Unexpected infection spikes in a model of Respiratory Syncytial Virus vaccination

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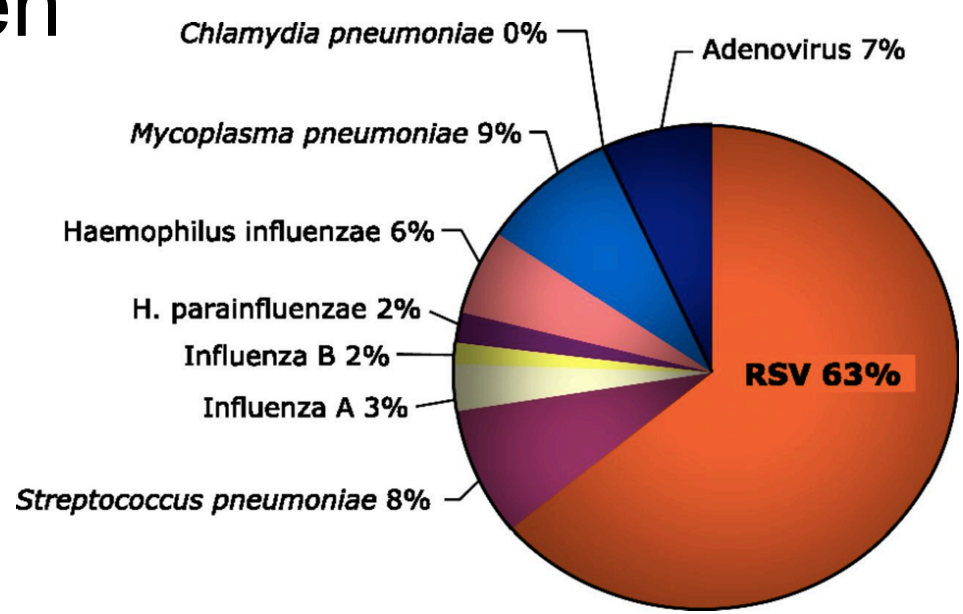
Respiratory Syncytial Virus (RSV)

- The main cause of acute lower respiratory infections in adults and young children
- Almost all children have been infected by age 2
- About 0.5–2% of infants require hospitalisation due to infection
- In 2005, 33.8 million new episodes of RSV occurred in children under 5 worldwide.

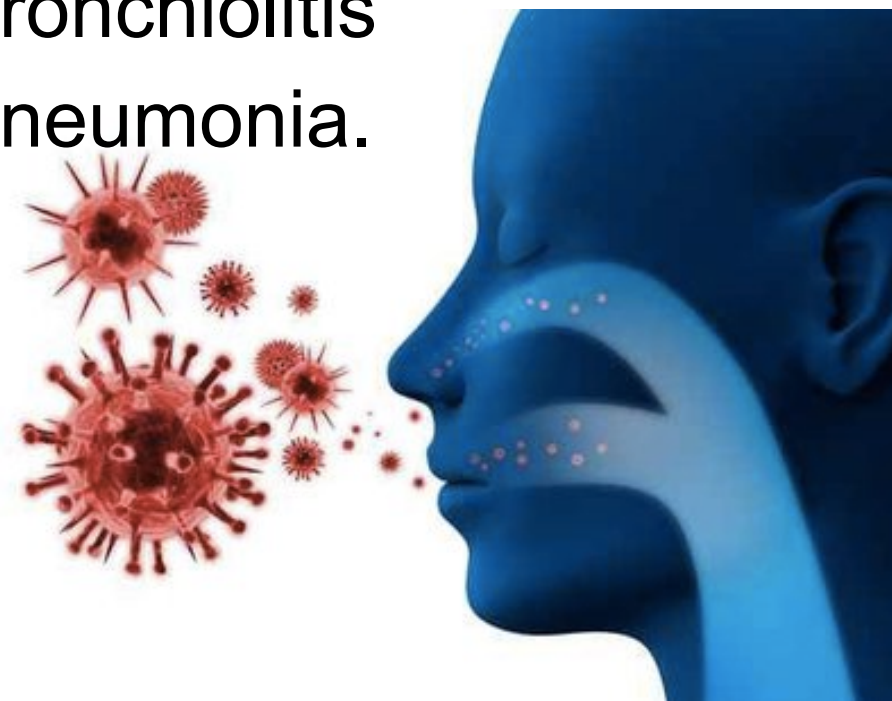


Etiology of acute respiratory infections in children.

Symptoms

- Mild symptoms:
  - cough
  - runny nose
  - sore throat
  - earache
  - fever

- Major symptoms:
  - difficulty breathing
  - blue skin due to lack of oxygen
  - bronchiolitis
  - pneumonia.

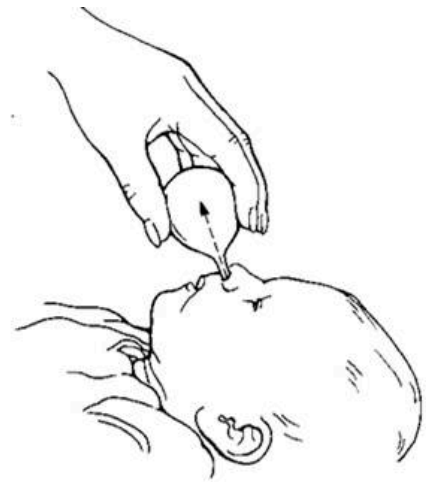


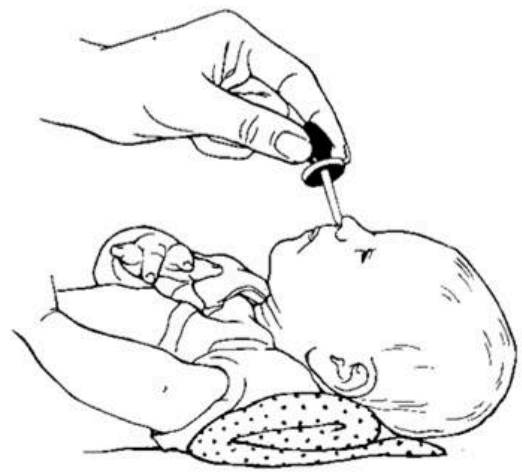
Burden of RSV

- Highest number of observed cases occurs in children aged six weeks to six months
- Morbidity occurs in <0.1% of cases
- Immunity is short-lasting
- Reinfection is common
- Hospitalisation costs are substantial
- Infection can occur throughout adult life
  - often a cause of mortality in the elderly
- RSV is a significant economic and healthcare system burden.

Seasonal patterns

- In temperate climates, RSV epidemics exhibit consistent seasonal patterns
- Most infections occur during winter months, whether wet or dry
- Outbreaks typically last 2–5 months
- In tropical climates, RSV is detected throughout the year, with less pronounced seasonal peaks
- The onset of RSV is typically associated with the rainy season.





Prophylaxis

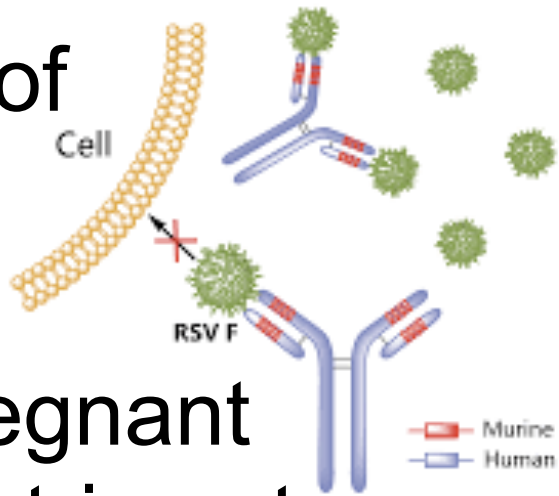
- Immunoprophylaxis with the monoclonal antibody Palivizumab has proven effective in reducing the severity of symptoms
- However, it cannot prevent the onset of infection
  - very expensive
  - $1416.48 for a 100mg vial
  - generally only administered to high-risk children.

Vaccination

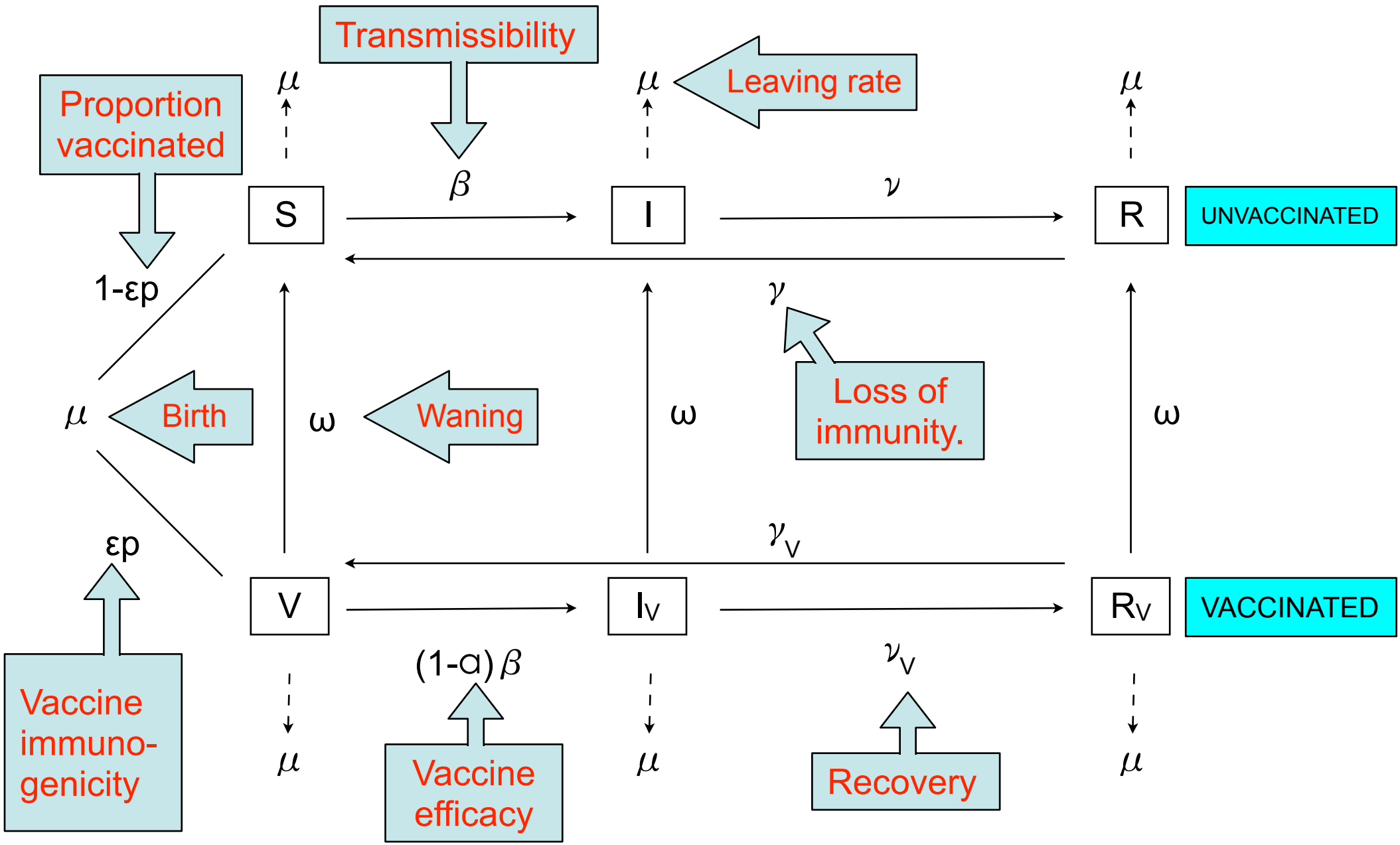
- Recent research has focused on the development of particle-based, subunit and vectored vaccines
- Several such vaccines are being evaluated in clinical trials
- Other vaccines are in pre-clinical development
- Live attenuated vaccines are also undergoing Phase I trials.

Model 1

- We extend an existing RSV model for a single age cohort to include vaccination
- We first assume a fixed proportion of individuals entering the model are temporarily immune to infection
- This reflects the situation where pregnant women are vaccinated in their third trimester
- Protective maternal antibodies are transferred placentally to the unborn infant
- This confers protection for the first few months of life.



Flow diagram



The continuous model

- The basic model with vaccination is

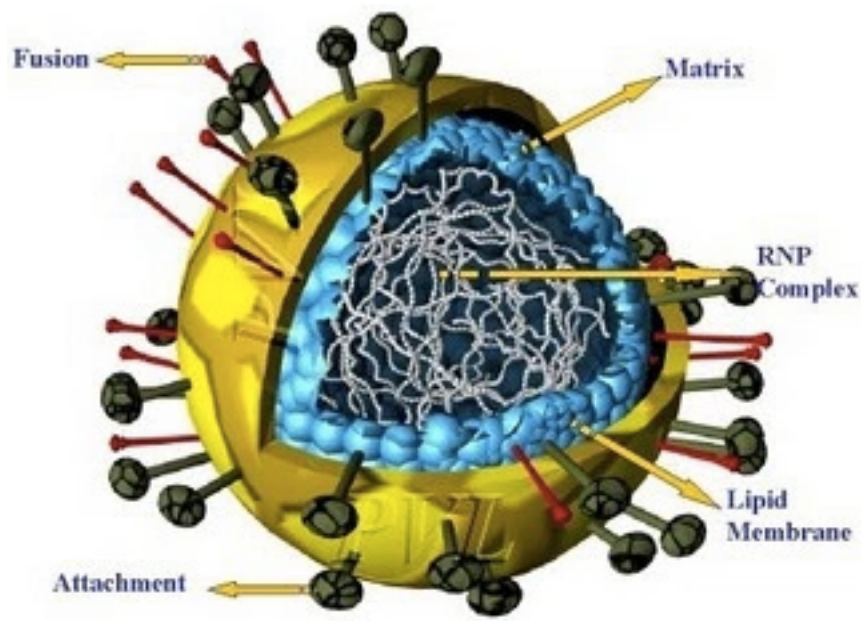
$$
\begin{aligned}
S' &= \mu(1-\epsilon p) - \mu S - \beta(t)S(I+I_V) + \gamma R + \omega V \\
I' &= \beta(t)S(I+I_V) - \nu I - \mu I + \omega I_V \\
R' &= \nu I - \mu R - \gamma R + \omega R_V \\
V' &= \epsilon p \mu - \mu V - \beta_V(t)V(I+I_V) + \gamma_V R_V - \omega V \\
I_V' &= \beta_V(t)V(I+I_V)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

with $\beta(t) = \beta_0(1+\beta_1\cos(2\pi t+\varphi))$
and $\beta_V(t) = (1-\alpha)\beta(t)$
(α may possibly be negative).

S=susceptible I, I_V=infected
R, R_V=recovered V=vaccinated
μ=background death ϵ=efficacy
p=coverage ω=waning
β, β_V=transmissibility
ν, ν_V=recovery γ, γ_V=loss of immunity

Key assumptions

- We assume
  - the leaving rate is unchanged across all classes
  - no disease-specific death
  - entry and leaving rates are scaled so the population is constant
  - transmissibility oscillates seasonally.



Constant transmission

- There is a DFE satisfying

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

- We can prove that this equilibrium is stable if

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

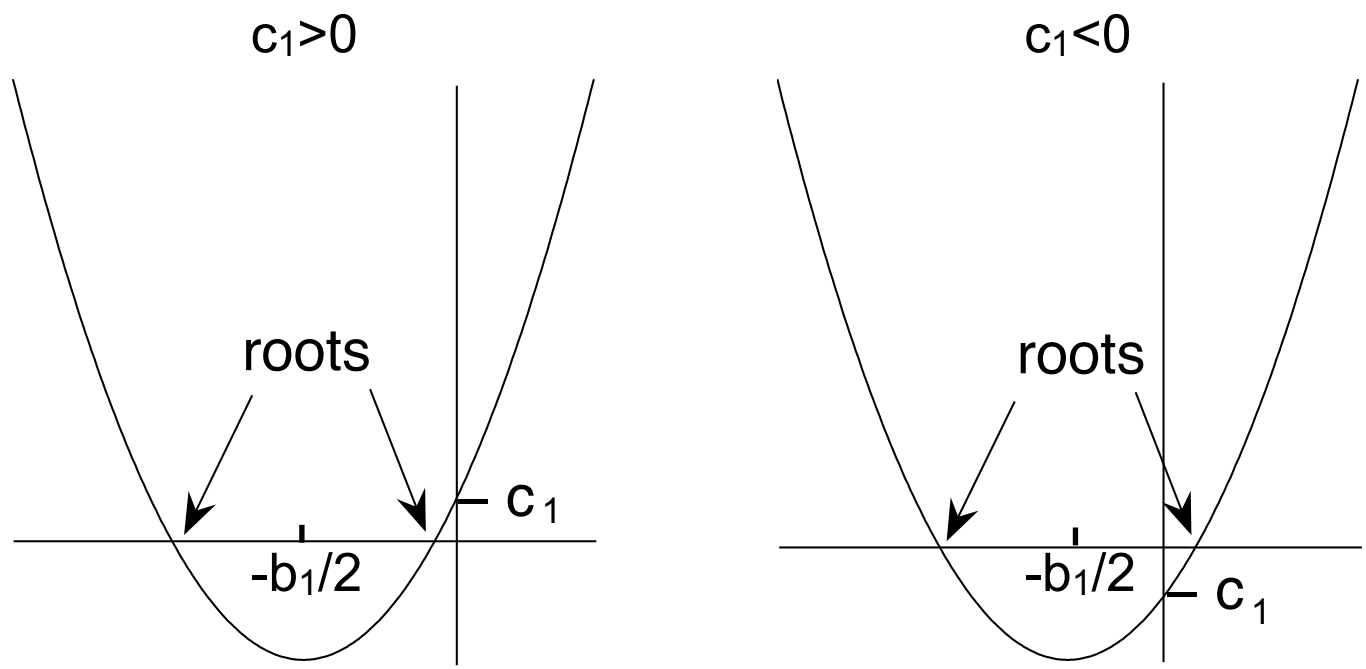
has roots with negative real part, where

$$b_1 = -\beta \bar{S} + \mu + \nu - \beta_V \bar{V} + \nu_V + \mu + \omega$$

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

S=susceptible I=infected R=recovered V=vaccinated susceptible I_V=vaccinated infected R_V=vaccinated recovered μ=background death ϵ=efficacy p=coverage ω=waning

Stability of eigenvalues



- If $b_1>0$, then c_1 is a proxy for the eigenvalues
- If $b_1<0$, then the DFE is unstable and c_1 is not a threshold.

b_1=vertex
c_1=intercept

Complex eigenvalues?

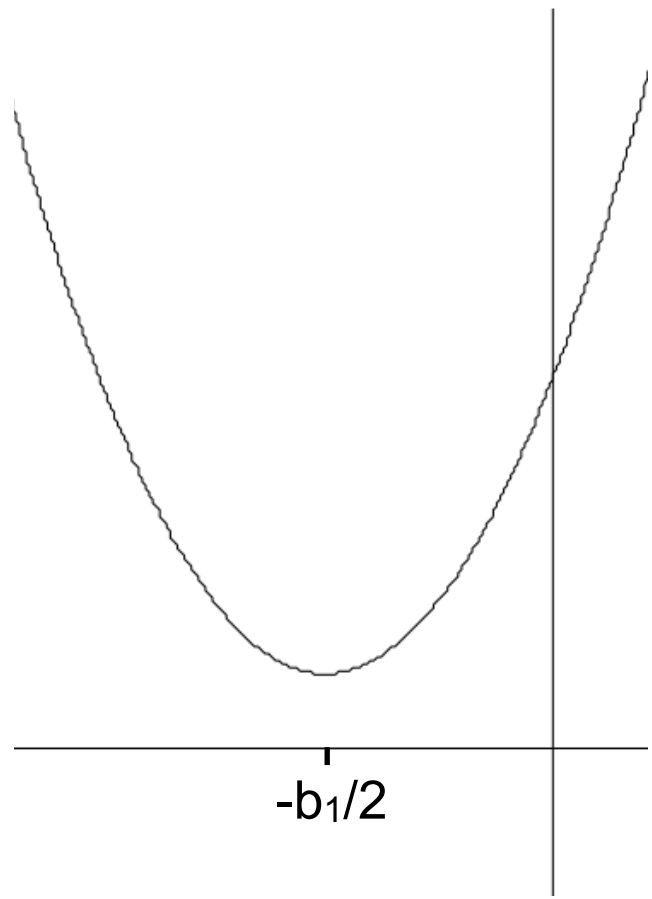
- If the roots are complex, then

$$\lambda = \frac{-b_1 \pm \sqrt{b_1^2 - 4c_1}}{2}$$

with the discriminant negative, and so

$$Re(\lambda) = -\frac{b_1}{2}$$

- It follows that stability in this case occurs if and only if $b_1>0$.



b_1=vertex
c_1=intercept

Basic reproduction number

- Rearranging the constant term leads to

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

- 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

  (as desired)
- However, it 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.

S=susceptible V=vaccinated
μ=background death ω=waning
β,β_V=transmissibility
ν,ν_V=recovery

Positive vertex

- 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 ν=ν_V (i.e., vaccination does not affect recovery) then b_1>0
- However, we expect that vaccinated individuals will recover faster than unvaccinated individuals
- Thus ν_V>ν
- It follows that b_1 could be negative.

V=vaccinated b_1=vertex
c_1=intercept
μ=background death
ω=waning
β_V=transmissibility
ν,ν_V=recovery

A possible turning point?

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

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

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

  we have f(ν)>0 and f(∞)>0
- Does f have a local minimum?
- If so, could it be negative?

V=vaccinated b_1=vertex
μ=background death
ω=waning
β_V=transmissibility
v,v_V=recovery

The turning point

- Differentiating, we have

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

- It follows that the turning point is

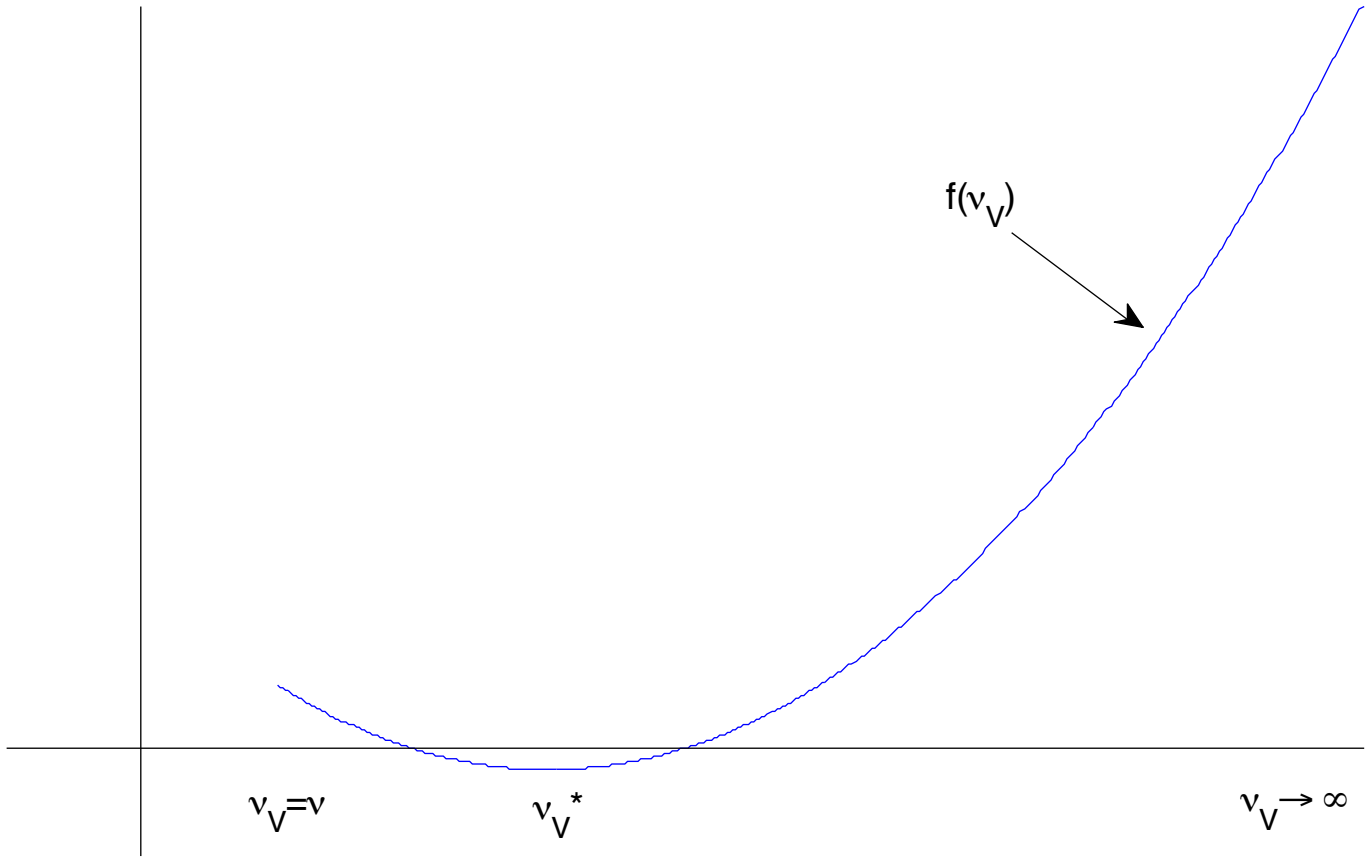
$$\nu_V^* = \sqrt{\beta_V \bar{V}(\omega+\mu+\nu)} - \omega - \mu$$

- There are three requirements for this to be meaningful:

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

V=vaccinated
μ=background death
ω=waning
β_V=transmissibility
v,v_V=recovery

Potential form of f(ν_V)

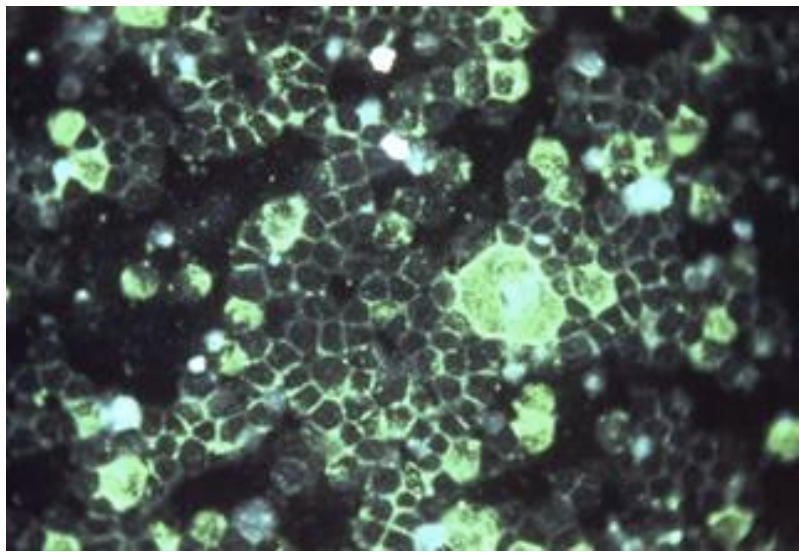


- We can prove that the turning point is a local minimum whenever it exists.

f=vertex
v,v_V=recovery

Regular vaccinations

- We now refine the continuous model
- Vaccination may not occur before birth
- It may also be administered at regular times
  - eg in schools or daycare centres
- We model a vaccine that reduces the susceptible population by a fixed proportion r
- This is described by a series of non-autonomous impulsive differential equations.



r=coverage

The impulsive model

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

where r is the coverage

and t_k are the vaccination times.

S=susceptible I, I_V=infected
R, R_V=recovered V=vaccinated
μ=background death ω=waning
β, β_V=transmissibility
ν, ν_V=recovery γ, γ_V=loss of immunity

Susceptible individuals

- Assuming transmission is constant, we can prove that solutions are bounded below by a stable impulsive periodic orbit with endpoints

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

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

- These correspond to the local maximum and minimum values for the unvaccinated susceptibles after a long time
- Note in particular that $\lim_{\tau\to 0} S_\infty^- = 0.$

S=susceptible μ=background death β=transmissibility r=coverage τ=period

Vaccinated individuals

- We can prove that vaccinated individuals are bounded below by the impulsive periodic orbit with endpoints

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

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

V=vaccinated μ=background death β=transmissibility ω=waning r=coverage τ=period

Infected individuals

- Assuming infected vaccinated individuals are negligible, we can prove that

$$I' \leq \frac{\beta\mu\left(1-e^{-(\mu+\beta)\tau}\right)}{(\mu+\beta)\left(1-(1-r)e^{-(\mu+\beta)\tau}\right)}I - \nu I - \mu I$$

- 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 $T_0<1$.

I=infected μ=background death
β=transmissibility v=recovery
r=coverage τ=period

Impulsive reproduction number

- From the condition 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

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

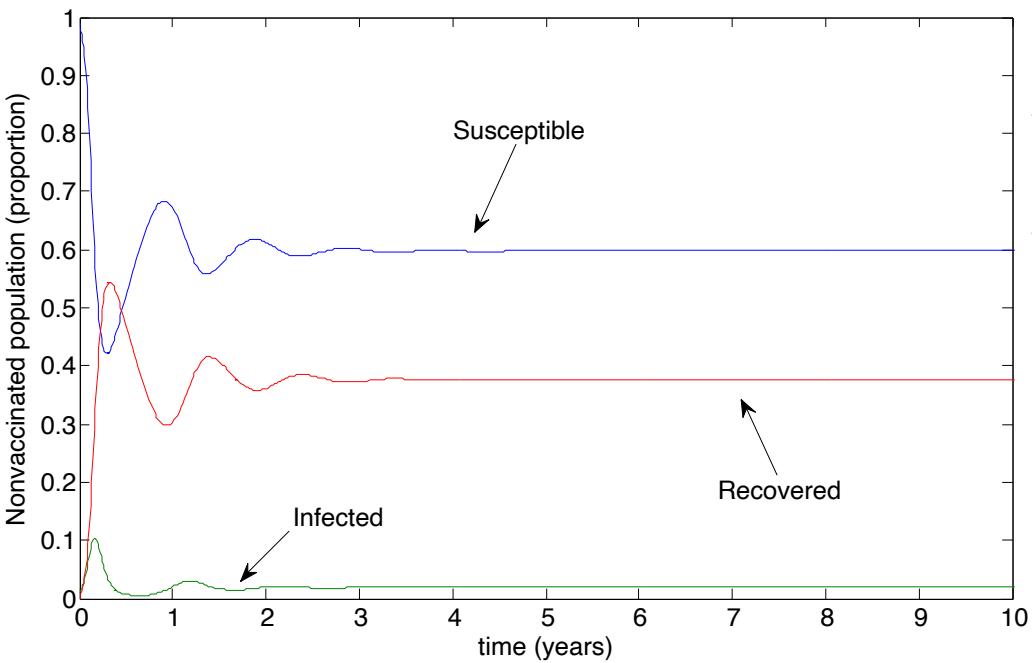
- We can show that T_0 is decreasing as r increases, for r<r*
  - the disease can then be controlled if $\tau < \hat{\tau}$
- For r>r*, T_0<1 and the disease is always controlled.

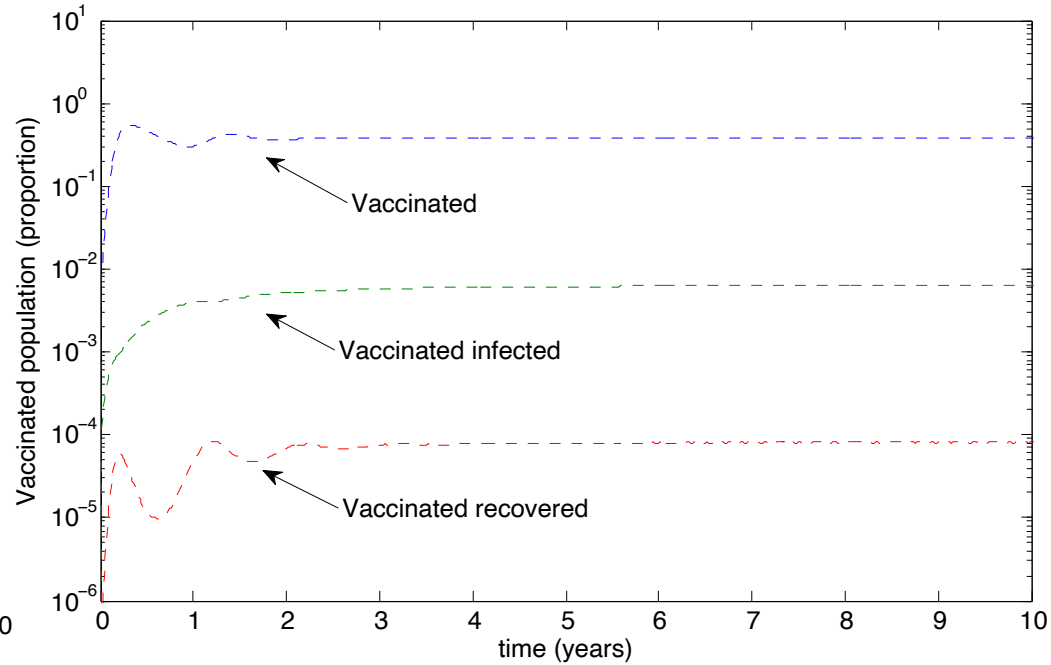
T_0=impulsive reproduction #
μ=background death
β=transmissibility v=recovery
r=coverage τ=period

Summary of theoretical results

- High coverage can thus control the disease
- If coverage is limited, then sufficiently frequent vaccinations can also achieve control
- Note that the impulsive reproduction number is conditional.

Continuous model, constant transmission

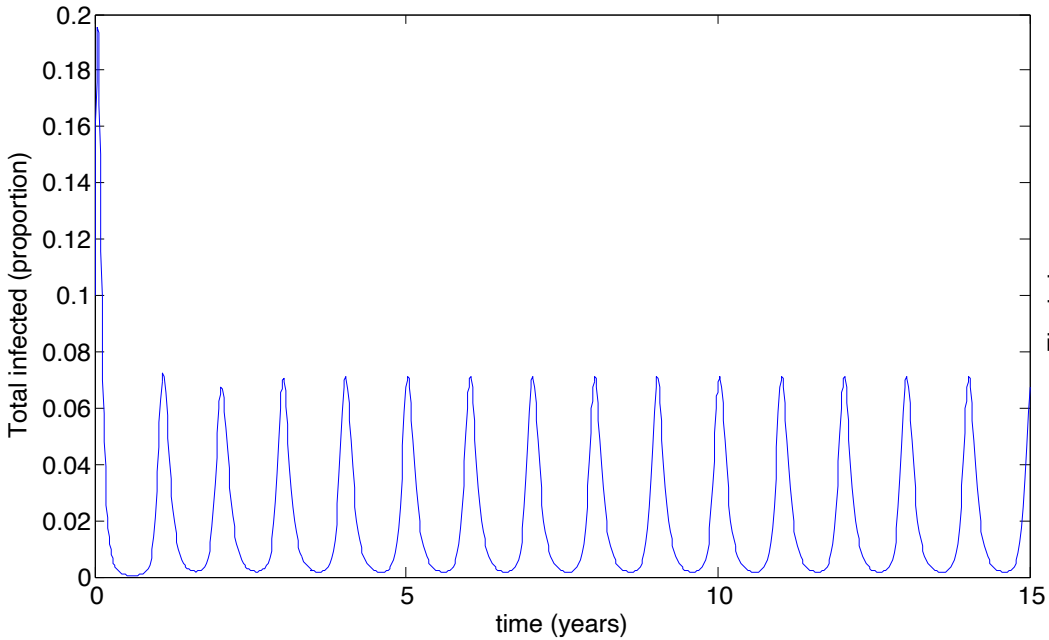


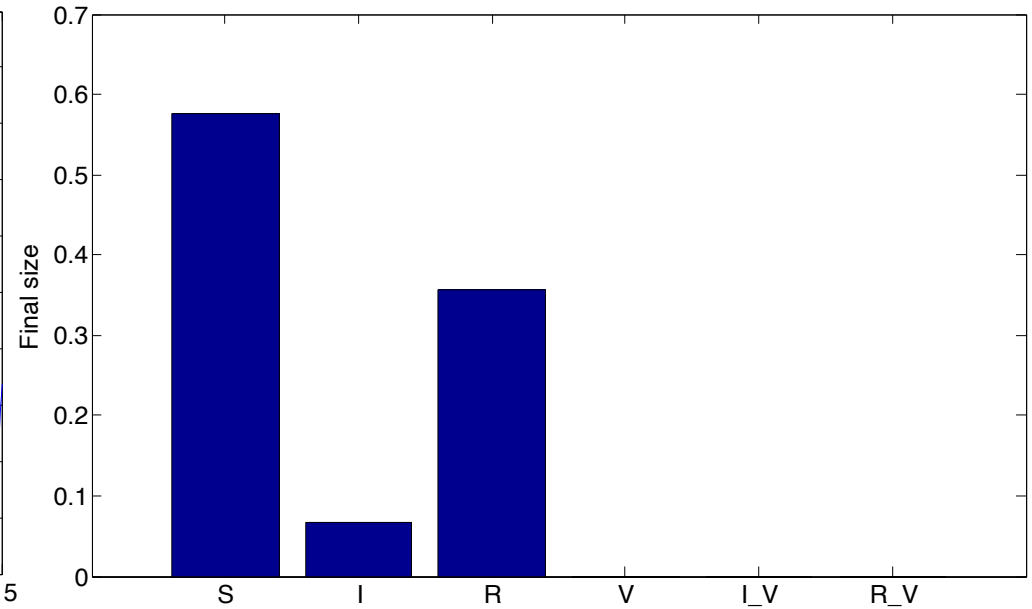


$\mu=1/70$, $\omega=0.1$, $\beta=50$, $\beta_V=0.5\beta$, $\varepsilon=0.9$, $p=0.5$, $\nu=36$, $\nu_V=1.2\nu$, $\gamma=1.8$, $\gamma_V=0.8\gamma$.

μ=background death ω=waning
β,β_V=transmissibility ϵ=efficacy
p=coverage v,v_V=recovery
γ,γ_V=loss of immunity

Impulsive model, no vaccine

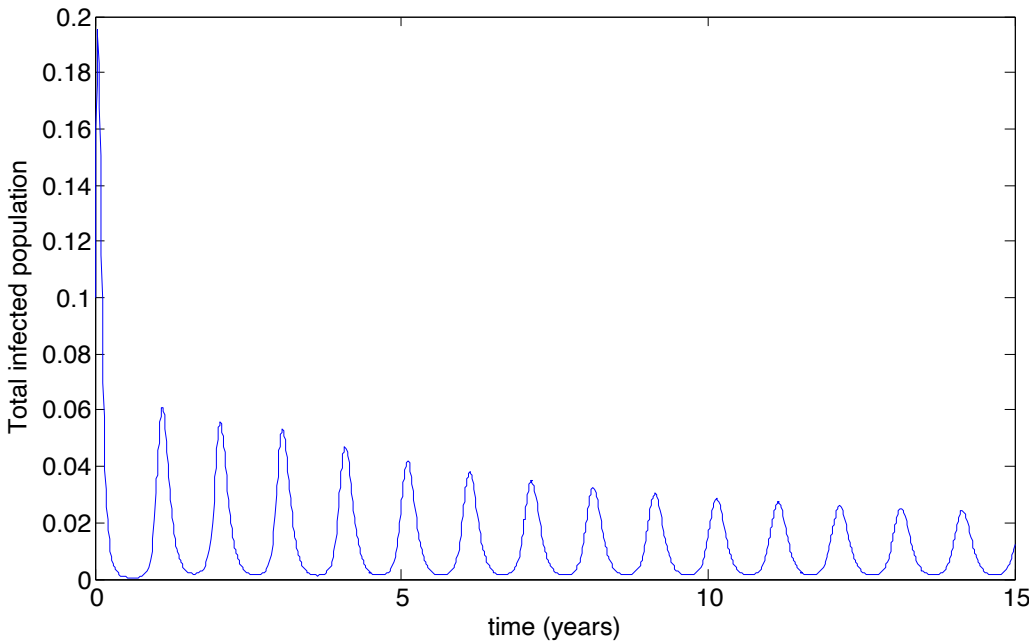


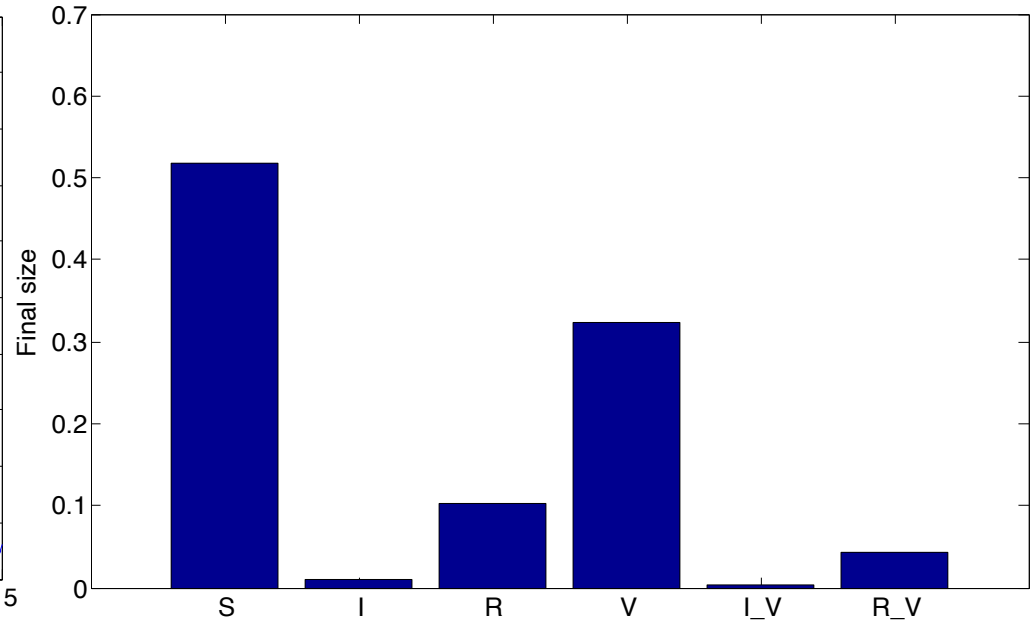


$\mu=1/70$, $\omega=0.1$, $b_0=60$, $b_1=0.16$, $\varphi=0.15$, $\beta_V=0.5\beta$, $\nu=36$, $\nu_V=1.2\nu$, $\gamma=1.8$, $\gamma_V=0.8\gamma$, $r=0$.

μ=background death ω=waning
b_0=average transmissibility
b_1=seasonal amplitude φ=phase
β_V=transmissibility ν,ν_V=recovery
γ,γ_V=loss of immunity, r=coverage

Impulsive model, 10% vaccination

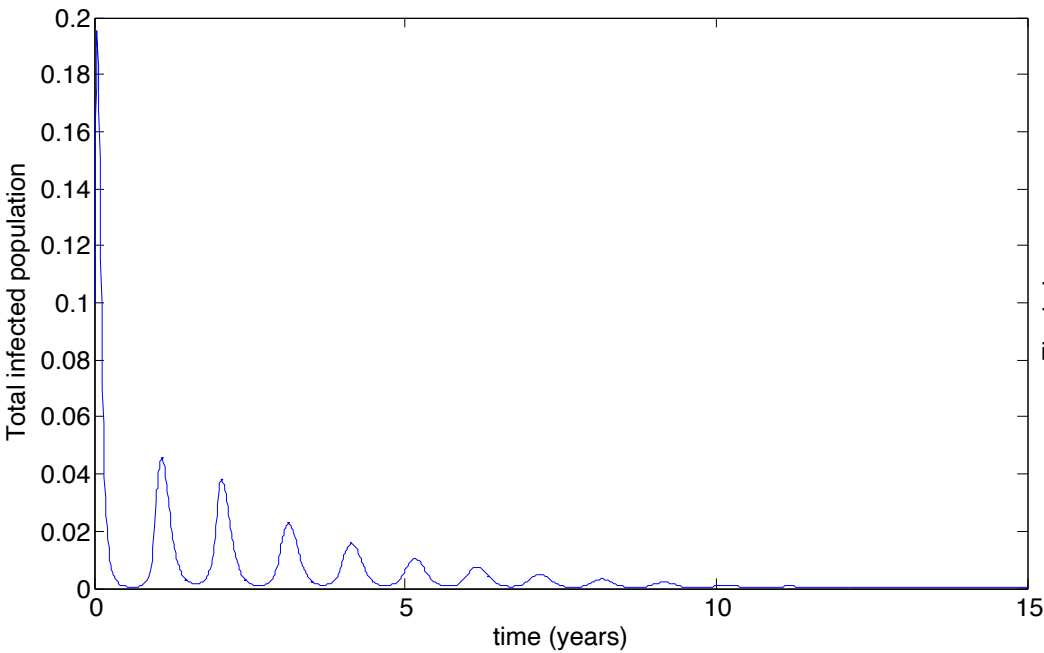


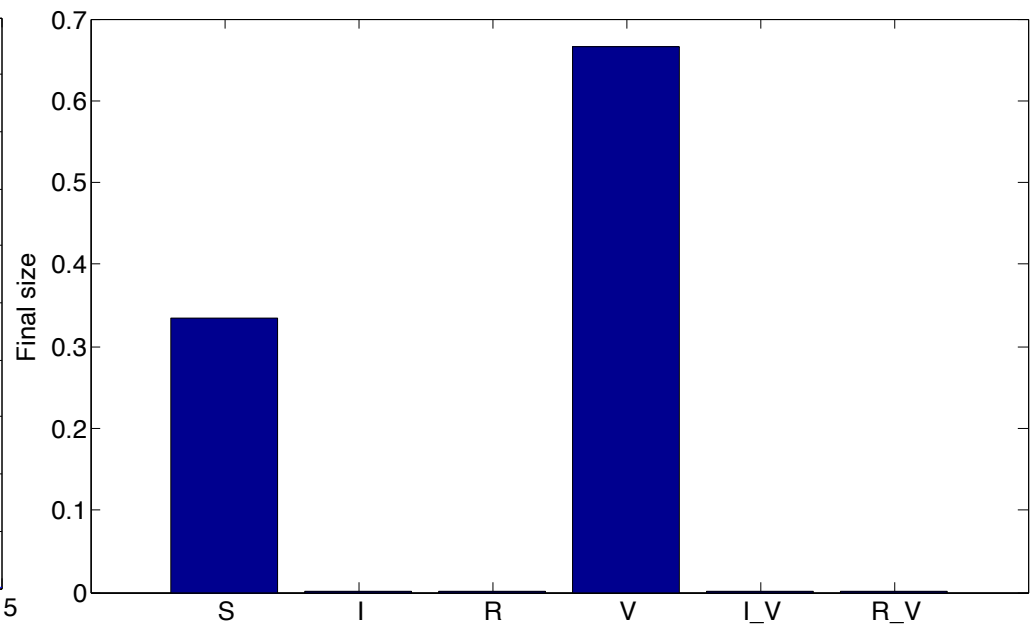


$\mu=1/70$, $\omega=0.1$, $b_0=60$, $b_1=0.16$, $\varphi=0.15$, $\beta_V=0.5\beta$, $\nu=36$, $\nu_V=1.2\nu$, $\gamma=1.8$, $\gamma_V=0.8\gamma$, $r=0.1$.

μ=background death ω=waning
b_0=average transmissibility
b_1=seasonal amplitude φ=phase
β_V=transmissibility ν,ν_V=recovery
γ,γ_V=loss of immunity, r=coverage

Impulsive model, 25% vaccination

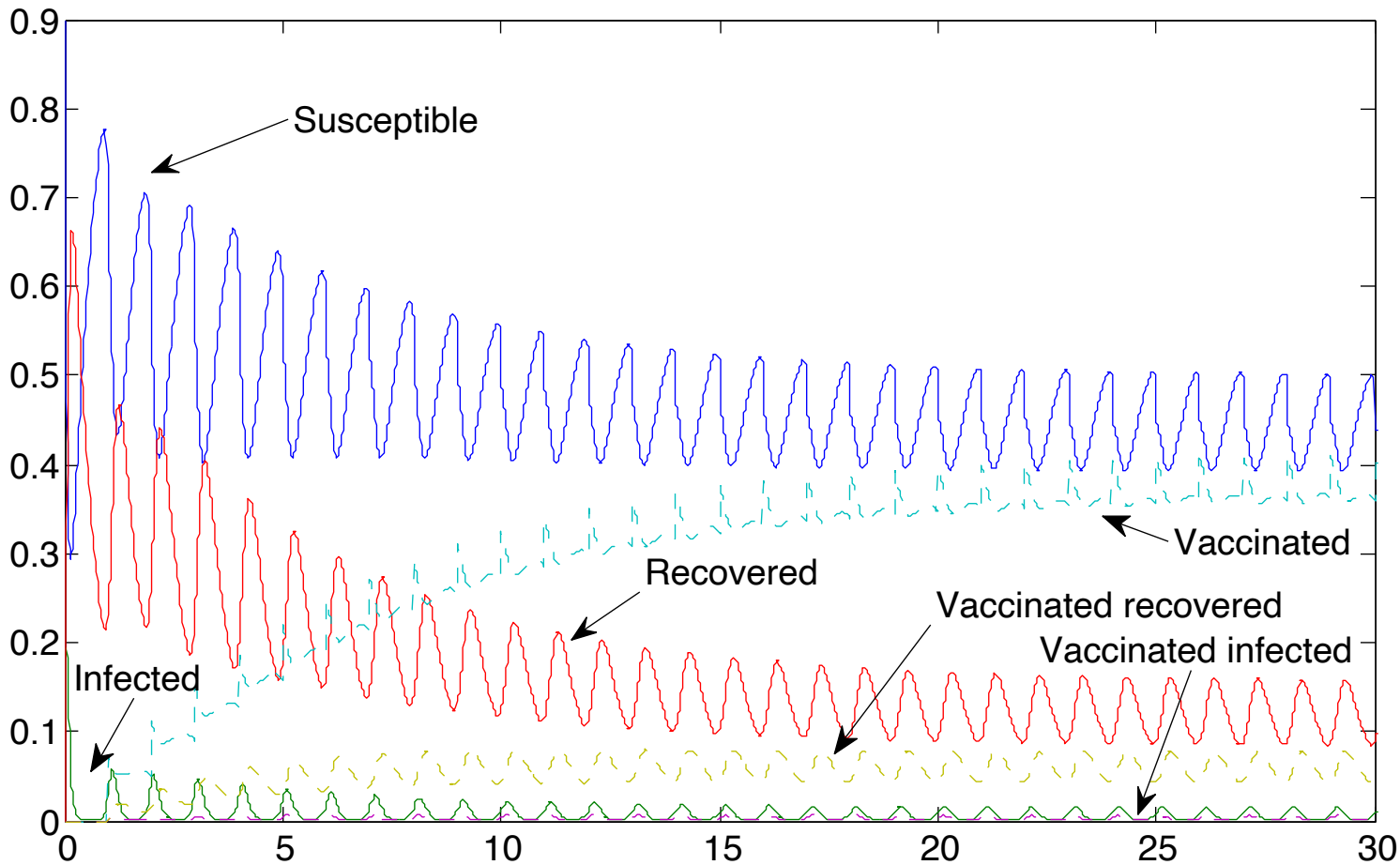




$\mu=1/70$, $\omega=0.1$, $b_0=60$, $b_1=0.16$, $\varphi=0.15$, $\beta_V=0.5\beta$, $\nu=36$, $\nu_V=1.2\nu$, $\gamma=1.8$, $\gamma_V=0.8\gamma$, $r=0.25$.

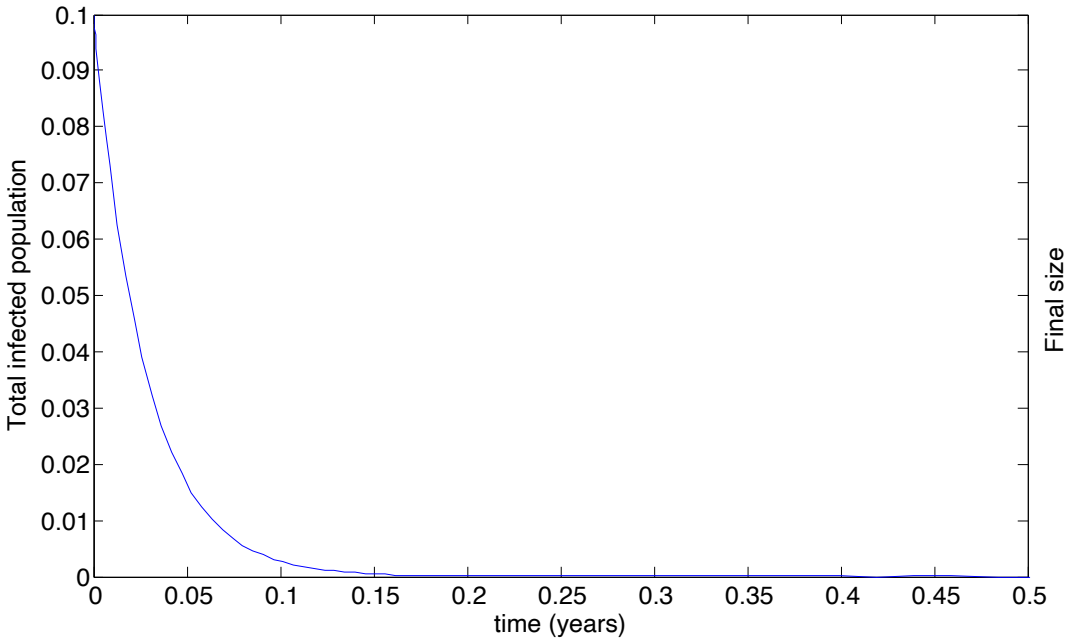
μ=background death ω=waning
b_0=average transmissibility
b_1=seasonal amplitude φ=phase
β_V=transmissibility ν,ν_V=recovery
γ,γ_V=loss of immunity, r=coverage

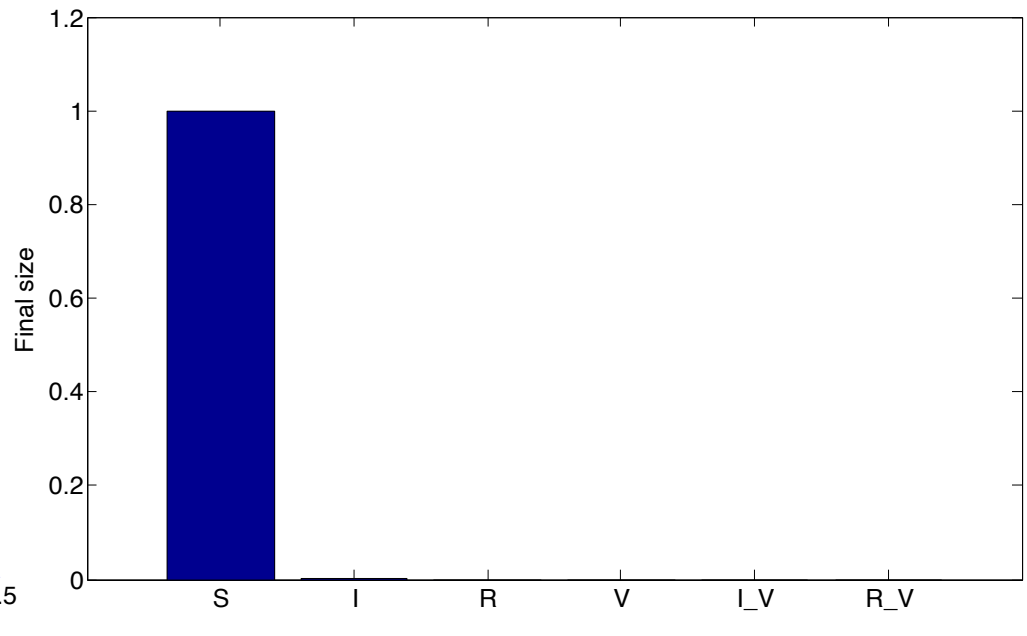
Population dynamics



- 10% vaccination
- Note the low-level oscillations in both infected classes.

Extreme parameters, no vaccine

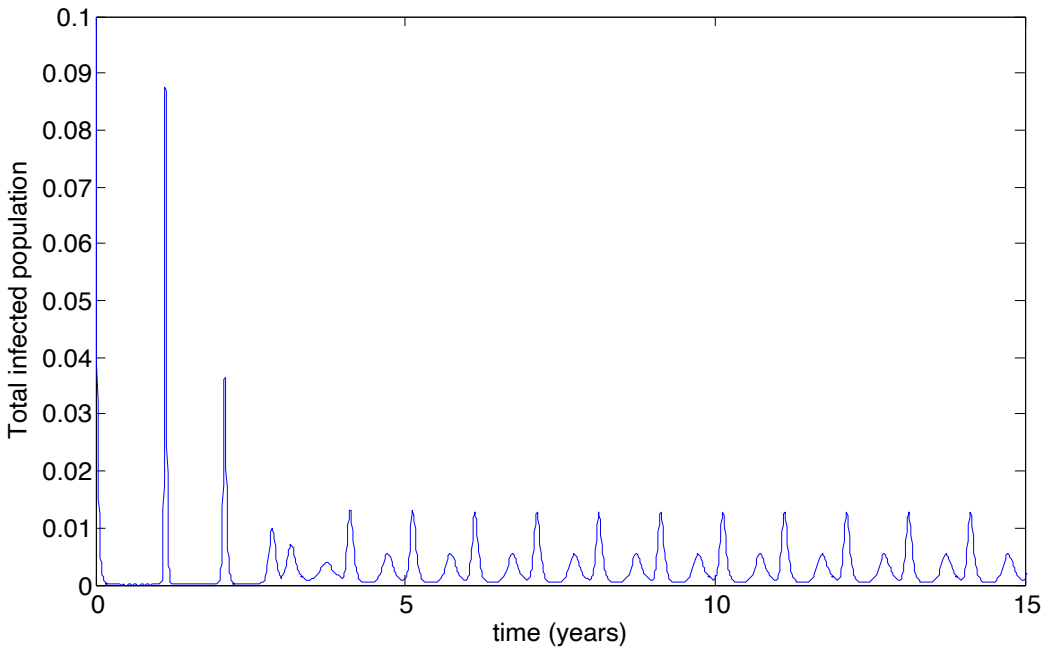


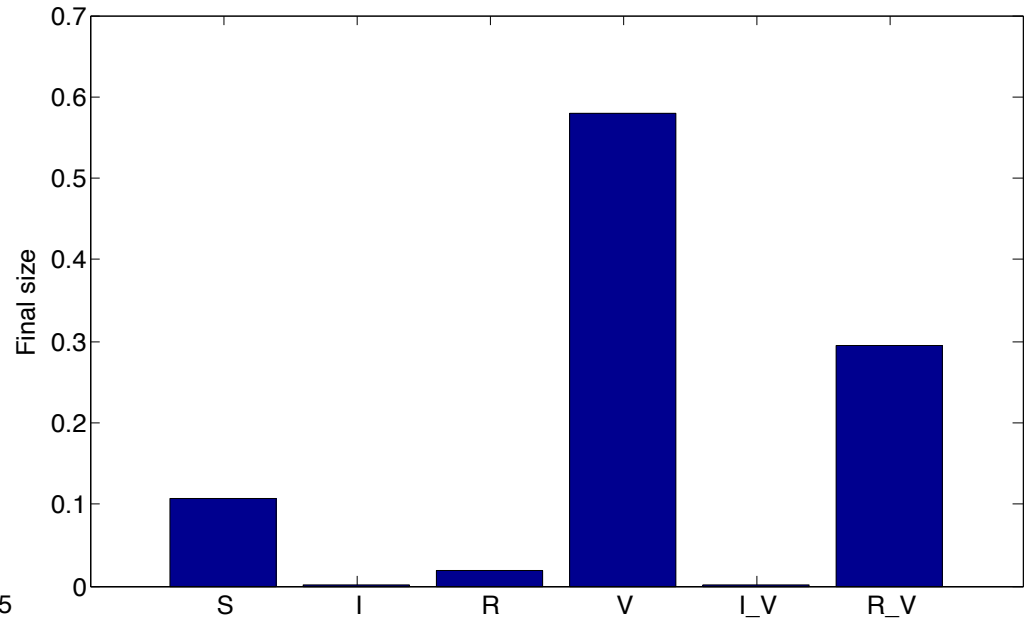


μ=1/70, ω=0.1, β=0.03, β_V=300, ν=36, ν_V=177, γ=1.8, γ_V=0.8γ, r=0.

μ=background death ω=waning
b_0=average transmissibility
b_1=seasonal amplitude φ=phase
β_V=transmissibility v,v_V=recovery
γ,γ_V=loss of immunity, r=coverage

Extreme parameters, 100% vaccination





μ=1/70, ω=0.1, β=0.03, β_V=300, ν=36, ν_V=177, γ=1.8, γ_V=0.8γ, r=1.

μ=background death ω=waning
b_0=average transmissibility
b_1=seasonal amplitude φ=phase
β_V=transmissibility v,v_V=recovery
γ,γ_V=loss of immunity, r=coverage

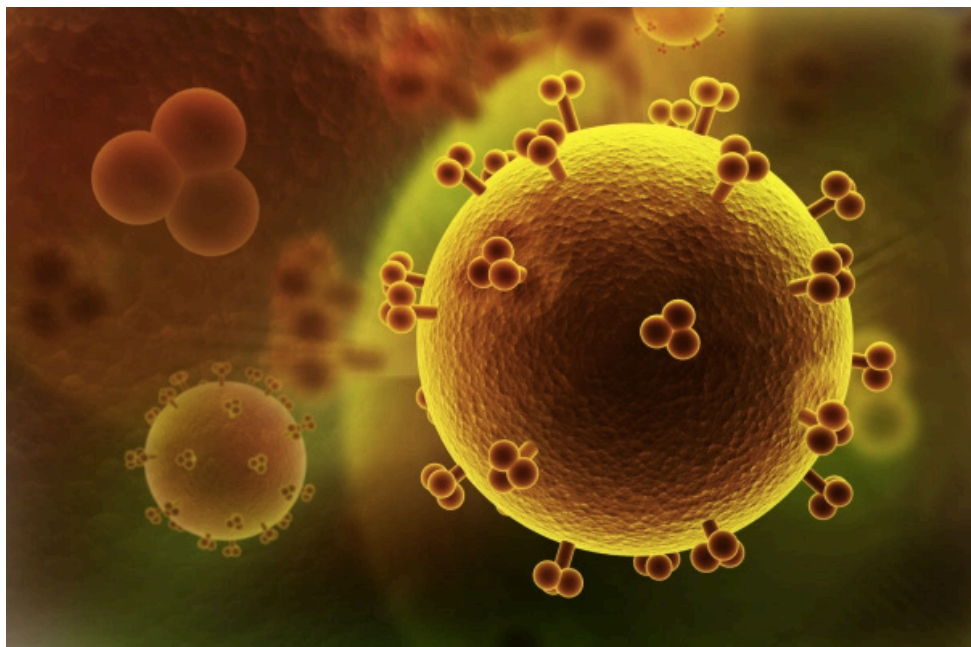
Unexpected infection spikes

- We used extreme vaccination parameters
- Transmission due to vaccinated individuals was extremely high
- But recovery was fast
- This allowed low-level infection spikes to occur in infected populations

- Note that this is not a backward bifurcation
- Rather, it is a destabilisation of the DFE.

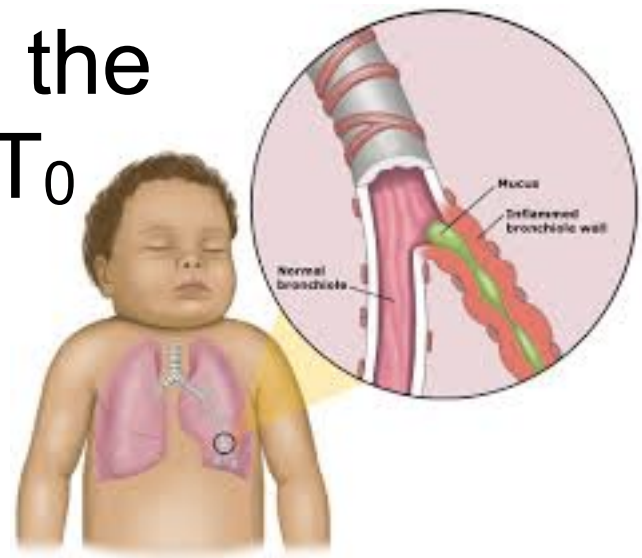
Summary

- We considered two forms of vaccination:
  - single administration before infection
    - e.g., a maternal vaccine
  - periodic vaccination
- Using impulsive differential equations, we were able to formulate conditions on the period and strength of vaccination to allow for disease control.



Impulsive reproduction number

- We also defined a new quantity, the impulsive reproduction number T_0
- This is a sufficient (but not necessary) condition that ensures eradication if $T_0<1$



- In this case, the infected population is contracting within each impulsive cycle
- The result is eventual eradication of the infection.

T_0=impulsive reproduction number

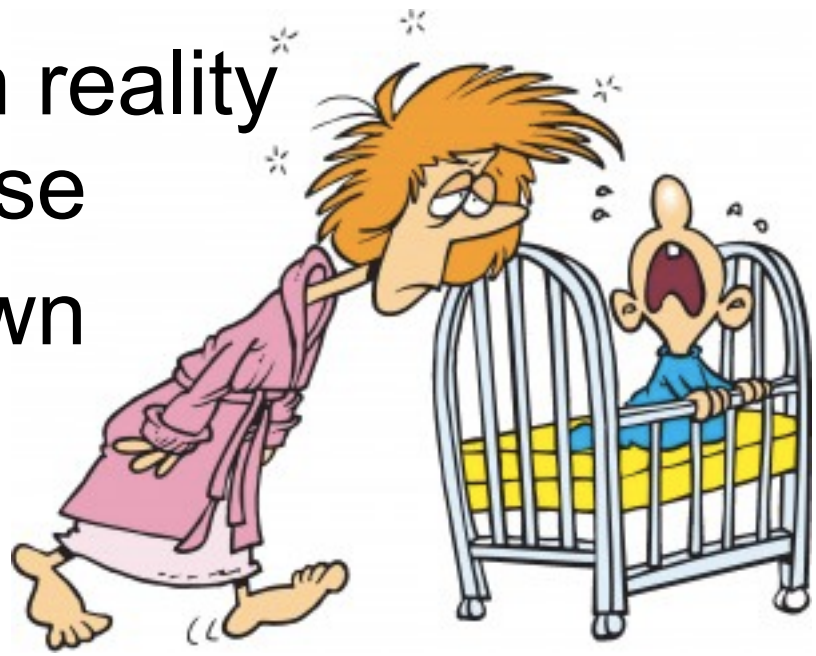
Constant vs seasonal transmission

- We assumed constant transmission for this derivation
- However, numerical simulations were performed using seasonal oscillations and demonstrated comparative results
- In particular, if the strength of periodic vaccination r is sufficiently high, the disease will be controlled
- If not, control can still be achieved if the vaccine is given with sufficient frequency.

r=coverage

Infection spikes

- The infection spikes occur when vaccine-induced transmission is extremely high but recovery is extremely fast
- They occur even when the transmission function is not oscillating
- They are unlikely to occur in reality with the parameters we chose
- Nevertheless, we have shown proof-of-concept that such an outcome is possible.



Limitations

We assumed:

- The time to administer the vaccine was significantly shorter than the time between vaccinations
- A well-mixed population
- A single age cohort
- A population of fixed size
- Constant birth and death
- Maternal vaccination in the first model.

Conclusions

- A vaccine that targets RSV infection has the potential to significantly reduce the overall prevalence of the disease
- Long-term, periodic vaccination can theoretically control the disease, but coverage needs to be high or administration sufficiently frequent
- Extreme parameters have the potential to induce unexpected infection spikes
- Care should be taken to understand long-term effects when introducing new vaccines.

Key reference

- R.J. Smith?, A.B. Hogan, G.N. Mercer *Unexpected infection spikes in a model of Respiratory Syncytial Virus vaccination* (Vaccines, 2017, 5:12).

http://mysite.science.uottawa.ca/rsmith43