How to write a modelling paper

RSV vaccination as an example

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Overview

- What this workshop is not

1. First Draft
2. The Introduction
3. Collation
4. Refinement
5. Responding to reviewers
6. What's next.

What this workshop is not

- I’m not telling you how to come up with ideas
- Or how to solve equations
- This is about how to present your work
- But more importantly how to refine it
- All writing is editing
- We’ll work through a successful example to illustrate the process
- Note that this is just one approach
- You may have a different one.

Part 1: First draft

- Brief statement of the problem
- Mathematical analysis
- Research question(s)
- Figures
- What it does not include:
  - introduction
  - references
  - discussion
  - abstract (always leave until last).

Preliminaries

- Coming up with the idea
  - what if we had a vaccine for RSV?
- Existing work in the literature
  - read the biology
- Creating the model
  - extending an existing one, in this case
- Initial analysis
  - DFE, simplifying assumptions, Jacobian, R_0
- This is all very standard
- *It does not make your results worth publishing!*

Draft title

More work to come later

The core idea.

Respiratory Syncytial Virus vaccination

Robert J. Smith?[1], Geoff Mercer

Part 2: impulsive model

1 Introduction

2 The model

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

Assumption [illegible] 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

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

Simplifying assumptions

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

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

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

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

where

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

Standard but necessary result.

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.)

Secondary analysis

- This is where you produce original insights
  - noticing b_1 may not be positive when $c_1=0$
  - one parameter could change the sign
  - it doesn't at the extremes
  - could there be a region where it does?
  - we just found our research question!
- Key question: What do we learn that we didn't know?
  - it's possible to destabilise the equilibrium in a new way (not a backward bifurcation)
- There's no algorithm for this part.

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,

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

Surprising result

May not happen...

...but it could!

Extreme case.

Refining the secondary analysis

- What are the implications?
  - Under what conditions does a critical point exist? Can we find it?
  - Is it definitely a local minimum? Can we prove that?
- Can we draw a picture?
- Diagrams are always helpful
- Some people will only read the abstract, the figure captions and the discussion
- The pictures need to tell the story
  - thus you need to have a narrative.

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

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

$$= \frac{(\omega + \mu + \nu_V)^2 - \beta_V \bar{V}[\omega + \mu + \nu]}{(\omega + \mu + \nu_V)^2}$$

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. $f(\nu^*) < 0$. See Figure 1.

[Is this definitely a local minimum?]

Yes, proven. Write up results.

Identify and solve key issues.

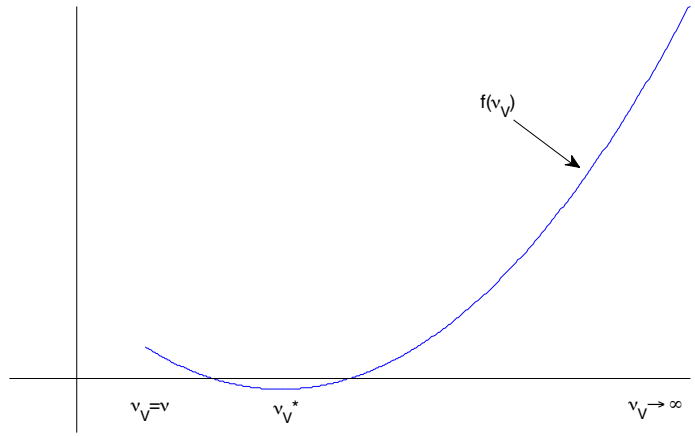


Figure 1: Possible sketch of the form of $f(\nu_V)$ with a negative minimum between two positive extremes.

Further ideas

- Possible future directions for this to go in
  - extending the model to an impulsive version
- Doesn't need to be completed yet
- Remember, the more depth you have in your paper, the more likely it is to be accepted

  (and read)
- If you want to change the world, you need to communicate your ideas
  - if you don't write it down, you didn't do it
- *Superficial or single results should not be published.*

4 Impulsive model

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

- Note that this is the entirety of Section 4 in the first draft.

Numerical simulations

- Used these to guide and reinforce the analysis
  - the possibility of $b_1<0$
  - trawl through parameter sets: can we see it?
- Parameters should be derived from the biological literature
- Not made up or drawn from mathematical models
- What do we learn that we didn't know?
  - extreme parameters can induce infection spikes, even with 100% vaccination.

Extreme parameters

Illustrates the surprising results

Identify any issues

A new result from simulations.

5 Numerical simulations

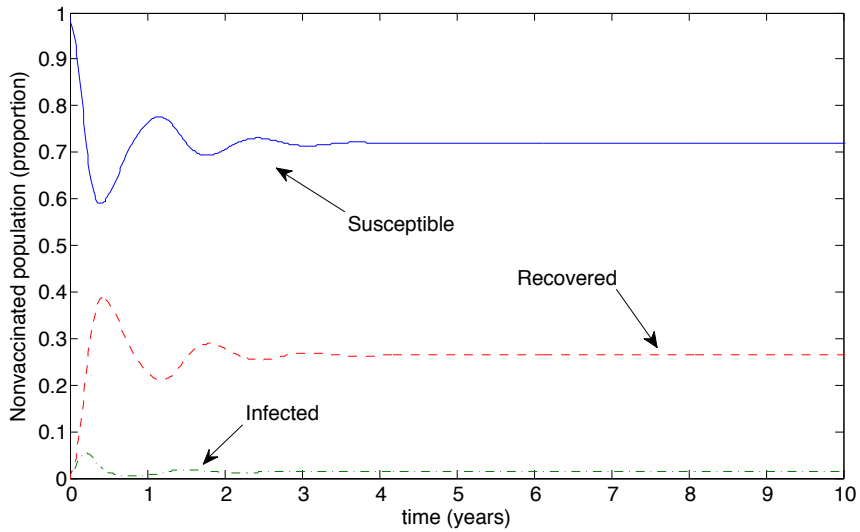
From Weber et al, we have $\beta = 0.03$ [illegible] 36. We add vaccination parameters $\omega = 0.1$, $\epsilon = 1$, $p =$ [illegible] $\nu_V = 177$ and $\beta_V = 3000$. We also have $\gamma = 1.8$ and impose $\gamma_V = 1.2\gamma$.) This repres[illegible]me with complete coverage and perfect efficacy 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 th[illegible] stable DFE can be destabilised by a vaccine.

Note that what we are dealing with here [illegible]not a backward bifurcation. [illegible]t 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 vacci[illegible]given to 50% of the eligible population, but waned after 0.01 years (**check this**). The data used were $\mu = 0.041; \omega = 100; \beta = 50; \beta_V = 0.8\beta; \epsilon = [illegible]; \nu = 36; \nu_V = 1.2\nu; \gamma = 1.8; \gamma_V = 1.2\gamma$.

Figure 3 illustrates the destabilisation of the DFE when extreme vaccination parameters are used. In this case, transmission of the vac[illegible]strain was extremely high but recovery extremely fast, allowing f[illegible] infection spikes to occur among a small proportion of vaccinated individuals bef[illegible]ection stabilises. Data used were $\mu = 0.041; \omega = 0.1; \beta = 0.03; \beta_V = 3000; \epsilon = 1; p = 0, 1; \nu = 36; \nu_V = 177; \gamma = 1.8; \gamma_V = 1.2.\gamma$.



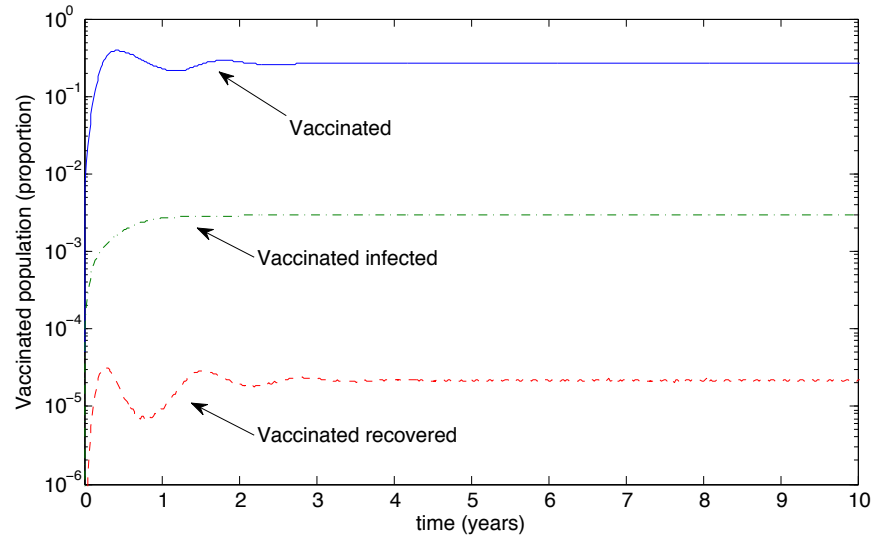


Figure 2: Results from the basic model with vaccination. There is an outbreak and the disease oscillates, eventually approaching an equilibrium. A small proportion of individuals are (and remain) vaccinated, with a low-level outbreak among vaccinated individuals.

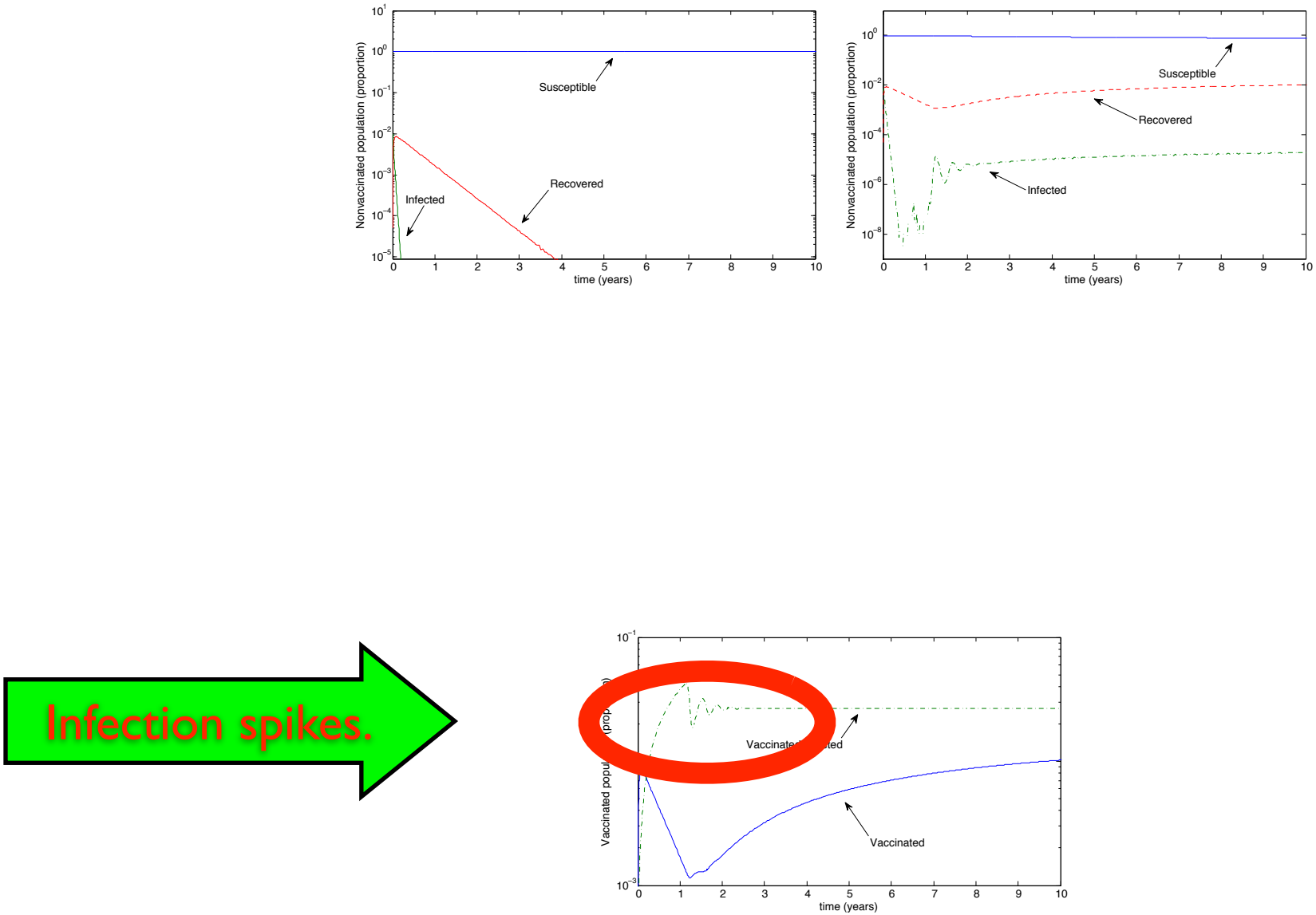


Figure 3: Extreme parameters show that perfect vaccination can induce infection spikes. A. With no vaccine, the result is that the infection clears and the entire population remains susceptible (note that the low-level fluctuations result from numerical limitations in MATLAB) B. With a vaccine given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

Refining numerical simulations

- More realism
  - include seasonal oscillations
- Apply stress tests
  - what if the coverage varied?
  - what happens when there's no vaccine?
  - what if the vaccine lasts for a lifetime?
- Identify key features
  - which is better, good coverage with a weak vaccine or a good vaccine given to only some people?
  - these should be issues people want to know.

More realism

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

Questions arise

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 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).

A key comparison

The take-home message.

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.

Baseline case

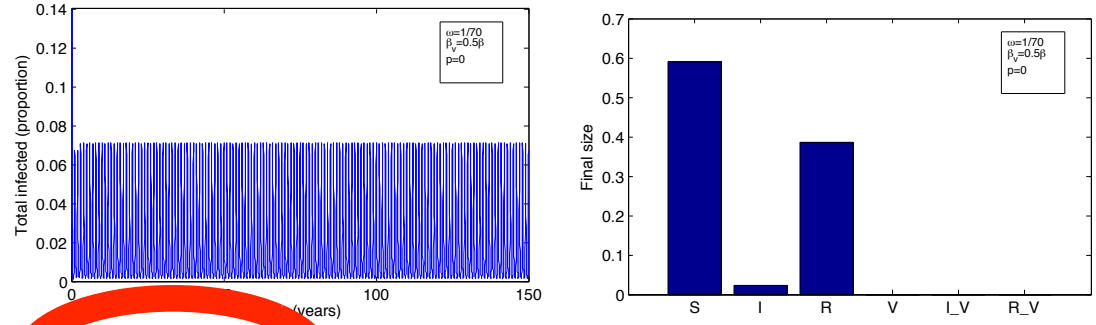


Figure : Without vaccination, t disease infects up to 7% of the population. A. The total infected population, includi cinated individ B. The final size in each population.

Intermediate case

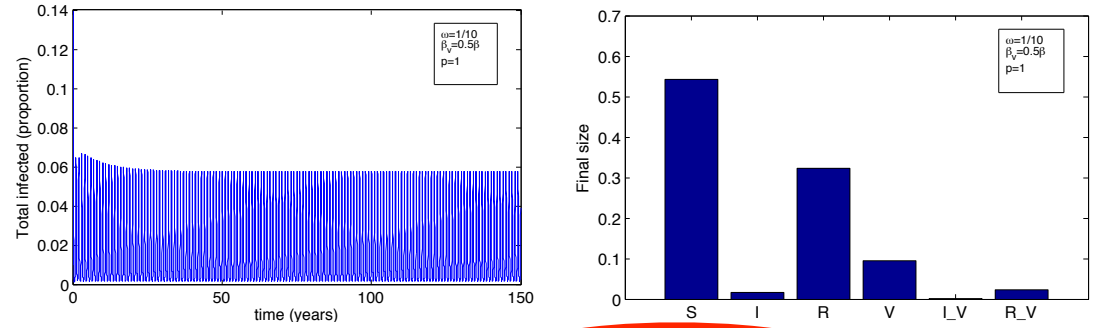


Figure 5: Complete coverage with a vaccine t did not wane for 10 years sults in a difference of 1% reduction in the disease. A. The total infected popu d individuals. B. The final size in each population.

Extreme case.

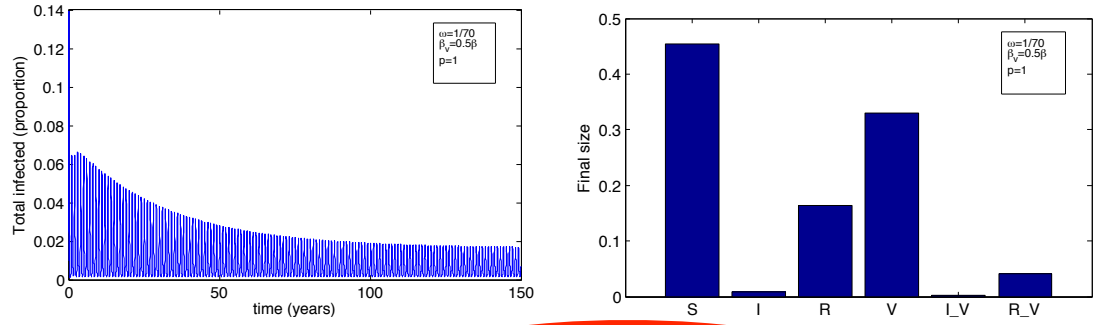
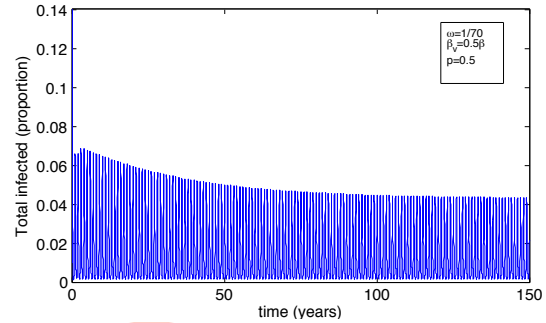


Figure 6: Complete coverage with a vaccin at did not wane for 70 years lts in a significant reduction in infection. A. The total infected population, incl B. The final size in each population.

Different case



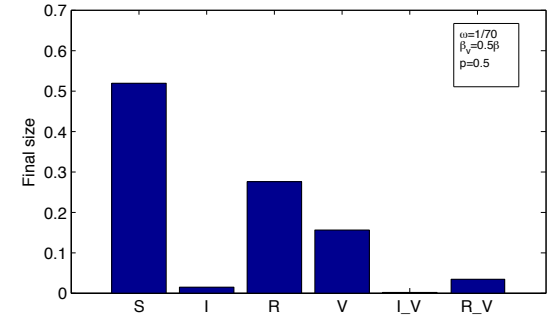
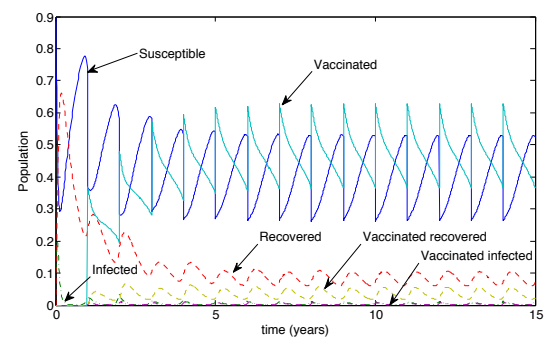


Figure 7: 50% coverage with a vaccine that did not wane for 70 years results in a significant reduction in infection. A. The [illegible], including vaccinated individuals. B. The final size in each population.



Identify issues.

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

Implications

- Do these results make sense?
  - if the entire population is vaccinated, who is susceptible?
  - is the vaccine realistic?
- What do we learn that we didn't know?
  - the waning rate is crucial
  - we see infection spikes that were not predicted
  - suddenly, we have a key result...

    ...and the title for the paper.

Understanding

- Why do we get these surprising results?
  - vaccinated individuals have a small chance of being infected
  - the transmission rate is very high, but the waning is very fast
  - the disease can thus act extremely intensely, but only in a small window of time
  - hence we see spikes
- If you can't explain surprising results biologically, they may be too good to be true
  - better that you find this out now than later.

Part 2: The Introduction

- Only a few, tight paragraphs
- Must be well written
  - find a native English speaker to read it
  - get a non-expert to read it
- Only things that are introductory should be in the Introduction
  - and things that are introductory should not be in other sections
- Don’t tell us how the paper is organised
  - unless the organisation is confusing
  - consider removing this confusion.

What to write

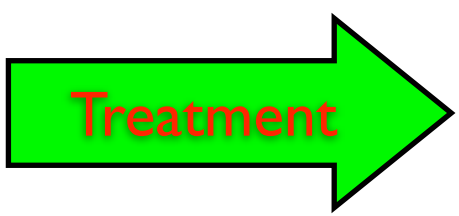
- Sketch a brief outline of each paragraph
  - what is RSV?
  - immunity
  - seasonal oscillations
  - treatment
  - previous models
- Do not write too little
- Do not write too much
- You are aiming to situate your work within the context of what's come before
  - needs to be tight.

I. Introduction

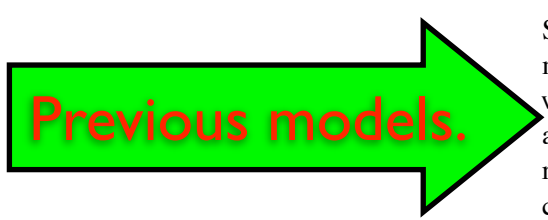
Respiratory syncytial virus (RSV) is the main cause of acute lower respiratory infections in infants and young children [22], with almost all children having been infected by two years of age [10, 25] and an estimated 0.5–2% of infants requiring hospitalisation due to infection [18]. One recent study estimated in that in 2005, 33.8 million new episodes of RSV occurred worldwide in children younger than five years of age [22]. Symptoms of RSV range from those of a cold, 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 [32], little data is published about RSV morbidity and mortality in developing countries [34]. However, estimates of the hospitalisation costs are substantial [14, 30, 36], 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 [8], and the highest number of observed RSV cases occur in children aged six weeks to six months [5, 27]. Immunity to RSV following an infection is short-lasting and reinfection in childhood is common [19]. Few studies have been undertaken to investigate transmission of RSV among adults, but it is thought that infection can occur throughout life [6, 15] and that in older children and adults, RSV manifests as a mild cold [10, 16]. RSV has been identified as a cause of mortality in the elderly with documented outbreaks in aged care settings [13, 31]; one such study found that up to 18% of pneumonia hospitalisation in adults aged above 65 years may be due to RSV infection [12].

In temperate climates RSV epidemics exhibit distinct and consistent seasonal patterns. Most RSV infections occur during the cooler winter months, whether wet or dry [34], and outbreaks typically last between two and five months [11, 23]. In a number of temperate regions a biennial pattern for RSV cases has been identified; see, for example, [4, 20, 28]. 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 [26, 34].



Immunoprophylaxis with the monoclonal antibody Palivizumab, while not preventing the onset of infection, has proven effective in reducing the severity of RSV-related symptoms [29]. 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 developed of live attenuated vaccines; several such vaccines are being evaluated in clinical trials, with other vaccines in preclinical development [9, 14]. With the possibility of a RSV vaccine becoming available, mathematical models can be powerful tools for planning vaccination roll-out strategies.



Several ordinary differential equation Susceptible-Exposed-Infectious-Recovered (SEIR) type mathematical models for RSV transmission have been published to date, such as those presented in [3, 7, 17, 21, 24, 33, 35] with a sine or cosine forcing term to account for seasonal variation in transmission. Weber *et al*. [33] present a SEIRS model which incorporates a gradual reduction in susceptibility to reinfection and maternally derived immunity, and fit the model to several data sets. Leecaster *et al*. [17] present a SEIDR model with both child and adult classes for the S, E and I compartments, and where the D class represents children in which

References

- Every sentence must be referenced
  - between 20–40 references
- Try to find interesting ways to present the information
  - sentences should not all have the same structure
- References concerning biology should be to the biological literature
  - not mathematical models
- Be consistent in your citation style
  - LaTeX can always change it later.

infection was detected. The model is fit to seven years of data from Salt Lake City, USA.

Moore *et al*. [21] present an age-structured SEIRS model for children under two years of age and the remaining population. The model is fit to data from Perth, Western Australia. Capistran *et al*. [7] outline a SIRS model with seasonal forcing and propose a method to estimate the model parameters, demonstrated by fitting models to data from The Gambia and Finland. Paynter *et al*. [24] investigate the ecological drivers of RSV seasonality in the Philippines, where the model includes a second partially susceptible class, and second classes for latent and infectious individuals with a subsequent RSV infection. This work also applies a square wave transmission term that accounts decreased transmissability over the summer holidays, as well as a seasonally driven birth rate.

White *et al*. [35] describe nested differential equation models for RSV transmission and fit these to RSV case data from different regions. In the work of Arenas *et al*. [3], randomness is introduced into the differential equation model and the model fit to RSV hospitalisation data for Valencia, Spain.

Few papers have so far explored vaccination strategies for RSV. A newborn vaccination strategy is outlined in [1] for the Spanish region of Valencia, in order to estimate the cost-effectiveness of potential RSV vaccination strategies. The modelling approach removes a fraction of susceptible newborns into a vaccinated class, where they remained until they reached the next age group, at which point they move to the second susceptible class. This strategy assumes booster doses of the vaccine in the first year of life, such that the immunisation period would be at least equal to the immunity of those who have recovered from RSV infection. In subsequent work, an RSV vaccine cost analysis is conducted based on a stochastic network model, with children vaccinated at two months, four months and one year of age [2].

Details of what we plan to do...

More than 30 references

Be consistent in citation style

E.g., use Google Scholar's " icon.

REFERENCES

[1] Acedo, L., J. Díez-Domingo, J.-A. Moraño, and R.-J. Villanueva (2010). Mathematical modelling of respiratory syncytial virus (RSV): vaccination strategies and budget applications. *Epidemiology and Infection 138*(6), 853–60.

[2] Acedo, L., J.-A. Moraño, and J. Díez-Domingo (2010). Cost analysis of a vaccination strategy for respiratory syncytial virus (RSV) in a network model. *Mathematical and Computer Modelling 52*(7-8), 1016–1022.

[3] Arenas, A. J., G. González-Parra, and L. Jódar (2010). Randomness in a mathematical model for the transmission of respiratory syncytial virus (). *Mathematics and Computers in Simulation 80*(5), 971–981.

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[5] Brandenburg, A. H., J. Groen, H. A. van Steensel-Moll, E. C. Claas, P. H. Rothbarth, H. J. Neijens, and A. D. Osterhaus (1997). Respiratory syncytial virus specific serum antibodies in infants under six months of age: limited serological response upon infection. *Journal of Medical Virology 52*(1), 97–104.

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Part 3: Collation

- Fill in any gaps
  - added impulsive model analysis
  - developed a new quantity, T_0, during a proof
  - added impulsive figures
- Should you add a co-author?
  - often this can save a paper that's flagging
- Discussion
  - this is for implications, not a summary
- Abstract
  - this is always the last thing you should write.

Title and Abstract

- The title should spring out of your most interesting results
- Abstracts should always follow the standard outline
  - Background (what is the problem?)
  - Methods (how did you approach it?)
  - Results (what did you find that was new?)
  - Conclusions (what are the implications?)
- 1–2 sentences for each
- Most people will ONLY read the abstract.

Unexpected infection spikes in a model of Respiratory Syncytial Virus vaccination

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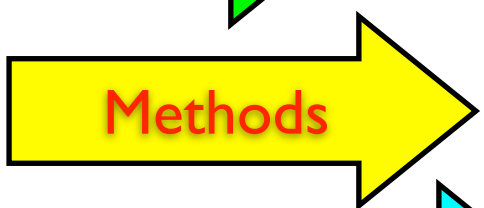
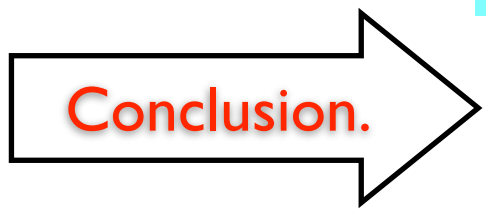
2. National Centre for Epidemiology and Population Health, Australian National University, Canberra, 2601, Australia



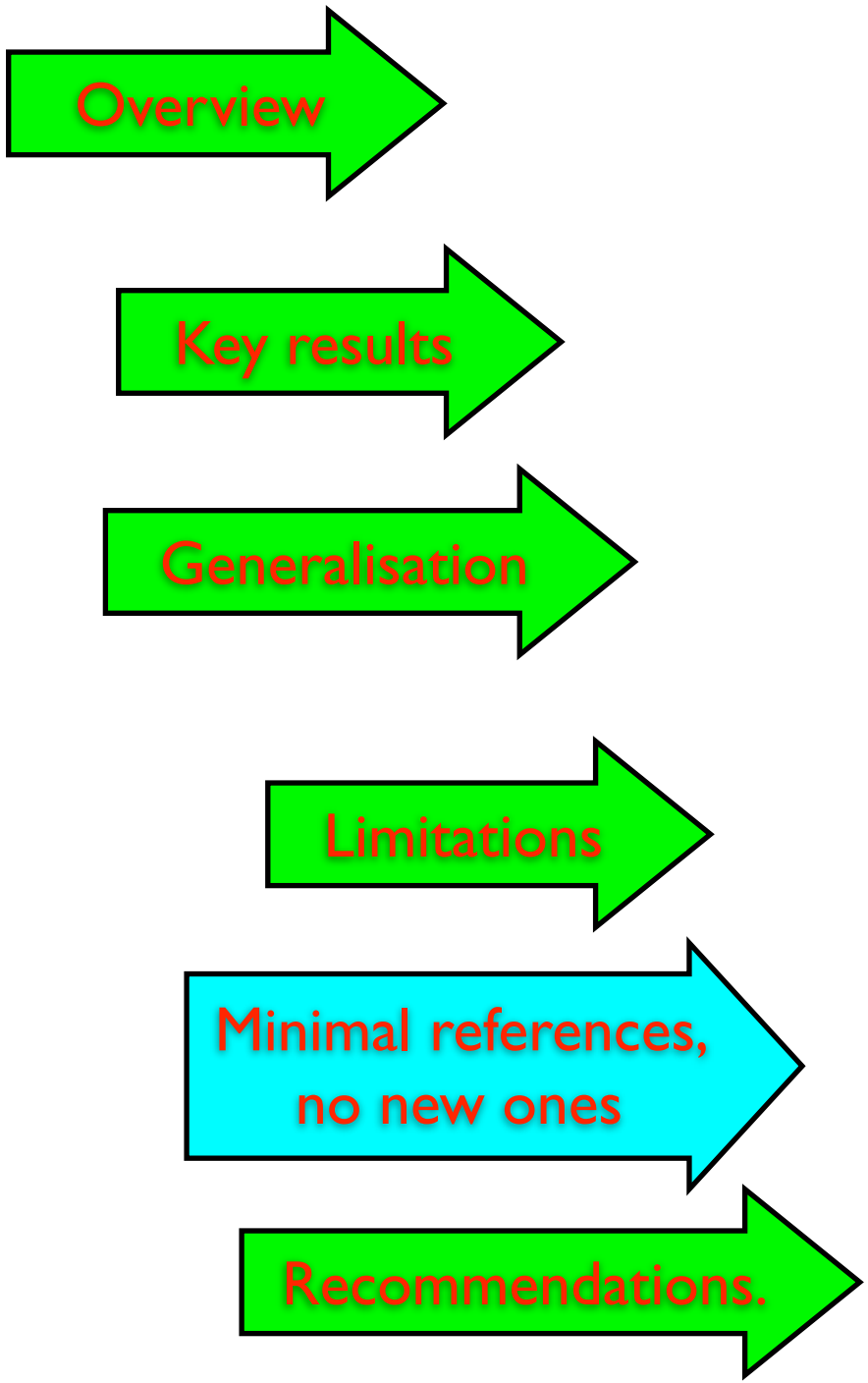


Abstract

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 live attentuated vaccines, several of which are 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. The waning rate of the vaccine is a critical parameter for long-term reduction in RSV prevalence, even more than coverage. We recommend that candidate vaccines be tested for sufficient duration before being released on the market.

Discussion

- The Discussion is for implications beyond your work
- It is not an extended summary of the results
- State any limitations of your model
  - impulsive assumptions
  - extreme parameters
  - well-mixed individuals
  - constant population
- Recommendations
- These must be biologically sensible.



5 Discussion

The introduction of a vaccine is always desirable, but new vaccines pose the risk of unintended consequences. We have highlighted some of the potential issues that may arise with vaccination against 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 good vaccine 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, which should be acknowledged. 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 [30], although can produce confounding effects in some situations [11]. 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 of 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.

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. If a durable vaccine can be developed, then we stand a chance of controlling this disease, assuming sufficiently widespread coverage.

Part 4: Refinement

- All writing is editing
- You need to cast a critical eye over it
  - and someone else's eye as well
  - e.g., a co-author, but also a non-expert
- What problems would a reviewer notice?
  (There will always be some!)
- Where are the gaps in logic?
- What is clear to you but not to the reader?
  - clarity is crucial.

Don't be afraid to make big cuts

Add new info for clarity.

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

Has more research come to light?

Ideas for better flow

Lots of small additions for clarity.

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.

Model diagram has been added

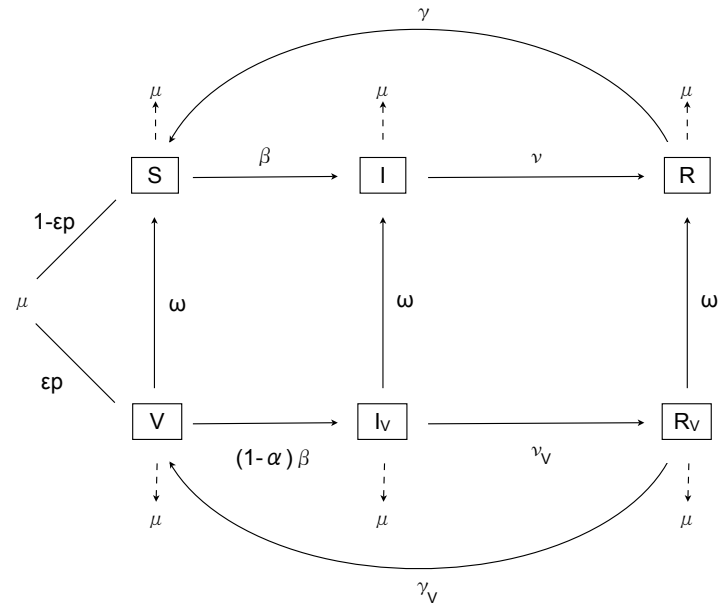


Figure 1: The model.

The basic model with vaccination is then

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

What may be clear to you but not others.

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?

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

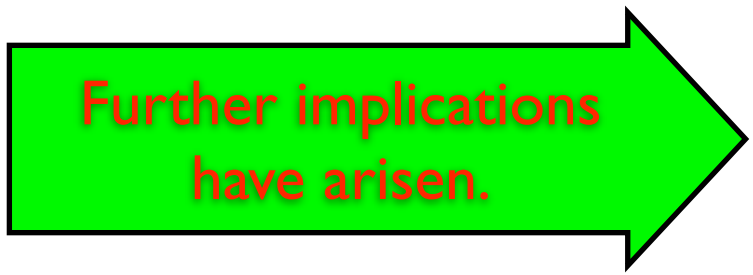
$$b_1\Big|_{c_1=0} = \frac{1}{\nu_V + \mu + \omega}\left[\beta_V\bar{V}(\nu - \nu_V) + (\nu_V + \mu + \omega)^2\right].$$

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 $f(\nu_V^*) < 0$.



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.

References

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Response

- If someone raises something, it needs to be addressed
- It doesn't have to be their solution, but it does mean you have a weakness
- Weaknesses need to be identified and strengthened
  - do this before submission
  - if the reviewers have to do this too much, you'll get rejected
- The goal is to make life easier for the reader.

Condenses the segue to one sentence

Justifies keeping the newborns paragraph.

tion in transmission [3, 11, 25, 30, 33, 46, 48]. 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 [8, 27], 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 [22, 35]. To the best of our knowledge, there are no theoretical models that examine the impact of an RSV vaccine analytically.

Here, we examine the effects of a prophylactic 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 SEIRS compartmental model for a single age cohort described by Weber *et al.* [46] to include a vaccine strategy for RSV where a fixed proportion of newborns are vaccinated before infection. (This is equivalent to the situation where pregnant mothers are vaccinated before giving birth.) 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.

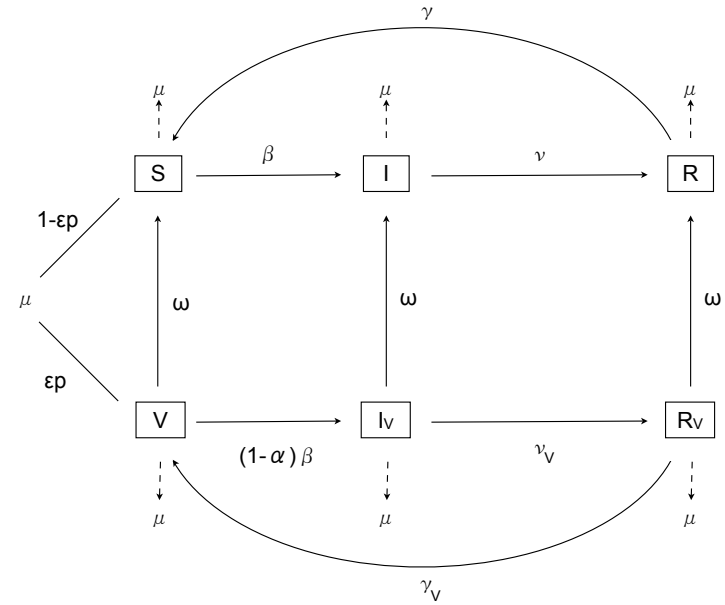

Figure 1: The model.

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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 \\
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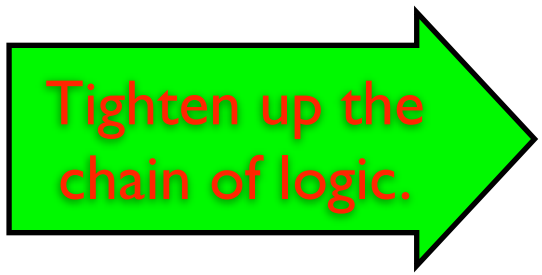
R_V' &= \nu_V I_V - \mu R_V - \gamma_V R_V - \omega R_V,
\end{aligned}
$$

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 the efficacy of vaccination in preventing infection. (We will relax the lower bound on α later in order to examine some theoretical scenarios.) The model is illustrated in Figure 1.

Explain and justify what was confusing.



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

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

where

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

We use the method of the constant term of the characteristic polynomial to determine the reproduction number [19]. Rearranging $c_1 = 0$, 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 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 $f(\nu_V^*) < 0$.

Part 5: Response to reviewers

- This is the most important writing you will ever do
- Be professional
  - don't argue back
- Address every point
  - a killer response is "we have done everything the reviewers requested"
  - only extremely large requests should be "outside the scope of our manuscript"
- Highlight changes in colour
  - make it easy for them to accept your paper.

Unexpected infection spikes in a model of Respiratory Syncytial Virus vaccination

Address the editor

Dear Dr. Yang,

We thank the Editor and R[illegible] manuscript on RSV vaccinati[illegible] We have done everything the reviewers requested [illegible]ere is a point-by-point response to th[illegible]

Reviewer 1

General This reviewer had four major comments and three minor comments.
Response: We have done everything this reviewer suggested. Changes due to this reviewer are in blue.

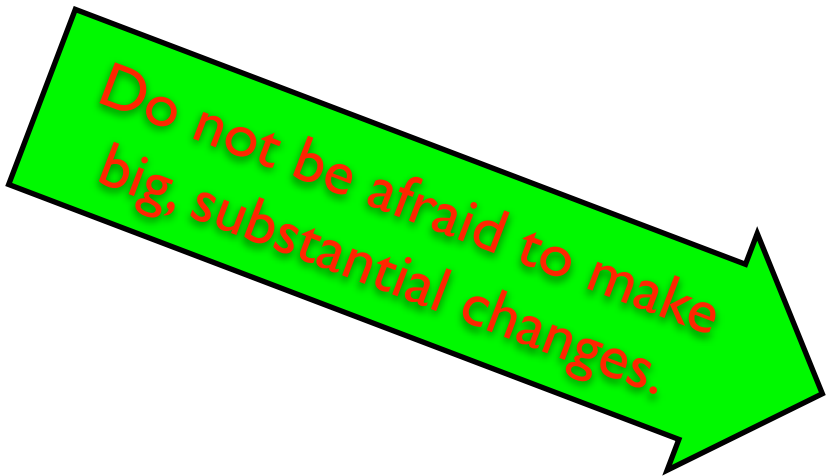
Indicate what you've changed and where to find it.

Comment (1) The authors describe current efforts at vaccine development as "focused on the development of particle-based and subunit vaccines (p.2, 3/4 down)". They do not mention, or consider, the continuing work on live attenuated vaccines or vectored vaccines both of which are supported by multiple large pharma companies.
Response: Good point. We have changed this sentence to: "focused on the development of particle-based, subunit and vectored vaccines. Live-attenuated vaccines are also undergoing phase 1 trials." This is based on the summary at `http://www.path.org/vaccineresources/files/RSV-snapshot-December2016.pdf` (Page 2)

Comment (2) The authors consider (p.3, middle) "a vaccine strategy for RSV where a fixed proportion of individuals entering the model are temporarily immune to infection. This reflects the situation where newborn children are vaccinated at birth." They do not mention, or consider, that the main vaccine strategy now being pursued for the youngest infants is not direct immunization, but is instead maternal immunization. Vaccination occurring during the third trimester generates antibodies in the mother that are transferred transplacentally to the infant, resulting in higher antibody titers in the infant at birth. The thought is that the higher antibody titers should protect the infant for approximately two months longer. Pre-formed antibodies decay with time, and by 6 months maternal antibodies are no longer detectable

Response: This is an excellent point, so we have changed the focus in this section to maternal vaccination and discussed this in some detail. Happily, by doing so, the results are unchanged from a mathematical perspective. (Pages 3, 7, 16, 17)

Comment (3) Vaccination of infants as soon as they are born is seldom successful for any pathogen because the infants immune system is immature. It is not currently being contemplated for RSV. However, MedImmune (owner of the prophylactic monoclonal antibody that is currently used for "at risk" infants to protect them against RSV) has developed a more potent RSV-neutralizing monoclonal antibody with increased stability that could be given at birth to protect infants for their first 6 months. This approach would avoid the uncertainties of individual maternal responses to RSV and the problem of premature birth which could result in incomplete transfer of the antibodies elicited by a maternal vaccine, depending on the time of vaccination relative to birth.
In general, the thinking in the field is that there will be two vaccines for RSV, one to protect infants during their first 6 months, and another to protect them from 6 months on. I realize that there may be too many variables for the authors to consider in one report, but they could choose one of these strategies and model that. Maternal vaccination before birth would seem to be the most important to study now since it is being pursued aggressively by the NIH and two big pharma companies and several smaller companies, and is being supported by the Bill and Melinda Gates Foundation. The MedImmune stabilized monoclonal antibody approach could be included as generally equivalent.
Response: This brings up a point that we realise was not clear: we are actually considering both options. The nonimpulsive model considers pre-infection vaccination only, while the impulsive model considers subsequent vaccination. We have added emphasis in several places to make this clear. (Pages 3, 7, 11, 16, 17)



Comment (4) But the protection of any of these approaches would cover only the first 6 months of life. Thereafter, immunization of the child with another vaccine would be needed to induce active immunity and a recall response that would provide future, more rapid protection upon infection. Right now, live attenuated or vectored (adenovirus) vaccines are the front runners, but direct immunization with a subunit vaccine might eventually be considered. A subunit vaccine has not been considered largely because of the initial formalin-inactivated vaccine trial in the 1960s resulted in much more severe disease following the first community acquired infection in the vaccinees.
While modeling a 10-year protective vaccine and a lifetime-protective vaccine can be done, even infection with the wild-type virus does not provide 10-year protection, so it is difficult to see how a long-term protective vaccine could be generated. Nevertheless, it is a laudable goal.
Response: This is a helpful observation. We have decided to change our focus away from long-lasting vaccines and instead mostly focus on short-term durations, as the

reviewer suggests. We have mostly restricted ourselves to vaccines lasting six months (corresponding to $\omega = 2$) and have instead moved the focus to vaccine coverage via the proportion of individuals who are vaccinated (r). We re-ran all our simulations and have thus updated all figures. The results are actually stronger with this new focus, so we are grateful to the reviewer for raising this. (Pages 12, 13, 14)

Comment (5) p.1, author list. Why is Robert J. Smith followed by a ? ?
Response: It is part of the author's name. See, for example:
`http://mysite.science.uottawa.ca/rsmith43/MDRHIV.pdf`

Comment (6) p.18, l.10. vaccination-induced
Response: Fixed (Page 16)

Comment (7) p.18, l.20.outcome than coverage
Response: We agree, although this sentence has now been deleted, so it no longer applies.

If the reviewer compliments your work, include it.

Reviewer 2

General This reviewer noted that the research questions examined in our manuscript are extremely important and relevant and that we use an innovative approach to address the question of potential vaccine efficacy. This reviewer had five major comments.
Response: We have done everything this reviewer suggested. Changes due to this reviewer are in red.

Comment (1) The authors base the model on the assumption that infants will be given the vaccine at birth. While this is true for a few vaccines, most are not given at birth. Additionally, the most advanced vaccines in development are not being targeted to infants. They are primarily targeting the elderly, and pregnant mothers to protect newborns. The authors need to address the fact that their assumption is very unlikely, or even false more than they have as the manuscript stands.
Response: This is a good point that was also raised by Reviewer #1. See our response to Comments (2) and (3) above. Note in particular that we are actually considering both and have made that more clear. (Pages 3, 12, 16, 17, in blue.)

Comment (2) The authors conclude that vaccine duration would be more important than vaccine coverage. They recommend that vaccine be tested for duration before approval. The authors need to discuss how the practicality of studying long term immunity is very challenging, especially regarding the time frames they test. Obviously 70, or even 10 years would be impossible to test during a clinical trial before licensure.

Response: This point was also raised by Reviewer #1. We have changed the focus to short-term durations and re-run our simulations. See our response to Comment (4) above. (Pages 12, 13, 14, in blue.)

Comment (3) Vaccine duration is a somewhat vague term, especially since the correlates of immunity have not been fully defined for RSV, and natural infection does not necessarily confer protection from reinfection.
Response: This isn't as important now, although we will note that it is a well-defined term mathematically, even if that is an approximation to a more fuzzy concept in reality. We have added a definition. (Pages 3–4)

Comment (4) The authors should cite other, already licensed vaccines that are in use where duration is more important than vaccine coverage.
Response: We have changed the focus away from this, although we did find that this is true for both pertussis and HPV.

If you can't change something, incorporate the concerns in the Discussion

Always be polite.

Comment (5) The endpoints of most RSV clinical trials are not sterilizing immunity, but a reduction in RSV-associated hospitalizations. The authors should consider incorporating this endpoint into their model or at least discuss this point.
Response: This is a good point that is worth mentioning. We have added a paragraph to the discussion addressing this. (Page 17)

In summary, we feel that these revisions have addressed all the points raised by the reviewers and hope that the manuscript is now acceptable.

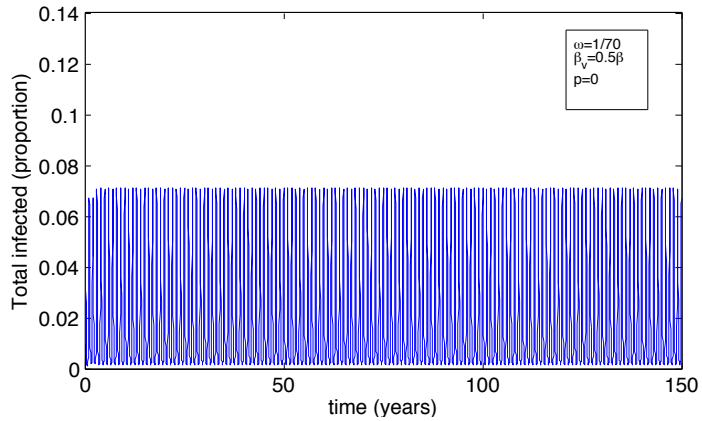
Yours sincerely,

Alexandra Hogan, Geoffry Mercer and Robert Smith?

Further polishing

- Often, the reviewers' questions can bring up issues that you find
  - infection spikes changed dramatically
- You may need to rework things significantly
- Don't be afraid of doing this
- Or you may just want to change for clarity
  - eg different timescales.

Old version



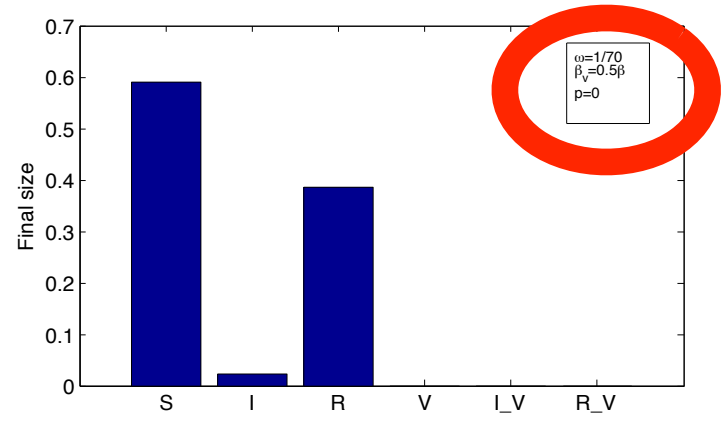
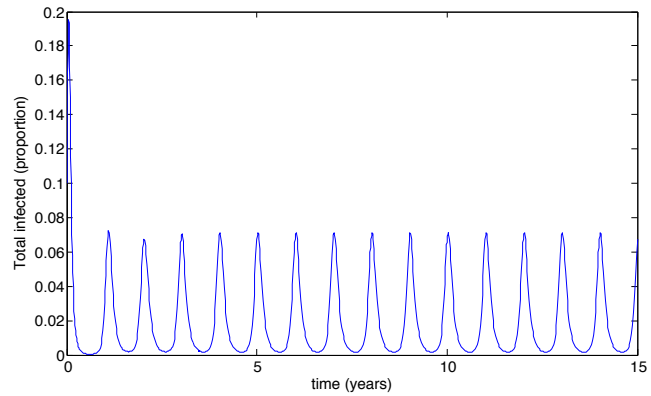


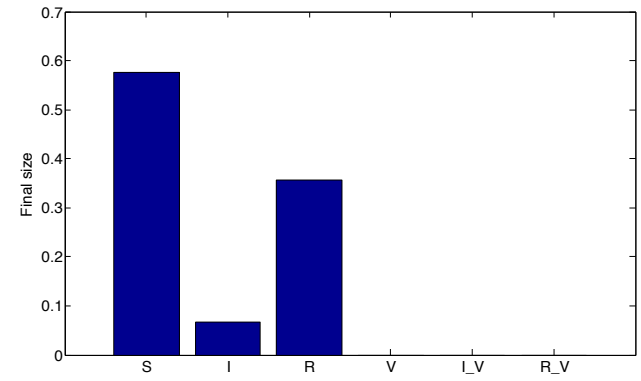
Figure 4: Without vaccination, the disease infects up to 7% of the population. A. The total infected population, including vaccinated individuals. B. The final size in each population.

New version

A



B



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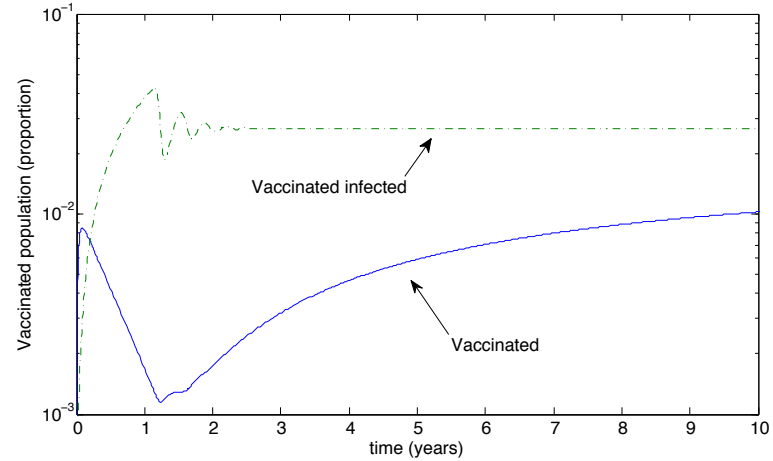
Old version



New version.

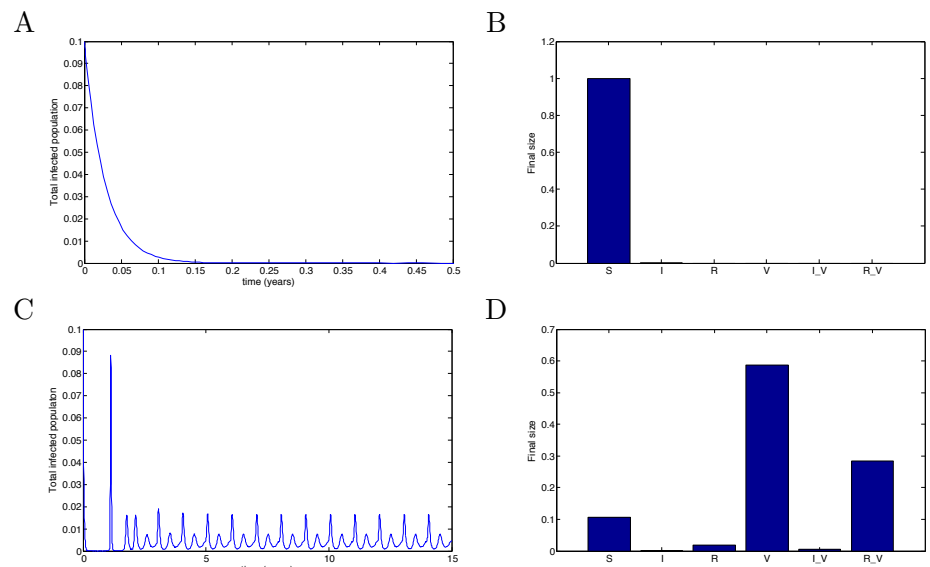


Figure 8: Extreme parameters show that perfect vaccination can induce unexpected infection spikes. A. With no vaccine ($r = 0$), the result is that the infection clears and the entire population remains susceptible. (Note that the timescale is given for only 0.5 years to show the decline but was run for 15 years.) B. The final size of each compartment in the case of no vaccine after 15 years. C. When an imperfect vaccine is given to the entire population ($r = 1$), the result is a series of disease spikes in the vaccinated population. Note that the transmission rate is not oscillating in this example. D. The final size of each compartment in the case of full vaccination after 15 years. Vaccination thus destabilises the DFE.

Part 6: What's next?

- Turn your paper into a 20-minute talk
- Present it to colleagues
- Ideally do this before the final version, to iron out any outstanding issues
  - you will likely find further weak spots
- Do any big questions come out of the presentation?
  - "Have you considered...?"
  - "What about...?"
- These may be the basis for your next paper
  - there's always more exciting research waiting.

Summary

- Research starts with an idea
- You find the paper through editing + refining
- *What did we learn that we didn't know?*
  - if you can't answer this question, don't publish
- The Abstract and Introduction must be tight
- The figures must tell the story
- The Discussion is for implications
- Use the reviews to help you find the narrative
- Ultimately, you're telling a story
- Make it a good one.

The Handout

mysite.science.uottawa.ca/rsmith43/paperwritinghandouts.htm

Includes links to:

- slides from this talk
- multiple drafts
- biological introduction
- response to reviewers
- final version.