Modelling the seasonality of respiratory syncytial virus in young children

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Abstract: Respiratory syncytial virus (RSV) is a major cause of acute lower respiratory tract infections in infants and young children. The transmission dynamics of RSV infection among young children are still poorly understood (Hall et al., 2009) and mathematical modelling can be used to better understand the seasonal behaviour of the virus. However, few mathematical models for RSV have been published to date (Moore et al., 2013; Weber et al., 2001; Leecaster et al., 2011) and these are relatively simple, in contrast to studies of other infectious diseases such as measles and influenza.

A simple SEIRS (Susceptible, Exposed, Infectious, Recovered, Susceptible) type deterministic ordinary differential equation model for RSV is constructed and then expanded to capture two separate age classes with different transmission parameters, to reflect the age specific dynamics known to exist for RSV. Parameters in the models are based on the available literature.

In temperate climates, RSV dynamics are highly seasonal with mid-winter peaks and very low levels of activity during summer months. Often there is an observed biennial seasonal pattern in southern Australia with alternating peak sizes in winter months. To model this seasonality the transmission parameter $\beta(t)$ is taken to vary sinusoidally with higher transmission during winter months, such as in models presented in Keeling and Rohani (2008) for infections such as measles and pertussis:

$$\beta(t) = \beta_0[1 + \beta_1 \sin(\frac{2\pi t}{52})]. \tag{1}$$

This seasonal forcing reflects increases in infectivity and susceptibility thought to be due to multiple factors including increased rainfall, variation in humidity, and decreased temperature (Cane, 2001; Weber et al., 1998).

Sinusoidally forced SIR-type models are known to support complex multi-periodic and even chaotic solutions. For realistic parameter values, obtained from the literature, and depending on the values selected for β_0 and β_1, the model predicts either annual peaks of the same magnitude, or the observed biennial pattern that can be explained by the interaction of the forcing frequency and the natural frequency of the system. This behaviour is in keeping with what is observed in different climatic zones.

Keywords: Mathematical model, infectious disease, respiratory syncytial virus, seasonality

1 INTRODUCTION

Respiratory syncytial virus (RSV) is a significant health and economic burden in Australia and internationally. Epidemics are strongly seasonal, occurring each winter in temperate climates (Cane, 2001) and during the rainy season in tropical climates (Simoes, 1999), usually lasting between two and five months (Hall, 1981; Kim et al., 1973).

There are only limited RSV data sets published and often these are only over short time spans. Recent data sets that span numerous years for Utah in the U.S.A. (Leecaster et al., 2011), southern Germany (Terletskaia-Ladwig et al., 2005) and Western Australia (Moore et al., 2013), show a distinct biennial seasonal pattern with higher peaks in alternate winter seasons. These regions all have a temperate climate and experience significant seasonal variation in climate. Other data sets, such as for Singapore (Chew et al., 1998) and the Spanish region of Valencia (Acedo et al., 2011) show annual seasonal behaviour, with peaks of the same magnitude each year.

While the mortality rate for previously healthy children is low, RSV causes high rates of hospitalisation for children under two years of age and has also been identified as a cause of mortality in the elderly (Faskey et al., 2005; Simoes, 1999; Hardelid et al., 2013). Clinical symptoms may vary from those of a mild infection to severe bronchiolitis or pneumonia (Hall, 1981).

In the young, infection with RSV does not cause long lasting protective immunity, meaning that individual children may be repeatedly infected. There is currently no licensed vaccine available, nor any antiviral treatments commonly used for RSV infection in Australia.

The aim of this study is to develop RSV models that reproduce the biennial pattern observed in temperate climates. In later work these models will be fitted to available data. Thus we present a SEIRS model for a single age class for RSV infection, where the transmission rate is seasonally forced, such as in models presented in Keeling and Rohani (2008). An investigation into the types of behaviour possible in this model is undertaken. To better reflect the known epidemiology of RSV, we then introduce a second age class into the model with a second transmission rate and investigate how this affects the transmission dynamics.

2 MODEL FOR A SINGLE AGE CLASS

A deterministic ordinary differential equation model is developed for the transmission of RSV for 0-23 month old children. This age group was chosen as the literature indicates that almost all children have been infected by the time they reach this age (Hall, 1981; Sorce, 2009). As it remains unclear to what degree adults carry and shed the virus, thereby infecting children, the adult population was not included in the model.

The population is divided into four compartments, where S represents the proportion of the population that is susceptible to infection; E represents the proportion of the population that is exposed but not yet infected; I represents the proportion that is infected with the virus; and R represents the proportion of the population that is recovered and temporarily immune to reinfection. The SEIRS-type model was selected for two reasons. Firstly, the virus is known to have a latency period between an individual being exposed to the infection and becoming infectious. This period is of the same order of magnitude as the infectious period and hence needs to be included to accurately represent the disease dynamics. Secondly, infection from the virus does not cause long-lasting immunity, hence recovered individuals may return to the susceptible class and be reinfected.
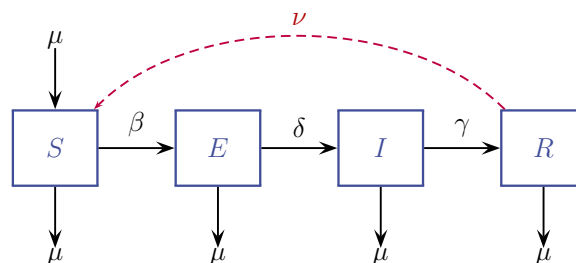

Figure 1. Schematic diagram for single age class SEIRS model for RSV transmission.

A schematic representation of the model is shown in Figure 1. The average recovery period is represented by $\frac{1}{\gamma}$,

the average latency period (the time between contracting the infection and becoming infectious) is represented by $\frac{1}{\delta}$ and the average duration of immunity is represented by $\frac{1}{\nu}$. The rate of entering the model (the birth rate) is equal to the rate at which individuals age out of the model, and is represented by μ. The virus is transmitted between individuals at rate β.

The differential equations, where time in weeks is represented by t, are

$$\frac{dS}{dt} = \mu - \beta SI - \mu S + \nu R \tag{2}$$

$$\frac{dE}{dt} = \beta SI - \delta E - \mu E \tag{3}$$

$$\frac{dI}{dt} = \delta E - \mu I - \gamma I \tag{4}$$

$$\frac{dR}{dt} = \gamma I - \mu R - \nu R. \tag{5}$$

2.1 Parameter values

The birth rate and ageing rate μ is chosen as in Moore et al. (2013) and is based on the average number of births per week in the metropolitan region of Western Australia. This gives an average weekly birth rate of 0.012. Assuming the birth and ageing rates are equal simplifies the calculations as it ensures the population size remains constant. Here this assumption does not change the overall dynamics of the system.

Based on the literature, the average latency period for RSV is assumed to be four days (Weber et al., 2001; Moore et al., 2013). Other models, such as those presented by Leecaster et al. (2011), assume a latency period of five days. A four day latency period equates to δ being 1.754 (or $\frac{1}{0.57}$).

Similarly, the average recovery period is based on estimates in previous models for RSV of 10 days (Weber et al., 2001; Moore et al., 2013; Acedo et al., 2010; Leecaster et al., 2011), and within the range of one to 21 days identified by Hall et al. (1976). This gives γ equal to 0.714 (or $\frac{1}{1.4}$).

The immunity period is the time between recovering from a RSV infection to becoming susceptible to the virus again. Although not currently well understood, there is some evidence that the immunity period is around 200 days which equates to ν being 0.035 (or $\frac{1}{28.57}$). This again is the value used in previous modelling of RSV (Weber et al., 2001; Moore et al., 2013; Acedo et al., 2010).
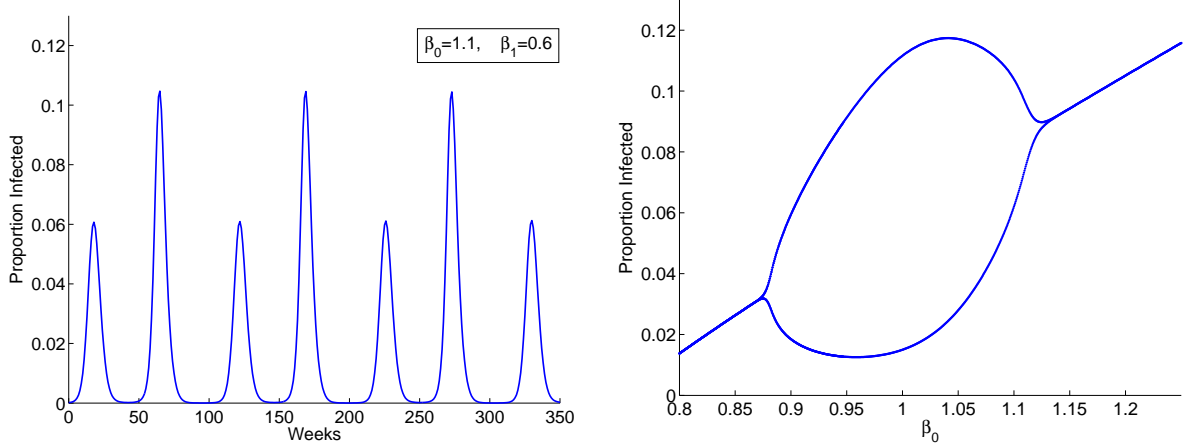
The transmission rate $\beta(t)$, given at Equation 1, was chosen to reflect the observed annual seasonality of RSV in temperate climates. Similar seasonal forcing has been applied in other models for RSV transmission (Weber et al., 2001; Moore et al., 2013; Acedo et al., 2010; Arenas et al., 2008; Leecaster et al., 2011). The sinusoidal function, with a period of 52 weeks, accounts for the observed higher transmission between children during the winter months. The term β_0 represents the average transmission rate and β_1 represents the amplitude of the seasonal fluctuation (Keeling and Rohani, 2008).

For the purpose of investigating the overall dynamics of this model, a range of values was considered for β_0. For β_1, a value of 0.6 was assumed (noting that $0 < \beta_1 \leq 1$), in order to replicate the conditions in temperate climates where strong seasonality is observed. For some seasonally forced models for RSV, values as high as 1 (Leecaster et al., 2011) have been assumed. Other models assume much lower values for β_1, such as between 0.10 and 0.36 (Arenas et al., 2008). In future work we will estimate these parameters β_0 and β_1 using longitudinal data from Western Australia.

2.2 Numerical solution

The system of differential equations was solved and plotted using MATLAB's ode45 routine. A burn in time of 80 years was used to allow the system to stabilise and thereby remove the dependence on the initial conditions. When there is no seasonality in the transmission rate (when β is constant, β_1=0), the natural oscillations in the system die out and the system reaches a steady state. With seasonality, there is either a distinct biennial pattern, with higher peaks in alternate winter seasons, or peaks of the same magnitude each year, depending on the values selected for β_0 and β_1. Figure 2(a) depicts a plot of a biennial pattern solution for the infected population, with β_0=1.1 and β_1=0.6.

As there are values of β_0 and β_1 where there is no biennial pattern but instead where the seasonal peak reaches the same maximum each year, adjacent seasonal peaks versus the parameter β_0 were plotted in order to better

(a) A numerical solution for the infected population of a single age class SEIRS model for RSV transmission with a sinusoidally forced transmission parameter.

(b) Maximum proportion of infectives at adjacent seasonal peaks versus the bifurcation parameter β_0, for the single age class system. The parameter determining the amplitude of the forcing, β_1, is 0.6

Figure 2.

understand the bifurcation patterns of the system. Figure 2(b) gives an impression of the bifurcation structure of the model, showing seasonal peaks over two adjacent years. Where the seasonal pattern is annual, only a single peak is shown, whereas biennial dynamics gives two distinct peaks. There is a specific range of possible values for β_0 for which the system will feature the biennial seasonal pattern. Outside this range, the system reverts to a regular annual seasonal pattern. These results are in keeping with what is observed in different climatic zones.

3 MODEL FOR TWO AGE CLASSES

Studies show that the transmission dynamics of RSV change as children age. That is, incidence is higher for children aged less than 12 months than those in the 12-23 month age class (Moore et al., 2010). It is still unclear why older children are less affected. Possible reasons are reduced susceptibility, or less severe symptoms (so less infections are reported), as a result of prior infection with the virus; or due to having better developed immune systems than younger children. Thus, we present a second set of differential equations to account for two age classes and two transmission parameters, β_A and β_B.

The second model is the set of differential equations

$$\frac{dS_1}{dt} = \mu - \beta_A S_1 (I_1 + I_2) - \eta S_1 + \nu R_1 \tag{6}$$

$$\frac{dE_1}{dt} = \beta_A S_1 (I_1 + I_2) - \delta E_1 - \eta E_1 \tag{7}$$

$$\frac{dI_1}{dt} = \delta E_1 - \eta I_1 - \gamma I_1 \tag{8}$$

$$\frac{dR_1}{dt} = \gamma I_1 - \eta R_1 - \nu R_1 \tag{9}$$

$$\frac{dS_2}{dt} = \eta S_1 - \beta_B S_2 (I_1 + I_2) - \eta S_2 + \nu R_2 \tag{10}$$

$$\frac{dE_2}{dt} = \eta E_1 + \beta_B S_2 (I_1 + I_2) - \delta E_2 - \eta E_2 \tag{11}$$

$$\frac{dI_2}{dt} = \eta I_1 + \delta E_2 - \eta I_2 - \gamma I_2 \tag{12}$$

$$\frac{dR_2}{dt} = \eta R_1 + \gamma I_2 - \eta R_2 - \nu R_2. \tag{13}$$
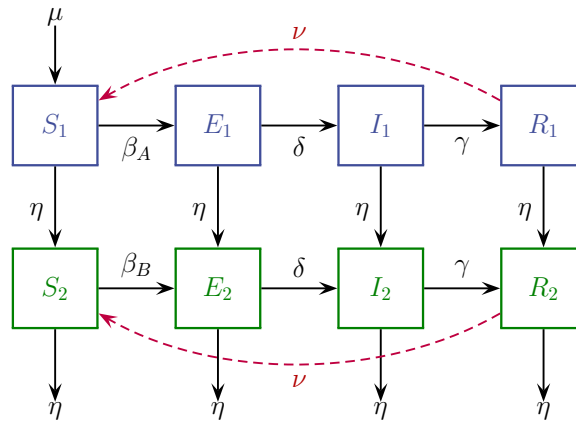
Figure 3. Schematic description of a SEIRS model for RSV transmission that takes into account two separate age classes: children aged <12 months, where the virus is transmitted at rate β_A; and 12-23 month old children, where the virus is transmitted at rate β_B.

The parameters μ, γ, δ and ν are as presented for the single age class model in Equations (2)-(5). An additional parameter η is introduced to reflect the ageing from the <12 month age class into the 12-23 month age class, and also to reflect the ageing out of the 12-23 month class. This rate is assumed to be equal and distributed evenly over time, therefore η is taken to be $\frac{1}{52}$. A schematic diagram of the two age class system is given in Figure 3.

The transmission rates are β_A, for the <12 month age class, and β_B, for the 12-23 month age class. Both are of the sinusoidal form presented for the single age class model at Equation (1). Here the parameter β_0 in β_B was selected to produce a reduced average transmission rate for the 12-23 month old age class, to better reflect the different transmission dynamics for older children. The β_1 parameter is the same for β_A and β_B, to represent the same climatic region.
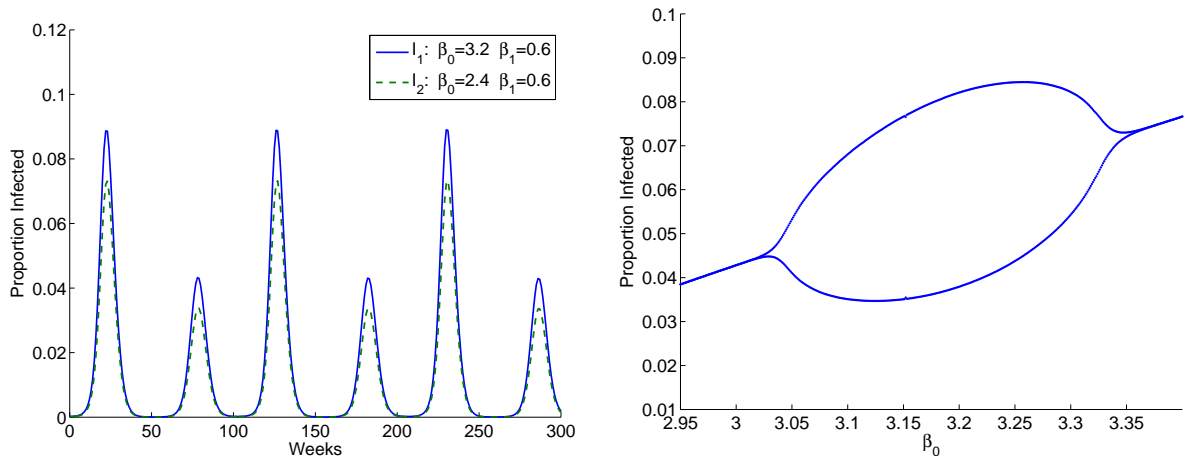
3.1 Numerical solution

The system of differential equations was solved using MATLAB's inbuilt ode45 routine, with a burn in time of 80 years. The model accurately mimics the expected lower number of infectives in the 12-23 month age class and again produces the biennial pattern for both age classes, as observed in the single age class system. Figure 4(a) shows a solution for the infected population for each age class. Adjacent seasonal peaks for increasing values of β_0 were again examined, showing that, as for the single age class system, there is a specific range of possible values for β_0 that produce the biennial seasonal pattern 4(b).

4 DISCUSSION

By sinusoidally forcing the transmission parameter, both models depict either a distinct biennial seasonality, or annual seasonal peaks of the same magnitude, for realistic parameter values depending on the values selected for β_0 and β_1. These results are in keeping with what is observed in different climatic zones. We showed that a simple single age class model, with demography, is sufficient to achieve these seasonal patterns. Both the single age class model, and the expanded model with two age classes, now provide a base on which to add complexities.

Future work will investigate varying the recovery, latency and immunity parameters for different age classes, as well as a more detailed bifurcation analysis of both systems. There is a possibility of more complex behaviour than the two-cycle pattern observed here being present. We will also investigate whether prior exposure is the reason for reduced susceptibility, through expanding the model and fitting with population-based linked laboratory data for the metropolitan region of Western Australia.

There is currently no licensed vaccine for RSV available in Australia. Vaccine development to date has been problematic due to lack of an ideal animal model for the the disease, and the challenges of immunising infants

(a) A numerical solution for the infected populations for the <12 month age class and the 12-23 month age class of a SEIRS model for RSV transmission, where the transmission parameter for each age class is sinusoidally forced.

(b) Maximum proportion of infectives at adjacent seasonal peaks versus β_0 (with $\beta_B = 0.75\beta_A$), demonstrating the biennial behaviour over a range of values. In this case, the parameter β_1 is 0.6.

Figure 4.

who are immunologically immature (Crowe Jr, 2002). However, with a new vaccine currently undergoing phase two trials (Anderson et al., 2013), we will also look at the optimal timing in the transmission cycle for the roll out of a vaccination program.

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