A mathematical model for the spread of *Streptococcus pneumoniae* with transmission dependent on serotype

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We examine a mathematical model for the transmission of *Streptococcus Pneumoniae* amongst young children when the carriage transmission coefficient depends on the serotype. Carriage means pneumococcal colonization. There are two sequence types (STs) spreading in a population each of which can be expressed as one of two serotypes. We derive the differential equation model for the carriage spread and perform an equilibrium and global stability analysis on it. A key parameter is the effective reproduction number $R_e$. For $R_e \leq 1$, there is only the carriage-free equilibrium (CFE) and the carriage will die out whatever be the starting values. For $R_e > 1$, unless the effective reproduction numbers of the two STs are equal, in addition to the CFE there are two carriage equilibria, one for each ST. If the ST with the largest effective reproduction number is initially present, then in the long-term the carriage will tend to the corresponding equilibrium.

**Keywords:** Steptococcus pneumoniae; equilibrium; global stability analysis; effective reproduction number; serotype

**AMS Subject Classification:** 34D05; 92B05; 34D20; 34D23; 37C75

1. Introduction

This paper is concerned with mathematical modelling of *Streptococcus pneumoniae* (*S. pneumoniae*) when the transmission is dependent on the serotype. The bacterium *S. pneumoniae* was simultaneously discovered in 1881 by Louis Pasteur and George Miller Sternberg. Pneumococcal serotypes are defined according to the structure of the polysaccharide capsule which encases the bacterium. This polysaccharide capsule protects the bacterium from the immune system, enabling it to cause infection and disease. The serotype is a known virulence factor with the level of virulence varying by the serotype [26]. Certain serotypes have similar antigens and are classified together in a serogroup. Currently at least 46 serogroups containing more than 90 distinct pneumococcal serotypes are known.

*S. pneumoniae* may also be categorized by the genetic sequence type (ST). This refers to the DNA structure of the bacterium. In practice, this can be identified by using the multi-locus sequence type to categorize the genetic material. Seven house-keeping genes within the genetic

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material are used to identify the pneumococcal ST [16]. These genes are relatively stable over time and hence used to determine the ST.

As the serotype is the outer bacterial coating and the ST is the inner genetic material it is not clear a priori whether these two methods of classifying the pneumococcus bacterium should be related. However, this does appear to be the case. It has been demonstrated that some STs are more associated with particular serotypes than others [4,22]. Brueggemann et al. [4], Clarke et al. [8] and Beall et al. [2] show that there is a correlation between invasive pneumococcal STs and invasive pneumococcal serotypes.

Pneumococcus is spread via coughs and sneezes or direct contact. Pneumococcus initially invades the body by colonizing the nasopharynx. As a common practice, we refer to (possibly asymptomatic) colonization with pneumococcus as carriage as this may or may not cause physical infection or disease symptoms. Pneumococcus can cause a wide range of infections such as ear infections, sinusitis and pneumonia. It is the most common cause of serious pneumonia [31]. More serious consequences can be invasive pneumococcal disease (IPD), such as meningitis and septicemia, where the virus invades further into the body. The main cause of pneumococcus transmission in a population is usually children. Carriage rates and spread are influenced by factors such as a frequent close contact with young children, especially those in day care centres, and high incidence of viral respiratory tract infections.

Although over 90 serotypes exist the majority of disease is attributable to around 20–30 serotypes [16]. Salisbury et al. [36] show that approximately two thirds of adult pneumococcal disease and 80% of disease in children is due to between 8 and 10 serotypes. The pattern of deaths due to pneumococcal disease shows a marked difference between developing and developed countries. Globally approximately 700,000 to one million children under 5 years of age die in a year and in total there are roughly one and a half million deaths yearly due to pneumococcus.

The first treatments used to combat pneumococcal disease and infection were antibiotics. However, resistance to these evolved and consequently pneumococcal vaccines were developed. Currently in the UK, the 23-valent pneumococcal polysaccharide vaccine PPV-23 is used with one dose per lifetime for healthy adults. This was first used in 1989. In people whose antibodies decay more quickly repeated vaccination may be introduced every five years. Additionally PPV-23 can be given to individuals older than two who are at a higher risk of pneumococcal infection. However, children under 2 years do not have a good antibody response to polysaccharide vaccinations [36] and so PPV-23 is not useful for this group.

Instead a 7-valent pneumococcal conjugate vaccine (PCV-7) was introduced in the UK in 2002 for children under two years most at risk of pneumococcal disease. In 2004, this was extended to children at risk under 5 years. PCV-7 was introduced to routine childhood immunization for the UK in 2006 [36]. Since then there has been a 90% effectiveness in preventing IPD due to the seven vaccine serotypes in healthy children [44]. The PCVs, in addition to preventing the disease in young children, who are one of the key risk groups, have another advantage. Not only do conjugate vaccines prevent invasive disease due to the vaccine serotypes, but they also prevent colonization with these serotypes [12,13].

A key concern is that of serotype replacement [28]. Here non-vaccine type (NVT) serotypes replace the eliminated vaccine type (VT) serotypes. There are two ways that this can happen. First, there could be an increase in the numbers infected with serotypes present in the population prior to the vaccine being introduced. Secondly, serotypes that were absent from the population before vaccination may be re-introduced once the VT serotypes disappear [38]. This affects long-term vaccine efficacy as it may lead to an increase in NVT disease and infection.

Another potential problem is capsular switching. This is where a bacterium that looks like one serotype can switch to another serotype through a swapping material with a second bacterium with a different serotype from the first [10]. It is believed that for a capsular switch to happen a person must be simultaneously colonized with two serotypes [6].
A key mathematical model for the spread of pneumococcal disease is due to Lipsitch [27]. There were two serotypes in circulation in the population, and co-colonization with both serotypes was possible. Infection with one serotype reduced the chances of infection with the second. A vaccine was available. This was completely effective against the first serotype and had variable effectiveness against the second. The two serotypes had different carriage (i.e. pneumococcal colonization) transmission coefficients. Note here that colonization with the pneumococcal bacteria is what is transmitted. Symptomatic infection or disease is a possible consequence of colonization with the bacteria. A fraction $f$ of the population was vaccinated at birth. Lipsitch used a differential equation model to describe the spread of disease.

His main conclusion was that if the vaccine specifically targets only one of the two serotypes, then reducing carriage of the VT serotype will result in an increase in carriage of the NVT serotype. However, the additional NVT serotype carriage will not be greater than the reduction in VT carriage. So total carriage could remain the same but will not increase. This is guaranteed only for the two-serotype model. If three or more serotypes are present and only one is a VT serotype, then total pneumococcal carriage may increase following vaccination.

The work of this paper builds on the work of Lamb et al. [25]. They discuss a simple mathematical model which uses differential equations to examine the relationship between STs and serotype. The model has a vaccination of a fraction $f$ of the population and one ST which can be expressed as both a vaccine and a non-vaccine serotype. The authors derive the effective reproduction number $R_e$ and carry out an equilibrium and global stability analysis. The carriage dies out if $R_e \leq 1$ but if $R_e > 1$, then provided that carriage is initially present it will tend to a unique endemic equilibrium. The results are confirmed by simulation with realistic parameter values. Here, we shall extend these results to include two STs where the transmission parameter depends on the serotype.

2. Mathematical model

It is assumed that hosts can become colonized with one of two STs, ST 1 and ST 2. For $i = 1, 2$, $T_i$ denotes the number of unvaccinated individuals and $V_T$ the number of vaccinated individuals carrying ST $i$ at time $t$. Each of ST 1 and ST 2 is associated with both of the two serotypes (1 and 2), but in different proportions. ST $i$ can manifest as serotypes 1 and 2 with numbers $P_iT_i$ and $(1 - P_i)T_i$, respectively. $X$ denotes the number of susceptibles, and $V$ the number of vaccinated individuals carrying neither ST at time $t$. As the vaccine is assumed to be 100% effective in preventing carriage of serotype 1, all vaccinated carriers of either ST must be carrying serotype 2.

A proportion $f$ of hosts entering the population are assumed to receive the vaccine. The total birth rate of hosts is $L$ and the average duration of pneumococcal colonization is $(1/\gamma)$ for both STs and whether or not individuals are vaccinated. We are modelling transmission amongst young children and the constant per capita rate at which individuals leave this group is $u$. This is independent of whether or not the individual is carrying pneumococcus and whether or not he or she has been vaccinated. The transmission is attributable to serotype not ST. Thus, the carriage transmission coefficient between an individual carrying serotype $i$ and a susceptible is $\beta_i$ per unit time, for $i = 1, 2$.

The differential equations which describe the spread of the disease are as follows:

$$\frac{dX}{dt} = L(1 - f) - uX - (P_1\beta_1 + (1 - P_1)\beta_2)XT_1 - (P_2\beta_1 + (1 - P_2)\beta_2)XT_2$$

$$- \beta_2XV_T - \beta_2XV_T + \gamma(T_1 + T_2),$$

(1a)
\[
\frac{dT_i}{dt} = (P_i \beta_1 + (1 - P_i) \beta_2) XT_i + \beta_2 X V T_i - (\gamma + u) T_i \quad \text{for } i = 1, 2, \quad (1b)
\]

\[
\frac{dV}{dt} = L f - u V - (P_1 \beta_1 + (1 - P_1) \beta_2) V T_1 - (P_2 \beta_1 + (1 - P_2) \beta_2) V T_2
- \beta_2 V V T_1 - \beta_2 V V T_2 + \gamma (V T_1 + V T_2)
\]

and \[
\frac{dV T_i}{dt} = (P_i \beta_1 + (1 - P_i) \beta_2) V T_i + \beta_2 V V T_i - (\gamma + u) V T_i \quad \text{for } i = 1, 2. \quad (1c)
\]

These differential equations are illustrated in Figure 1 which shows the different classes and the transitions into and out of compartments. In this figure, \(Y_i\) is the number of children in that compartment manifesting as serotype \(i\), for \(i = 1, 2\).

In the above model, the total population size \(N = X + V + T_1 + T_2 + V T_1 + V T_2\) is not necessarily constant, but it is straightforward to show that \(N \to L/u\) as \(t \to \infty\).

The model assumes that for \(i = 1, 2\) when a bacterium of ST \(i\) 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 ST is transmitted to a vaccinated individual, then it cannot manifest itself as serotype 1 so it automatically manifests as serotype 2, again possibly by capsular switch. Thus, vaccinated children will be colonized with the same chance as unvaccinated children but with a different serotype. The vaccine targets the serotypes which have the most serious consequences for IPD, not the most transmissible serotypes. As far as we are aware there is no association between the transmissibility of a serotype and its inclusion in the vaccine. Thus \(\beta_1\) may be greater than, equal to, or less than, \(\beta_2\).

Figure 1. Model of two STs, both associated with two serotypes. Transmission is due to the serotype and the vaccine is assumed to be effective against one serotype.
3. Equilibrium solutions

For \(i = 1, 2\) define \(K_i = P_i \beta_1 + (1 - P_i) \beta_2, \xi_i = L/u - (\gamma + u)/(1 - f)K_i + f \beta_2\) and

\[
R_{ei} = \frac{(1 - f)K_i + f \beta_2}{\gamma + u} L / u. \tag{2}
\]

We have the following theorem:

**Theorem 3.1** For \(K_1 \neq K_2\), there are three equilibria:

(i) First the carriage-free equilibrium (CFE):

\[
(X, T_1, T_2, V, V_{T_1}, V_{T_2}) = \left( (1 - f) \frac{L}{u}, 0, 0, \frac{L}{u}, 0, 0 \right). \tag{3}
\]

This is always possible.

(ii) Second there is the ST \(1\) carriage equilibrium (CE 1):

\[
(X, T_1, T_2, V, V_{T_1}, V_{T_2}) = \left( (1 - f) \left( \frac{L}{u} - \xi_1 \right), (1 - f) \xi_1, 0, f \left( \frac{L}{u} - \xi_1 \right), f \xi_1, 0 \right). \tag{4}
\]

This equilibrium is possible provided \(R_{e1} > 1\).

(iii) Third, there is the ST \(2\) carriage equilibrium (CE 2):

\[
(X, T_1, T_2, V, V_{T_1}, V_{T_2}) = \left( (1 - f) \left( \frac{L}{u} - \xi_2 \right), 0, (1 - f) \xi_2, f \left( \frac{L}{u} - \xi_2 \right), 0, f \xi_2 \right). \tag{5}
\]

This equilibrium is possible provided \(R_{e2} > 1\).

(iv) If \(K_1 = K_2\), then \(\xi_1 = \xi_2 = \xi\) and the above solutions are still possible, but provided that \(R_{e1} = R_{e2} > 1\) then any point on the line joining CE 1 and CE 2:

\[
(X, T_1, T_2, V, V_{T_1}, V_{T_2}) = \left( (1 - f) \left( \frac{L}{u} - \xi \right), \alpha(1 - f)\xi, (1 - \alpha)(1 - f)\xi, f \left( \frac{L}{u} - \xi \right), \alpha f \xi, (1 - \alpha) f \xi \right) \tag{6}
\]

with \(0 \leq \alpha \leq 1\) is also a possible equilibrium solution.

**Proof** Suppose that \(K_1 \neq K_2\). Then from (1b, \(i = 1\)) \(T_1 = \beta_2 XV_{T_1}/(\gamma + u - K_1 X)\). Substituting into Equation (1d, \(i = 1\)) and solving gives \(V_{T_1} = 0\) or

\[
V = \frac{\gamma + u - K_1 X}{\beta_2}. \tag{7}
\]

Now substituting Equation (7) into Equation (1d, \(i = 2\)) gives \(X = 0\) or

\[
V_{T_2} = \left( \frac{\gamma + u - K_1 X}{\beta_2} \right) \frac{K_2 T_2}{K_1 X}. \tag{8}
\]

If \(X = 0\), then from (1b) \(T_1 = T_2 = 0\) which contradicts \(X + T_1 + T_2 = L(1 - f)/u\), obtained from adding Equations (1a)–(1b). So Equation (8) holds. Substituting Equation (8) into Equation (1b, \(i = 2\)) gives that \(T_2 = 0\).
If $V T_1 = 0$, then (1d, $i = 1$) implies that $V = 0$ or $T_1 = 0$.

If $V T_1 = V = 0$, then (1d, $i = 2$) implies that $V T_1 = 0$. Next adding Equations (1c)–(1d) gives $V + V T_1 + V T_2 = L f / u$ a contradiction. Hence $T_1 = V T_1 = 0$. Adding Equations (1a)–(1b) and (1c)–(1d) gives $X + T_2 = L (1 - f) / u$ and $V + V T_2 = L f / u$. Dividing Equation (1b, $i = 2$) by Equation (1d, $i = 2$), we deduce that $T_2 = V T_2 = 0$ or

$$
\frac{T_2}{V T_2} = \frac{X}{V} = \frac{(L / u) (1 - f) - T_2}{(L / u) f - V T_2}.
$$

Hence $f T_2 = (1 - f) V T_2$. Therefore, $T_2 = (1 - f) v$ and $V T_2 = f v$, where $T_2 + V T_2 = v$ and so $X = (1 - f) (L / u - v)$ and $V = f (L / u - v)$. Substituting these expressions into Equation (1b, $i = 2$) added to Equation (1d, $i = 2$) and solving gives $v = 0$ or

$$
v = \xi_2 = \frac{L}{u} - \frac{\gamma + u}{(1 - f) K_2 + f \beta_2}.
$$

$v = 0$ gives the CFE, whereas Equation (9) gives CE 2.

When $T_2 = 0$, from Equation (1b, $i = 2$) either $X = 0$ or $V T_2 = 0$. However, as before $X = 0$ leads to a contradiction. Hence $T_2 = V T_2 = 0$ and an argument similar to the above shows that this solution is either the CFE or CE 1.

Finally, if $K_1 = K_2$ then once again we have $V + V T_1 + V T_2 = L f / u$. Then from Equation (1b, $i = 1$) divided by Equation (1d, $i = 1$) $T_1 / V T_1 = X / V$ unless $T_1 = V T_1 = 0$. Similarly, $T_2 / V T_2 = X / V$ unless $T_2 = V T_2 = 0$. So when $T_1$ or $V T_1 \neq 0$, and $T_2$ or $V T_2 \neq 0$,

$$
\frac{T_1}{V T_1} = \frac{T_2}{V T_2} = \frac{X}{V} = \pi.
$$

So

$$
\pi = \frac{X + T_1 + T_2}{V + V T_1 + V T_2} = \frac{1 - f}{f}.
$$

Hence

$$
\frac{X}{V} = \frac{T_1 + T_2}{V T_1 + V T_2} = \frac{1 - f}{f}.
$$

So if $T_1 + T_2 = (1 - f) \xi$ and $V T_1 + V T_2 = f \xi$,

$$
\xi = T_1 + T_2 + V T_1 + V T_2 = \frac{L}{u} - (X + V) = \frac{L}{u} - X \left(1 + \frac{f}{1 - f}\right).
$$

Therefore, $X = (1 - f) (L / u - \xi)$ and $V = f (L / u - \xi)$. Substituting these expressions into Equation (1a) and simplifying gives $\xi = 0$ or

$$
\xi = \frac{L}{u} - \frac{\gamma + u}{K_1 (1 - f) + \beta_2 f}.
$$

$\xi = 0$ corresponds to the CFE. If $\xi \neq 0$ and $R_{c1} = R_{c2} > 1$, then pick $\alpha < 1$ so that $V T_1 = \alpha f \xi$. Then $V T_1 = (1 - \alpha) f \xi$, $T_1 = (1 - f) V T_1 / f = \alpha (1 - f) \xi$, $T_2 = (1 - \alpha) (1 - f) \xi$ and we have Equation (6). It is straightforward to show that Equation (6) is an equilibrium solution for any value of $\alpha$.

If $T_2 = V T_2 = 0$ and $T_1$ or $V T_1 \neq 0$

$$
\frac{T_1}{V T_1} = \frac{X}{V} = \pi \quad \text{so} \quad \pi = \frac{X + T_1}{V + V T_1} = \frac{1 - f}{f}.
$$

Hence if $T_1 = (1 - f) \xi$ and $V T_1 = f \xi$, $\xi = T_1 + V T_1 = L / u - (X + V)$. Thus, $\xi = L / u - X (1 + f / (1 - f))$, $X = (1 - f) (L / u - \xi)$ and $V = f (L / u - \xi)$. Therefore, we get CE 1. Similarly, when $T_1 = V T_1 = 0$, $T_2$ or $V T_2 \neq 0$ we get CE 2.
There are four classes of infected individuals in this model, $T_1, T_2, V_{T_1}$ and $V_{T_2}$. The $(i,j)$’th entry of the next generation matrix $[14]$ gives the expected number of type $i$ infected individuals caused by a single newly infected type $j$ individual entering the CFE. Thus, here

$$M = \begin{bmatrix}
\frac{K_1L(1-f)}{u(\gamma+u)} & 0 & \frac{\beta_2L(1-f)}{u(\gamma+u)} & 0 \\
0 & \frac{K_2L(1-f)}{u(\gamma+u)} & 0 & \frac{\beta_2L(1-f)}{u(\gamma+u)} \\
\frac{K_1f}{u(\gamma+u)} & 0 & \frac{\beta_2f}{u(\gamma+u)} & 0 \\
0 & \frac{K_2f}{u(\gamma+u)} & 0 & \frac{\beta_2f}{u(\gamma+u)}
\end{bmatrix}.$$

Recall that for $i = 1, 2, R_{ci} = (((1-f)K_1+f\beta_2)/((\gamma+u))L/u$. The largest eigenvalue of $M$ is $R_e = \max(R_{c1}, R_{c2})$ the effective reproduction number $[14,25]$.

5. Global stability analysis

(i) When $T_1(0) = V_{T_1}(0) = T_2(0) = V_{T_2}(0) = 0$ then $T_1(t) = V_{T_1}(t) = T_2(t) = V_{T_2}(t) = 0, \forall t$. It is then straightforward that the system approaches the CFE.

(ii) Next suppose that $R_e \leq 1$ and at least one of $T_1(0), T_2(0), V_{T_1}(0)$ or $V_{T_2}(0) > 0$. From (1a)–(1b)

$$\frac{d}{dt}(X + T_1 + T_2) = L(1 - f) - u(X + T_1 + T_2),$$

so $X + T_1 + T_2 \to L(1 - f)u$ as $t \to \infty$. Similarly $V + V_{T_1} + V_{T_2} \to Lf/u$ as $t \to \infty$. This means that given $\epsilon > 0, \exists t_0$ such that for $t \geq t_0, X + T_1 + T_2 \leq L(1 - f)u + \epsilon$ and $V + V_{T_1} + V_{T_2} \leq Lf/u + \epsilon$.

Define $B(\epsilon) = \begin{bmatrix} K_1\left(\frac{L(1-f)}{u} + \epsilon\right) & K_1\left(\frac{Lf}{u} + \epsilon\right) \\
K_1\left(\frac{L(1-f)}{u} + \epsilon\right) & K_1\left(\frac{Lf}{u} + \epsilon\right) \end{bmatrix}$ and $T = \begin{pmatrix} T_1 \\
V_{T_1} \end{pmatrix}$.

$\rho(B(0)^T) = (\gamma + u)R_{c1} \leq (\gamma + u)$ as $R_{c1} \leq 1$. By Lemma 2.1 of [32], there is an $e = (e_1, e_2) > 0$ such that $B(0)^Te^T = \rho(B(0)^Te^T)$. We have

$$\frac{dT}{dt} \leq \begin{bmatrix} K_1\left(\frac{L(1-f)}{u} + \epsilon - T_1\right) & K_1\left(\frac{Lf}{u} + \epsilon - V_{T_1}\right) \\
K_1\left(\frac{L(1-f)}{u} + \epsilon - T_1\right) & K_1\left(\frac{Lf}{u} + \epsilon - V_{T_1}\right) \end{bmatrix} T - (\gamma + u)T,$$

$$\frac{d[e.T]}{dt} \leq e \begin{bmatrix} K_1(\epsilon - T_1) & K_1(\epsilon - V_{T_1}) \\
K_1(\epsilon - T_1) & K_1(\epsilon - V_{T_1}) \end{bmatrix} T - (\gamma + u)e.T$$

$$\leq (K_1T_1 + \beta_2V_{T_1})(\epsilon_1 + \epsilon_2)e - e.T.$$

Hence for $e.T \geq (\epsilon_1 + \epsilon_2)e, (d/dt)(e.T)$ is decreasing so $\exists t_1 \geq t_0$ such that for $t \geq t_1, 0 \leq e.T \leq 2(\epsilon_1 + \epsilon_2)e$. But $\epsilon > 0$ is arbitrary and $e_1 > 0$ and $e_2 > 0$, so $T_1$ and $V_{T_1} \to 0$ as
\( t \rightarrow \infty \). A similar argument shows that \( T_2 \) and \( V_{T_2} \) → 0 as \( t \rightarrow \infty \). So \( X \rightarrow L(1-f)/u \) and \( V \rightarrow Lf/u \) as \( t \rightarrow \infty \), and the system approaches the CFE.

(iii) Next suppose that \( R_e > 1 \), and ST 2 is not initially present but ST 1 is. It is easily shown that no hosts will ever carry ST 2 and that

\[
X + T_1 \rightarrow \frac{L}{u} (1-f) \quad \text{and} \quad V + V_{T_1} \rightarrow \frac{L}{u} f \quad \text{as} \quad t \rightarrow \infty.
\]

Let \( T = K_1 T_1 + \beta_2 V_{T_1} \). It is easy to show that \( T(t) > 0 \) for all \( t \). Then

\[
\frac{1}{T} \frac{dT}{dt} = [K_1 X + \beta_2 V - (\gamma + u)] \rightarrow K_1 \frac{L(1-f)}{u} + \beta_2 \frac{Lf}{u} - (\gamma + u) - T \quad \text{as} \quad t \rightarrow \infty.
\]

Hence if \( R_{e1} \leq 1 \), given \( \epsilon > 0 \) there exists \( t_2 \geq t_0 \) such that

\[
\frac{1}{T} \frac{dT}{dt} \leq \epsilon - T
\]

for \( t \geq t_2 \). So by standard comparison theorems \([3]\) \( T \geq 0 \) is bounded above by \( \bar{T} \) where \( \bar{T} \) satisfies

\[
\frac{d\bar{T}}{dt} = (\epsilon - \bar{T})\bar{T}
\]

and \( \bar{T}(0) = T(0) \). It is straightforward that \( \bar{T} \rightarrow \limsup_{t \rightarrow \infty} \bar{T} \leq \epsilon \). So \( 0 \leq \limsup_{t \rightarrow \infty} T \leq \epsilon \) and as \( \epsilon > 0 \) is arbitrary \( T \rightarrow 0 \) as \( t \rightarrow \infty \). Thus, \( T_1 \rightarrow 0 \) and \( V_{T_1} \rightarrow 0 \) as \( t \rightarrow \infty \) and the system approaches the CFE.

When \( R_{e1} > 1 \), similar comparison arguments show that if \( \epsilon > 0 \),

\[
K_1 \frac{L(1-f)}{u} + \beta_2 \frac{Lf}{u} + \epsilon - (\gamma + u) \geq \limsup_{t \rightarrow \infty} T,
\]

\[
\geq \liminf_{t \rightarrow \infty} T,
\]

\[
\geq K_1 \frac{L(1-f)}{u} + \beta_2 \frac{Lf}{u} - \epsilon - (\gamma + u).
\]

So

\[
T \rightarrow K_1 \frac{L(1-f)}{u} + \beta_2 \frac{Lf}{u} - (\gamma + u) \quad \text{as} \quad t \rightarrow \infty.
\]

When \( R_{e1} > 1 \) from Equations \((1b, i = 1), (10) \) and \((11) \) as \( t \rightarrow \infty \)

\[
\frac{dT_1}{dt} \rightarrow \frac{L(1-f)}{u} \left( K_1 \frac{L(1-f)}{u} + \beta_2 \frac{Lf}{u} - (\gamma + u) \right) - \left( K_1 \frac{L(1-f)}{u} + \beta_2 \frac{Lf}{u} \right) T_1.
\]

A similar argument to the one used to obtain Equation \((11) \) shows that \( T_1 \rightarrow (1-f)\xi_1 \) as \( t \rightarrow \infty \). From Equation \((10) \) \( X \rightarrow (1-f)(L/u - \xi_1) \) as \( t \rightarrow \infty \). We likewise deduce that \( V_{T_1} \rightarrow f\xi_1 \) as \( t \rightarrow \infty \) and \( V \rightarrow f(L/u - \xi_1) \) as \( t \rightarrow \infty \) so the system approaches CE 1 as \( t \rightarrow \infty \).

(iv) Similarly to above if \( R_e > 1 \), and ST 1 is not initially present but ST 2 is then it is easily shown that as \( t \rightarrow \infty \) then the system approaches the CFE if \( R_{e2} \leq 1 \) and CE 2 if \( R_{e2} > 1 \).
Now suppose that \( K_1 > K_2, R_{c1} > \max(1, R_{c2}) \) and both STs are initially present. As

\[
\frac{d}{dt}(K_1 T_1 + \beta_2 V_{T_1}) = [(K_1 X + \beta_2 V) - (\gamma + u)](K_1 T_1 + \beta_2 V_{T_1})
\]

and \((K_1 T_1 + \beta_2 V_{T_1})(0) > 0\) it is straightforward that \((K_1 T_1 + \beta_2 V_{T_1})(t) > 0\) for all \( t \). Similarly \((K_2 T_2 + \beta_2 V_{T_2})(t) > 0\) for all \( t \). Write \( \eta = (K_1 T_1 + \beta_2 V_{T_1})/(K_2 T_2 + \beta_2 V_{T_2}) \). Then

\[
\frac{d\eta}{dt} = (K_1 - K_2)X\eta. \tag{12}
\]

We need the following lemma which shows that we can bound \( X \) strictly away from zero, provided that the time is large.

**Lemma 5.1** \( \exists \epsilon > 0 \) and \( t_3 > 0 \) such that \( X \geq \epsilon > 0 \) for \( t \geq t_3 \).

**Proof** We know that \( X + V + T_1 + V_{T_1} + T_2 + V_{T_2} \to L/u \) as \( t \to \infty \). Therefore \( \exists t_4 \) such that for \( t \geq t_4, X + V + T_1 + V_{T_1} + T_2 + V_{T_2} \leq 2L/u \). For \( t \geq t_4, \)

\[
\frac{dX}{dt} \geq L(1 - f) - (u + K_1 T_1 + \beta_2 V_{T_1} + K_2 T_2 + \beta_2 V_{T_2})X,
\]

\[
\geq L(1 - f) - \left( u + \max(K_1, K_2, \beta_2)\frac{L}{u}\right)X.
\]

For \( X \leq \frac{1}{2}L(1 - f)/(u + \max(K_1, K_2, \beta_2)2L/u), \) \( dX/dt \geq \frac{1}{2}L(1 - f) > 0 \), so \( \exists t_3 > t_4 \) such that \( X \geq \frac{1}{2}L(1 - f)/(u + \max(K_1, K_2, \beta_2)2L/u) > 0 \) for \( t \geq t_3 \). \( \Box \)

From Equation (12), using Lemma 5.1, we deduce that \( \eta \to \infty \) as \( t \to \infty \). Hence given \( \epsilon > 0 \) \( \exists t_5 \) such that for \( t \geq t_5, \)

\[
\frac{K_2 T_2 + \beta_2 V_{T_2}}{K_1 T_1 + \beta_2 V_{T_1}} \leq \epsilon \quad \text{and} \quad K_1 T_1 + \beta_2 V_{T_1} \leq 2\max(K_1, \beta_2)\frac{L}{u}.
\]

So

\[
0 \leq K_2 T_2 + \beta_2 V_{T_2} \leq 2\epsilon \frac{L}{u} \max(K_1, \beta_2).
\]

We deduce that \( T_2 \) and \( V_{T_2} \) tend to zero as \( t \to \infty \). By adding Equations (1a)–(1b) we see that

\[
\frac{d}{dt}(X + T_1 + T_2) = L(1 - f) - u(X + T_1 + T_2)
\]

so \( X + T_1 + T_2 \to L(1 - f)/u \) as \( t \to \infty \). Hence \( X + T_1 \to L/u(1 - f) \) as \( t \to \infty \). Similarly \( V + V_{T_1} \to Lf/u \) as \( t \to \infty \). Then the argument given in (iii) for \( R_e > 1 \) shows that the system approaches CE 1 as \( t \to \infty \).

In the same way, if \( K_2 > K_1, R_{c2} > \max(1, R_{c1}) \) and there are initially hosts carrying both STs then the system approaches CE 2 as \( t \to \infty \).
Now suppose that $K_1 = K_2, R_c > 1$ and there are initially hosts carrying both STs. Then Equations (1) become

$$\frac{dX}{dt} = L(1 - f) - uX - K_1X(T_1 + T_2) - \beta_2X(V_{T_1} + V_{T_2}) + \gamma(T_1 + T_2),$$

$$\frac{dT_1 + T_2}{dt} = K_1X(T_1 + T_2) + \beta_2X(V_{T_1} + V_{T_2}) - (\gamma + u)(T_1 + T_2),$$

(13)

$$\frac{dV}{dt} = LF - uV - K_1V(T_1 + T_2) - \beta_2V(V_{T_1} + V_{T_2}) + \gamma(V_{T_1} + V_{T_2})$$

and

$$\frac{d(V_{T_1} + V_{T_2})}{dt} = K_1V(T_1 + T_2) + \beta_2V(V_{T_1} + V_{T_2}) - (\gamma + u)(V_{T_1} + V_{T_2}).$$

These equations have the same form as in Case (iii) with $T_1$ replaced by $T_1 + T_2$ and $V_{T_1}$ replaced by $V_{T_1} + V_{T_2}$. We deduce that $X, T_1, T_2, V, V_{T_1},$ and $V_{T_2}$ tend to the surface given by $X = (1 - f)(L/u - \xi), T_1 + T_2 = (1 - f)\xi, V = f(L/u - \xi)$ and $V_{T_1} + V_{T_2} = f\xi$. Furthermore from Equation (12) $K_1T_2 + \beta_2V_{T_2} = k(K_1T_1 + \beta_2V_{T_1})$ where $k > 0$ is a constant. On the above surface, if $V_{T_1} = \alpha_1f\xi,$ then $0 \leq \alpha_1 \leq 1$ and $V_{T_2} = (1 - \alpha_1)f\xi.$ Similarly, if $T_1 = \alpha_2(1 - f)\xi$ then $0 \leq \alpha_2 \leq 1$ and $T_2 = (1 - \alpha_2)(1 - f)\xi.$ Now

$$\frac{d}{dt} \left( \frac{T_1}{T_2} \right) = \frac{XT}{T_2} \left( 1 - \frac{T_1k}{T_2} \right).$$

(14)

We need the following lemma to show that we can bound the term $XT/T_2$ away from zero, again provided that the time is large.

**Lemma 5.2** $\exists t_6 > 0$ and $\epsilon, \epsilon_1 > 0$ such that for $t \geq t_6,$ $X \geq \epsilon > 0,$ $T \geq \epsilon_1 > 0$ and $T_2 \leq 2\frac{L}{u}.$

**Proof** $X + V \to (L/u - \xi) < L/u$ as $t \to \infty.$ So $\exists \epsilon_2 > 0$ and $t_7$ such that for $t \geq t_7$

$$\left| X + V - \frac{L}{u} \right| > \epsilon_2 > 0.$$

$\exists t_8 \geq t_7$ such that for $t \geq t_8, |N - L/u| < \epsilon_2/2.$ For $t \geq t_8,$

$$(k + 1)T = |K_1T_1 + \beta_2V_{T_1} + K_1T_2 + \beta_2V_{T_2}|,$$

$$\geq \min(K_1, \beta_2)(T_1 + V_{T_1} + T_2 + V_{T_2}) = \min(K_1, \beta_2)|N - (X + V)|,$$

$$\geq \min(K_1, \beta_2) \left\{ \left| \frac{L}{u} - (X + V) \right| - \left| N - \frac{L}{u} \right| \right\} > \min(K_1, \beta_2) \frac{\epsilon_2}{2}.$$ 

So

$$T \geq \epsilon_1 = \frac{\min(K_1, \beta_2)}{2(k + 1)} \epsilon_2 > 0.$$

The result follows. $\blacksquare$

Using Lemma 5.2 and Equation (14) it is straightforward to show that $T_1/T_2 \to 1/k$ as $t \to \infty.$ Now

$$\beta_2(kV_{T_1} - V_{T_2}) = k(K_1T_1 + \beta_2V_{T_1}) - (K_1T_2 + \beta_2V_{T_2}) - K_1(kT_1 - T_2),$$

$$= -K_1(kT_1 - T_2) \to 0 \quad \text{as} \quad t \to \infty.$$

So $V_{T_1}/V_{T_2} \to 1/k$ as $t \to \infty.$ Hence $\alpha_1/(1 - \alpha_1)$ and $\alpha_2/(1 - \alpha_2) \to 1/k$ as $t \to \infty.$ Hence $\alpha_1, \alpha_2 \to 1(k + 1)$ as $t \to \infty.$ Therefore, $X, V, T_1, T_2, V_{T_1}$ and $V_{T_2}$ approach the
Figure 2. Bifurcation diagram illustrating Theorem 5.3.

point (6) where $\alpha = 1/(1 + k)$ and $0 < \alpha < 1$. $k$ is given in terms of the initial conditions by $(K_1 T_2(0) + \beta_2 V T_2(0))/(K_1 T_1(0) + \beta_2 V T_1(0))$. To summarize we have shown the following theorem:

**Theorem 5.3**

(i) When $R_e \leq 1$ the CFE is the only possible equilibrium. In this situation, regardless of the number of children initially carrying either ST, both STs will die out in the long-term. The number of susceptibles and vaccinateds will tend to the CFE values.

(ii a) When $R_e > 1$, if there are no children initially carrying either of the STs, there will never be any children carrying either ST. The system approaches the CFE.

(ii b) If $R_e = R_e_1 > 1 > R_e_2$, then if initially ST 2 is present but ST 1 is not, then ST 1 will never be present and the number of children carrying ST 2 will tend to zero. The system tends to the CFE. If $R_e = R_e_1 > R_e_2 > 1$ then under the same initial conditions the system tends to CE 2.

(ii c) However, if $R_e_1 > \max(1, R_e_2)$ and ST 1 is initially present, regardless of whether or not ST 2 is initially present, in the long-term ST 2 will die out and the system will tend to CE 1.

(ii d) If $R_e_2 > \max(1, R_e_1)$ the situations in (ii b) and (ii c) are reversed.

(ii e) If $R_e_2 = R_e_1 > 1$ then the possible CEs are a line of equilibria and in the long-term coexistence of both STs is possible along this line if both are initially present. Provided that at least one ST is initially present $X, T_1, T_2, V, V T_1$ and $V T_2$ approach the equilibrium point (6) for $\alpha = 1/(1 + k)$ and $0 \leq \alpha \leq 1$. Here $k = (K_1 T_2(0) + \beta_2 V T_2(0))/(K_1 T_1(0) + \beta_2 V T_1(0))$ and $\xi = L/u - (\gamma + u)/(K_1 (1 - f)) + \beta_2 f$.

This theorem is summarized by the bifurcation diagram shown in Figure 2.

The results for this ST model show three possible equilibria, in general. There is the CFE, a CE 1 corresponding to ST 1 and one corresponding to ST 2, CE 2. Assuming that both STs are initially present, in region A the carriage dies out, in region B the carriage tends to CE 1 and in region C the carriage tends to CE 2. On the line which is the boundary between B and C the carriage approaches a coexistence equilibrium as given in Theorem 5.3.

6. Discussion

We may ask what the biological significance of $R_e$ is. Consider the population at the CFE and also a new carriage case entering the population. For $i = 1, 2$, if this child is carrying ST $i$ (i.e. in class $T_i$ or $V T_i$) then he or she will carry the bacteria for total time $1/(\gamma + u)$. During this time he or she will pass the bacteria to an average $K_1 (1 - f) L/u$ unvaccinated susceptibles and $\beta_2 f L/u$ vaccinated
susceptibles. Hence $R_{ei}$ is the total expected number of secondary carriage cases produced by such a newly colonized child. $R_e$ thus has a biological interpretation as the maximum expected number of secondary carriage cases produced by a newly colonized child entering the CFE, over all types of carrying children.

If $K_1 > K_2$, then $R_e = R_{e1}$ and if this value is less than or equal to one then both STs will die out in the long-term, irrespective of the initial conditions. When $R_e = R_{e1} > 1$ the population size will tend to CE 1 as ST 1 dominates when $K_1 > K_2$ provided that ST 1 is present initially. If no STs are initially present and $R_e > 1$ then the populations will tend to the CFE. If initially there are children carrying ST 2 but not ST 1, and $R_{e2} \leq 1$, the population again tends to the CFE, but with the same initial conditions and $R_{e2} > 1$ the system approaches CE 2. If $K_2 > K_1$ then the situation is reversed.

We may ask what is the effect of changing $f$, the fraction vaccinated, on the dynamic behaviour of the system. If we alter $f$, then it makes no difference as to which of $K_1$ and $K_2$ is largest and hence no difference as to which of the two CEs dominate. If $\beta_1 > \beta_2$, then increasing $f$ makes each $R_{ei}$ smaller and so it is more likely that the disease will die out, and if it persists then there will be less carriage at the dominant CE. Conversely, if $\beta_1 < \beta_2$ then increasing $f$ makes each $R_{ei}$ bigger and so it is less likely that the disease will die out and if it persists then there will be more carriage at the dominant CE. If $\beta_1 = \beta_2$, then $K_1 = K_2$ and then increasing $f$ makes no difference to the final total amount of carriage, but means that at the limiting value more of the children carrying pneumococcus will be vaccinated.

Note that although this concept of serotype replacement seems anti-intuitive, that NVT serotypes can replace VT serotypes, possibly increasing prevalence has widely been observed in practice. For example, Vestrheim et al. [42] document this phenomenon in Norway, Huang et al. [20] reported a similar phenomenon in the USA and Park et al. [34] observed a similar result in Alaska. See also Singleton et al. [37], Beall et al. [2] and Albrich et al. [1]. There are many other papers which document that serotype replacement often occurs following a pneumococcal vaccination campaign. The phenomenon of serotype replacement has also been predicted by the mathematical models of Lipsitch [27] and Temime et al. [40], discussed later. One reason for this is believed to be capsular switch [5]. Beall et al. [2] report extensive evidence of capsular switching between PCV7 VT and NVT serotypes in the same serogroup. Coffey et al. [9], Mbelle et al. [30] and Klugman [23] also suggest capsular switch as a possible explanation for serotype replacement.

Our model also assumes that vaccinated children will be colonized with the same chance as unvaccinated children but with a different serotype. There are few studies of pneumococcal carriage before and after vaccination but a paper by Yeh et al. [44] lends some support to this. The paper reports that there was no significant increase in nasopharyngeal carriage of S. pneumoniae between a group of children vaccinated with PCV7 and a control group although the numbers in the study were relatively small. Data from Obaro et al. [33] and Mbelle et al. [30] also lend support to this hypothesis.

As both STs are able to manifest in both serotypes then even though STs have been shown unable to coexist in the population, the two serotypes should be able to coexist, assuming that there are unvaccinated hosts. If $f = 1$, then all children will receive the conjugate vaccine, assumed to be 100% effective in preventing carriage of serotype 1. In this case, regardless of whether or not individuals are colonized with ST 1 or ST 2 all hosts must be carrying serotype 2. In the case of no vaccine intervention $f = 0$ and $V = V_{T_1} = V_{T_2} = 0$. All of the results obtained formally by putting $f = 0$ in Theorems 3.1 and 5.3 and the expression for $R_e$ (now the basic reproduction number $R_0$) can be shown still to be valid.

Only one of the serotypes is assumed to be a VT serotype. Vaccinated hosts are still able to be colonized with either ST as the vaccine is serotype-specific, not ST specific. The vaccine would result in the elimination of the ST only if it was solely associated with the VT serotype. The model
did not consider STs solely associated with a VT serotype as it was created to assess what would occur in the population following a vaccine intervention should STs be able to manifest as both a virulent VT and a NVT serotype.

The assumption that the vaccine is 100% effective in preventing carriage of VT serotypes is likely to be an overestimate of the vaccine effectiveness, with studies in France and the USA showing a reduction in carriage of VT serotypes but not total elimination [10,20]. Similarly in a South African trial of PCV-7, the carriage of VT serotypes observed for vaccinated hosts was half that observed for unvaccinated hosts but VT serotypes were still carried by vaccinated hosts [31]. Thus, a topic for future study would be to modify these models accordingly. However, other published mathematical models of pneumococcus assume that the vaccine is 100% effective in preventing colonization with VT strains [27,40].

The model considered transmission due to serotype, not ST. Biologically it is not clear whether this is true. It is difficult to address this question through the literature as most other established pneumococcal models do not consider STs and concentrate only on the serotype. Buckee et al. [7] discuss a stochastic simulation model for evolution of STs in Nesseiria meningitidis. Their model assumes that transmissibility is determined by ST, not serotype, but they do not seem to discuss the biological reason for this. An alternative model discussed by Lamb [24] also assumes that transmission is due to ST. The models of Lipsitch [27] and Lipsitch et al. [29] assume that transmission is attributable to serotype. It makes sense to model from the serotype perspective as the serotype is a known virulence factor of the bacterium and penicillin resistance has been observed for different serotypes involved in disease.

We may ask how our results compare with other published literature on pneumococcus models, particularly Lipsitch’s results. There are several other mathematical models of pneumococcal spread (for example [21,39]), but most of them are trying to model different aspects of the disease, in particular, penicillin resistance, so their results do not directly compare with ours. Lipsitch considers only serotypes but allows an individual to be dually colonized with both serotypes. We consider the interaction between serotypes and STs but do not allow dual colonization. As the models are different so are the conclusions, in particular Lipsitch’s model has an equilibrium where the two serotypes coexist. As our model is mathematically simpler we can get more complete mathematical results.

Lipsitch observed numerically that if the vaccine targets one of the two serotypes then reducing carriage of the VT serotype resulted in an increased carriage of the NVT serotype. The total carriage could remain the same but was not increased. If there were three serotypes then vaccination could actually increase pneumococcal carriage. In our model serotype replacement also occurs as vaccination shifts carriage of the VT serotype to the NVT serotype but the total carriage remains the same.

Temime et al. [40] study the effect of a vaccine on penicillin resistance. They use an age-structured compartmental model. This model does not consider the possibility of coexistence of strains within the population, or an individual. The model focuses on VT and NVT serotypes and considers varying degrees of resistance. It does not allow for variation in transmission or carriage duration for different pneumococcal serotypes. Although their assumptions are not directly comparable with our model or Lipsitch’s their results on serotype replacement are qualitatively the same as in Lipsitch’s [27] model.

Temime et al. [41] also model the impact of pneumococcal vaccines. Individuals can be dually colonized. They also use an age-structured model and consider capsular switching. Temime et al. perform a numerical simulation assuming that the vaccine coverage rate is 90% and they used parameter estimates from a literature search to explore the effect that capsular switch has on the impact of a vaccine. Their results suggest that capsular switch should not significantly affect the benefits obtained through the use of a vaccine indicating that the reduction in disease incidence should not decrease due to switching.
Our model assumes that $P_1$ and $P_2$ are constants determined by the genetic material. Thus, when an individual is newly colonized with ST $i$ the or she manifests as serotype 1 with probability $P_i$ and serotype 2 with probability $1 - P_i$, possibly by capsular switch, whatever the serotype of the individual who transmitted the bacteria. An alternative model without capsular switch would be to assume that a newly colonized individual has both the same ST and serotype as the transmitting individual. This would lead to a different model which could be analysed similarly.

The model discussed in this paper did not show the possibility of coexistence of STs in the population except at special parameter values. However, coexistence of STs or serotypes within an individual host was not considered in this model. Multiple carriage of serotypes has been documented, but in one study appears rare [19] with a longitudinal study of pneumococcus in 82 children less than 2 years old in the USA showing carriage of two serotypes in 4% of isolates examined and three serotypes in 0.3%. Multiple pneumococcal colonization has been observed in other studies [19,17,11]. Hence if co-infection is indeed rare, our model may be valuable as an approximation to the real situation where co-infection is possible and in any case our model is a basis on which to build future work (currently in progress, but mathematically far more difficult) with co-infection included. Longitudinal carriage studies have assessed serotypes colonizing but no studies with appropriate ST and serotype data could be identified to obtain an idea of what happens from the genetic perspective in dual colonization. This type of longitudinal study is required to establish an appropriate model for further analysis.

Coexistence of STs or serotypes within an individual appears to be a necessary prerequisite for coexistence of STs within a population. By excluding the possibility of coexistence within an individual in the model coexistence of the two STs is not possible in the population at equilibrium. This is a significant conclusion in spite of the simplifying assumptions.

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