A Mathematical Model of Pneumococcal Carriage and Transmission

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Abstract

Streptococcus pneumoniae is a bacterium commonly found in the path from the noses to the throats of young children. Pneumococcal serotypes can cause a variety of diseases such as meningitis. One major problem when attempting to introduce appropriate vaccines is that the sequence types (genetic material found in the serotypes) which are associated with the disease can be present in a number of different serotypes. The aim of the project is to examine a system of ordinary differential equations that has been proposed as a simple model of the case when a sequence type is able to manifest itself in one vaccine serotype and one non-vaccine serotype. The analytical results are carried out where equilibrium solutions, effective reproductive number, local stability analysis and global stability analysis are determined. To confirm the analytical results, simulations with real-life parameter values are performed.

Declaration

I, the undersigned, hereby declare that the work contained in this research project is my original work, and that any work done by others or by myself previously has been acknowledged and referenced accordingly.

Pie Sinangwanabose, 22 May 2014

Contents

1. Introduction

Streptococcus pneumoniae is a bacterium commonly found in the nasopharynx (a space in the upper throat that lies behind the nose) of young children. It was discovered simultaneously and independently by an American physician George Miller Sternberg and a French chemist Louis Pasteur in 1881 (Lamb et al., 2011). Pneumococcus can cause a number of different infections such as ear infection, sinusitis and pneumonia, and diseases like meningitis and septicaemia. It is spread through direct contact with infected individuals or via coughs and sneezes. Worldwide, there are approximately one and half million deaths each year due to the pneumococcal disease, including $700,000$ to one million children under the age of 5 years (Greenhalgh et al., 2011). Pneumococcal carriage rate and transmission within a community depend on several factors such as frequent close contact with other individuals, particularly young children in environments such as child care centres, and high incidence of viral respiratory tract infections (Lamb, 2009).

Pneumococcal serotypes are defined according to the structure of the polysaccharide capsule which encases the bacterium. The capsule protects the bacterium from the body immunity and enables it to cause infection and disease (Greenhalgh et al., 2012). The level of virulence of the bacterium will depend on the capsule meaning that some serotypes will be more virulent than others.

The serotypes are classified in a serogroup according to their antigens. These are the substances that can cause the immune body to produce antibodies against them. At least 46 serogroups containing more than 90 distinct pneumococcal serotypes are known but the majority of pneumococcal disease is caused by $20-30$ serotypes (Greenhalgh et al., 2012).

According to the DNA structure, the streptococcus pneumoniae bacterium may also be categorised by multi-locus sequence types MLSTs (Lamb, 2009). There are hundreds different pneumococcal MLSTs and some of these can be associated with more than one serotype (Lamb et al., 2011). The pneumococcal sequence types are defined according to the 7 house-keeping genes identified within genetic material. These genes are relatively stable over time and are used to determine the sequence type (Lamb, 2009). The serotype classification is based on the outer bacterial coating, whereas the sequence type depends on the inner genetic material. It has been demonstrated that some sequence types are more associated with particular serotypes than others. Therefore, there is a correlation between invasive sequence types and invasive serotypes, with the most invasive sequence types corresponding to the most invasive serotypes (Greenhalgh et al., 2012).

The first treatments used to combat against pneumococcal infection and disease were antibiotics (Greenhalgh et al., 2012). In order to stop the pneumococcal infection and disease, two kinds of vaccines have been developed; a 23-valent polysaccharide vaccine which has purified capsular polysaccharide from 23 different pneumococcal serotypes and a 7-valent conjugate vaccine with purified capsular polysaccharide from 7 different pneumococcal serotypes conjugated to protein. The latter is more effective in preventing pneumococcal infection amongst children under two years of age (Lamb et al., 2011).

The 23-valent is $60\%-70\%$ effective against the 23 vaccine serotypes which account for $85\%-90\%$ of the circulating pneumococcal strains. The 7-valent conjugate vaccine is much more effective, but against only 7 vaccine serotypes. But one advantage of the 7-valent vaccine is that, in preventing carriage, it has the potential to produce herd immunity in the population (Lamb et al., 2011).

The advantage of pneumococcal conjugate vaccine is to prevent the disease in the risk group (young children) and the carriage of the serotypes which are causing the invasive disease. In preventing carriage, the 7-valent pneumococcal conjugate vaccine allows herd immunity to occur in the population. This

occurs when the vaccinated group brings protection to the whole population. Since the conjugate vaccine reduces the carriage of the 7-valent vaccine type serotypes in children less than two years of old, then the transmission of these serotypes to adult population will be prevented (Lamb, 2009).

The key problem that we are interested in is that the sequence types are able to manifest themselves in more than one serotype. This is a problem if an invasive sequence type is associated with non-vaccine type serotypes. So, this could result in a loss in effectiveness of the vaccine.

The study done in Scotland was concerned with serotype 14 which was potentially characterised by the increasing of invasive disease and was found to be associated with ten different sequence types. Six of these sequence types can manifest themselves in many different serotypes including five serotypes that are not included in the conjugate vaccine (Lamb et al., 2011).

In (Lamb et al., 2011) and (Greenhalgh et al., 2012), mathematical models have been developed to investigate this problem of sequence types being associated with multiple serotypes, some of which are not included in the vaccine. In the simplest case (Lamb et al., 2011), a single sequence type which is associated with a vaccine-type serotype and a non-vaccine type serotype is considered. The underlying host population is then subdivided into four classes, namely unvaccinated and vaccinated susceptibles, unvaccinated carriers, and, finally, individuals, who despite having been vaccinated, carry the disease through the manifestation of the sequence type in the non-vaccine serotype. The transmission of the disease between the different classes is then represented by a system of four ordinary differential equations. In the more complicated model examined in (Greenhalgh et al., 2012), the case of two sequence types and two serotypes is considered, resulting in a model involving a system of six differential equations.

In the population of the simple model, two serotypes are considered where the infection with one serotype reduces the probability of the infection with another serotype. The vaccination of an individual is completely effective against the first serotype and varies the effectiveness against the second. For that the two serotypes have different carriage transmission coefficients. A constant fraction of the population is assumed to be vaccinated at birth (Greenhalgh et al., 2011).

2. Mathematical modelling of pneumococcal carriage and transmission in children

Several mathematical models have been developed to show the problem of sequence types being associated with multiple serotypes. This chapter describes the simplest model developed in (Lamb et al., 2011). It consists of one sequence type associated with two serotypes.

The model considers four compartments of individuals and takes the form of a system of ordinary differential equations involving the following variables:

$X(t)$: population size of unvaccinated susceptible individuals at time t,

$V(t)$: population size of vaccinated susceptible individuals at time t,

$T(t)$: population size of unvaccinated individuals at time who are carrying the sequence type,

$V_T(t)$: population size of vaccinated individuals at time who are carrying the sequence type.

2.1 Model assumptions

In this model, we assume that the proportion f of children who receive the vaccine is constant. The sequence type can express itself as either serotype 1 (Y_1) or serotype 2 (Y_2) with proportions pT and $(1-p)T$ respectively. Vaccinated children are completely protected against serotype 1 but only partially or not at all against serotype 2 (Lipsitch, 1997). The susceptible children enter the population of interest at a constant rate L and they leave the population at a per capita rate u. The transmission is determined by the sequence type not the serotype (Lamb et al., 2011). For that, the unvaccinated and vaccinated susceptibles are infected at a rate $\beta X(T+V_T)$ and $\beta V(T+V_T)$ respectively. The children who were carrying the sequence type become susceptible again at a rate γ.

2.2 Mathematical model

From the assumptions, we can construct a diagram showing the process of the system; see Figure 2.1.

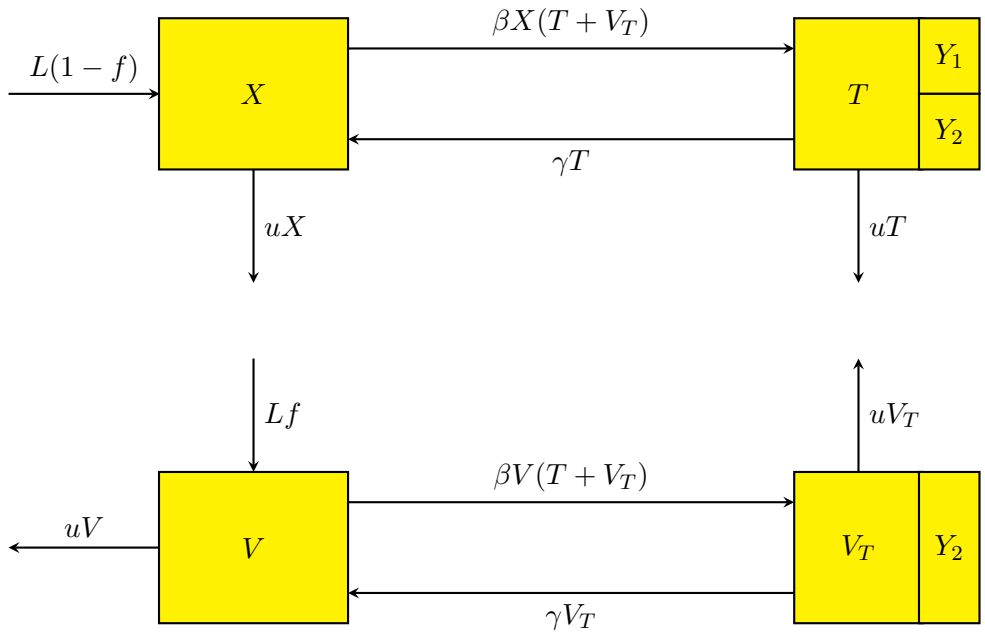

Figure 2.1: Flow diagram for the model

The ordinary differential equations (ODEs) that describe the process illustrated in Figure 2.1 are

$$\begin{aligned}
\frac{dX}{dt} &= L(1-f) - uX - \beta X(T+V_T) + \gamma T \quad &= f_1(\underline{W}) \\
\frac{dT}{dt} &= \beta X(T+V_T) - (\gamma+u)T &= f_2(\underline{W}) \\
\frac{dV}{dt} &= Lf - uV - \beta V(T+V_T) + \gamma V_T &= f_3(\underline{W}) \\
\frac{dV_T}{dt} &= \beta V(T+V_T) - (\gamma+u)V_T &= f_4(\underline{W}),
\end{aligned} \tag{2.2.1}$$

where $\underline{W} = (X, T, V, V_T)$.

The time evolution of the population of unvaccinated susceptibles is governed by the first of these equations. As t increases, the population size $X(t)$ can increase through the introduction of new unvaccinated children ($L(1-f)$) and also through unvaccinated carriers returning to the unvaccinated class (γT). Equally, $X(t)$ can decrease due to unvaccinated susceptibles becoming unvaccinated carriers through contact with either unvaccinated carriers ($-\beta XT$) or vaccinated carriers ($-\beta XV_T$), and also due to the natural migration of individuals from this class ($-uX$).

However, the second equation is representing the time evolution of the population of unvaccinated carrying sequence type which manifests itself as two serotypes (Y_1 and Y_2). The population size $T(t)$ can increase due to unvaccinated susceptibles becoming infected by unvaccinated carriers (βXT) or vaccinated carriers (βXV_T). Similarly, the population can decrease through the unvaccinated carriers coming back to the unvaccinated susceptibles ($-\gamma T$) and also through the natural migration of individuals from this compartment ($-uT$).

If we let the total population size at time t be represented by $N(t)$, so that $N(t) = X(t) + T(t) + V(t) + V_T(t)$, then, on adding the four equations in (2.2.1), we find that

$$\frac{dN}{dt} = L - uN. \tag{2.2.2}$$

The equation (2.2.2) will play a useful role in the analysis that follows.

3. Model analysis

In this chapter, we identify the equilibrium solutions, or steady states, of the system (2.2.1). In addition, the effective reproductive number will be discussed to show whether a disease spreads or dies out. Then a local stability analysis is carried out to determine whether small perturbations from a steady state decay to zero or grow. And again, we shall perform a global stability analysis aimed at finding the set of initial states from which solutions will converge to a given steady state. Finally, with specific initial conditions and realistic values of parameters, simulations will be done to emphasize the analytical results.

3.1 Equilibrium solutions

We need to solve the system of algebraic equations $f_i(\underline{\hat{W}}) = 0$, $i = 1, 2, 3, 4$, where, for each i, f_i is the function appearing in the system (2.2.1). Thus, at equilibrium, (2.2.1) becomes

$$\begin{aligned} L(1-f) - u\hat{X} - \beta\hat{X}(\hat{T} + \hat{V}_T) + \gamma\hat{T} &= 0 \\ \beta\hat{X}(\hat{T} + \hat{V}_T) - (\gamma + u)\hat{T} &= 0 \\ Lf - u\hat{V} - \beta\hat{V}(\hat{T} + \hat{V}_T) + \gamma\hat{V}_T &= 0 \\ \beta\hat{V}(\hat{T} + \hat{V}_T) - (\gamma + u)\hat{V}_T &= 0. \end{aligned} \tag{3.1.1}$$

By adding the first two equations of (3.1.1), we get $\hat{X} + \hat{T} = \dfrac{L}{u}(1-f)$. Similarly, combining the last two equations yields $\hat{V} + \hat{V}_T = \dfrac{L}{u}f$.

From (2.2.2), the total population $N(t)$ satisfies the equation $\dfrac{d\hat{N}}{dt} = L - uN$.

When $f(N) = L - uN > 0$ then $\dfrac{dN}{dt} > 0$ and this implies that $N(t)$ is increasing. But if $f(N) < 0$ then $\dfrac{dN}{dt} < 0$, and so, $N(t)$ is decreasing; see Figure 3.1. Consequently, $N(t) \longrightarrow \dfrac{L}{u}$ as $t \longrightarrow \infty$. At equilibrium, the total number of hosts in the population is $\dfrac{L}{u}$.

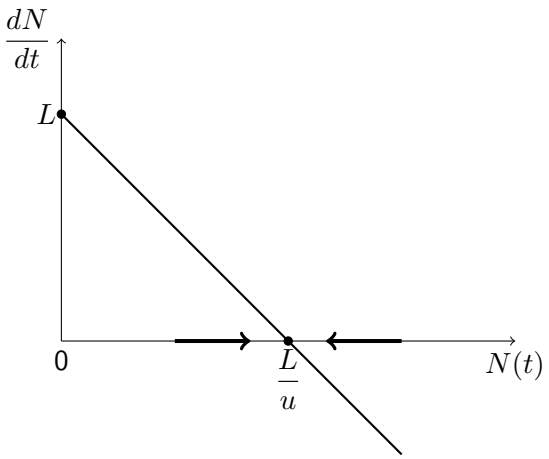

Figure 3.1: Phase-line plot diagram

Substituting $\hat{X} = \frac{L}{u}(1-f) - \hat{T}$ into the second equation of (3.1.1) and $\hat{V} = \frac{L}{u}f - \hat{V}_T$ into the last equation of (3.1.1), leads to

$$\beta\left(\frac{L}{u}(1-f) - \hat{T}\right)(\hat{T} + \hat{V}_T) - (\gamma + u)\hat{T} = 0 \tag{3.1.2}$$

and

$$\beta\left(\frac{L}{u}f - \hat{V}_T\right)(\hat{T} + \hat{V}_T) - (\gamma + u)\hat{V}_T = 0. \tag{3.1.3}$$

Adding (3.1.2) and (3.1.3), we obtain

$$(\hat{T} + \hat{V}_T)\left[\beta\left(\frac{L}{u} - (\hat{T} + \hat{V}_T)\right) - (\gamma + u)\right] = 0,$$

which means that either $(\hat{T}+\hat{V}_T) = 0$ or $\beta\left(\frac{L}{u} - (\hat{T} + \hat{V}_T)\right) - (\gamma+u) = 0$. Since we are only interested in physically meaningful equilibria, if $(\hat{T} + \hat{V}_T) = 0$ then we must have $\hat{T} = 0$, $\hat{V}_T = 0$ and hence, $\hat{X} = \frac{L}{u}(1-f)$ and $\hat{V} = \frac{L}{u}f$.

Hence, the carriage-free equilibrium (CFE) solution is given by:

$$\left(\hat{X}, \hat{T}, \hat{V}, \hat{V}_T\right) = \left(\frac{L}{u}(1-f), 0, \frac{L}{u}f, 0\right).$$

It follows that at CFE, there are no children carrying the sequence type. The total population at this equilibrium consists only of unvaccinated and vaccinated susceptibles.

If $\hat{T} + \hat{V}_T \neq 0$, then $\beta\left(\frac{L}{u} - (\hat{T} + \hat{V}_T)\right) - (\gamma + u) = 0$, and so

$$\hat{T} + \hat{V}_T = \frac{L}{u} - \frac{\gamma + u}{\beta}. \tag{3.1.4}$$

Dividing the second and last equations of (3.1.1) and using $\hat{X}+\hat{T}=\frac{L}{u}(1-f)$, $\hat{V}+\hat{V}_T=\frac{L}{u}f$ gives

$$\frac{\hat{T}}{\hat{V}_T}=\frac{\hat{X}}{\hat{V}}=\frac{\frac{L}{u}(1-f)-\hat{T}}{\frac{L}{u}f-\hat{V}_T}.$$

It follows that

$$\hat{T}\left(\frac{L}{u}f-\hat{V}_T\right)=\hat{V}_T\left(\frac{L}{u}(1-f)-\hat{T}\right)$$

and then

$$\hat{T}f=\hat{V}_T(1-f).$$

Thus $\hat{V}_T=(\hat{T}+\hat{V}_T)f$ and $f\hat{T}=\hat{V}_T(1-f)$. Since $\hat{T}+\hat{V}_T=\frac{L}{u}-\frac{\gamma+u}{\beta}$, then $\hat{V}_T=f\left(\frac{L}{u}-\frac{\gamma+u}{\beta}\right)$ and $\hat{T}=(1-f)\left(\frac{L}{u}-\frac{\gamma+u}{\beta}\right)$.

Again, It has been shown that $\hat{X}+\hat{T}=(1-f)\frac{L}{u}$ and $\hat{V}+\hat{V}_T=f\frac{L}{u}$. Then $\hat{X}=(1-f)\frac{L}{u}-(1-f)\left(\frac{L}{u}-\frac{\gamma+u}{\beta}\right)=(1-f)\frac{\gamma+u}{\beta}$ and $\hat{V}=f\frac{L}{u}-f\left(\frac{L}{u}-\frac{\gamma+u}{\beta}\right)=f\frac{\gamma+u}{\beta}$.

Therefore, the carriage equilibrium solution (CE) is

$$\left(\hat{X},\hat{T},\hat{V},\hat{V}_T\right)=\left((1-f)\frac{\gamma+u}{\beta},(1-f)\left(\frac{L}{u}-\frac{\gamma+u}{\beta}\right),f\frac{\gamma+u}{\beta},f\left(\frac{L}{u}-\frac{\gamma+u}{\beta}\right)\right).$$

The CE will have biological meaning if $\frac{L}{u}\geq\frac{\gamma+u}{\beta}$ and this is equivalent to $\frac{L\beta}{u(\gamma+u)}\geq 1$. So, the basic reproductive number which is a number of secondary infections caused by a single primary infection (Lamb, 2014) is $R=\frac{L\beta}{u(\gamma+u)}$.

Therefore, if $R>1$, both the CFE and CE exist but if $R\leq 1$, there is only the CFE.

In addition, if there is no vaccination in the population ($f=0$), at the CFE all children $\left(\frac{L}{u}\right)$ will be found only in the unvaccinated susceptible compartment (X). At the CE, $\frac{\gamma+u}{\beta}$ children will be found in the unvaccinated susceptible compartment X and $\frac{L}{u}-\frac{\gamma+u}{\beta}$ children are in the unvaccinated carrying compartment (T).

However, if all children are vaccinated ($f=1$), at CFE, all children are in the vaccinated susceptible compartment (V) and at CE, $\frac{\gamma+u}{\beta}$ children are in the vaccinated susceptible compartment (V) and $\frac{L}{u}-\frac{\gamma+u}{\beta}$ children are in the vaccinated carrying compartment (V_T).

At CE, the number of children carrying serotypes 1 and 2 is given, respectively, by

$$\begin{aligned}\hat{Y_1} &= p\hat{T} = p(1-f)\left(\frac{L}{u} - \frac{\gamma+u}{\beta}\right),\\ \hat{Y_2} &= (1-p)\hat{T} + \hat{V}_T\\ &= (1-p)(1-f)\left(\frac{L}{u} - \frac{\gamma+u}{\beta}\right) + f\left(\frac{L}{u} - \frac{\gamma+u}{\beta}\right)\\ &= (1-p(1-f))\left(\frac{L}{u} - \frac{\gamma+u}{\beta}\right).\end{aligned}$$

3.2 Effective reproductive number (R_e)

The effective reproductive number is the expected number of secondary cases caused by a typical infected individual entering a completely susceptible population at equilibrium (Lamb et al., 2011). It is called effective because of the vaccine effect that is built into the model.

The average carriage duration of a serotype is $\frac{1}{\gamma+u}$ for both vaccinated and unvaccinated children. In our case, there are two types of infected individuals, unvaccinated (type 1) and vaccinated (type 2). Let m_{ij} denote the expected number of type i infected individuals caused by a single type j infected individual entering the CFE during his or her infectious period, where i, j can take values 1 and 2. Thus, the matrix $M = (m_{ij})$ is given by

$$M = \begin{pmatrix} \frac{\beta L(1-f)}{u(\gamma+u)} & \frac{\beta L(1-f)}{u(\gamma+u)} \\ \frac{\beta L f}{u(\gamma+u)} & \frac{\beta L f}{u(\gamma+u)} \end{pmatrix}.$$

The characteristic equation of the matrix M is given by

$$\begin{vmatrix} \frac{\beta L(1-f)}{u(\gamma+u)} - \lambda & \frac{\beta L(1-f)}{u(\gamma+u)} \\ \frac{\beta L f}{u(\gamma+u)} & \frac{\beta L f}{u(\gamma+u)} - \lambda \end{vmatrix} = 0$$

from which we obtain

$$\left(\frac{\beta L(1-f)}{u(\gamma+u)} - \lambda\right)\left(\frac{\beta L f}{u(\gamma+u)} - \lambda\right) - \left(\frac{\beta L(1-f)}{u(\gamma+u)}\right)\left(\frac{\beta L f}{u(\gamma+u)}\right) = 0.$$

Simplifying then leads to

$$\lambda^2 - \left(\frac{\beta L f}{u(\gamma+u)} + \frac{\beta L(1-f)}{u(\gamma+u)}\right)\lambda = \left(\lambda - \frac{\beta L}{u(\gamma+u)}\right)\lambda = 0$$

and therefore M has eigenvalues

$$\lambda_1 = 0 \quad \text{and} \quad \lambda_2 = \frac{\beta L}{u(\gamma+u)}.$$

The effective reproductive number R_e corresponds to the largest eigenvalue and hence $R_e = \dfrac{\beta L}{u(\gamma+u)}$, since $\dfrac{\beta L}{u(\gamma+u)} > 0$. It follows that the basic and effective reproductive numbers are equal. Note that the effective reproductive number does not depend on the vaccination fraction f because the sequence type can express itself as serotype 2.

3.3 Local stability analysis

In order to find out what happens to the number of unvaccinated and vaccinated susceptibles and carriers in the long term, a linear local stability analysis is implemented.

The Jacobian matrix of the model (2.2.1) is given by

$$J = \begin{bmatrix} \dfrac{\partial f_1}{\partial X} & \dfrac{\partial f_1}{\partial T} & \dfrac{\partial f_1}{\partial V} & \dfrac{\partial f_1}{\partial V_T} \\ \dfrac{\partial f_2}{\partial X} & \dfrac{\partial f_2}{\partial T} & \dfrac{\partial f_2}{\partial V} & \dfrac{\partial f_2}{\partial V_T} \\ \dfrac{\partial f_3}{\partial X} & \dfrac{\partial f_3}{\partial T} & \dfrac{\partial f_3}{\partial V} & \dfrac{\partial f_3}{\partial V_T} \\ \dfrac{\partial f_4}{\partial X} & \dfrac{\partial f_4}{\partial T} & \dfrac{\partial f_4}{\partial V} & \dfrac{\partial f_4}{\partial V_T} \end{bmatrix}$$

and so

$$J = \begin{bmatrix} -u-\beta(T+V_T) & \gamma-\beta X & 0 & -\beta X \\ \beta(T+V_T) & \beta X-(\gamma+u) & 0 & \beta X \\ 0 & -\beta V & -u-\beta(T+V_T) & \gamma-\beta V \\ 0 & \beta V & \beta(T+V_T) & \beta V-(\gamma+u) \end{bmatrix}. \tag{3.3.1}$$

At the CFE $\left(\dfrac{L}{u}(1-f), 0, \dfrac{L}{u}f, 0\right)$, (3.3.1) becomes

$$J_{CFE} = \begin{bmatrix} -u & \gamma-\beta\dfrac{L}{u}(1-f) & 0 & -\beta\dfrac{L}{u}(1-f) \\ 0 & \beta\dfrac{L}{u}(1-f)-(\gamma+u) & 0 & \beta\dfrac{L}{u}(1-f) \\ 0 & -\beta\dfrac{L}{u}f & -u & \gamma-\beta\dfrac{L}{u}(1-f) \\ 0 & \beta\dfrac{L}{u}f & 0 & \beta\dfrac{L}{u}f-(\gamma+u) \end{bmatrix}.$$

The characteristic equation is $det(J_{CFE}-\lambda I)=0$. Thus

$$\begin{vmatrix} -u-\lambda & \gamma-\beta\dfrac{L}{u}(1-f) & 0 & -\beta\dfrac{L}{u}(1-f) \\ 0 & \beta\dfrac{L}{u}(1-f)-(\gamma+u)-\lambda & 0 & \beta\dfrac{L}{u}(1-f) \\ 0 & -\beta\dfrac{L}{u}f & -u-\lambda & \gamma-\beta\dfrac{L}{u}(1-f) \\ 0 & \beta\dfrac{L}{u}f & 0 & \beta\dfrac{L}{u}f-(\gamma+u)-\lambda \end{vmatrix} = 0$$

and, expanding by column 1, we obtain

$$det(J_{CFE}-\lambda I) = -(u+\lambda)\begin{vmatrix} \beta\frac{L}{u}(1-f)-(\gamma+u)-\lambda & 0 & \beta\frac{L}{u}(1-f) \\ -\beta\frac{L}{u}f & -u-\lambda & \gamma-\beta\frac{L}{u}(1-f) \\ \beta\frac{L}{u}f & 0 & \beta\frac{L}{u}f-(\gamma+u)-\lambda \end{vmatrix}$$

$$= -(u+\lambda)\begin{vmatrix} -(\gamma+u)-\lambda & 0 & \beta\frac{L}{u}(1-f) \\ -\beta\frac{L}{u}f-\gamma+\beta\frac{L}{u}(1-f) & -u-\lambda & \gamma-\beta\frac{L}{u}(1-f) \\ (\gamma+u)+\lambda & 0 & \beta\frac{L}{u}f-(\gamma+u)-\lambda \end{vmatrix}$$

(where we have applied the column transformation $c_1 \to c_1 - c_3$ in the 3×3 determinant)

$$= (u+\lambda)^2(\gamma+u+\lambda)\left(\beta\frac{L}{u}f-(u+\gamma)-\lambda+\beta\frac{L}{u}(1-f)\right)$$
$$= (u+\lambda)^2(\gamma+u+\lambda)\left(\beta\frac{L}{u}-(u+\gamma)-\lambda\right).$$

Consequently, the eigenvalues of J_{CFE} are $\lambda_{1,2}=-u$, $\lambda_3=-(\gamma+u)$ and $\lambda_4=\beta\frac{L}{u}-(\gamma+u)$. The eigenvalues $\lambda_{1,2}$, and λ_3 are clearly negative and λ_4 is negative if $\beta\frac{L}{u}<(\gamma+u)$.

Therefore, the CFE is locally asymptotically stable if $R_e<1$ and it is unstable if $R_e>1$.

At the CE $\left((1-f)\frac{\gamma+u}{\beta},(1-f)\left(\frac{L}{u}-\frac{\gamma+u}{\beta}\right),f\frac{\gamma+u}{\beta},f\left(\frac{L}{u}-\frac{\gamma+u}{\beta}\right)\right)$, (3.3.1) becomes

$$J_{CE}=\begin{bmatrix} \gamma-\beta\frac{L}{u} & \gamma-(1-f)(\gamma+u) & 0 & -(1-f)(\gamma+u) \\ \beta\frac{L}{u}-(\gamma+u) & -f(\gamma+u) & 0 & (1-f)(\gamma+u) \\ 0 & -f(\gamma+u) & \left(\gamma-\beta\frac{L}{u}\right) & \gamma-f(\gamma+u) \\ 0 & f(\gamma+u) & \beta\frac{L}{u}-(\gamma+u) & (f-1)(\gamma+u) \end{bmatrix}. \tag{3.3.2}$$

Using Sage, the eigenvalues of the matrix (3.3.2) are $\lambda_{1,2}=-u$, $\lambda_3=-\beta\frac{L}{u}$ and $\lambda_4=-\beta\frac{L}{u}+(\gamma+u)$. All these eigenvalues are negative if $\beta\frac{L}{u}>(\gamma+u)$. Therefore, for $R_e>1$, the CE is locally asymptotically stable and it doesn't exist as a physical equilibrium when $R_e<1$.

3.4 Global stability analysis

It is known that solutions which start sufficiently close to a locally asymptotically stable equilibrium converge to the equilibrium as $t\longrightarrow\infty$. But we do not know, quantitatively, what "sufficiently close"

means. Consequently, given a set of initial conditions $X(0)$, $T(0)$, $V(0)$, $V_T(0)$, we cannot say what is going to happen to the corresponding unique solution as $t \longrightarrow \infty$. Although we can compute the distance from this initial state to the equilibrium, how do we know if the distance is small enough?

The aim of the global stability analysis is to improve these results. We want to determine all the physically meaningful initial states that produce solutions converging to a given equilibrium. This is done by using the differential inequalities and comparison theorem to compare the solutions of the system at each moment with solutions of simpler differential equations.

It has been shown that the total population $N(t) = X(t) + T(t) + V(t) + V_T(t)$ satisfies the scalar ODE

$$\frac{dN(t)}{dt} = L - uN(t)$$

and so $N(t) \longrightarrow \frac{L}{u}$ from below as $t \longrightarrow \infty$ when $N(0) < \frac{L}{u}$, and $N(t) \longrightarrow \frac{L}{u}$ from above as $t \longrightarrow \infty$ when $N(0) > \frac{L}{u}$; see Figure 3.1.

A key part of the global analysis strategy is to investigate the coupled pair of ODEs that govern the dynamics of the combined susceptible class $X + V$ and combined carrying class $T + V_T$.

From (2.2.1), the population of the susceptible children to carriage of the sequence type and the carriers satisfy

$$\frac{d}{dt}(X + V) = L - u(X + V) - \beta(X + V)(T + V_T) + \gamma(T + V_T) \tag{3.4.1}$$

and

$$\frac{d}{dt}(T + V_T) = \beta(X + V)(T + V_T) - (\gamma + u)(T + V_T) \tag{3.4.2}$$

respectively.

Taking $S = X + V$ and $C = T + V_T$, (3.4.1) and (3.4.2) can be written as

$$\begin{aligned} S' &= L - uS - \beta SC + \gamma C = F(S, C), \\ C' &= \beta SC - (\gamma + u)C = G(S, C). \end{aligned} \tag{3.4.3}$$

Let us consider two cases; when $R_e = \frac{L\beta}{u(\gamma + u)} \leq 1$ and when $R_e = \frac{L\beta}{u(\gamma + u)} > 1$.

(i) When $R_e = \frac{L\beta}{u(\gamma + u)} \leq 1$.

To determine equilibrium solutions (S^*, C^*) of the system (3.4.3) we solve $F(S^*, C^*) = 0$ and $G(S^*, C^*) = 0$, obtaining

$$\begin{aligned} L - uS^* - \beta S^*C^* + \gamma C^* &= 0 \\ \beta S^*C^* - (\gamma + u)C^* &= 0. \end{aligned} \tag{3.4.4}$$

Adding both equations of (3.4.4) leads to $S^* + C^* = \frac{L}{u}$.

Taking $S^* = \frac{L}{u} - C^*$ in the second equation of the system (3.4.4), we get

$$C^* \left(\beta \frac{L}{u} - (\gamma + u) - \beta C^* \right) = 0.$$

So, $C^* = 0$ or $C^* = \frac{L}{u} - \frac{\gamma + u}{\beta}$.

It follows that

$$(S^*, C^*) = \left(\frac{L}{u}, 0 \right) \quad \text{or} \quad \left(\frac{\gamma + u}{\beta}, \frac{L}{u} - \frac{\gamma + u}{\beta} \right).$$

Since $\frac{L\beta}{u(\gamma + u)} \leq 1$, $\frac{L}{u} \leq \frac{\gamma + u}{\beta}$ and then $\frac{L}{u} - \frac{\gamma + u}{\beta} \leq 0$.

Therefore, when $R_e \leq 1$, there exists only one physical meaningful equilibrium and this is $\left(\frac{L}{u}, 0 \right)$. This could have been deduced from the CFE $\left(\frac{L}{u}(1 - f), 0, f\frac{L}{u}, 0 \right)$ by taking $\frac{L}{u}(1-f) + f\frac{L}{u} = \frac{L}{u}$ and $0 + 0 = 0$.

A local stability analysis can be carried out using the Jacobian matrix

$$\begin{bmatrix} \frac{\partial F}{\partial S} & \frac{\partial F}{\partial C} \\ \frac{\partial G}{\partial S} & \frac{\partial G}{\partial C} \end{bmatrix},$$

and this shows that the equilibrium solution $\left(\frac{L}{u}, 0 \right)$ is locally asymptotically stable when $R_e < 1$.

We want to verify that $S(0) \geq 0$ and $C(0) \geq 0$ implies that $S(t) \geq 0$ and $C(t) \geq 0$ so that the solutions $S(t)$ and $C(t)$ are biologically meaningful.

Consider what happens on the S and C axes. If $C = 0$ then we get $C' = 0$ and $S' = L - uS$. By uniqueness of the solutions, the unique solution $(S(t), C(t))$ of the system of ODEs with initial conditions $(S(0), C(0)) = (S_0, 0)$ is $(S(t), 0)$, where $S(t)$ satisfies $S' = L - uS$, $S(0) = S_0$. So, the S axis is made up entirely of trajectories, and so trajectories starting in the first quadrant cannot break through the S-axis. This means that $C(t)$ can never be negative.

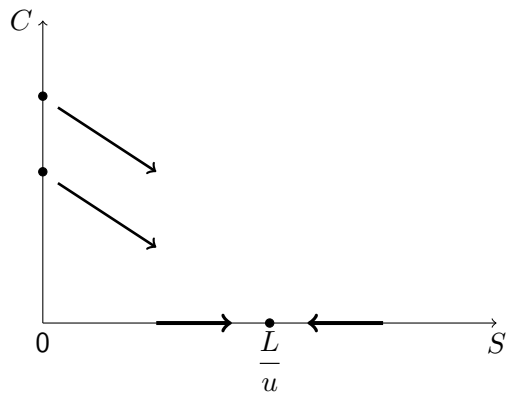

Figure 3.2: Phase-line analysis

If $S = 0$ then $S' = L + \gamma C$ and $C' = -(\gamma + u)C$ which shows that $S(t)$ increases, and $C(t)$ decreases, away from C axis. This means that trajectories do not pass through to the second quadrant; see Figure 3.2.

For the chosen parameter values, $L = 0.5$, $\beta = 8 \times 10^{-4}$, $u = 0.001$, $\gamma = 0.8$, the phase portraits of the system (3.4.3) provide some evidence about the long term behaviour of the solutions from different initial conditions and suggest that global stability results may be possible; see Figure 3.3.

Figure 3.3 confirms that $(S(t), C(t)) \longrightarrow \left(\frac{L}{u}, 0\right) = (500, 0)$ when $R_e < 1$ and $(S(0), C(0))$ is sufficiently close to $(500, 0)$.

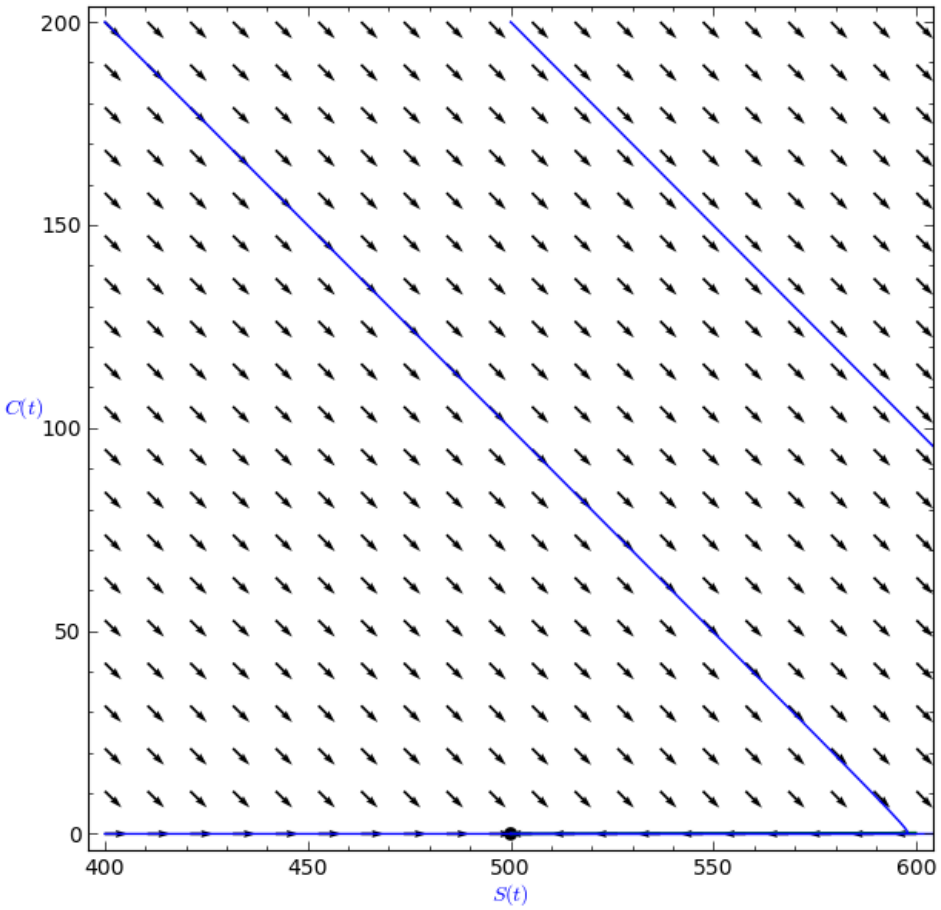

Figure 3.3: Phase portraits with the case $R_e < 1$

When $R_e = \dfrac{L\beta}{u(\gamma + u)} = 1$, the local stability analysis fails but the phase portraits again suggest global stability. For the chosen parameter values , $L = 0.5$, $\beta = 5 \times 10^{-6}$, $u = 0.001$, $\gamma = 0.0015$, the system approaches the CFE $(500, 0)$; see Figure 3.4.

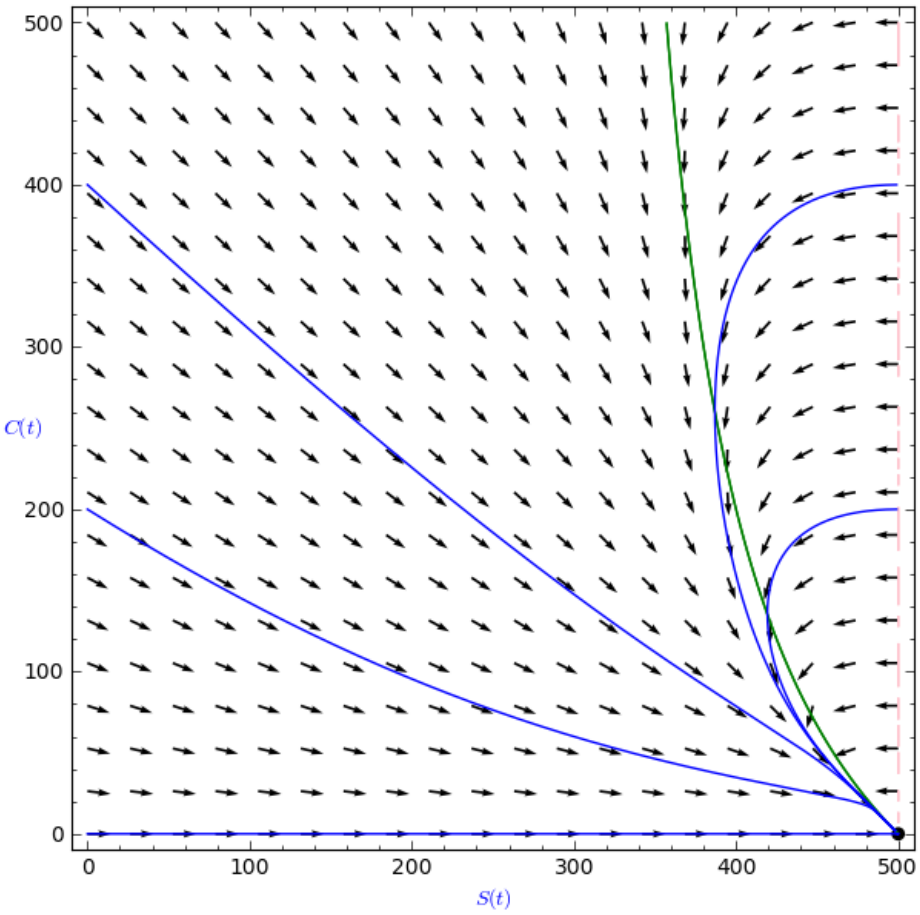

Figure 3.4: Phase portraits with the case $R_e = 1$

(ii) When $R_e = \dfrac{L\beta}{u(\gamma + u)} > 1$.

In this case, both equilibria are physical but now $\left(\dfrac{L}{u}, 0\right)$ is no longer stable; instead $\left(\dfrac{\gamma + u}{\beta}, \dfrac{L}{u} - \dfrac{\gamma + u}{\beta}\right)$ is locally asymptotically stable.

For the chosen parameter values, $L = 0.5$, $\beta = 8 \times 10^{-4}$, $u = 0.001$, $\gamma = 0.15$, Figure 3.5 confirms that $(S(t), C(t)) \longrightarrow \left(\dfrac{\gamma + u}{\beta}, \dfrac{L}{u} - \dfrac{\gamma + u}{\beta}\right) = (189, 311)$ when $R_e > 1$ and $(S(0), C(0))$ is sufficiently close to $(189, 311)$. And it also indicates that most solutions converge to the locally asymptotically stable equilibrium.

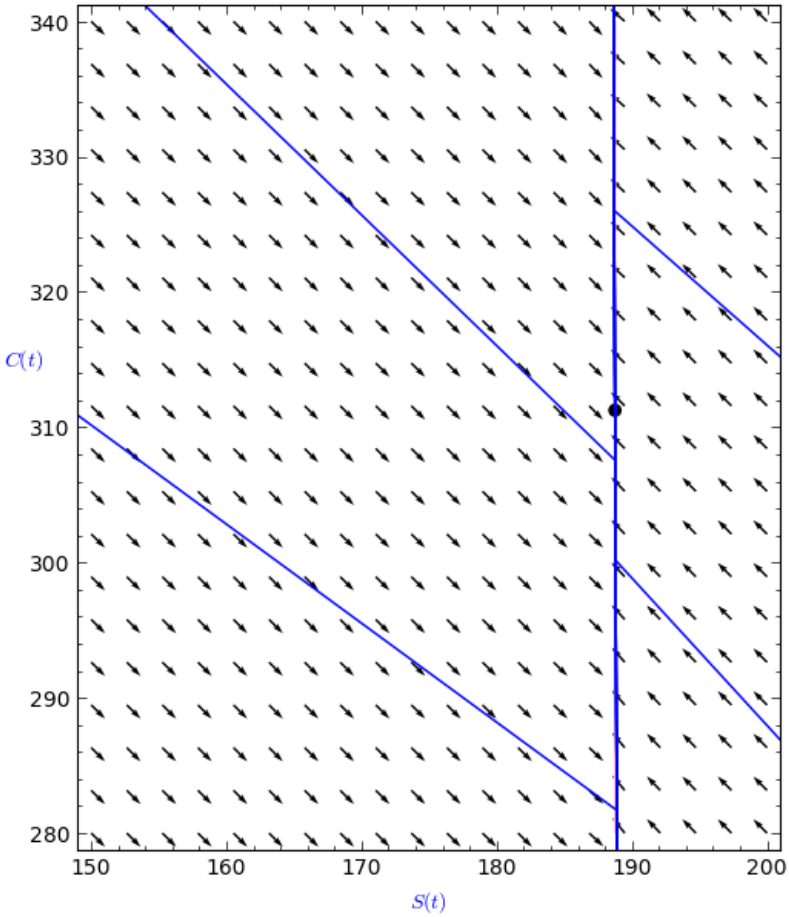

Figure 3.5: Phase portraits with the case $R_e > 1$

To analyse the global stability, three cases are again considered.

i) $R_e < 1$.

In this case, there is only the CFE. By using differential inequalities and some estimations, we can establish that the system is approaching the equilibrium solution. This means that $(X(t), T(t), V(t), V_T(t)) \longrightarrow \left(\frac{L}{u}(1-f), 0, \frac{L}{u}f, 0\right)$ for any $X(0) \geq 0$, $T(0) \geq 0$, $V(0) \geq 0$, $V_T(0) \geq 0$.

Now, let us prove that $S(0) \geq 0, C(0) \geq 0 \Rightarrow (S(t), C(t)) \longrightarrow \left(\frac{L}{u}, 0\right)$ as $t \longrightarrow \infty$.

We can start by showing that $C(t) \longrightarrow 0$ as $t \longrightarrow \infty$. This will involve the use of differential inequalities together with the following estimates:

(1) Since $N(t) \longrightarrow \frac{L}{u}$ as $t \longrightarrow \infty$ and $N(t) = S(t) + C(t)$, with $S(t) \geq 0, C(t) \geq 0$, given any $\epsilon > 0$, $\exists t \geq t_0 (= t_0(\epsilon))$ such that

$$S(t) \leq N(t) \leq \frac{L}{u} + \epsilon \quad \forall t \geq t_0. \tag{3.4.5}$$

(2) Since $R_e < 1$ and $\gamma, u, \beta > 0$, there exists $\epsilon > 0$ such that

$$-k_0 = (\gamma + u)(R_e - 1) + \beta\varepsilon = \beta\frac{L}{u} - (\gamma + u) + \beta\epsilon < 0. \tag{3.4.6}$$

We choose ϵ and $t_0 = t_0(\epsilon)$ so that both (3.4.5) and (3.4.6) hold.

Then, for $t \geq t_0$,

$$\begin{aligned}\frac{1}{C(t)}\frac{d}{dt}C(t) &= \beta S(t) - (\gamma + u)\\ &\leq \beta\left(\frac{L}{u} + \varepsilon\right) - (\gamma + u)\\ &= \beta\frac{L}{u} - (\gamma + u) + \beta\varepsilon = -k_0 < 0,\end{aligned}$$

and so

$$\frac{1}{C(t)}\frac{d}{dt}C(t) \leq -k_0, \quad \forall t \geq t_0. \tag{3.4.7}$$

Integrating both sides of (3.4.7) gives

$$\begin{aligned}\int_{t_0}^{t}\left(\frac{1}{C(t)}\frac{d}{dt}C(t)\right)ds &\leq \int_{t_0}^{t} -k_0 ds\\ \ln\left(\frac{C(t)}{C(t_0)}\right) &\leq -k_0(t - t_0),\end{aligned}$$

and it follows that, for all $t \geq t_0$,

$$C(t) \leq C(t_0)\exp(-k_0(t - t_0)).$$

Consequently, $C(t) \longrightarrow 0$ as $t \longrightarrow \infty$. Since $N(t) = S(t) + C(t) \longrightarrow \frac{L}{u}$ as $t \longrightarrow \infty$, we deduce that $S(t) \longrightarrow \frac{L}{u}$ as $t \longrightarrow \infty$.

Having established the long term behaviour of $S(t)$ and $C(t)$, we now consider the separate components $X(t), T(t), V(t)$ and $V_T(t)$. Since X, T, V, V_T are non-negative and $T(t) + V_T(t) \longrightarrow 0$, it follows immediately that $T(t) \longrightarrow 0$ and $V_T(t) \longrightarrow 0$ as $t \longrightarrow \infty$.

To determine what happens to $(X(t), V(t))$ as $t \longrightarrow \infty$, we must consider the first equation of the system (2.2.1).

Given any $\epsilon > 0$, there exists $t_1 = t_1(\epsilon) > 0$ such that

$$L(1 - f) - uX - \epsilon < \frac{dX}{dt} < L(1 - f) - uX + \epsilon \quad \forall t \geq t_1.$$

Let $X_{-\epsilon}$ and X_ϵ be the solutions of the initial value problems.

$$\begin{aligned}X'_{-\epsilon} &= L(1 - f) - uX - \epsilon, \quad X_{-\epsilon}(t_1) = X(t_1)\\ X'_{\epsilon} &= L(1 - f) - uX + \epsilon, \quad X_{\epsilon}(t_1) = X(t_1).\end{aligned}$$

By the comparison theorem (Birkhoff and Rota, 1982), $X_{-\epsilon}(t) \leq X(t) \leq X_{\epsilon}(t)\ \forall t \geq t_1$. Now $X_{-\epsilon}(t) \longrightarrow \dfrac{L(1-f)-\epsilon}{u}$ and $X_{\epsilon}(t) \longrightarrow \dfrac{L(1-f)+\epsilon}{u}$ as $t \longrightarrow \infty$.

Hence $\exists t_2 = t_2(\epsilon)$, $t_2 > t_1$, such that

$$X_{-\epsilon}(t) > \frac{L(1-f)-\varepsilon}{u} - \frac{\epsilon}{u} = \frac{L(1-f)-2\varepsilon}{u}$$

and

$$X_{\epsilon}(t) < \frac{L(1-f)+\varepsilon}{u} + \frac{\epsilon}{u} = \frac{L(1-f)+2\varepsilon}{u}.$$

It follows that

$$\frac{L(1-f)-2\varepsilon}{u} \leq X(t) \leq \frac{L(1-f)+2\varepsilon}{u}$$

and since $\epsilon > 0$ can be chosen arbitrarily small, we deduce that

$$X(t) \longrightarrow \frac{L(1-f)}{u} \quad \text{as} \quad t \longrightarrow \infty.$$

Moreover, since $X(t) + V(t) \longrightarrow \dfrac{L}{u}$ as $t \longrightarrow \infty$, then

$$V \longrightarrow \frac{L}{u} - \frac{L(1-f)}{u} = \frac{Lf}{u} \quad \text{as} \quad t \longrightarrow \infty.$$

Therefore, for the epidemic case, since

$$(X(t), T(t), V(t), V_T(t)) \longrightarrow \left(\frac{L}{u}(1-f), 0, \frac{L}{u}f, 0\right),$$

the CFE is globally asymptotically stable .

ii) $R_e > 1$.

It has been shown that in this case, there are both the CFE and the CE. But the CFE is unstable whilst the CE is locally asymptotically stable. Figure 3.5 shows that the system approaches the CE $\left((1-f)\dfrac{\gamma+u}{\beta}, (1-f)\left(\dfrac{L}{u} - \dfrac{\gamma+u}{\beta}\right), f\dfrac{\gamma+u}{\beta}, f\left(\dfrac{L}{u} - \dfrac{\gamma+u}{\beta}\right)\right)$. Again using differential inequalities and the comparison theorem, we can show that global stability occurs.

To prove that $S(0) \geq 0$, $C(0) \geq 0 \Rightarrow (S(t), C(t)) \longrightarrow \left(\dfrac{\gamma+u}{\beta}, \dfrac{L}{u} - \dfrac{\gamma+u}{\beta}\right)$ as $t \longrightarrow \infty$, let us begin by showing that $C(t) \longrightarrow \dfrac{L}{u} - \dfrac{\gamma+u}{\beta}$ as $t \longrightarrow \infty$.

Once again, differential inequalities and some estimations are involved as follows:

Since $N(t) \longrightarrow \dfrac{L}{u}$ as $t \longrightarrow \infty$ and $N(t) = S(t) + C(t)$, with $S(t) \geq 0, C(t) \geq 0$, given any $\epsilon > 0$, $\exists t \geq t_0 (= t_0(\epsilon))$ such that

$$\frac{L}{u} - \epsilon \leq N(t) \leq \frac{L}{u} + \epsilon \quad \forall t \geq t_0. \tag{3.4.8}$$

Figure 3.5 indicates that as $t \longrightarrow \infty$, $C(t)$ can be either decreasing or increasing to get its value at the CE. When $C(t)$ is decreasing, then, from (3.4.8), it can be deduced that

$$\begin{aligned}\frac{1}{C(t)}\frac{d}{dt}C(t) &= \beta(N - C(t)) - (\gamma + u) \\ &\leq \beta\left(\left(\frac{L}{u} + \epsilon\right) - C(t)\right) - (\gamma + u) = \beta\left(\frac{L}{u} + \epsilon\right) - \beta C(t) - (\gamma + u).\end{aligned}$$

Again, when $C(t)$ is increasing, then

$$\begin{aligned}\frac{1}{C(t)}\frac{d}{dt}C(t) &= \beta(N - C(t)) - (\gamma + u) \\ &\geq \beta\left(\left(\frac{L}{u} - \epsilon\right) - C(t)\right) - (\gamma + u) = \beta\left(\frac{L}{u} - \epsilon\right) - \beta C(t) - (\gamma + u).\end{aligned}$$

Hence

$$C(t)\left(\beta\left(\frac{L}{u} - \epsilon\right) - \beta C(t) - (\gamma + u)\right) \leq \frac{dC(t)}{dt} \leq C(t)\left(\beta\left(\frac{L}{u} + \epsilon\right) - \beta C(t) - (\gamma + u)\right) \quad \forall t \geq t_0.$$

Let $C_{-\epsilon}$ and C_ϵ be solutions of the initial value problems.

$$\begin{aligned}C'_{-\epsilon} &= \left(\beta\left(\frac{L}{u} - \epsilon\right) - \beta C(t) - (\gamma + u)\right) C(t), \quad C_{-\epsilon}(t_0) = C(t_0) \\ C'_{\epsilon} &= \left(\beta\left(\frac{L}{u} + \epsilon\right) - \beta C(t) - (\gamma + u)\right) C(t), \quad C_{\epsilon}(t_0) = C(t_0).\end{aligned}$$

Then $C_{-\epsilon}(t) \leq C(t) \leq C_\epsilon(t)\ \forall t \geq t_0$.

Now the equations for $C'_{-\epsilon}$ and C'_ϵ are of the form $Z' = (a - bZ)Z$. Two equilibria are $Z^* = 0$ and $Z^* = \frac{a}{b}$.

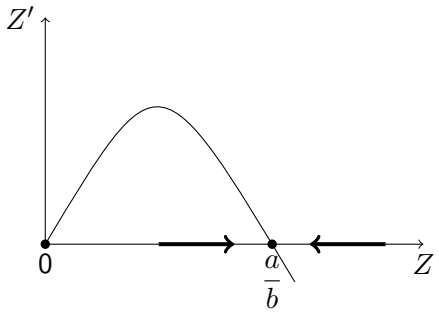

Figure 3.6: Phase-line

Figure 3.6 shows that $Z(t) \longrightarrow \frac{a}{b}$ as $t \longrightarrow \infty$.

Applying this to $C_{-\epsilon}$, C_{ϵ}, we get

$$C_{-\epsilon}(t) \longrightarrow \frac{\beta\left(\frac{L}{u}-\epsilon\right)-(\gamma+u)}{\beta} = \frac{L}{u} - \frac{\gamma+u}{\beta} - \epsilon$$
$$C_{\epsilon}(t) \longrightarrow \frac{\beta\left(\frac{L}{u}+\epsilon\right)-(\gamma+u)}{\beta} = \frac{L}{u} - \frac{\gamma+u}{\beta} + \epsilon.$$

Hence, $\exists t_1 = t_1(\epsilon) > t_0$ such that

$$C_{-\epsilon}(t) > \frac{L}{u} - \frac{\gamma+u}{\beta} - 2\epsilon$$
$$C_{\epsilon}(t) < \frac{L}{u} - \frac{\gamma+u}{\beta} + 2\epsilon$$

and so

$$C(t) \longrightarrow \frac{L}{u} - \frac{\gamma+u}{\beta} \quad \text{as} \quad t \longrightarrow \infty.$$

This means that $T(t) + V_T(t) \longrightarrow \frac{L}{u} - \frac{\gamma+u}{\beta}$ as $t \longrightarrow \infty$.

Since $N(t) \longrightarrow \frac{L}{u}$, then $X(t) + V(t) \longrightarrow \frac{L}{u} - \left(\frac{L}{u} - \frac{\gamma+u}{\beta}\right)$.

So, $X(t) + V(t) \longrightarrow \frac{\gamma+u}{\beta}$ as $t \longrightarrow \infty$.

To determine what happens to $X(t)$, $T(t)$, $V(t)$, $V_T(t)$, let $X(t) = (1-f)\bar{X}(t)$, $T(t) = (1-f)\bar{T}(t)$, $V(t) = f\bar{V}(t)$ and $V_T(t) = f\bar{V}_T(t)$.

Hence the first two equations of the system (2.2.1) become

$$\frac{d}{dt}\bar{X}(t) = L - u\bar{X}(t) - \beta\bar{X}(t)(T(t) + V_T(t)) + \gamma\bar{T}(t)$$
$$\frac{d}{dt}\bar{T}(t) = \beta\bar{X}(t)(T(t) + V_T(t)) - (\gamma+u)\bar{T}(t)$$

and adding them leads to

$$\frac{d}{dt}(\bar{X}(t) + \bar{T}(t)) = L - u(\bar{X}(t) + \bar{T}(t)).$$

Therefore,

$$\bar{X}(t) + \bar{T}(t) \longrightarrow \frac{L}{u}.$$

From that,

$$\frac{d}{dt}\bar{T}(t) \longrightarrow \beta\left(\frac{L}{u} - \bar{T}\right)\left(\frac{L}{u} - \frac{\gamma+u}{\beta}\right) - (\gamma+u)\bar{T}$$
$$= \beta\frac{L}{u}\left(\frac{L}{u} - \frac{\gamma+u}{\beta}\right) - \beta\frac{L}{u}\bar{T}.$$

Given any $\epsilon > 0$, $\exists t_2 = t_2(\epsilon) > 0$ such that

$$\beta\frac{L}{u}\left(\frac{L}{u} - \frac{\gamma+u}{\beta}\right) - \beta\frac{L}{u}\bar{T} - \epsilon < \frac{d\bar{T}}{dt} < \beta\frac{L}{u}\left(\frac{L}{u} - \frac{\gamma+u}{\beta}\right) - \beta\frac{L}{u}\bar{T} + \epsilon, \quad \forall t \geq t_2.$$

Let $\bar{T}_{-\epsilon}$ and $\bar{T}_{\epsilon}$ be the solutions of the initial value problems.

$$\bar{T}'_{-\epsilon} = \beta\frac{L}{u}\left(\frac{L}{u} - \frac{\gamma+u}{\beta}\right) - \beta\frac{L}{u}\bar{T} - \epsilon, \quad \bar{T}_{-\epsilon}(t_2) = \bar{T}(t_2)$$
$$\bar{T}'_{\epsilon} = \beta\frac{L}{u}\left(\frac{L}{u} - \frac{\gamma+u}{\beta}\right) - \beta\frac{L}{u}\bar{T} + \epsilon, \quad \bar{T}_{\epsilon}(t_2) = \bar{T}(t_2).$$

By the comparison theorem, $\bar{T}_{-\epsilon}(t) \leq \bar{T}(t) \leq \bar{T}_{\epsilon}(t)$, $\forall t \geq t_2$.

Now $\bar{T}_{-\epsilon}(t) \longrightarrow \left(\frac{L}{u} - \frac{\gamma+u}{\beta}\right) - \frac{\epsilon u}{\beta L}$ and $\bar{T}_{\epsilon}(t) \longrightarrow \left(\frac{L}{u} - \frac{\gamma+u}{\beta}\right) + \frac{\epsilon u}{\beta L}$.

Hence $\exists t_3 = t_3(\epsilon), t_3 > t_2$ such that

$$\bar{T}_{-\epsilon}(t) > \left(\frac{L}{u} - \frac{\gamma+u}{\beta}\right) - \frac{2\epsilon u}{\beta L} \quad \forall t \geq t_3$$

and

$$\bar{T}_{\epsilon}(t) < \left(\frac{L}{u} - \frac{\gamma+u}{\beta}\right) + \frac{2\epsilon u}{\beta L} \quad \forall t \geq t_3.$$

This shows that

$$\left(\frac{L}{u} - \frac{\gamma+u}{\beta}\right) - \frac{2\epsilon u}{\beta L} \leq \bar{T}(t) \leq \left(\frac{L}{u} - \frac{\gamma+u}{\beta}\right) + \frac{2\epsilon u}{\beta L}$$

and since $\epsilon > 0$ can be chosen arbitrarily small, we deduce that

$$\bar{T}(t) \longrightarrow \left(\frac{L}{u} - \frac{\gamma+u}{\beta}\right)$$

and then

$$T(t) \longrightarrow (1-f)\left(\frac{L}{u} - \frac{\gamma+u}{\beta}\right) \quad \text{as} \quad t \longrightarrow \infty.$$

Since $C(t) \longrightarrow \frac{L}{u} - \frac{\gamma+u}{\beta}$ and $V_T(t) = C(t) - T(t)$, then $V_T(t) \longrightarrow C(t) - T(t)$. This is

$$V_T(t) \longrightarrow \frac{L}{u} - \frac{\gamma+u}{\beta} - (1-f)\left(\frac{L}{u} - \frac{\gamma+u}{\beta}\right)$$
$$= f\left(\frac{L}{u} - \frac{\gamma+u}{\beta}\right) \quad \text{as} \quad t \longrightarrow \infty.$$

Similarly, since $\bar{X}(t) + \bar{T}(t) \longrightarrow \frac{L}{u}$, then $X(t) + T(t) \longrightarrow (1-f)\frac{L}{u}$, and

$$X(t) \longrightarrow \frac{L}{u}(1-f) - (1-f)\left(\frac{L}{u} - \frac{\gamma+u}{\beta}\right).$$

So,

$$X(t) \longrightarrow (1-f)\frac{\gamma+u}{\beta} \quad \text{as} \quad t \longrightarrow \infty.$$

It has been shown that $X(t)+V(t) \longrightarrow \frac{\gamma+u}{\beta}$ as $t \longrightarrow \infty$, and hence

$$\begin{aligned} V(t) &\longrightarrow \frac{\gamma+u}{\beta} - (1-f)\frac{\gamma+u}{\beta} \\ &= f\frac{\gamma+u}{\beta} \quad \text{as} \quad t \longrightarrow \infty. \end{aligned}$$

Therefore, for the endemic case, since

$$(X(t),T(t),V(t),V_T(t)) \longrightarrow \left((1-f)\frac{\gamma+u}{\beta}, (1-f)\left(\frac{L}{u}-\frac{\gamma+u}{\beta}\right), f\frac{\gamma+u}{\beta}, f\left(\frac{L}{u}-\frac{\gamma+u}{\beta}\right)\right),$$

the CE is globally asymptotically stable.

iii) $R_e = 1$.

It has been shown that $R_e = 1$ if

$$\frac{L}{u} = \frac{\gamma+u}{\beta}. \tag{3.4.9}$$

In addition, the Figure 3.4 indicates that the system approaches the equilibrium solution $(S^*, C^*) = \left(\frac{L}{u}, 0\right)$. Substituting the condition (3.4.9) in the equilibrium, in ii), it follows that

$$(X(t),T(t),V(t),V_T(t)) \longrightarrow \left(\frac{L}{u}(1-f), 0, \frac{L}{u}f, 0\right) \quad \text{as} \quad t \longrightarrow \infty,$$

and then CFE is globally asymptotically stable even when $R_e = 1$.

Therefore, if $R_e \leq 1$, the system approaches the CFE and if $R_e > 1$, it approaches the CE.

3.5 Simulations

The aim of this part is to illustrate the analytical results by using real-life parameter values.

In (Lamb et al., 2011), the population of children under 2 years old from Scotland is considered. The size of this population is $N = 150000$ and it is assumed to be at equilibrium. The unit of time is one week. The illustrative parameter values are

$$u = \frac{1}{104}/\text{week}, \quad \gamma = 0.1408/\text{week}, \quad \beta = 1.5041 \times 10^{-6}/\text{week} \quad \text{and} \quad f = 0.6.$$

From these values, the effective reproductive number is

$$\begin{aligned} R_e &= \frac{\beta L}{u(\gamma+u)} \quad \text{with} \quad L = uN = 1442.31 \\ &= \frac{1.5041 \times 10^{-6} * 1442.31}{\frac{1}{104}\left(0.1408+\frac{1}{104}\right)} = 1.5. \end{aligned}$$

The CFE is

$$\left(\frac{L}{u}(1-f), 0, \frac{L}{u}f, 0\right) = (0.4 * 150000, 0, 0.6 * 150000, 0) = (60000, 0, 90000, 0).$$

The CE is

$$\left((1-f)\frac{\gamma+u}{\beta}, (1-f)\left(\frac{L}{u} - \frac{\gamma+u}{\beta}\right), f\frac{\gamma+u}{\beta}, f\left(\frac{L}{u} - \frac{\gamma+u}{\beta}\right)\right)$$

$$= \left(0.4 * \eta, 0.4 * (150000 - \eta), 0.6 * \frac{0.1408 + \frac{1}{104}}{1.5041 \times 10^{-6}}, 0.6 * (150000 - \eta)\right), \quad \text{where} \quad \eta = \frac{0.1408 + \frac{1}{104}}{1.5041 \times 10^{-6}}$$

$$= (40000, 20000, 60000, 30000).$$

Taking the initial conditions; $X(0) = 149000$, $T(0) = 1000$, $V(0) = 0$ and $V_T(0) = 0$, Figure 3.7 shows that only the carriage equilibrium exists when $R_e > 1$.

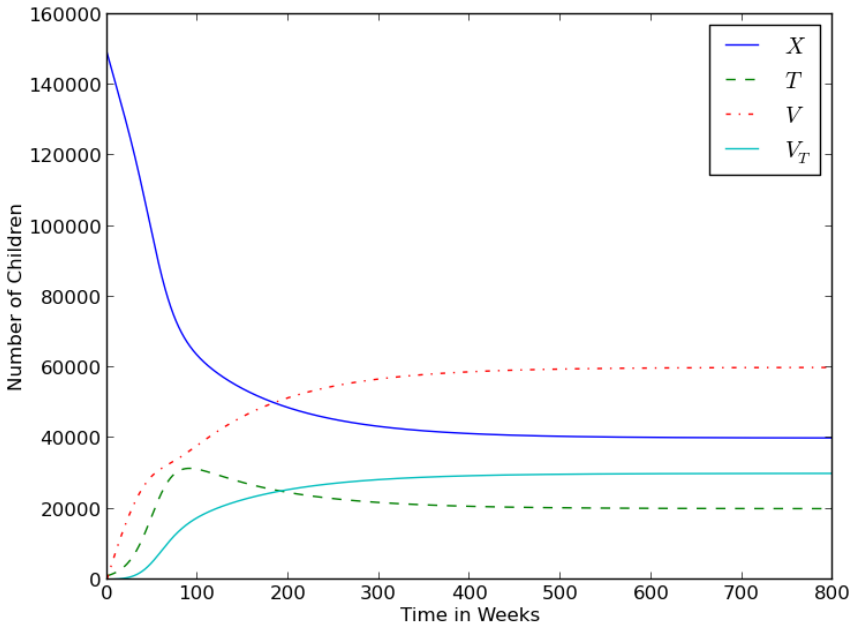

Figure 3.7: Simulation with the case $R_e > 1$

4. Conclusion

In this work, the simple mathematical model for the carriage and transmission of pneumococcal disease in a population of children under two years old is considered to understand the concept of sequence type colonization. The sequence type is able to manifest itself as a vaccine type and a non-vaccine type serotype.

The analytical results of the model show that there exist two equilibria; CFE and CE. In addition, the effective reproductive number was determined to investigate the behaviour of the disease. When $R_e \leq 1$, there is only the CFE which is globally asymptotically stable and, in the long term, there are no children carrying the sequence type. At this steady state, all children, in the four compartments (vaccinated susceptible, unvaccinated susceptible, vaccinated carriers and unvaccinated carriers), are susceptible to carriage of the sequence type. In addition, regardless of the number of vaccinated and unvaccinated carriers in the population, the disease will die out in the long term. Contrariwise, when $R_e > 1$ the disease spreads out and two equilibrium solutions exist; the CE is globally asymptotically stable whereas the CFE is unstable. If there are no initial carriers of sequence type in the population, there will be again the vaccinated and unvaccinated susceptible compartments only. But if there are some initial carriers, the population will be subdivided into the four compartments and the number of carriers approaches $\frac{L}{u} - \frac{\gamma + u}{\beta}$ children.

Moreover, since the sequence type plays a role in the spread of disease and it manifests itself as two serotypes, then the disease will continue to appear in the population as the vaccine prevents only one serotype.

This work can be extended by considering multiple sequence types that can manifest themselves in more than one serotype. So, two sequence types associated with two serotypes can be taken into account and this results in a model of six ordinary differential equations; (Greenhalgh et al., 2012).

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