium and (global) stability analysis on the model. We show that in general there are only three equilibria, the carriage-free equilibrium and two carriage equilibria. If the effective reproduction number $R_e$ is less than or equal to one, then the carriage will die out. If $R_e > 1$, then the carriage will tend to the carriage equilibrium corresponding to the multi-locus sequence type with the largest transmission parameter. In the case where both multi-locus sequence types have the same transmission parameter then there is a line of carriage equilibria. Provided that carriage is initially present then as time progresses the carriage will approach a point on this line. The results generalise to many competing sequence types. Simulations with realistic parameter values confirm the analytical results.

1. Introduction. Streptococcus pneumoniae, (S. pneumoniae), or pneumococcus, is a bacterium. Over 90 different pneumococcal serotypes within 46 serogroups have been identified. Serotypes are distinct variations of S. pneumoniae. Determination of serotypes can be based on a wide variety of characteristics. Virulence varies by serotype. Similar serotypes are classified together in a serogroup. S. pneumoniae may also be classified by multi-locus sequence type (MLST). Pneumococcal sequence types are defined according to 7 house-keeping genes [12]. There are many different types of MLSTs and some MLSTs can manifest in more than one serotype. The relationship between pneumococcal serotypes and MLSTs is difficult to define as no direct correlation has been established. However, certain MLSTs have been shown to be more associated with particular serotypes than others. Some MLSTs have been shown to be associated with invasive pneumococcal disease [2, 7].

Pneumococcal strains may be spread through direct contact, or via airborne respiratory droplets such as coughs and sneezes. Children are the primary carriers.

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and the main cause of transmission [18]. Carriage rates and transmission within a population depend on several factors such as frequent close contact with other individuals, particularly young children in child-care centres and high incidence of viral respiratory tract infections [10].

Pneumococcus causes many diseases, such as otitis media, sinusitis and pneumonia. Disease is sometimes but not always preceded by nasopharyngeal colonization [14]. A more serious consequence can be invasive pneumococcal disease (IPD) such as meningitis, or septicaemia. Worldwide there are approximately one and a half million deaths per year attributable to pneumococcal disease, with an estimated 700,000 to one million in children under the age of five years [30].

Antibiotics are used to treat pneumococcal infections and disease. However, this has led to an increase in antibiotic resistant pneumococcal strains, particularly in the United States beginning in the 1990s [4]. In order to prevent pneumococcal disease and infection, pneumococcal conjugate vaccines (PCVs) were developed for use in children only, with serotypes included in these vaccines identified as those most commonly associated with resistance [9]. A vaccine with a different mechanism from PCVs, the pneumococcal polysaccharide vaccine (PPV) is used for vaccination of elderly people.

A potential problem due to the use of PCVs is that capsular switching may occur. This is where an organism that is expressing one particular serotype is able to express another serotype through large recombinatorial exchanges with a different donor serotype [8]. It is likely that in order for capsular switch to take place, an individual must become dually colonized with two different pneumococcal serotypes [6].

This paper develops a simple mathematical model to describe the spread of \emph{S. pneumoniae} in a population, and the effect of vaccination against it. Previous models have concentrated on the transmission of different serotypes in a population. However it is plausible that the genetic structure of the bacterium is also important [5]. Another factor which is important is that if a vaccine is introduced it may force the vaccine serotype (VT) to express as a non-vaccine serotype (NVT) by capsular switching. Our model aims to capture the possible consequences of this by considering the simplest possible situation where there are two MLSTs and the transmissibility of a bacterium is determined by its MLST. The results extend to the case of many competing MLSTs. The paper extends the existing literature by considering the implications of genetic effects in the spread of the pneumococcus and vaccination against it.

We shall now survey previous mathematical modeling work on \emph{S. pneumoniae}. Most of this, with the exception of the work of Lipsitch and coworkers [19, 21] and Lamb, Greenhalgh and Robertson [17] uses numerical simulation models rather than mathematical analysis. Moreover some of the models concentrate on antibiotic resistance rather than vaccination.

A key deterministic model of the carriage of \emph{S. pneumoniae} described in [19] is a set of equations that details the dynamics of two serotypes and the effect of vaccination against one of the serotypes. Individuals may either be susceptible, infected with serotype \(i\), \((i = 1,2)\), coinfected with both serotypes, vaccinated and uninfected with serotype 2 and vaccinated and infected with serotype 2. The main conclusion is that if the vaccine specifically targets only one of the two serotypes in the population, then the reduction in carriage of the VT serotype will result in an increase in carriage of the NVT serotype. However, the increase in carriage of
the NVT serotype will be smaller than the size of the reduction of VT carriage. Thus the vaccine will still ultimately be beneficial. This result is limited to the two serotype model. If two or more serotypes are considered in the population and only one is a VT serotype, one of the NVT may be able to replace the VT serotype.

Temime et al. [25] consider a deterministic compartmental model to assess the development of antibiotic resistance to penicillin. They model the spread of disease (both S. pneumoniae and Neisseria meningitidis) in a population but the emphasis is on antibiotic resistance and vaccination is not included. Temime et al. do not consider the possibility of a coexistence of strains within a population or individual. The model focuses on only one serotype and considers varying degrees of resistance. It does not allow for variation in transmission or carriage duration for different serotypes.

Temime et al. [28] extend this model to consider a vaccine effect. The population is age-structured. The model considers the interaction of the vaccine and antibiotic resistance. The results suggest a similar picture to that of the two serotype model in [19]. Temime et al. conclude that an increase in NVT pneumococcal carriage occurs as a result of the decrease in carriage of VT serotypes. However, as in [19] the increase in carriage of NVTs is not as great as the decrease in VT carriage. Thus overall carriage in the population is reduced upon introduction of PCV. Penicillin resistance is unaffected by the vaccine.

Temime et al. [27] focus on one of the severe outcomes of pneumococcal colonization, community-acquired bacterial meningitis. They consider both antibiotic resistance and a vaccine effect. The model results suggest that the length of time that a host carries a pneumococcal serotype is the crucial parameter in determining meningitis incidence from antibiotic resistant strains. Antibiotic exposure also proved to be important. The limitations of this model are that it does not consider coexistence of serotypes within an individual so the possibility of serotype replacement was not addressed. Additionally the incidence of bacterial meningitis for those aged under 2 years is underestimated.

Temime et al. [26] consider the impact of vaccination without antibiotic resistance, but considering capsular switching. Again an age-structured model is used. Capsular switch occurs amongst vaccinated hosts who are colonized with both a vaccine and a non-vaccine serotype. The natural switch process that occurs is not specifically defined in the model as Temime et al. state that among unvaccinated hosts the switches to and from vaccine strains should be balanced and it is unnecessary to have an additional mechanism to account for the switch in the model. There was a competition effect. The results suggest that capsular switch should not significantly affect the benefits obtained through the use of the vaccine, indicating that the reduction in disease incidence should not decrease due to capsular switching. This is partly because of the competition effect. The drawbacks of the model are that there is a lack of reliable data on the occurrence of capsular switch. Also the model assumes that capsular switching has no effect on the virulence of the bacterium. This may not be true.

Sutton et al. [24] expand on the ideas of Lipsitch [19] to consider those who continue to develop pneumococcal infection following colonization. The model also includes rates of waning of vaccine-induced immunity, vaccine effectiveness, reduction in the disease due to the vaccine, the proportion of susceptibles at risk and seasonality in infection. They use Australian surveillance data to investigate vaccination effects. The model performs well for 2005, but underestimates disease burden in
2006 and 2007. The authors conclude that widespread PCV immunization is likely to have an effect on the epidemiology of \textit{S. pneumoniae}.

Huang et al. [15] consider a pneumococcal transmission model which takes into account the risk of higher rates for children who attend child-care centres or who are often forced to spend time with children who attend these centres. This carriage model does not consider coexistence as children are assumed to be able to carry only one serotype at a time. In addition the model considers a closed community and does not allow new children to enter or existing children to leave. The results stress the importance of child-care centres.

Lipsitch et al. [21] revisit the issue of coexistence of serotypes in a population. This paper stresses the importance of correctly modeling the possibility of a host being able to become simultaneously invaded with more than one strain, taking into account difficulties in obtaining a second strain if already colonized and considering acquired immunity of new strains. Lipsitch et al. present the notion of a neutral null model which requires two criteria to be met in order to allow strain coexistence of two identical strains. There are two other mathematical models which describe the spread of \textit{S. pneumoniae} [1, 22] but these concentrate on antibiotic resistance rather than the effect of vaccination.

Lamb, Greenhalgh and Robertson [17] present a basic differential equation model to explore the relationship between sequence types and serotypes. There is a single sequence type and a vaccine. The sequence type is able to manifest itself in one vaccine serotype and one non-vaccine serotype. In this model $X$ denotes unvaccinated susceptibles, $T_1$ individuals carrying sequence type 1, $V$ vaccinated susceptibles, and $V_T$, vaccinated individuals carrying sequence type 1.

A constant fraction $f$ of newborn children are vaccinated. The sequence $T_1$ can express itself either as serotype 1 ($Y_1$) or serotype 2 ($Y_2$) with proportions $p T_1$ or $(1 - p) T_1$ respectively. New children are born at a constant rate $L$ and children exit the modeled population at per capita rate $u$. $\beta_1$ is the disease transmission term coefficient. The differential equations which describe the progress of the disease are:

$$ \frac{dX}{dt} = L(1 - f) u X \beta_1 (T_1 + V_T) + \gamma T_1, \quad (1) $$

$$ \frac{dT_1}{dt} = \beta_1 X (T_1 + V_T) - (\gamma + u) T_1, $$

$$ \frac{dV}{dt} = L f u V \beta_1 (T_1 + V_T) + \gamma V_T, $$

$$ \frac{dV_T}{dt} = \beta_1 V (T_1 + V_T) - (\gamma + u) V_T. $$

An equilibrium and stability analysis is carried out. It is found that if the threshold value

$$ R_{eq} = \frac{\beta_1 L}{u(\gamma + u)} $$

is less than or equal to one, then the disease will die out, but if $R_{eq} > 1$, then the carriage will tend to the unique endemic equilibrium if it is initially present. They prove the following theorem:
Theorem 1.1. (i) For $R_{01} > 1$ System 1 has only the CFE given by

$$(X, T_1, V, V_t, \xi) = (1 - f) \frac{L}{u}, 0, f \frac{L}{u}, 0$$

which is GAS as time becomes large.

(ii) For $R_{01} > 1$ there are two equilibria, the CFE and a unique CE given by

$$(X, T_1, V, V_t, \xi_1) = (1 - f) \frac{\gamma + u}{\beta_1}, (1 - f) \xi_1, f \frac{\gamma + u}{\beta_1}, f \xi_1$$

where $\xi_1 = \frac{1}{u} \frac{\gamma + u}{\beta_1}$. If there is no disease initially present, then the system goes to the CFE. If there is disease initially present, then the system goes to the CE as time gets large.

Simulations with realistic parameter values are used to confirm the analytical results.

Hence this model completely describes the situation where a single genetic type of bacterium, modeled as a single MLST, spreads in a vaccinated population. This MLST is able to express as two serotypes. However in reality there are many different genetic types of S. pneumoniae. We now develop these results to include two competing MLSTs, if the disease transmission parameter depends on MLST. We shall see later that the results generalize easily to many different genetic sequence types.

2. Mathematical Model. We build upon previous models [17, 19] to study the dynamics of two sequence types $T_1$ and $T_2$. In unvaccinated individuals for $i = 1, 2$ sequence type $i$ is associated with two serotypes in the proportions $p_i T_i$ and $(1 - p_i) T_i$ respectively. Transmission is determined by sequence type. There is a vaccine which is 100% effective in preventing carriage of serotype 1 but ineffective in preventing carriage of serotype 2. The model assumes that for $i = 1, 2$ when a bacterium of sequence type $i$ is transmitted to an unvaccinated host it manifests itself in the new host as serotype 1 with probability $p_i$ and serotype 2 with probability $1 - p_i$, possibly by capsular switch with very low levels of the other serotype. If a bacterium of either sequence type is transmitted to a vaccinated individual, then it cannot manifest itself as serotype 1 so it automatically manifests itself as serotype 2, again possibly by capsular switch.

There are $X$ susceptible individuals and $V$ vaccinated uninfected individuals at time $t$, with $T_i$ individuals carrying sequence type $i$ for $i = 1, 2$. $V_t$ denotes the number of vaccinated individuals carrying sequence type $i$. The spread of the disease is represented by the following set of differential equations:

$$\frac{dX}{dt} = L(1 - f) u X \beta_1 X (T_1 + V_t) - \beta_2 X (T_2 + V_t) + \gamma (T_1 + T_2), \quad (2a)$$

$$\frac{dT_1}{dt} = \beta_1 X (T_1 + V_t) - (\gamma + u) T_1, \quad (2b)$$

$$\frac{dT_2}{dt} = \beta_2 X (T_2 + V_t) - (\gamma + u) T_2, \quad (2c)$$

$$\frac{dV}{dt} = Lf u V \beta_1 V (T_1 + V_t) - \beta_2 V (T_2 + V_t) + \gamma (V_t + V_t), \quad (2d)$$
\[
\frac{dV_{T_1}}{dt} = \beta_1 V(T_1 + V_{T_1}) \ (\gamma + u) V_{T_1}, \tag{2e}
\]

\[
\frac{dV_{T_2}}{dt} = \beta_2 V(T_2 + V_{T_2}) \ (\gamma + u) V_{T_2}, \tag{2f}
\]

with appropriate initial conditions.

\( L \) denotes the total rate per unit time and \( u \) the per capita death rate. The equilibrium total population size is \( (L/u) \). A proportion \( f, \ 0 < f < 1 \), of newborn individuals are vaccinated. For \( i = 1, 2 \), \( \beta_i \) is the carriage transmission coefficient associated with infection with serotype \( i \). \( (1/\gamma) \) is the average infectious period, assumed the same for both sequence types and serotypes.

The effective reproduction number \( R_{ei} \) if a fraction \( f \) of newborn individuals are steadily vaccinated, is defined as the expected number of secondary carriage cases caused by a single new carriage case entering the carriage-free population at equilibrium. Here, a secondary case is a case caused by direct contact with the original infected individual. In [17] the effective reproduction number (for sequence type 1) is the threshold value

\[
R_{e1} = \frac{\beta_1 L}{u(\gamma + u)}. \tag{3}
\]

Similarly

\[
R_{e2} = \frac{\beta_2 L}{u(\gamma + u)} \tag{4}
\]

is the effective reproduction number for sequence type 2. Our next step is to look for the equilibrium solutions.

3. Equilibrium Solutions. From setting the right-hand side of the Differential Equations 2a to 2f to zero we deduce that, adding Equations 2b and 2e and then adding Equations 2c and 2f for \( i = 1, 2 \) either (a) \( T_i + V_{T_i} = 0 \) or (b) \( X + V = \frac{L-f}{\gamma + u} \).

Hence if \( \beta_1 \neq \beta_2 \), either:

(i) \( T_1 = V_{T_1} = T_2 = V_{T_2} = 0 \) giving the carriage-free equilibrium point (CFE)

\[
(X, T_1, T_2, V, V_{T_1}, V_{T_2}) = \left(\frac{L}{u}(1-f), 0, 0, \frac{L}{u} f, 0, 0 \right) .
\]

(ii) \( T_1 + V_{T_1} = 0, T_2 = V_{T_2} = 0 \) then using Theorem 1.1 we have the sequence type 1 carriage equilibrium (CE1) \( (X, T_1, T_2, V, V_{T_1}, V_{T_2}) = \left(1-f\right) \frac{\gamma + u}{\beta_1}, (1-f)\xi_1, 0, f \frac{\gamma + u}{\beta_1}, f\xi_1, 0 \). Recall that \( \xi_1 = \frac{L}{u} - \frac{-u}{\gamma + u} \). For this equilibrium to be feasible we need \( R_{e1} > 1 \). The number of individuals carrying serotypes 1 and 2 are \( Y_1 = p_1(1-f)\xi_1 \) and \( Y_2 = (1-p_1(1-f))\xi_1 \), respectively.

(iii) Similarly if \( T_1 = V_{T_1} = 0, T_2 + V_{T_2} = 0 \), then we have the sequence type 2 carriage equilibrium \( (X, T_1, T_2, V, V_{T_1}, V_{T_2}) = \left(1-f\right) \frac{\gamma + u}{\beta_2}, 0, (1-f)\xi_2, f \frac{\gamma + u}{\beta_2}, 0, f\xi_2 \) provided that \( R_{e2} > 1 \). \( \xi_2 \) is defined as \( \frac{L}{u} - \frac{-u}{\gamma + u} \). \( Y_1 = p_2(1-f)\xi_2 \) and \( Y_2 = (1-p_2(1-f))\xi_2 \).
If $\beta_1 = \beta_2 = \beta$, then case (i) is possible but provided that $R_{e1} = R_{e2} > 1$, then any solution of the form $(X, T_1, T_2, V, V_1, V_2) =$

$$(1 + f)^{\frac{\gamma + u}{\beta}}, (1 + f)^{\alpha \xi}, (1 + f)^{\gamma + u}, f(1 + \alpha)\xi$$

is a possible equilibrium solution. Here, $\xi = \frac{1}{u} - \frac{4u}{\beta}$ and $\alpha$ is any number between zero and one. These are the only equilibria. $Y_1 = (p_1 \alpha + p_2(1 - \alpha))(1 + f)\xi$ and $Y_2 = (1 - \alpha)(p_1 \alpha + p_2(1 - \alpha))(1 + f)\xi$.

Hence if $\beta_1 \neq \beta_2$, the two serotypes cannot coexist at equilibrium and there are three possible equilibria, the CFE, CE1 and CE2. If $\beta_1 = \beta_2 = \beta$, there is the CFE and a line of possible carriage equilibria connecting CE1 and CE2. Next, we shall look at the effective reproduction number.

4. The Effective Reproduction Number. In our model there are four classes of infected individuals $T_1, T_2, V_1,$ and $V_2$. The $(i, j)^{th}$ entry of the next generation matrix [11] gives the expected number of type $i$ infected individuals caused by a single newly infected type $j$ individual entering the CFE. Thus here,

$$M = \begin{pmatrix} \frac{l + (1 - f)}{u(\gamma + u)} & 0 & \frac{l + (1 - f)}{u(\gamma + u)} & 0 \\ 0 & \frac{l + (1 - f)}{u(\gamma + u)} & 0 & \frac{l + (1 - f)}{u(\gamma + u)} \\ \frac{l + (1 - f)}{u(\gamma + u)} & 0 & \frac{l + (1 - f)}{u(\gamma + u)} & 0 \\ 0 & \frac{l + (1 - f)}{u(\gamma + u)} & 0 & \frac{l + (1 - f)}{u(\gamma + u)} \end{pmatrix}$$

For example, if a single newly infected unvaccinated individual enters the CFE, then he or she is infected for average time $\frac{1}{u}$. There are $\frac{l + (1 - f)}{u}$ unvaccinated susceptible individuals in the CFE each of whom is infected at rate $\beta_1$. Thus the average number of new unvaccinated sequence type $1$ cases caused over this time is $M_{11} = \frac{\beta_1 l (1 - f)}{u(\gamma + u)}$.

The other elements of the matrix $M$ are explained similarly. The largest eigenvalue of $M$ is $R_e = \max(R_{e1}, R_{e2})$ the effective reproduction number [11].

5. Global Stability Analysis. Suppose that $\beta_1 \neq \beta_2$. Thus $R_{e1} = R_{e2} = R_e = R_{e1} = \frac{l + (1 - f)}{u(\gamma + u)}$. We have

$$\frac{d(X + V)}{dt} = L(X + V)(\beta_1 (T_1 + V_1) + \beta_2 (T_2 + V_2))$$

$$+ \gamma(T_1 + T_2 + V_1 + V_2),$$

$$\frac{dT_1 + V_1}{dt} = \beta_1 (X + V)(T_1 + V_1) + (\gamma + u)(T_1 + V_1),$$

$$\frac{dT_2 + V_2}{dt} = \beta_2 (X + V)(T_2 + V_2) + (\gamma + u)(T_2 + V_2).$$

The analysis has similarities with the single MLST model discussed by [17]. We first consider the case where $R_e = 1$.

(i) $(T_1 + V_1)(0) = (T_2 + V_2)(0)$. In this case $(T_1 + V_1)(t) = (T_2 + V_2)(t) = 0$ for all $t$. Thus $T_1 = V_1 = T_2 = V_2 = 0$ for all $t$ and from Equations 2a and 2d we deduce that $X = \frac{l + (1 - f)}{u}$ and $V = \frac{l + (1 - f)}{u}$ as $t \uparrow 1$. 

(ii) \((T_1 + V_{T_1})(0) = 0, (T_2 + V_{T_2})(0) > 0\). Then \((T_1 + V_{T_1})(t) = 0\) for all \(t\). Thus \(T_1 = V_{T_1} = 0\) for all \(t\). Theorem 1.1 then shows that \(X! \frac{L^*(f)}{u}, T_2! 0, V! \frac{L}{u}\) as \(t! 1\).

(iii) \((T_1 + V_{T_1})(0) > 0, (T_2 + V_{T_2})(0) = 0\). This is similar to (ii).

(iv) \((T_1+V_{T_1})(0) > 0, (T_2+V_{T_2})(0) > 0\). From Equations 5b and 5c it is straightforward to show that \((T_1+V_{T_1})(t) > 0\) for all \(t\). Define \(T = T_1+V_{T_1}+T_2+V_{T_2}\). If \(R_0 < 1\), choose \(\epsilon > 0\) such that \(k_0 = (\gamma + u)(R_0 - 1) + \beta_1 \epsilon < 0\). As \(N = X + V + T + \frac{L}{u}\) as \(t! 1\), there exists a \(t_0\) such that \(X + V + \frac{L}{u} + \epsilon\) for \(t! t_0\). Since \(\beta_1 < \beta_2\)

\[
\frac{dT}{dt} \beta_1 \frac{L}{u} + \epsilon \ T \ (\gamma + u)T = k_0T.
\]

Therefore, \(0 \ T(t) T(t_0) \exp( k_0(t - t_0)) \). So, \(T(t) ! 0\) as \(t! 1\) and \(T_1, V_{T_1}, T_2\) and \(V_{T_2}\) all tend to zero as \(t\) becomes large.

In the case where \(R_0 = 1\) and \(\epsilon_1 > 0\), then there exists a \(t_1\) such that \(N + \frac{L}{u} + \epsilon_1 = \frac{L}{u} = \frac{L}{u} + \epsilon_1\) for \(t! t_1\).

\[
\frac{dT}{dt} \beta_1 (N - T) T \ (\gamma + u)T \ \beta_3 \frac{L}{u} + \epsilon_1 \ T \ T \ (\gamma + u)T = \beta_1 (\epsilon_1 - T)T. (6)
\]

Hence, for \(T = 2\epsilon_1, \frac{dT}{dt} = \beta_1 \epsilon_1 T\). It is straightforward to show that there exists a \(t_2 = t_1\) such that for \(t! t_2, T = 3\epsilon_1\). But \(\epsilon_1\) is arbitrary. Hence, here also \(T(t) ! 0\) as \(t! 1\).

Since \(X + V = N - T, X + V! \frac{L}{u}\) as \(t! 1\). Hence, from Equation 2a given \(\epsilon_2 > 0\) there exists a \(t_3\) such that for \(t! t_3\)

\[
\frac{dX}{dt} < L(1 - f) \ uX + \epsilon_2.
\]

Therefore, using standard comparison theorems [3] we conclude that for \(t! t_3\), \(X\) is bounded above by \(X_0(t)\) where \(X_0(t)\) is the solution to

\[
\frac{dX_0}{dt} = L(1 - f) \ uX_0 + \epsilon_2.
\]

and \(X_0(t_3) = X(t_3)\). As \(X_0(t) + \frac{(1 - f)k + z}{u}\) as \(t! 1\) we deduce that \(\limsup_{t \to 1} X(t) + \frac{(1 - f)k + z}{u}\). Similarly, \(\liminf_{t \to 1} X(t) + \frac{(1 - f)k + z}{u}\). As \(\epsilon_2\) is arbitrary \(X! (1 - f)\frac{L}{u}\) and \(V = X + V\) as \(t! 1\). So, for \(R_0 > 1\) the system approaches the CFE.

Next consider the case \(R_0 > 1\).

(i) \((T_1 + V_{T_1})(0) = (T_2 + V_{T_2})(0)\). As in Case (i) above the system approaches the CFE.

(ii) \((T_1 + V_{T_1})(0) = 0, (T_2 + V_{T_2})(0) > 0\). Then \(T_1 = V_{T_1} = 0\) for all \(t\). Theorem 1.1 shows that if \(R_{e_2} = 1\), then the system approaches the CFE whereas if \(R_{e_2} > 1\), the system approaches CE2.

(iii) \((T_1 + V_{T_1})(0) > 0, (T_2 + V_{T_2})(0) = 0\). This is the same as Case (ii) with the sequence types switched over.

(iv) \((T_1 + V_{T_1})(0) > 0, (T_2 + V_{T_2})(0) > 0\).
(1) $\beta_1 \leq \beta_2$. As $t \rightarrow 1$ the system approaches CE1 if $\beta_1 > \beta_2$, or CE2 if $\beta_2 > \beta_1$. The proof is given in Appendix 1.

(2) $\beta_1 = \beta_2$. In this case $X, T_1, T_2, V, V_{T_1}$, and $V_{T_2}$ approach the equilibrium point where

$$X = (1 - f) \frac{L}{u} \xi, \quad T_1 = (1 - f) \alpha \xi, \quad T_2 = (1 - f)(1 - \alpha) \xi, \quad V = f \frac{L}{u} \xi,$$

$$V_{T_1} = f \alpha \xi \quad \text{and} \quad V_{T_2} = f(1 - \alpha) \xi, \quad \text{for} \quad \alpha = \frac{1}{1 + k} \quad \text{and} \quad 0 < \alpha < 1.$$ 

Here, $\xi = \frac{L}{u} \left( \frac{1}{T_2(0) + V_{T_2}(0)} \right)$. The proof is given in Appendix 2.

To summarise, we have shown the following results [16]:

Theorem 5.1. (i) When $R_e > 1$ the CFE is the only possible equilibrium. The carriage will tend to the CFE in the long-term.

(ii) (1) When $R_e > 1$, if there are no hosts carrying either of the MLSTs, there will never be any hosts carrying either MLST.

(ii) (2) If $R_e = R_{e1} > 1 \quad R_{e2}$, then if there are initially hosts carrying MLST2 but not MLST1, then there will never be any hosts carrying MLST1 and the number of hosts carrying MLST2 will tend to zero. If $R_e = R_{e1} > R_{e2} > 1$, then under the same initial conditions the system will tend to CE2.

(iii) (3) If $R_{e1} > R_{e2}$ and there are initially hosts carrying MLST1, then in the long-term the system will tend to CE1.

(iv) (4) If $R_{e2} > R_{e1}$, the situation is the same with the sequence types reversed.

(v) (5) If $R_{e2} = R_{e1} > 1$, then the CE is a line of equilibria and in the long-term both MLSTs will coexist along this line if both are present initially.

It is possible to use the same techniques to extend the results to the situation where there are $n$ competing sequence types although the situation where several of the transmission coefficients are equal is complicated to express. Again the sequence type with the highest

$$R_{ei} = \frac{\beta_i L}{u(\gamma + u)} \quad i = 1, 2, \ldots, n,$$

competitively excludes the other sequence types, provided that this $R_{ei}$ value exceeds one and this sequence type is initially present. In the case where several transmission coefficients are equal, that is

$$\beta_1 = \beta_2 = \ldots = \beta_q = \beta \quad (q \quad n)$$

and all of the other sequence types that are initially present have strictly lower $\beta$ values then $X, T_1, T_2, \ldots, T_n, V, V_{T_1}, V_{T_2}, \ldots, V_{T_n}$, and $V_{T_n}$ approach the equilibrium point where
\[ X = (1 \ f) \frac{L}{u} \xi , \ T_1 = (1 \ f) \alpha_1 \xi , \ T_2 = (1 \ f) \alpha_2 \xi , \ldots , \ T_q = (1 \ f) \alpha_q \xi , \]

\[ T_{q+1} = \ldots = T_n = 0, \ V = f \frac{L}{u} \xi , \ V_T = f \alpha_1 \xi , \ V_{T_2} = f \alpha_2 \xi , \ldots , \ V_{T_n} = f \alpha_n \xi , \]

and \( V_{T_{q+1}} = \ldots = V_{T_n} = 0. \)

Here, \( \alpha_j = \frac{1}{\prod_{l=1}^{q} k_{lj}} \) where \( k_{lj} = \frac{T_l(0) + V_{T_l}(0)}{T_j(0) + V_{T_j}(0)} \) for \( l = 1, 2, \ldots q. \)

6. Simulations. We shall aim to use real-life parameter values in our simulations although our aim is more to illustrate the analytical results rather than to try to model any particular situation in detail. We have in mind the set of Scottish children under two years of age to model pneumococcal carriage transmission. This population contains roughly \( \bar{N} = 150,000 \) children and we assume that it is at equilibrium. We have that \( u = \frac{1}{104} \text{wk} = 9.615 \) \( 10^{-3} \text{wk} \) and \( L = u\bar{N} = 1442.31 \text{wk}. \)

In her thesis Weir [29] performs a systematic review on the average length of pneumococcal carriage for children under two years and finds \( \gamma = 0.1408/\text{wk} \) (so \( 1/\gamma = 7.1 \text{ wks} \)). Estimates for \( R_0 \) for \( S. \) pneumoniae are 1.49 [13] and 1.8 - 2.2 [31]. For illustrative purposes we take \( R_{e1} = 1.5 \) and \( R_{e2} = 1.8 \), which using Equations 3 and 4 gives \( \beta_1 = 1.5041 \) \( 10^{-6}/\text{wk} \) and \( \beta_2 = 1.8050 \) \( 10^{-6}/\text{wk} \). We also take \( f = 0.7. \) These parameters give a CFE of \( (45,000, 0, 0, 0, 0, 0, 0), \) CE1 = \( (30,000, 15,000, 0, 70,000, 35,000, 0) \) and CE2 = \( (25,000, 0, 20,000, 58,333.33, 0, 46,666.67) \).

Simulations were undertaken with a large selection of initial conditions and different parameter values. These simulations were undertaken using the numerical integration package SOLVER. In each case for \( R_0 > 1 \) the system tended to the carriage equilibrium corresponding to the largest \( R_0 \) value. For \( R_0 < 1 \) the disease always died out. This confirms our analytical results. Figure 1 shows a typical simulation with \( R_0 > 1. \) The initial values were \( X(0) = 145,900, \ T_1(0) = 2,000, \ T_2(0) = 100, \ V(0) = 0, \ V_T(0) = 2,000 \) and \( V_{T_2}(0) = 0. \)

7. Summary and Conclusions. There have been quite a few mathematical and simulation models for how \( S. \) pneumoniae will spread in a population. Some of these included vaccination. However up to now all of them have concentrated on the serotype as the key determining feature of the bacterium rather than its inner genetic material. The latter may be important as when a vaccine is introduced there may be pressure for a VT serotype to switch to an associated NVT serotype by capsular switching. It may also be important in invasive disease [5].

The model was created to examine what would occur in a population following a vaccine intervention should MLSTs be able to express as both a VT and a NVT serotype. We considered the simplest possible case of one VT serotype and a NVT serotype. The model described in [17] considered one MLST, able to express as two serotypes, in a vaccinated population. We extended this to the case of two competing MLSTs in a vaccinated population. The results extend easily to many MLSTs. The conclusions are that apart from a few special cases the MLST with
the strictly highest effective reproduction number will in the long-term competitively exclude the other MLSTs, provided that its effective reproduction number exceeds one and it is initially present. Thus with this model long-term coexistence of different MLSTs in a population was not possible.

Our model is a first step in including genetic effects into \textit{S. pneumoniae} modeling and makes many simplifications. One of these is that co-infection of an individual with more than one MLST is not possible. The model predicts that long-term coexistence of MLSTs in the population is not possible. Hence an important conclusion of our model is that in order to have coexistence of MLSTs at a population level, one of the assumptions of the model must be invalid. This could be a coinfection of an individual with more than one MLST, or some other explanation, for example stochastic effects or heterogeneity in the population. We are interested in extending this model to look at the implications of coinfection of an individual with more than one MLST. This would be a desirable and realistic development but would considerably complicate the model.

\textbf{Appendix 1} Suppose that $\beta_1 > \beta_2$. Recall that $T = T_1 + V_1 + T_2 + V_2$ and $\mathcal{N} = X + V + T$. Given $\epsilon > 0$, there exists a $t_1$ such that for $t > t_1$, $\frac{\mathcal{N}}{\mathcal{N}} < \frac{L}{\mathcal{N}} + \frac{\epsilon}{\mathcal{N}}$.

$$\frac{dT}{dt} = \beta_1 (X + V)T - (\gamma + u)T - \beta_1 \frac{L}{u} + \frac{\epsilon}{\beta_1} T - (\gamma + u) T.$$

By standard comparison theorems $T$ is bounded above by $\mathcal{T}$ where $\mathcal{T}$ is the solution to

$$\frac{d\mathcal{T}}{dt} = \beta_1 \frac{L}{u} + \frac{\epsilon}{\beta_1} \mathcal{T} - (\gamma + u) \mathcal{T}.$$
with \( T(t_1) = \overline{T}(t_1) > 0 \). But it is straightforward that

\[
\frac{(\gamma + u)(R_e 1)}{\beta_1} + \frac{\epsilon}{\beta_1} \text{ as } t \to 1.
\]

Hence, there exists a \( t_2 \) such that for \( t \to t_2 \)

\[
T \to \frac{(\gamma + u)(R_e 1)}{\beta_1} + \epsilon 1 + \frac{1}{\beta_1}.
\]

So,

\[
X + V = N \quad T = \frac{L}{u} \frac{(\gamma + u)(R_e 1)}{\beta_1} \quad 1 + \frac{1}{\beta_1} + \frac{1}{\beta_2}.
\]

Similarly for \( t_1 \),

\[
\frac{dT}{dt} = \frac{L}{u} \frac{\epsilon}{\beta_2} \quad T \to (\gamma + u) T.
\]

A similar argument shows that there exists a \( t_3 \) such that for \( t \to t_3 \)

\[
X + V \to \frac{\gamma + u}{\beta_2} + \epsilon 1 + \frac{1}{\beta_1} + \frac{1}{\beta_2}.
\]

Now there exists a \( t_4 \) such that for \( t \to t_4 \), \( X + V \to \frac{\gamma + u}{\beta_1} > 0 \). Write \( \eta = \frac{T_1 + V_{T_1}}{T_2 + V_{T_2}} \).

\( \eta \) is well-defined as \( (T_2 + V_{T_2})(t) > 0 \). Consider

\[
\frac{d\eta}{dt} = (\beta_1 \beta_2)(X + V)\eta \quad (\beta_1 \beta_2) \quad \frac{1}{2} \frac{\gamma + u}{\beta_1} \quad \text{ for } t \to t_4.
\]

We deduce that \( \eta \to 1 \) as \( t \to 1 \). Hence, \( \frac{T_2 + V_{T_2}}{T_1 + V_{T_1}} \to 0 \) as \( t \to 1 \). So given \( \epsilon > 0 \), there exists a \( t_5 \) such that \( \frac{T_2 + V_{T_2}}{T_1 + V_{T_1}} < \epsilon \), \( 8t \to t_5 \). Thus \( 0 \to \frac{V_{T_2}}{T_2 + V_{T_2}} \to 0 \) for \( t \to t_6 \) for some \( t_6 > 0 \). Hence, \( T_2 + V_{T_2} > 0 \) as \( t \to 1 \).

Given \( \epsilon > 0 \), there exists a \( t_7 > t_1 \) such that for \( t \to t_7 \), \( T_2 + V_{T_2} \to \epsilon \). For \( t \to t_7 \)

\[
\frac{1}{T_1 + V_{T_1}} \frac{d}{dt}(T_1 + V_{T_1}) = \beta_1(X + V) \quad (\gamma + u),
\]

\[
= \beta_1 \left( \frac{L}{u} \frac{T_1 + V_{T_1}}{T_2 + V_{T_2}} \right) \quad (\gamma + u),
\]

\[
\frac{\epsilon}{\beta_1} \quad T_1 \quad V_{T_1} \quad \gamma + u \quad \beta_1.
\]

A comparison theorem argument similar to the one used before shows that there exists a \( t_8 \) such that for \( t \to t_8 \)

\[
T_1 + V_{T_1} \quad \frac{L}{u} \quad \frac{\gamma + u}{\beta_1} + 1 + \frac{1}{\beta_1} \epsilon.
\]

Similarly for \( t_7 \),

\[
\frac{1}{T_1 + V_{T_1}} \frac{d}{dt}(T_1 + V_{T_1}) \quad \beta_1 \quad \frac{L}{u} \frac{\epsilon}{\beta_2} \quad T_1 \quad V_{T_1} \quad \epsilon \quad \frac{\gamma + u}{\beta_1}.
\]

so there exists a \( t_9 \) such that

\[
T_1 + V_{T_1} \quad \frac{L}{u} \quad \frac{\gamma + u}{\beta_1} \quad 2 \quad 1 + \frac{1}{\beta_2} \epsilon \quad \text{ for } t \to t_9.
\]
We deduce that \( T_1 + V T_1 \downarrow \frac{b_1}{\beta} \downarrow \downarrow \frac{u}{\gamma} \) and \( X + V = N \) \( T_1 \) \( V T_1 \) \( T_2 \) \( V T_2 \downarrow \frac{u}{\gamma} \) as \( t \uparrow 1 \).

As \( \frac{d}{dt}(X + T_1 + T_2) = L(1 \ f) \ u(X + T_1 + T_2), \)
\( X + T_1 + T_2 \downarrow \frac{(1 - t)}{u} \) as \( t \uparrow 1 \). So \( X + T_1 = (X + T_1 + T_2) \) \( T_2 \downarrow \frac{(1 - t)}{u} \) as \( t \uparrow 1 \). Similarly \( V + V T_1 \downarrow \frac{u}{\gamma} \) as \( t \uparrow 1 \).

We write \( X = (1 \ f)X, T_1 = (1 \ f)T_1, T_2 = (1 \ f)T_2, V = fV, V T_1 = fV T_1, \) and \( V T_2 = fV T_2 \). We have

\[
\frac{dX}{dt} = L \ uX \ \beta_1 X(T_1 + V T_1) + \gamma(T_1 + T_2) \ \beta_2 X(T_2 + V T_2),
\]
\[
\frac{dT_1}{dt} = \beta_1 X(T_1 + V T_1) \ (\gamma + u)T_1, \text{ for } i = 1, 2.
\]
\( \bar{X} + T_1 \downarrow \frac{u}{\gamma} \) as \( t \uparrow 1 \).

Hence, \( \frac{dT_1}{dt} \downarrow \frac{\beta_1 L \ u \ \gamma + u \beta_1}{u} \ T_1 \ (\gamma + u)T_1 = \frac{\beta_1 L \ u \ \gamma + u}{\beta_1} \ T_1 + \epsilon. \)

Given \( \epsilon > 0 \), there exists a \( t_{10} \) such that for \( t \geq t_{10} \)

\[
\frac{dT_1}{dt} \downarrow \frac{\beta_1 L \ u \ \gamma + u \beta_1}{u} \ T_1 + \epsilon,
\]

i.e. \( T_1 \downarrow \frac{\beta_1 L \ u \ \gamma + u \beta_1}{u} \ T_1 + \epsilon \). A similar argument shows that \( T_{1:1} \downarrow \frac{\beta_1 L \ u \ \gamma + u \beta_1}{u} \ T_1 \downarrow \frac{\beta_1 L \ u \ \gamma + u \beta_1}{u} \ T_1 + \epsilon \)

and as \( \epsilon \) is arbitrary we deduce that \( T_{1:1} \downarrow \frac{\beta_1 L \ u \ \gamma + u \beta_1}{u} \ T_1 \downarrow \frac{u}{\gamma} \) as \( t \uparrow 1 \). Hence, \( T_1 \downarrow \frac{\beta_1 L \ u \ \gamma + u \beta_1}{u} \ T_1 \downarrow \frac{u}{\gamma} \) as \( t \uparrow 1 \).

Appendix 2 From Appendix 1, \( X + V \downarrow \frac{\beta_1 L \ u \ \gamma + u \beta_1}{u} \ T_1 \downarrow \frac{u}{\gamma} \) and \( \eta = \frac{T_{1:1} + V T_1}{T_{1:1} + V T_2} \) is a constant \( \frac{u}{\beta_1} \) say. The equations become

\[
\frac{dX}{dt} = L(1 \ f) \ uX \ \beta X(T_1 + T_2 + V T_1 + V T_2) + \gamma(T_1 + T_2),
\]
\[
\frac{dT_1}{dt} = \beta X(T_1 + T_2 + V T_1 + V T_2) \ (\gamma + u)(T_1 + T_2),
\]
\[
\frac{dV}{dt} = L f \ uV \ \beta V(T_1 + T_2 + V T_1 + V T_2) + \gamma(V T_1 + V T_2),
\]
\[
\frac{dV}{dt} = \beta V(T_1 + T_2 + V T_1 + V T_2) \ (\gamma + u)(V T_1 + V T_2).
\]

From Theorem 1.1 we deduce that \( X, T_1, T_2, V, V T_1, \) and \( V T_2 \) tend to the surface where\( T_1 + T_2 = (1 \ f)\xi, X = (1 \ f)(\frac{\beta_1}{\beta_2} \xi), V T_1 + V T_2 = f\xi \) and \( V = f(\frac{\beta_1}{\beta_2} \xi) \) as \( t \uparrow 1 \).
If $T_1 = \alpha_1(1 - f)\xi$ and $V_1 = \alpha_2(1 - f)\xi$, then $0 < \alpha_1, \alpha_2 < 1$. $T_2 = (1 - \alpha_1)(1 - f)\xi$ and $V_2 = (1 - \alpha_2)(1 - f)\xi$. It is straightforward to show that $T_2(t) > 0$ for $t > 0$. Now

$$\frac{dT_1}{dT_2} = \frac{T_1T_2}{T_2^2} = \frac{\beta X(T_1 + V_1)}{T_2}$$

There exists $t_0 > 0$ and $\epsilon > 0$ such that for $t \geq t_0, \min(X, T_1 + V_1) \geq \epsilon > 0$ and $T_2 < \frac{\beta \epsilon}{k}$. Thus if $\frac{k}{\beta \epsilon} > 1$, then $\frac{T_1}{T_2}$ is decreasing and if $\frac{k}{\beta \epsilon} < 1$, then $\frac{T_1}{T_2}$ is increasing. Thus $\frac{T_1}{T_2} = \frac{1}{k} + \frac{1}{k}$ as $t \to 1$. Hence, $\frac{T_1}{T_2} \to \frac{1}{k}$ as $t \to 1$ and $\alpha_1 \to \frac{1}{k}$ as $t \to 1$. Similarly $\alpha_2 \to \frac{1}{k}$ as $t \to 1$. The result follows.

REFERENCES


A MATHEMATICAL MODEL FOR STREPTOCOCCUS PNEUMONIAE


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