Respiratory Syncytial Virus vaccination

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Part 2: impulsive model

1 Introduction

2 The model

We extend the basic model from Weber et al to include vaccination.

Assumptions: The leaving rate μ is unchanged across all classes. There is no disease-specific death rate. We scale the entry and leaving rates so that the population is constant.

The basic model with vaccination is

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

with $\beta(t) = b_0(1 + b_1\cos(2\pi t + \phi))$ and $\beta_V(t) = (1-\alpha)\beta(t)$, for $0 \le \alpha \le 1$. (We may relax the lower bound on α later.)

3 Analysis

There is a disease-free equilibrium that satisfies

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

3.1 Constant transmission

If we assume transmisison is constant so that β and β_V are independent of time, then the Jacobian is

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

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

$$\det(J-\lambda I) = (-\mu-\lambda)(-\mu-\gamma-\lambda)(-\mu-\omega-\lambda)(-\mu-\gamma_V-\omega-\lambda)\det\begin{bmatrix}\beta\bar{S}-\mu-\nu-\lambda & \beta\bar{S}+\omega \\ \beta_V\bar{V} & \beta_V\bar{V}-\nu_V-\mu-\omega-\lambda\end{bmatrix}$$

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

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

(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 point 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, we expect that vaccinated individuals 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 we would like to know whether f has a turning point ν_V^* such that $f(\nu_V^*) < 0$.

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 two requirements we need for this to be meaningful: 1. $\nu_V^* > \nu$ and 2. $f(\nu_V^*) < 0$. See Figure 1.

[Is this definitely a local minimum?]

Yes, proven. Write up results.

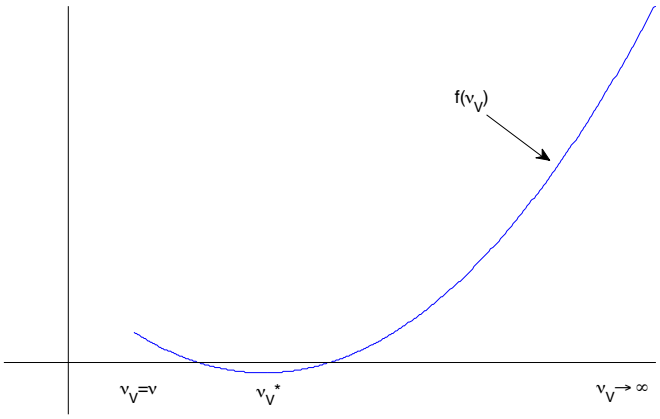

Figure 1: Possible sketch of the form of $f(\nu_V)$ with a negative minimum between two positive extremes.

4 Impulsive model

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

5 Numerical simulations

From Weber et al, we have $\beta = 0.03$, $\mu = 0.041$ 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 efficacy that wanes after ten years, but vaccinated individuals can be infected with a high transmission rate, but recover very quickly.

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

Note that what we are dealing with here is not a backward bifurcation, but rather a destabilisation of the equilibrium.

Figure 2 shows the results of transmission using data from Weber et al 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 **(check this)** The data 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 illustrates the destabilisation of the DFE when extreme vaccination parameters are used. In this case, transmission of the vaccinated strain was extremely high but recovery extremely fast, allowing for infection spikes to occur among a small proportion of vaccinated individuals before the infection stabilises. Data used were $\mu = 0.041; \omega = 0.1; \beta = 0.03; \beta_V = 3000; \epsilon = 1; p = 0, 1; \nu = 36; \nu_V = 177; \gamma = 1.8; \gamma_V = 1.2.\gamma$.

Next, following Weber et al, 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. Data used was $\mu = 1/70; \omega = 1/10; b_0 = 60; b_1 = 0.16; \phi = 0.15; \beta_V = 0.5\beta; \epsilon = 1; p = 0; \nu = 36; \nu_V = 1.2\nu; \gamma = 1.8; \gamma_V = 1.2\gamma$. See Figure 4.

A vaccine given to the entire population with 50% transmission that did not wane for ten years resulted in about 6% of the population infected. Data used was identical to Figure 4 except that $p = 1$. See Figure 5. In

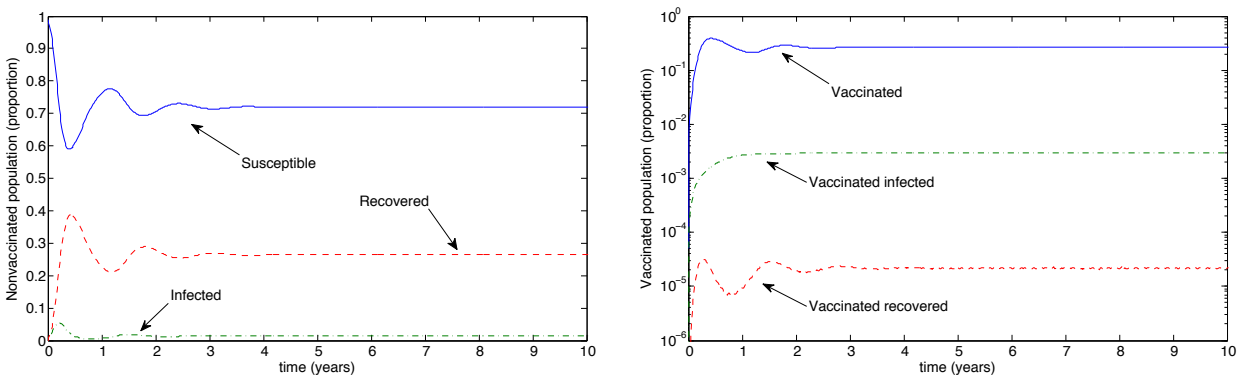

Figure 2: Results from the basic model with vaccination. There is an outbreak and the disease oscillates, eventually approaching an equilibrium. A small proportion of individuals are (and remain) vaccinated, with a low-level outbreak among vaccinated individuals.

this case, there is only a slight decrease in the maximum disease burden, despite complete vaccination coverage.

[If the entire population is vaccinated, who is susceptible?]

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 5 except that $\omega = 1/70$. See Figure 6. In this case, there is a significant reduction in the total disease burden, reducing the maximum to less than 2% of the total population.

Of course, complete vaccination coverage is not realistic. Consequently, we examined the effect of 50% coverage with a vaccine that did not wane for 70 years. Data used was identical to Figure 6 except that $p = 0.5$. See Figure 7. 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 5).

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 8 illustrates the population dynamics when such a vaccine is introduced.

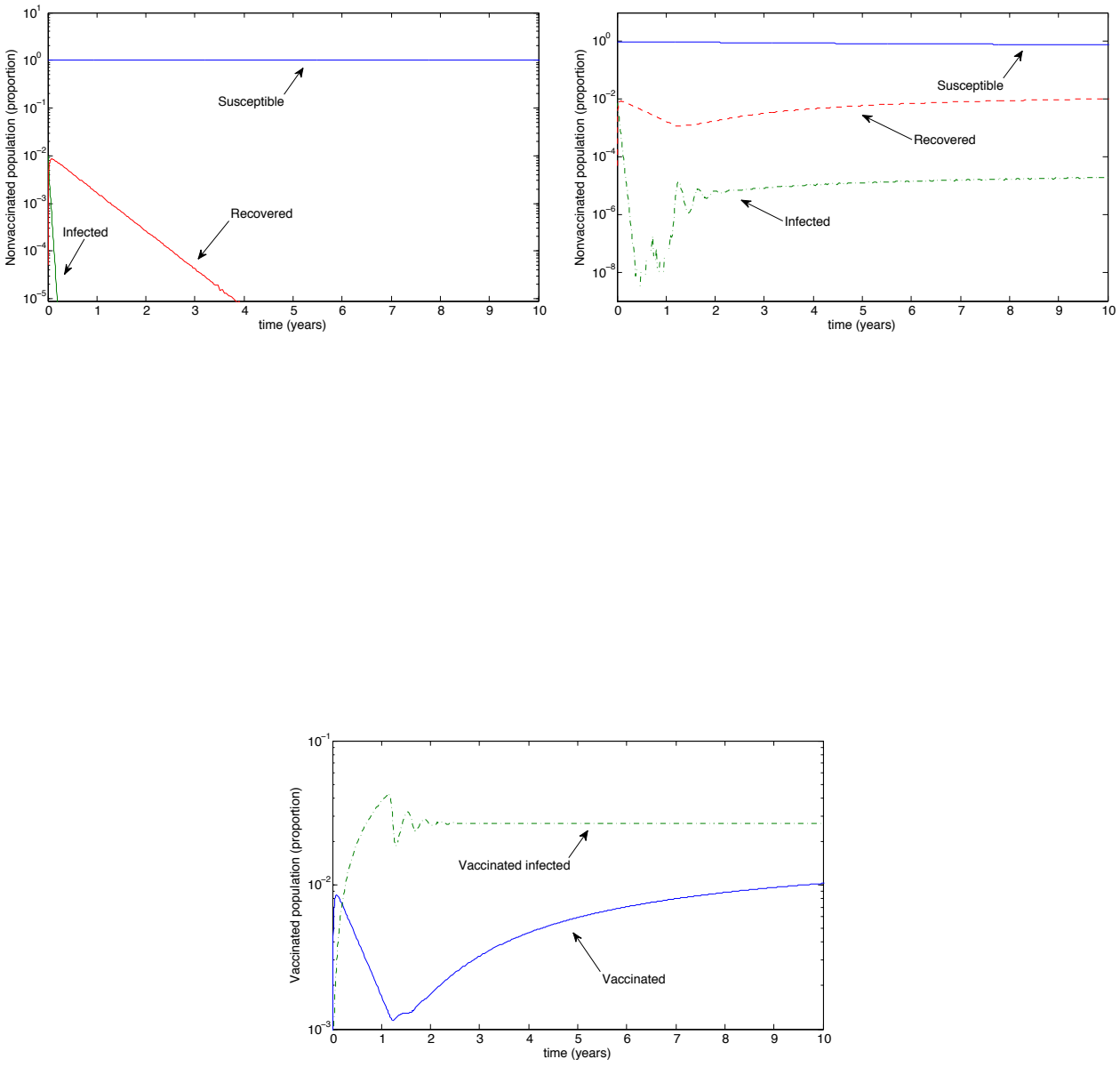

Figure 3: Extreme parameters show that perfect vaccination can induce infection spikes. A. With no vaccine, the result is that the infection clears and the entire population remains susceptible (note that the low-level fluctuations result from numerical limitations in MATLAB) B. With a vaccine given 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.

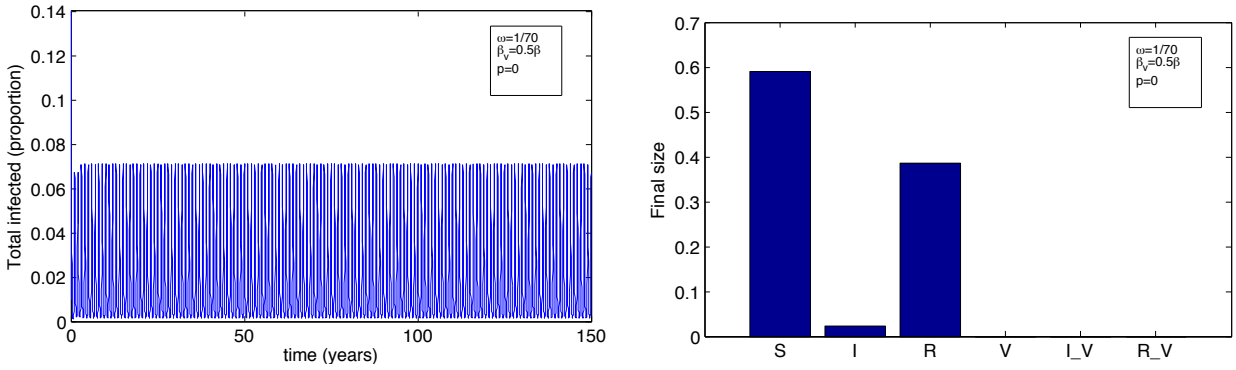

Figure 4: Without vaccination, the disease infects up to 7% of the population. A. The total infected population, including vaccinated individuals. B. The final size in each population.

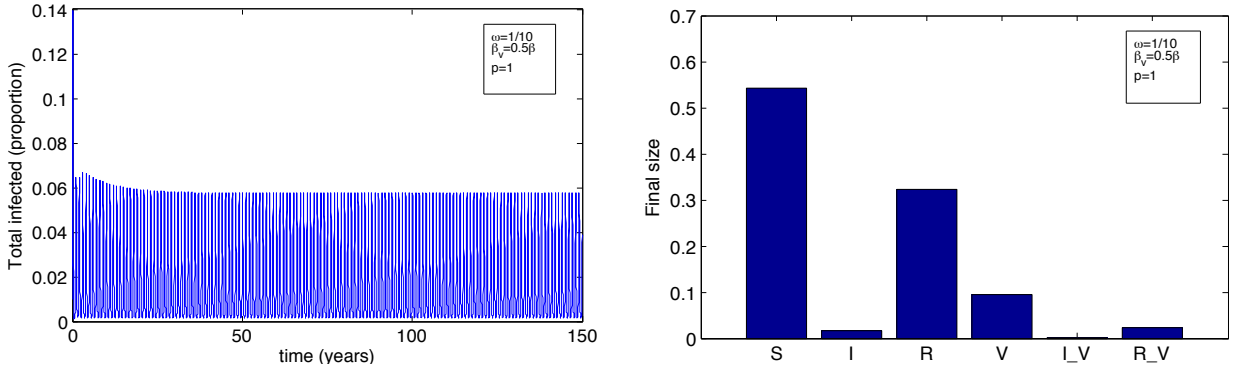

Figure 5: Complete coverage with a vaccine that did not wane for 10 years results in a difference of 1% reduction in the disease. A. The total infected population, including vaccinated individuals. B. The final size in each population.

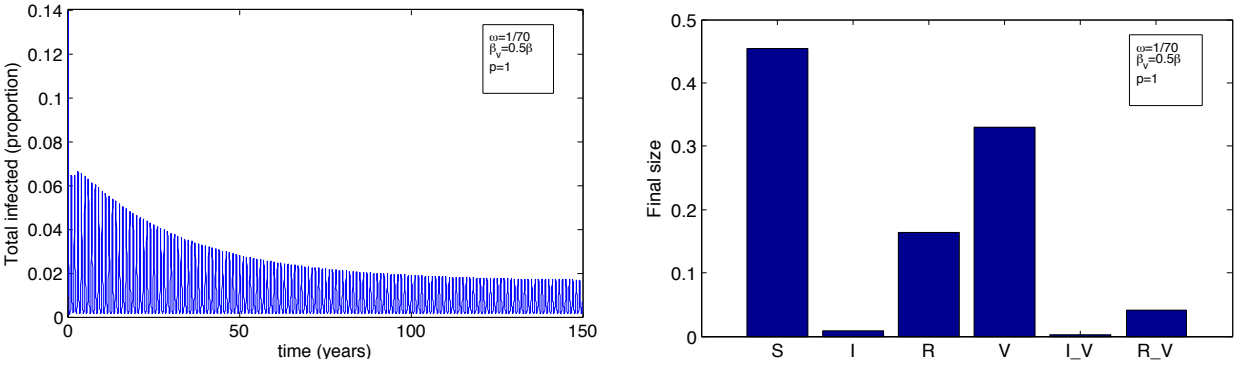

Figure 6: Complete coverage with a vaccine that did not wane for 70 years results in a significant reduction in infection. A. The total infected population, including vaccinated individuals. B. The final size in each population.

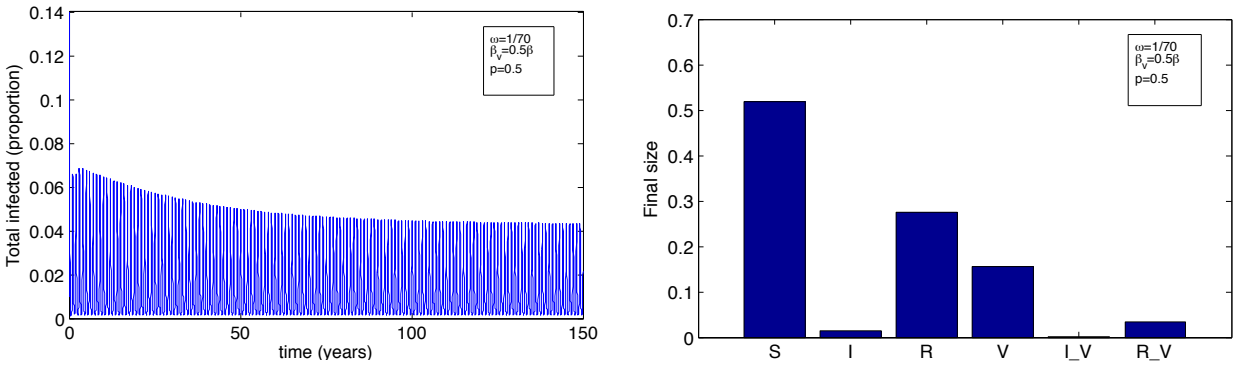

Figure 7: 50% coverage with a vaccine that did not wane for 70 years results in a significant reduction in infection. A. The total infected population, including vaccinated individuals. B. The final size in each population.

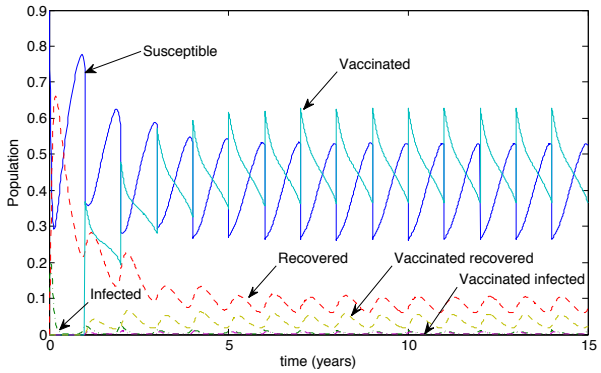

Figure 8: Population dynamics for a lifelong vaccine with complete coverage. Note that the vaccinated infected are too small to appear on the figure. [**Fix figure; the lowest arrow is regular infected.**]