Unexpected infection spikes in a model of Respiratory Syncytial Virus vaccination

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Abstract

Respiratory Syncytial Virus (RSV) is an actute respiratory infection that infects millions of children and infants worldwide. Recent research has shown promise for the development of a vaccine, with a range of vaccine types now in clinical trials or preclinical development. We extend an existing mathematical model with seasonal transmission to include vaccination. We model vaccination both as a continuous process and as a discrete one, using impulsive differential equations. We develop conditions for the stability of the disease-free equilibrium and show that this equilibrium can be destabilised under certain (extreme) conditions. Using impulsive differential equations and introducing a new quantity, the *impulsive reproduction number*, we determine conditions for the period and strength of vaccination that will control (but not eradicate) RSV. In our model, the vaccine waning rate is a critical parameter and more important than coverage for long-term reduction in RSV prevalence. We recommend that candidate vaccines be tested for sufficient duration of protection before being released.

1 Introduction

Respiratory syncytial virus (RSV) is the main cause of acute lower respiratory infections in infants and young children [25], with almost all children having been infected by two years of age [10, 31] and an estimated 0.5–2% of infants requiring hospitalisation due to infection [20]. It has been estimated that in 2005, 33.8 million new episodes of RSV occurred worldwide in children younger than five years of age [25]. Symptoms of RSV range from those of a cold to more severe afflictions such as bronchiolitis and pneumonia [10]. While mortality due to RSV infection in developed countries is low, occurring in less than 0.1% of cases [38], few data have been published about RSV morbidity and mortality in developing countries [40]. However, estimates of the hospitalisation costs are substantial [14, 36, 42], making RSV a significant economic and health care system burden.

Newborn infants are typically protected from RSV infection by maternal antibodies until about six weeks of age [9], and the highest number of observed RSV cases occur in children aged six weeks to six months [6, 33]. Immunity to RSV following an infection is short-lasting, and reinfection in childhood is common [22]. Few studies have been undertaken to investigate transmission of RSV among adults, but it is thought that infection can occur throughout life [7, 15] and that, in older children and adults, RSV manifests as a mild cold [10, 18]. RSV has been identified as a cause of mortality in the elderly, with documented outbreaks in aged-care settings [13, 37]; one such study found that up to 18% of pneumonia hospitalisation in adults aged above 65 years may be due to RSV infection [12] *could take out this paragraph?.

In temperate climates RSV epidemics exhibit distinct and consistent seasonal patterns. Most RSV infections occur during the cooler winter months, whether wet or dry [40], and outbreaks typically last between two and five months [11, 26]. In a number of temperate regions, a biennial pattern for RSV cases has been identified [4, 23, 34]. In tropical climates, RSV is detected throughout the year with less pronounced seasonal peaks, and the onset of RSV is typically associated with the wet season [32, 40].

Immunoprophylaxis with the monoclonal antibody Palivizumab, while not preventing the onset of infection, has proven effective in reducing the severity of RSV-related symptoms [35]. However, prophylaxis is expensive and generally only administered to high-risk children, with recommendations varying across jurisdictions. There is currently no licensed vaccine to prevent RSV infection, despite about 50 years of vaccine research. Recent research has focused on the development of particle-based and subunit vaccines; several such vaccines are being evaluated in clinical trials, with other vaccines in preclinical development [28, 30]. With the possibility of an RSV vaccine becoming available, mathematical models are powerful tools for assessing the impacts of different vaccine characteristics.

Several ordinary differential equation mathematical models for RSV transmission have been published to date, most using Susceptible–Exposed–Infectious–Recovered (SEIR) dynamics and with a sine or cosine forcing term to account for seasonal variation in transmission [3, 8, 19, 24, 27, 39, 41]. Few papers have so far used dynamic models to explore vaccination strategies for RSV, and these have generally investigated RSV vaccination from a cost-effectiveness perspective [5, 21], for example in the context of a newborn vaccination strategy in the Spanish region of Valencia [1, 2]. More recent studies conducted for the setting of rural Kenya have focussed on the likely benefits of vaccination for particular target groups [17, 29]. *A nice segue here would be to say that we have not identified any RSV vaccination models that examine the impact of a theoretical vaccine analytically, and look at the stability of different scenarios - but can't think right now how to word this.

Here, we examine the effects of a theoretical vaccine on the transmission of RSV in a single age class. We consider several vaccination scenarios, including differing levels of coverage, seasonal oscillations in the transmission rate and a waning of the vaccine. We also compare continuous vaccination to impulsive vaccination in order to determine conditions on the vaccination strength and duration? that will control the virus.

2 The model

We extend the basic compartmental model for a single age cohort described by Weber *et al.* [39] to include a vaccine strategy for RSV where a fixed proportion of newborns are vaccinated?. We assume that the leaving rate μ is unchanged across all classes and that there is no disease-specific death rate. We scale the entry and leaving rates so that the population is constant.

Let S represent susceptible, I represent infected and R represent recovered individuals, with V, I_V and R_V the corresponding compartments for vaccinated individuals. The birth rate is μ, with a proportion p vaccinated, of whom ϵ successfully mount an immune response; the death rate is equal to the birth rate. The time-dependent transmissibility function is $\beta(t)$, with recovery ν and loss of immunity γ. The transmissibility of infected vaccinated individuals is described by $\beta_V(t)$, and the recovery and loss of immunity rates for vaccinated individuals are ν_V and γ_V respectively. Finally, the waning of the vaccine protectiveness? is given by ω.

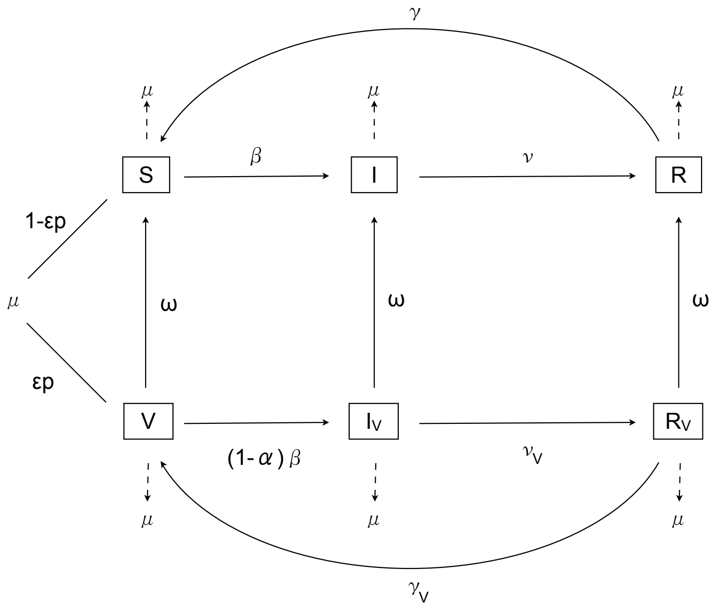

Figure 1: The model.

The basic model with vaccination is then

$$\begin{aligned}
S' &= \mu(1-\epsilon p) - \mu S - \beta(t)S(I+I_V) + \gamma R + \omega V\\
I' &= \beta(t)S(I+I_V) - \nu I - \mu I + \omega I_V\\
R' &= \nu I - \mu R - \gamma R + \omega R_V\\
V' &= \epsilon p \mu - \mu V - \beta_V(t)V(I+I_V) + \gamma_V R_V - \omega V\\
I_V' &= \beta_V(t)V(I+I_V) - \nu_V I_V - \mu I_V - \omega I_V\\
R_V' &= \nu_V I_V - \mu R_V - \gamma_V R_V - \omega R_V,
\end{aligned}$$

with $\beta(t) = b_0(1 + b_1\cos(2\pi t + \phi))$ and $\beta_V(t) = (1-\alpha)\beta(t)$, for $0 \le \alpha \le 1$, where α represents.... (We may relax the lower bound on α later.) The model is illustrated in Figure 1. *I'm confused about the rationale for relaxing the lower bound on α?

3 Analysis

There is a disease-free equilibrium that satisfies

$$(\bar{S}, \bar{I}, \bar{R}, \bar{V}, \bar{I}_V, \bar{R}_V) = \left(\frac{(1-\epsilon p)\mu + \omega}{\mu + \omega}, 0, 0, \frac{\epsilon p \mu}{\mu + \omega}, 0, 0\right).$$

3.1 Constant transmission

If we assume transmission is constant, so that β and β_V are independent of time, then the Jacobian is $J = [J_1|J_2]$, where

$$J_1 = \begin{bmatrix} -\mu - \beta(I + I_V) & -\beta\bar{S} & \gamma \\ \beta(I + I_V) & \beta\bar{S} - \mu - \nu & 0 \\ 0 & \nu & -\mu - \gamma \\ 0 & -\beta_V\bar{V} & 0 \\ 0 & \beta_V\bar{V} & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

$$J_2 = \begin{bmatrix} \omega & -\beta\bar{S} & 0 \\ 0 & \beta\bar{S} + \omega & 0 \\ 0 & 0 & \omega \\ -\mu - \beta_V(I + I_V) - \omega & -\beta_V\bar{V} & \gamma_V \\ \beta_V(I + I_V) & \beta_V\bar{V} - \nu_V - \mu - \omega & 0 \\ 0 & \nu_V & -\mu - \gamma_V - \omega \end{bmatrix}.$$

At the DFE, we have

$$J\Big|_{DFE} = \begin{bmatrix} -\mu & -\beta\bar{S} & \gamma & \omega & -\beta\bar{S} & 0 \\ 0 & \beta\bar{S} - \mu - \nu & 0 & 0 & \beta\bar{S} + \omega & 0 \\ 0 & \nu & -\mu - \gamma & 0 & 0 & \omega \\ 0 & -\beta_V\bar{V} & 0 & -\mu - \omega & -\beta_V\bar{V} & \gamma_V \\ 0 & \beta_V\bar{V} & 0 & 0 & \beta_V\bar{V} - \nu_V - \mu - \omega & 0 \\ 0 & 0 & 0 & 0 & \nu_V & -\mu - \gamma_V - \omega \end{bmatrix}.$$

The characteristic polynomial satisfies

$$\det(J - \lambda I) = (-\mu - \lambda)(-\mu - \gamma - \lambda)(-\mu - \omega - \lambda)(-\mu - \gamma_V - \omega - \lambda)\det M,$$

where

$$M = \begin{bmatrix} \beta\bar{S} - \mu - \nu - \lambda & \beta\bar{S} + \omega \\ \beta_V\bar{V} & \beta_V\bar{V} - \nu_V - \mu - \omega - \lambda \end{bmatrix}.$$

The first four eigenvalues are always negative. The nontrivial part of characteristic equation satisfies

$$\lambda^2 + b_1\lambda + c_1 = 0,$$

where

$$\begin{aligned}
b_1 &= -\beta\bar{S} + \mu + \nu - \beta_V\bar{V} + \nu_V + \mu + \omega \\
c_1 &= (\beta\bar{S} - \mu - \nu)(\beta_V\bar{V} - \nu_V - \mu - \omega) - \beta_V\bar{V}(\beta\bar{S} + \omega) \\
&= \beta\bar{S}(-\nu_V - \mu - \omega) - (\mu + \nu)(\beta_V\bar{V} - \nu_V - \mu - \omega) - \beta_V\bar{V}\omega.
\end{aligned}$$

From $c_1 = 0$, we find I am confused about this step here, sorry! How did we get from setting $c_1 = 0$ to determining R_0?

$$R_0 = \frac{\beta\bar{S}(\nu_V + \mu + \omega) + \beta_V\bar{V}(\mu + \nu + \omega)}{(\mu + \nu)(\mu + \nu_V + \omega)}$$

(This is equivalent to the value found using the next-generation method.)

If $c_1 = 0$ and $b_1 > 0$, then we have a bifurcation with the property that the DFE is stable if $R_0 < 1$ and unstable if $R_0 > 1$

However, it is possible that when $c_1 = 0$, $b_1 < 0$. In this case, R_0 is not a threshold and the disease can persist if $R_0 < 1$.

When $c_1 = 0$, we have

$$b_1\Big|_{c_1=0} = \frac{1}{\nu_V + \mu + \omega}\left[\beta_V\bar{V}(\nu - \nu_V) + (\nu_V + \mu + \omega)^2\right].$$

Note that if $\nu = \nu_V$, then $b_1 > 0$. However, it is plausible that vaccinated individuals infected with RSV will recover faster than unvaccinated individuals. Thus $\nu_V > \nu$. This raises the possibility that b_1 could be negative.

If $\nu_V \to \infty$, then this is equivalent to vaccinated individuals recovering instantaneously. In this case,

$$\begin{aligned}
\lim_{\nu_V\to\infty} b_1 &= \lim_{\nu_V\to\infty} \frac{\beta_V\bar{V}(\nu - \nu_V)}{\omega + \mu + \nu_V} + \omega + \mu + \nu_V \\
&= \infty - \beta_V\bar{V} > 0
\end{aligned}$$

Hence if we define $f(\nu_V) = \frac{\beta_V\bar{V}(\nu-\nu_V)+(\omega+\mu+\nu_V)^2}{\omega+\mu+\nu_V}$, then it is clear that $f(0) > 0$ and $f(\infty) > 0$. So we would like to know whether f has a turning point ν_V^* such that $f(\nu_V^*) < 0$.

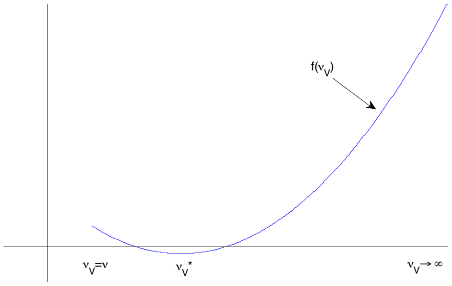

Figure 2: Possible sketch of the form of $f(\nu_V)$ with a negative minimum between two positive extremes.

We have

$$\begin{aligned} f'(\nu_V) &= \frac{(\omega+\mu+\nu_V)[-\beta_V\bar{V}+2(\omega+\mu+\nu_V)]-[\beta_V\bar{V}(\nu-nu_V)+(\omega+\mu+\nu_V)^2]}{(\omega+\mu+\nu_V)^2} \\ &= \frac{(\omega+\mu+\nu_V)^2-\beta_V\bar{V}[\omega+\mu+\nu]}{(\omega+\mu+\nu_V)^2} \end{aligned}$$

It follows that $\nu_V^* = \sqrt{\beta_V\bar{V}(\omega+\mu+\nu)}-\omega-\mu$. There are three requirements we need for this to be meaningful (Figure 2):

1. $\nu_V^* > \nu$
2. $f(\nu_V^*) < 0$ and
3. ν_V^* is a local minimum.

The first and second criteria determine whether such a ν_V^* exists. To prove the third, we can differentiate again:

$$f''(\nu_V) = \frac{(\omega+\mu+\nu_V)^2+\beta_V(\omega+\mu+\nu)}{(\omega+\mu+\nu_V)} > 0.$$

It follows that ν_V^* is a local minimum whenever it exists.

4 Impulsive model

Previously, we assumed that vaccination occurred at birth and that a fixed proportion of newborns were vaccinated. Are we assuming that the vaccine is administered after birth, or that the vaccine is administered to pregnant women and therefore newborns are born vaccinated? I know it doesn't make any difference from a modelling point of view but could be a question asked by a finicky person. This is effectively continuous vaccination. However, vaccination may occur later and may be administered at regular times (for example, in schools or daycare centres). We assume that the effect of the vaccine is to reduce the susceptible population by a fixed proportion. Such a model is described by a system of non-autonomous impulsive differential equations [**? ? ? ?**].

The impulsive model is given by

$$\begin{aligned}
S' &= \mu - \mu S - \beta(t)S(I + I_V) + \gamma R + \omega V && t \neq t_k\\
I' &= \beta(t)S(I + I_V) - \nu I - \mu I + \omega I_V && t \neq t_k\\
R' &= \nu I - \mu R - \gamma R + \omega R_V && t \neq t_k\\
V' &= -\mu V - \beta_V(t)V(I + I_V) + \gamma_V R_V - \omega V && t \neq t_k\\
I_V' &= \beta_V V(I + I_V) - \nu_V I_V - \mu I_V - \omega I_V && t \neq t_k\\
R_V' &= \nu_V I_V - \mu R_V - \gamma_V R_V - \omega R_V && t \neq t_k\\
\Delta S &= -rS && t = t_k\\
\Delta V &= rS && t = t_k
\end{aligned}$$

Here t_k are the vaccination times. They may be fixed or non-fixed, although for our purposes we will consider them fixed.

4.1 Impulsive analysis

We will set β to be constant for mathematical convenience, and therefore consider the system in the absence of seasonal transmission. In order to analyse the impulsive system, we need to solve the differential equations for finite time. Since this is not possible in general, we will develop several overestimates in order to determine bounds for the long-term numbers of susceptible, infected and vaccinated individuals, under several assumptions.

Susceptible individuals

First we consider the overestimate $I + I_V \leq 1$ (i.e., maximal infection). Then we have

$$S' \geq \mu - \mu S - \beta S.$$

Integrating and applying the "initial" condition $S(t_k^+)$ in the $(k+1)$st cycle, we have

$$\begin{aligned} S(t) &\geq e^{-(\mu+\beta)(t-t_k)} S(t_k^+) + \frac{\mu}{\mu+\beta}\left(1-e^{-(\mu+\beta)(t-t_k)}\right), \text{ for } t_k < t \leq t_{k+1} \\ S(t_{k+1}^-) &\geq e^{-(\mu+\beta)\tau} S(t_k^+) + \frac{\mu}{\mu+\beta}\left(1-e^{-(\mu+\beta)\tau}\right). \end{aligned}$$

Applying the impulsive condition, we have

$$\begin{aligned} S(t_{k+1}^+) &= (1-r)S(t_k^-) \\ S(t_{k+1}^+) &\geq (1-r)e^{-(\mu+\beta)\tau} S(t_k^+) + \frac{\mu}{\mu+\beta}(1-r)\left(1-e^{-(\mu+\beta)\tau}\right). \end{aligned}$$

This is a recurrence relation in the form $x_{n+1} = ax_n + b$, which has equilibrium $\bar{x} = \frac{b}{1-a}$, and the equilibrium is stable if $|a| < 1$. In our case, we have $a = (1-r)e^{-(\mu+\beta)\tau} < 1$, so the equilibrium is stable. It follows that solutions converge to a stable impulsive periodic orbit with endpoints

$$\begin{aligned} S_\infty^- &= \frac{\mu\left(1-e^{-(\mu+\beta)\tau}\right)}{(\mu+\beta)\left(1-(1-r)e^{-(\mu+\beta)\tau}\right)} \\ S_\infty^+ &= \frac{\mu(1-r)\left(1-e^{-(\mu+\beta)\tau}\right)}{(\mu+\beta)\left(1-(1-r)e^{-(\mu+\beta)\tau}\right)}. \end{aligned}$$

These values correspond to the local maximum and minimum values for the unvaccinated susceptibles after a long time. These values are well-defined, since both the numerator and the denominator are always positive.

Note in particular that

$$\lim_{\tau\to 0} S_\infty^- = 0.$$

That is, if the period between vaccinations shrinks to zero, then the number of susceptibles would shrink to zero. (Note that this is a theoretical result only, since the impulsive assumptions of long cycle times relative to instantaneous approximation would break down [**?**].)

Vaccinated individuals

Second, we turn our attention to vaccination. Using the inequalities $I + I_V \leq 1$ and $R_V \geq 0$, we have

$$V' \geq -\mu V - \beta V - \omega V.$$

Integrating and applying the "initial" condition $V(t_k^+)$ in the $(k+1)$st cycle, we have

$$\begin{aligned} V(t) &\geq V(t_k^+)e^{-(\mu+\beta+\omega)(t-t_k)}, \text{ for } t_k < t \leq t_{k+1} \\ V(t_{k+1}^-) &\geq V(t_k^+)e^{-(\mu+\beta+\omega)\tau}. \end{aligned}$$

Applying the impulsive condition, we have

$$\begin{aligned} V(t_{k+1}^+) &= V(t_{k+1}^-) + rS(t_{k+1}^1) \\ V(t_{k+1}^+) &\geq V(t_{k+1}^-) + \frac{r\mu\left(1-e^{-(\mu+\beta)\tau}\right)}{(\mu+\beta)\left(1-(1-r)e^{-(\mu+\beta)\tau}\right)} \\ &\geq V(t_k^-)e^{-(\mu+\beta+\omega)\tau} + \frac{r\mu\left(1-e^{-(\mu+\beta)\tau}\right)}{(\mu+\beta)\left(1-(1-r)e^{-(\mu+\beta)\tau}\right)}. \end{aligned}$$

Since $e^{-(\mu+\beta+\omega)\tau} < 1$, this recurrence relation has a stable equilibrium and hence solutions converge to the impulsive periodic orbit with endpoints

$$\begin{aligned} V_\infty^- &= \frac{r\mu\left(1-e^{-(\mu+\beta)\tau}\right)e^{-(\mu+\beta+\omega)\tau}}{(\mu+\beta)\left(1-(1-r)e^{-(\mu+\beta)\tau}\right)\left(1-e^{(\mu+\beta+\omega)\tau}\right)} \\ V_\infty^+ &= \frac{r\mu\left(1-e^{-(\mu+\beta)\tau}\right)}{(\mu+\beta)\left(1-(1-r)e^{-(\mu+\beta)\tau}\right)\left(1-e^{(\mu+\beta+\omega)\tau}\right)}. \end{aligned}$$

Infected vaccinated individuals

Next we calculate the number of infected vaccinated individuals. Using the overestimate $I \leq 1$, we can write

$$\begin{aligned} I' &\leq \beta_V V(1+I_V) - \nu_V I_V - \mu I_V - \omega I_V \\ &\leq \beta_V V_\infty^+(1+I_V) - \nu_V I_V - \mu I_V - \omega I_V \end{aligned}$$

over a long period of time. Integrating and applying the initial condition $I(0) = 0$, we have

$$I_V = \frac{\beta V_\infty^+}{\nu_V + \mu + \omega - \beta_V V_\infty^+}\left(1 - e^{(\beta_V V_\infty^+ - \nu_V - \mu - \omega)t}\right).$$

This converges if $\nu_V + \mu + \omega - \beta_V V_\infty^+ > 0$. If this holds, then

$$\nu_V + \mu + \omega > \frac{\beta_V r\mu\left(1-e^{-(\mu+\beta)\tau}\right)}{(\mu+\beta)\left(1-(1-r)e^{-(\mu+\beta)\tau}\right)\left(1-e^{(\mu+\beta+\omega)\tau}\right)}.$$

Rearranging, we have

$$(\mu+\beta)\left(1-(1-r)e^{-(\mu+\beta)\tau}\right)(\nu_V+\mu+\omega) > \beta_V r\mu\left(1-e^{-(\mu+\beta)\tau}\right)$$
$$\left[-(\mu+\beta)(1-r)(\nu_V+\mu+\omega)+\beta_V r\mu\right]e^{-(\mu+\beta)\tau} > \beta_V r\mu-(\mu+\beta)(\nu_V+\mu+\omega).$$

This inequality has no solution unless

$$r < \bar{r} = \frac{(\mu+\beta)(\nu_V+\mu+\omega)}{\beta_V r\mu+(\mu+\beta)(\nu_V+\mu+\omega)} < 1$$

If $r > \bar{r}$, then I_V converges to

$$\lim_{t\to\infty} I_V = \frac{\beta_V V_\infty^+}{\nu_V+\mu+\omega-\beta_V V_\infty^+} \equiv I_V^\infty$$

We are interested in the size of this value of I_V^∞. We have

$$I_V^\infty = \frac{\beta_V r\mu\left(1-e^{-(\mu+\beta)\tau}\right)}{\mu+\beta\left(1-(1-r)e^{-(\mu+\beta)\tau}\right)\left(1-e^{-(\mu+\beta+\omega)\tau}\right)\left(\nu_V+\mu+\omega-\frac{\beta_V r\mu\left(1-e^{-(\mu+\beta)\tau}\right)}{(\mu+\beta)\left(1-(1-r)e^{-(\mu+\beta)\tau}\right)}\right)}.$$

To estimate the size of this value for frequent vaccinations, we use L'Hôpital's rule to find

$$\begin{aligned}\lim_{\tau\to 0} I_V^\infty &= \frac{\beta_V\mu}{(\mu+\beta+\omega)(\nu_V+\mu+\omega)}\\ &= \frac{(1-\alpha)\beta\mu}{(\mu+\beta+\omega)(\nu_V+\mu+\omega)} \ll 1-\alpha < 1.\end{aligned}$$

It follows that I_V is small if the vaccine significantly reduces transmissibility and is applied frequently.

Infected individuals

Finally, we examine the number of infected individuals under the assumption that infected vaccinated individuals are negligible (so $I_V \approx 0$). We then have

$$\begin{aligned}I' &\approx \beta SI-\nu I-\mu I\\ &\leq \beta S_\infty^- I-\nu I-\mu I\\ &= \frac{\beta\mu\left(1-e^{-(\mu+\beta)\tau}\right)}{(\mu+\beta)\left(1-(1-r)e^{-(\mu+\beta)\tau}\right)}I-\nu I-\mu I.\end{aligned}$$

It follows that, after sufficient time, the disease will be contracting *not sure what this means if

$$q = \frac{\beta\mu\left(1 - e^{-(\mu+\beta)\tau}\right)}{(\mu+\beta)\left(1-(1-r)e^{-(\mu+\beta)\tau}\right)} - \nu - \mu < 0.$$

We thus define a new quantity, the *impulsive reproduction number*

$$T_0 = \frac{\beta\mu\left(1 - e^{-(\mu+\beta)\tau}\right)}{(\nu+\mu)(\mu+\beta)\left(1-(1-r)e^{-(\mu+\beta)\tau}\right)},$$

which has the condition that the disease will be controlled if $T_0 < 1$.

Solving the equation $T_0 = 1$, we can define the maximal period as

$$\hat{\tau} = \frac{1}{\mu+\beta} \ln \frac{(1-r)(\nu+\mu)(\mu+\beta) - \beta\mu}{(\nu+\mu)(\mu+\beta) - \beta\mu}.$$

This is defined only if

$$r < r^* \equiv 1 - \frac{\beta\mu}{(\nu+\mu)(\mu+\beta)}. \tag{1}$$

Differentiating, we have

$$\frac{\partial T_0}{\partial r} = \frac{\beta\mu\left(1 - e^{-\mu+\beta\tau}\right)}{(\nu+\mu)(\mu+\beta)}\left[-\left(1-(1-r)e^{-(\mu+\beta)\tau}\right)e^{-(\mu+\beta)\tau}\right] < 0.$$

It follows that T_0 is decreasing as r increases, for $r < r^*$.

Now let $r = r^* + \epsilon$ in order to determine what happens beyond r^*. We have

$$r = \frac{(\nu+\mu)(\mu+\beta) - \beta\mu}{(\nu+\mu)(\mu+\beta)} + \epsilon.$$

Substituting into q and taking a common denominator, we find that the numerator of q is

$$(\nu+\mu)^2(\mu+\beta)^2\left[(1-\epsilon)e^{-(\mu+\beta)\tau} - 1\right] < 0.$$

It follows that $T_0 < 1$ whenever $r > r^*$.

In summary, assuming the number of infected vaccinated individuals is negligible, if $r > r^*$, where r^* is defined by (1), then the disease will be controlled, whereas if $r < r^*$, then the disease can be controlled, assuming the period between vaccinations satisfies $\tau < \hat{\tau}$.

5 Numerical simulations

From Weber *et al.* [39], we assume the parameter values $\beta = 0.03$, $\mu = 0.041$ and $\nu = 36$. We add vaccination parameters $\omega = 0.1$, $\epsilon = 1$, $p = 1$, $\nu_V = 177$ and $\beta_V = 3000$. (We also have $\gamma = 1.8$ and impose $\gamma_V = 1.2\gamma$.) This represents a vaccine with complete coverage and perfect effectiveness that wanes after ten years, where vaccinated individuals can be infected with a high transmission rate, but recover very quickly.

Figure 3 shows the results of transmission using disease parameters from Weber *et al.* [39] and assumed vaccination parameters such that recovery was slightly faster and transmission slightly less likely. The vaccine was given to 50% of the eligible population, but waned after 0.01 years (3.65 days) is this the extreme parameter value for vaccine waning? May need to justify why this parameter choice is so low. The parameters used were $\mu = 0.041; \omega = 100; \beta = 50; \beta_V = 0.8\beta; \epsilon = 0.9; p = 0.5; \nu = 36; \nu_V = 1.2\nu; \gamma = 1.8; \gamma_V = 1.2\gamma$.

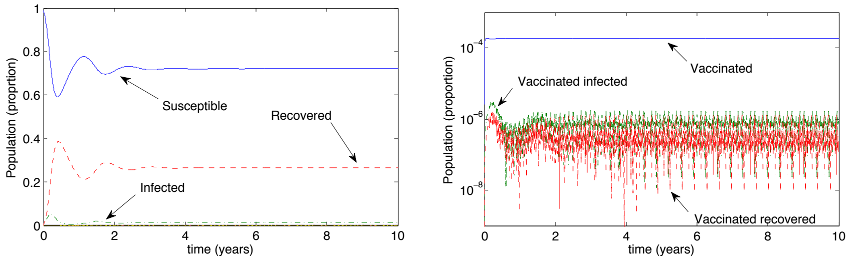

Figure 3: Results from the basic model with vaccination. There is an outbreak and the infectious population oscillates, eventually approaching an equilibrium. A small proportion of individuals are (and remain) vaccinated, with a low-level outbreak among vaccinated individuals.

Figure 4 illustrates the destabilisation of the DFE when extreme vaccination parameters are used. In this case, transmission of the vaccinated strain *what does the vaccinated strain mean? was extremely high but recovery fast, allowing for infection spikes to occur among a small proportion of vaccinated individuals before the infection stabilised. Data used were $\mu = 0.041; \omega = 0.1; \beta = 0.03; \beta_V = 3000; \epsilon = 1; p = 0, 1?; \nu = 36; \nu_V = 177; \gamma = 1.8; \gamma_V = 1.2\gamma$.

Although the transmission rate is unrealistically high, this nevertheless demonstrates that a stable DFE can be destabilised by a vaccine. Note that

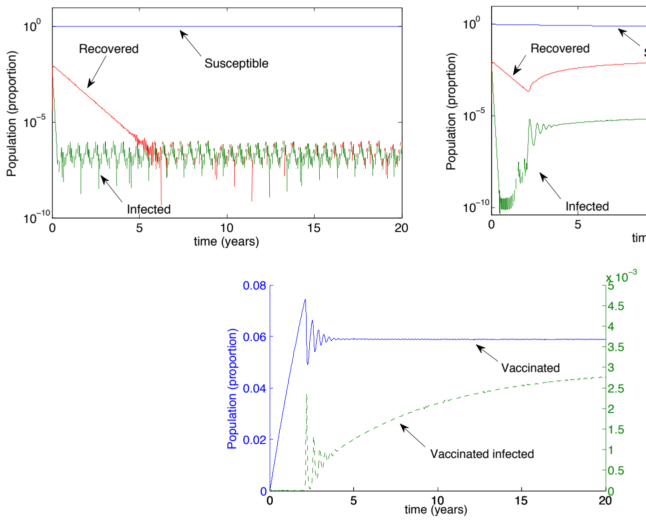

Figure 4: Extreme parameters show that perfect vaccination can induce infection spikes. A. With no vaccine, the result is that the infection clears and the entire population remains susceptible (note that the low-level fluctuations result from numerical limitations in MATLAB) B. With a vaccine given to the entire population, the susceptible population dips slightly as infection takes hold. C. Infection in the vaccinated population initially takes the form of infection spikes before stabilising. Note that vaccination thus destabilises the disease-free equilibrium.

this point of interest is not a backward bifurcation, but rather a destabilisation of the equilibrium.

Next, following Weber *et al.* [39], we examined the more realistic case when the transmission rate oscillated. Since the waning rate of the vaccine was not known, we decided to investigate several options for ω.

When there is no vaccine, the disease results in a maximum of 7% of the population infected. Parameters used were $\mu = 1/70; \omega = 1/10; b_0 = 60; b_1 = 0.16; \phi = 0.15; \beta_V = 0.5\beta; \epsilon = 1; p = 0; \nu = 36; \nu_V = 1.2\nu; \gamma = 1.8; \gamma_V = 1.2\gamma$ (see Figure 5).

A vaccine administered to the entire population with 50% transmission that did not wane for ten years resulted in about 6% of the population infected. Data used were identical to Figure 5 except that $p = 1$ (see Figure 6). In this case, there is only a slight decrease in the maximum disease burden, despite complete vaccination coverage.

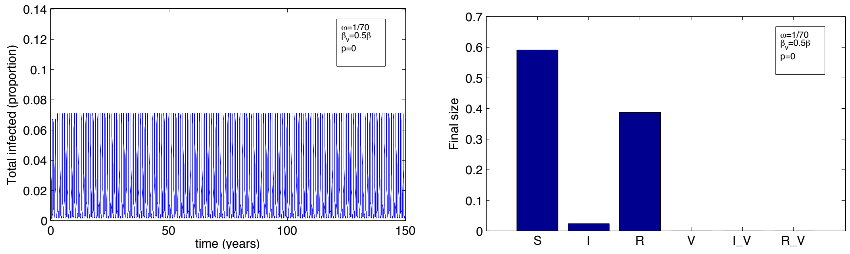

Figure 5: Without vaccination, the disease infects up to 7% of the population. A. The total infected population, including vaccinated individuals. B. The final size in each population.

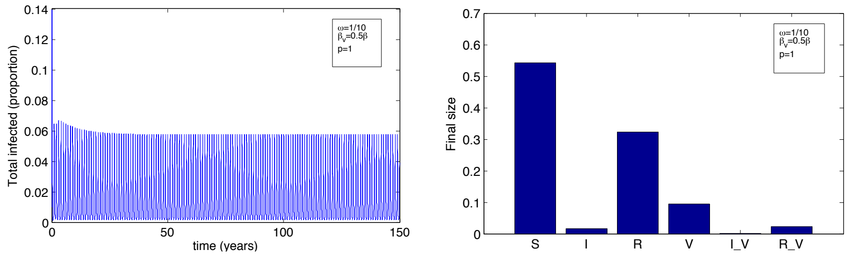

Figure 6: Complete coverage with a vaccine that did not wane for 10 years results in a 1% reduction in the disease compared to not vaccinating. A. The total infected population, including vaccinated individuals. B. The final size in each population.

A vaccine given to the entire population with 50% transmission that did not wane for 70 years resulted in a significant reduction in the infected population. Data used was identical to Figure 6 except that $\omega = 1/70$. See Figure 7. In this case, there is a significant reduction in the total disease burden, reducing the maximum to less than 2% of the total population.

Note that, even with perfect coverage with a lifelong vaccine (so that $\epsilon = p = 1$ and $\mu = \omega = \frac{1}{70}$), the DFE still satisfies

$$\bar{S} = \frac{\omega}{\mu + \omega} = \frac{1}{2}$$
$$\bar{V} = \frac{\mu}{\mu + \omega} = \frac{1}{2},$$

so the population without infection would eventually split into equal num-

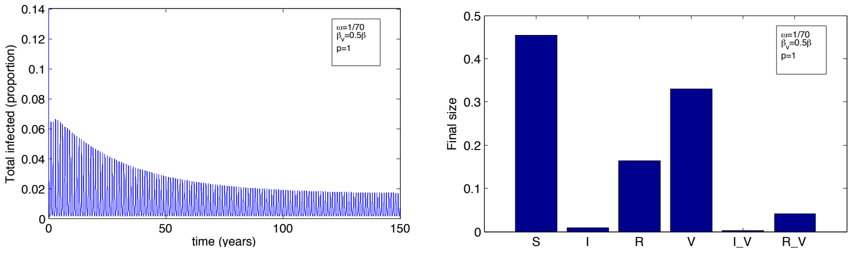

Figure 7: Complete coverage with a vaccine that did not wane for 70 years results in a significant reduction in infection. A. The total infected population, including vaccinated individuals. B. The final size in each population.

bers of vaccinated and unvaccinated susceptible individuals. With infection included and oscillating transmission, explicitly calculating the final size in each compartment is not possible. However, we expect that higher coverage with a lifelong vaccine would tend to a final size with similar numbers; Figure 7 shows that this is indeed the case.

Of course, complete vaccination coverage is unrealistic. Consequently, we examined the effect of 50% coverage with a vaccine that did not wane for 70 years. Parameter values used were identical to those in Figure 7 except that $p = 0.5$. See Figure 8. In this case, there is still a significant reduction in total disease burden. Note that significantly greater reduction is achieved with 50% coverage and a lifelong vaccine than was achieved with 100% coverage and a vaccine that lasted 10 years (see Figure 6).

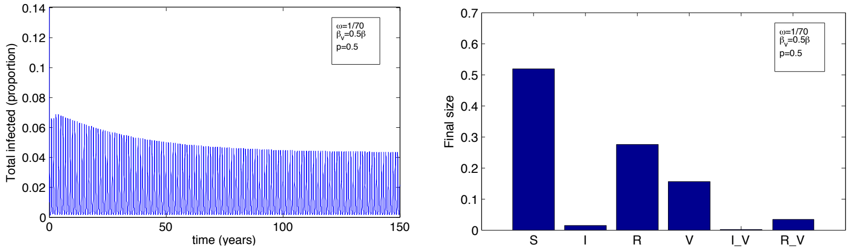

Figure 8: 50% coverage with a vaccine that did not wane for 70 years results in a moderate reduction in infection. A. The total infected population, including vaccinated individuals. B. The final size in each population.

It follows that the waning rate of the vaccine is crucial. Even if complete coverage could be achieved, a vaccine with a moderate duration (eg 10 years) results in very little reduction of infection. Conversely, a vaccine that does not wane over a lifetime results in significant reduction in disease burden.

The best-case scenario involves complete coverage with a vaccine that does not wane for 70 years. Figure 9 illustrates the population dynamics when such a vaccine is introduced.

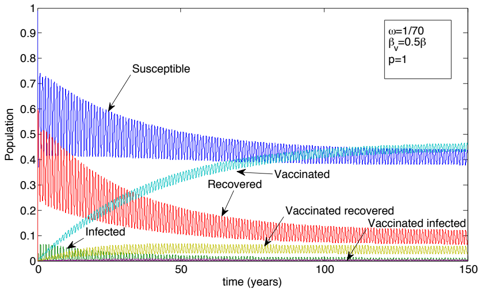

Figure 9: Population dynamics for a lifelong vaccine with complete coverage. Note that the vaccinated infected are too small to appear on the figure.

Figure 10 illustrates the effect of pulse vaccination on the dynamics over a ten-year period. The infection is kept low, with a small outbreak among the vaccinated. Overall, however, there is an exchange with the majority of individuals gradually transforming from susceptible to vaccinated.

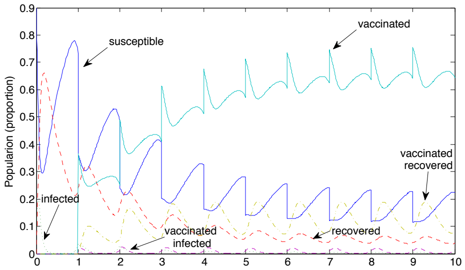

Figure 10: Population dynamics for an impulsive vaccine given annually to 50% of the population, with a waning of 10 years. Note that the seasonal oscillations and the impulses combine to produce a double period.

6 Discussion

Before a new vaccine is introduced, anticipated benefits and issues are assessed. Mathematical models can provide information about the population-level effects of a vaccine, and therefore assist in the decision-making process. We have highlighted potential issues that may arise with vaccination for RSV. In particular, we determine conditions under which a destabilisation of the disease-free equilibrium is possible. This is not in the form of a backward bifurcation, as is sometimes seen, but rather occurs when the vaccine causes sufficiently fast recovery and transmission is extremely high. An infection-free population that is effectively vaccinated against RSV can nevertheless produce vaccination-innduced spikes of infection. Although such a case is unlikely to occur with the unrealistic parameters we chose, we have shown proof-of-concept that it is possible and determined conditions on the recovery rate due to vaccinaton that allow for the possibility.

Using impulsive differential equations, we were able to formulate conditions on the period and the strength of vaccination to allow for disease control (though not eradication). If the vaccine reduces transmissibility and is applied frequently, then vaccinated infected individuals can be reduced to low numbers. We relaxed the assumption of constant transmission. We demonstrated that the waning of the vaccine has a greater effect on the outcome that coverage. Hence it is imperative that a vaccine that provides a sufficient duration of protection be developed before being released for general use.

We also defined a new quantity, the impulsive reproduction number T_0. This is a sufficient (but not necessary) condition, based on an overestimate of the infected population, that ensures eradication if $T_0 < 1$. If $T_0 < 1$, then the infected population is contracting within each impulsive cycle. Since the infected population is then reduced at each impulse point, the result is the eventual eradication of the infection. Note that we assumed constant transmission for this derivation; however, numerical simulations were performed using seasonal oscillations. The result was a double period: one from the impulsive periodic orbit and the other from the seasonal oscillations.

Our model has some limitations. Firstly, we assumed that time to administer the vaccine was significantly shorter than the time between vaccine administrations in order to justify the impulsive approximation. Such assumptions are reasonable in many cases [**?**], although can produce confounding effects in some situations [**?**]. The extreme parameters that we used to illustrate the vaccination spikes operated under the assumption that the transmission rate for infected vaccinatied individuals was significantly higher than the transmission rate without vaccination. Since we extended the model introduced by Weber *et al.* [39], our model inherited many of the assumptions from that model, such as mass-action transmission, a constant birth rate and that the birth and death rates were matched, resulting in a constant population.

In our model we considered RSV transmission dynamics for a single age class, in order to allow for the model to be analytically tractable. Given we were examining the broad popoulation-level impacts in a large population, we considered this a reasonable model simplification. Further, it has been shown that for a similar compartmental RSV model, including multiple age classes did not change the bifurcation structure of the model [16]. However, different vaccine candidates for RSV are being developed for distinct key age groups – infants, young children, pregnant women, and the elderly [30]. This means that future models that explore the specific implications of vaccines for these target groups may need to incorporate additional age classes.

A vaccine that targets RSV infection has the potential to significantly reduce the overall prevalence of the disease, but it has to be sufficiently long-lasting. Coverage and effectiveness of the vaccine is important, but the critical parameter that our modelling identified is the waning rate of the vaccine. We thus recommend that candidate vaccines be tested for sufficient duration before being released to the public.

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