Unexpected infection spikes in a model of Respiratory Syncytial Virus vaccination

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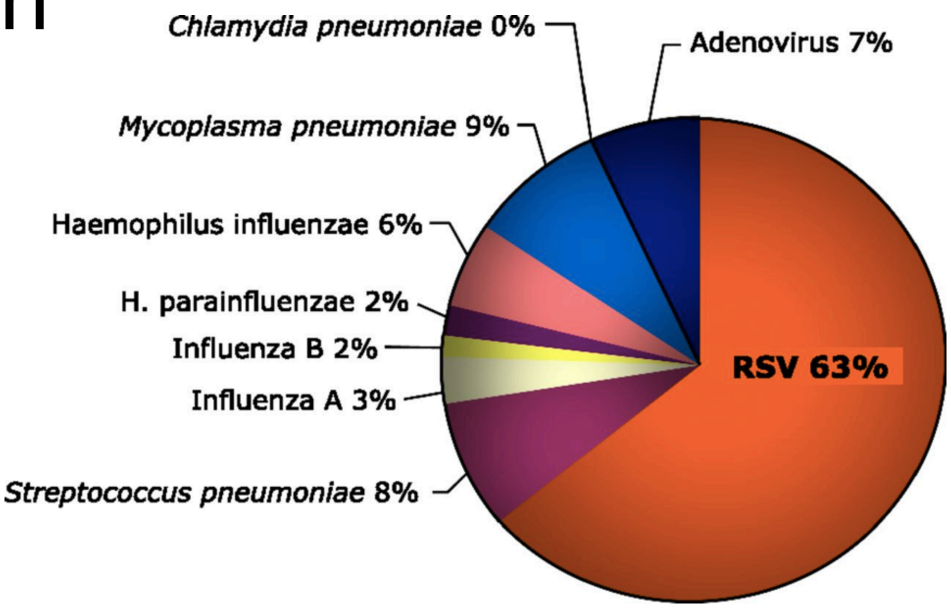
- The main cause of acute lower respiratory infections in adults and young children



Etiology of acute respiratory infections in children.

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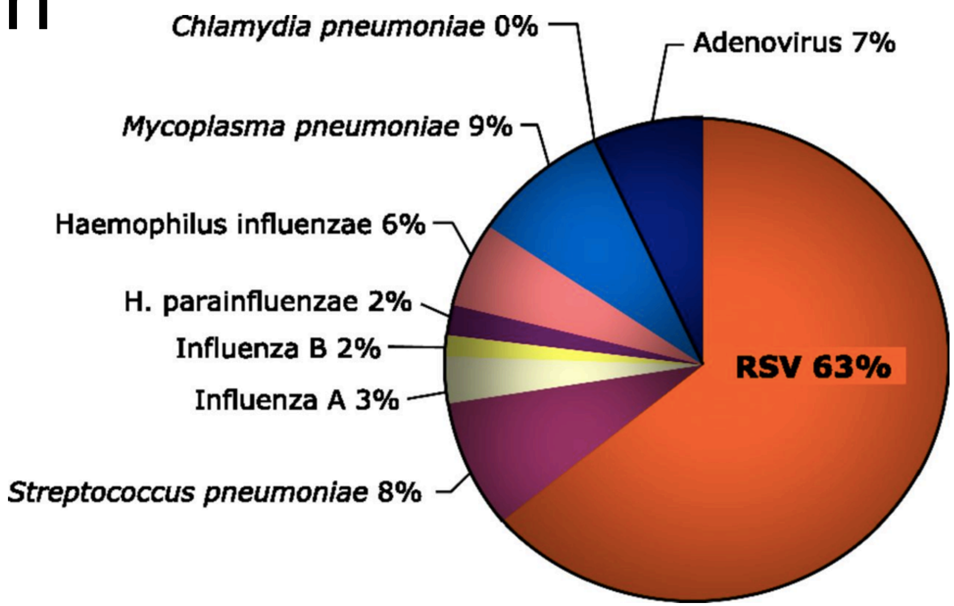

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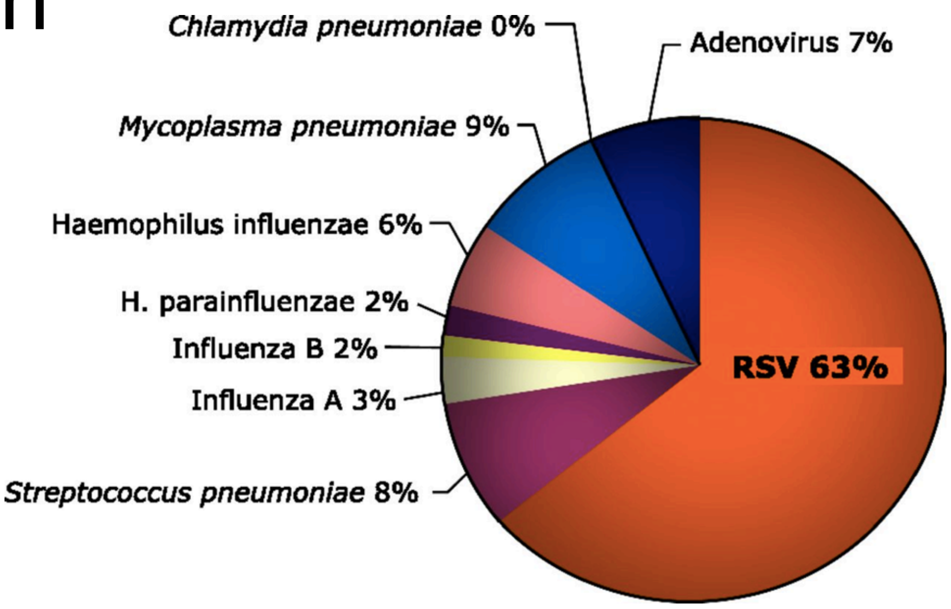

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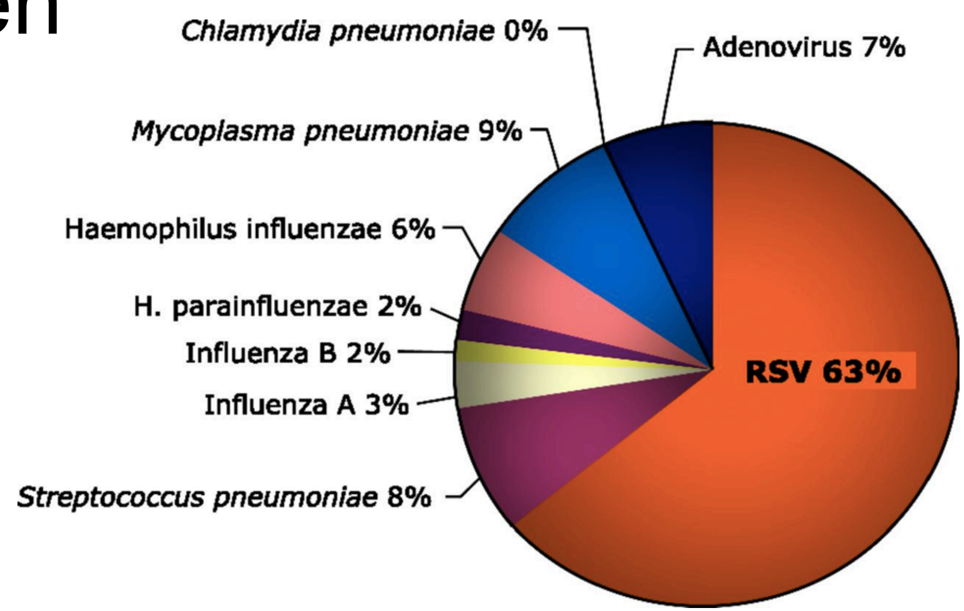
- In 2005, 33.8 million new episodes of RSV occurred in children under 5 worldwide.



Etiology of acute respiratory infections in children.

Symptoms

- Mild symptoms:

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  - cough

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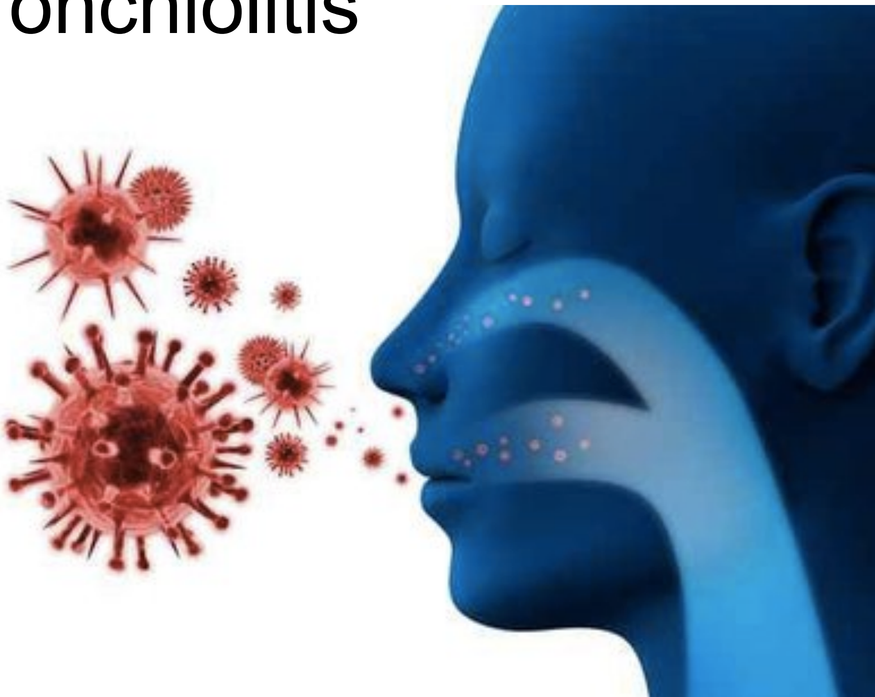

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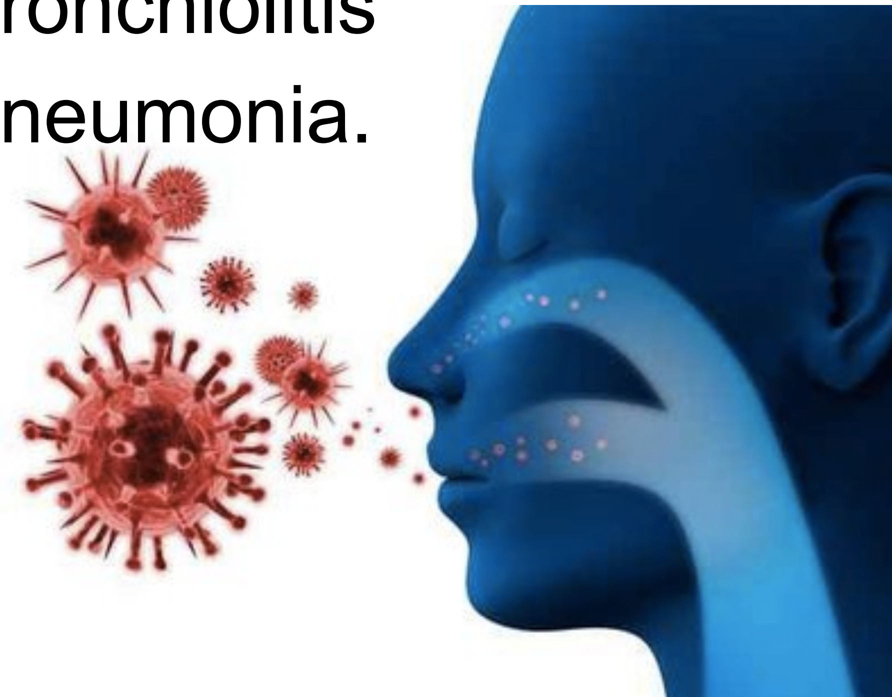
  - pneumonia.



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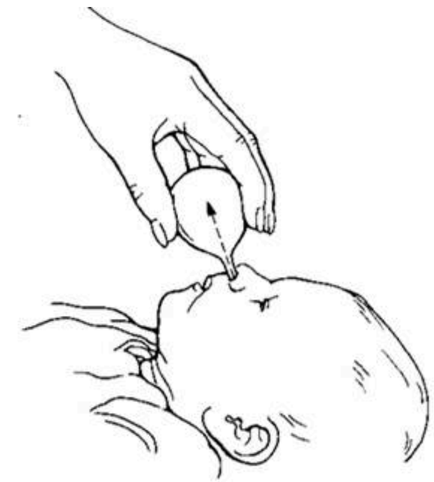
- RSV is a significant economic and healthcare system burden.

Seasonal patterns

- In temperate climates, RSV epidemics exhibit consistent seasonal patterns



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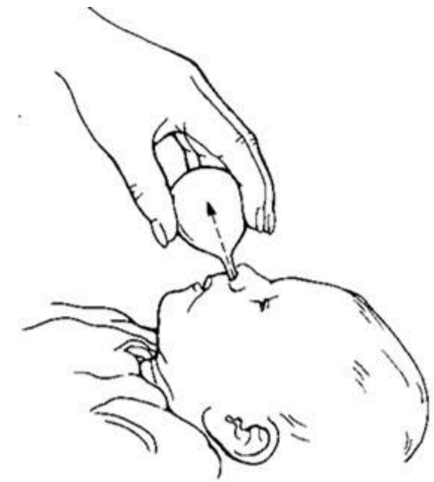

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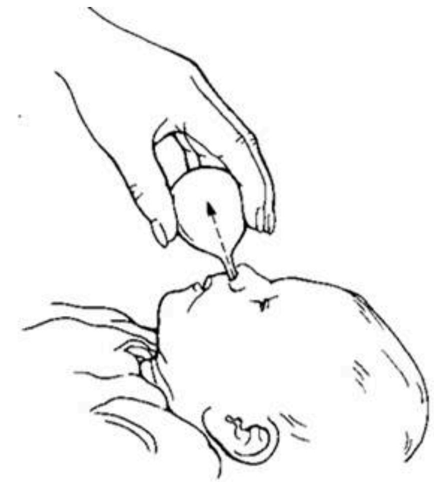

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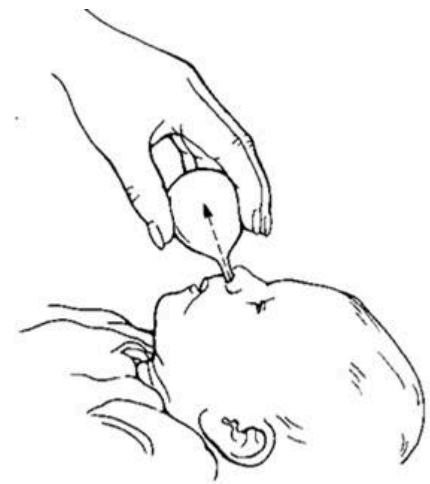
- The onset of RSV is typically associated with the rainy season.



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  - generally only administered to high-risk children.

Vaccination

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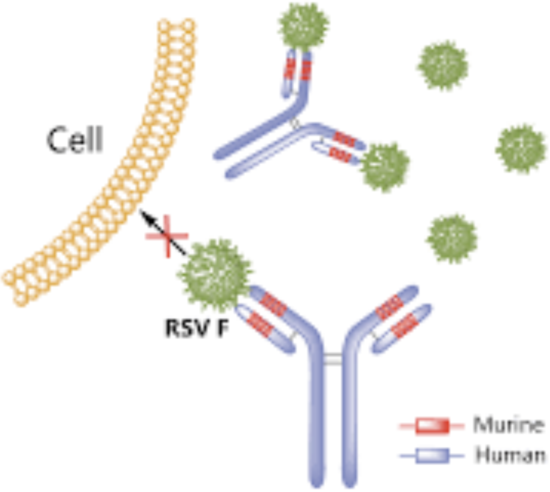
- Live attenuated vaccines are also undergoing Phase I trials.

Model 1

- We extend an existing RSV model for a single age cohort to include vaccination



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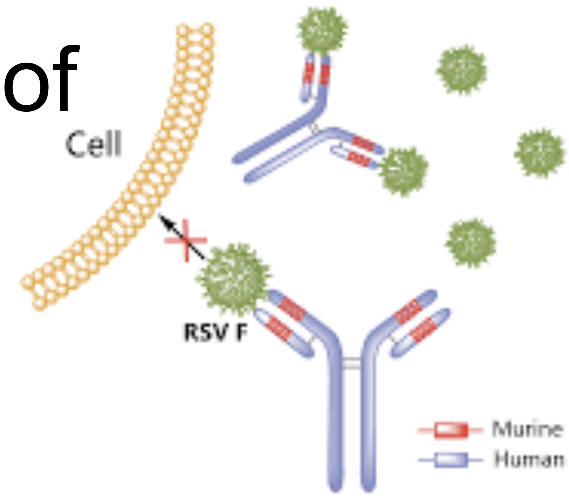

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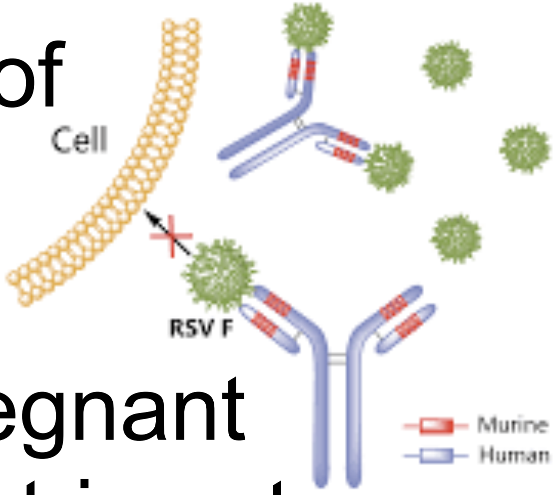

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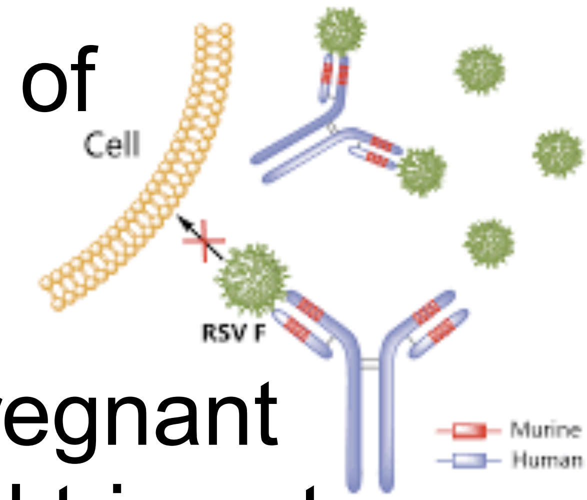

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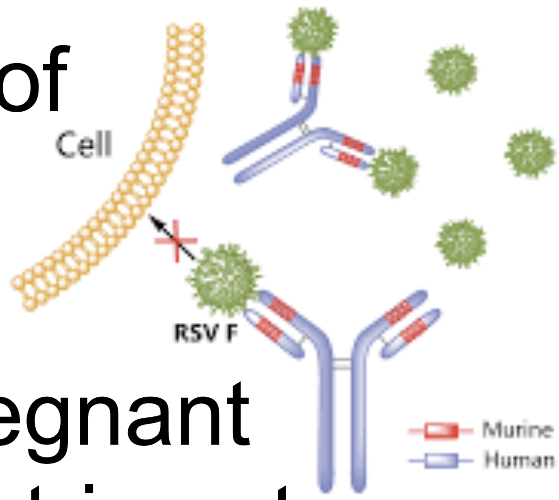
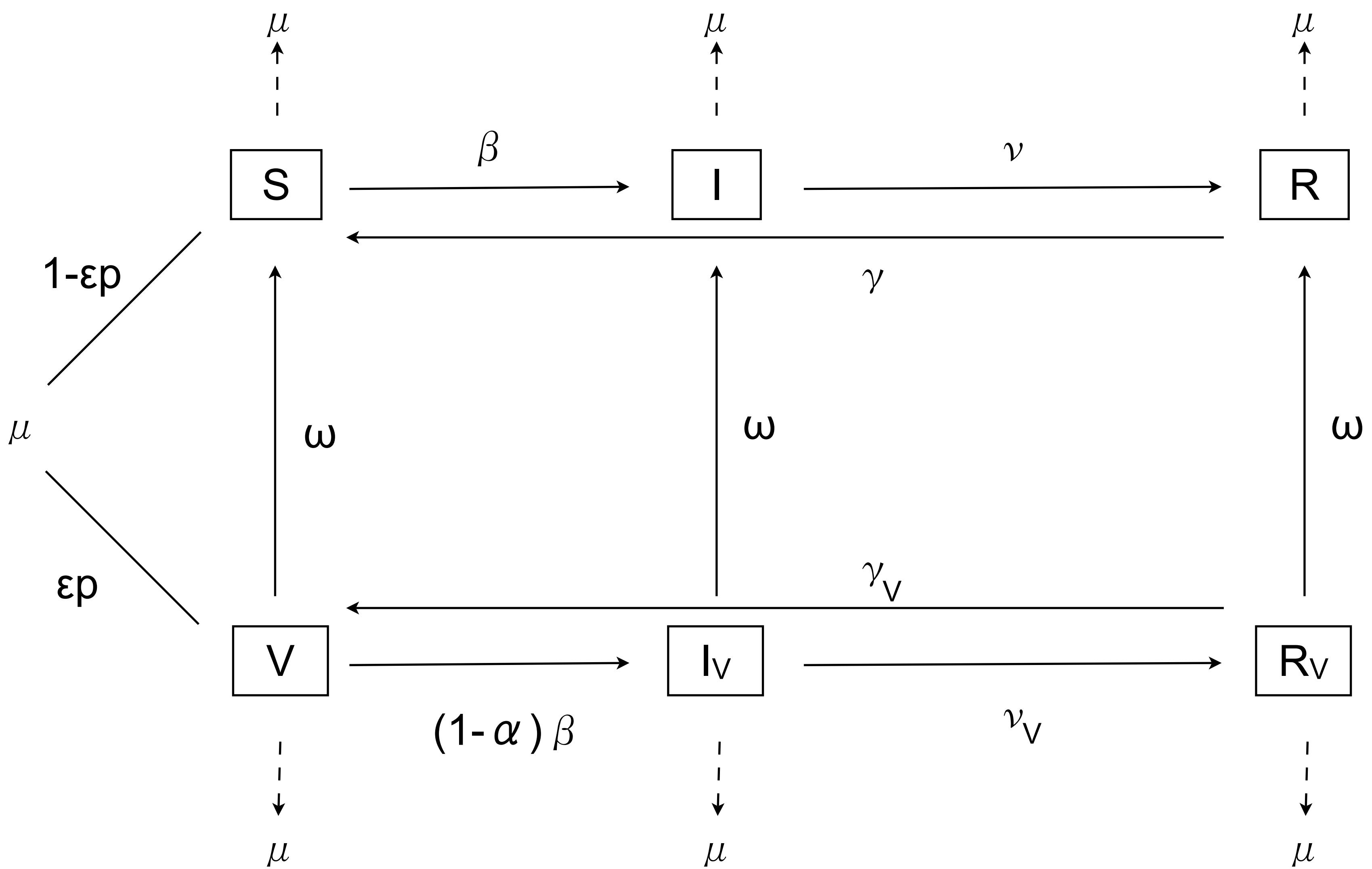


- This reflects the situation where pregnant women are vaccinated in their third trimester
- Protective maternal antibodies are transferred placentally to the unborn infant
- This confers protection for the first few months of life.

Flow diagram



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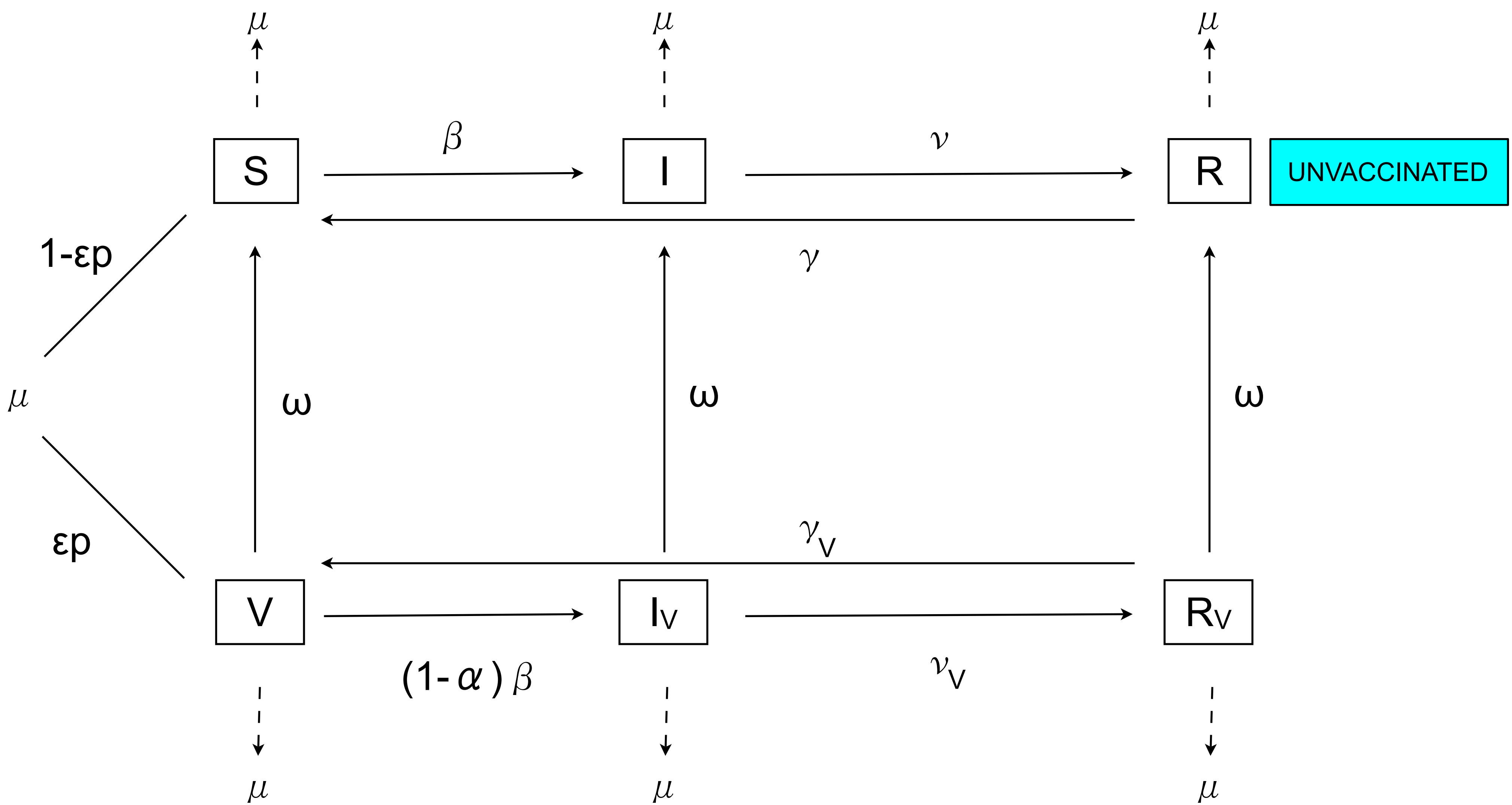

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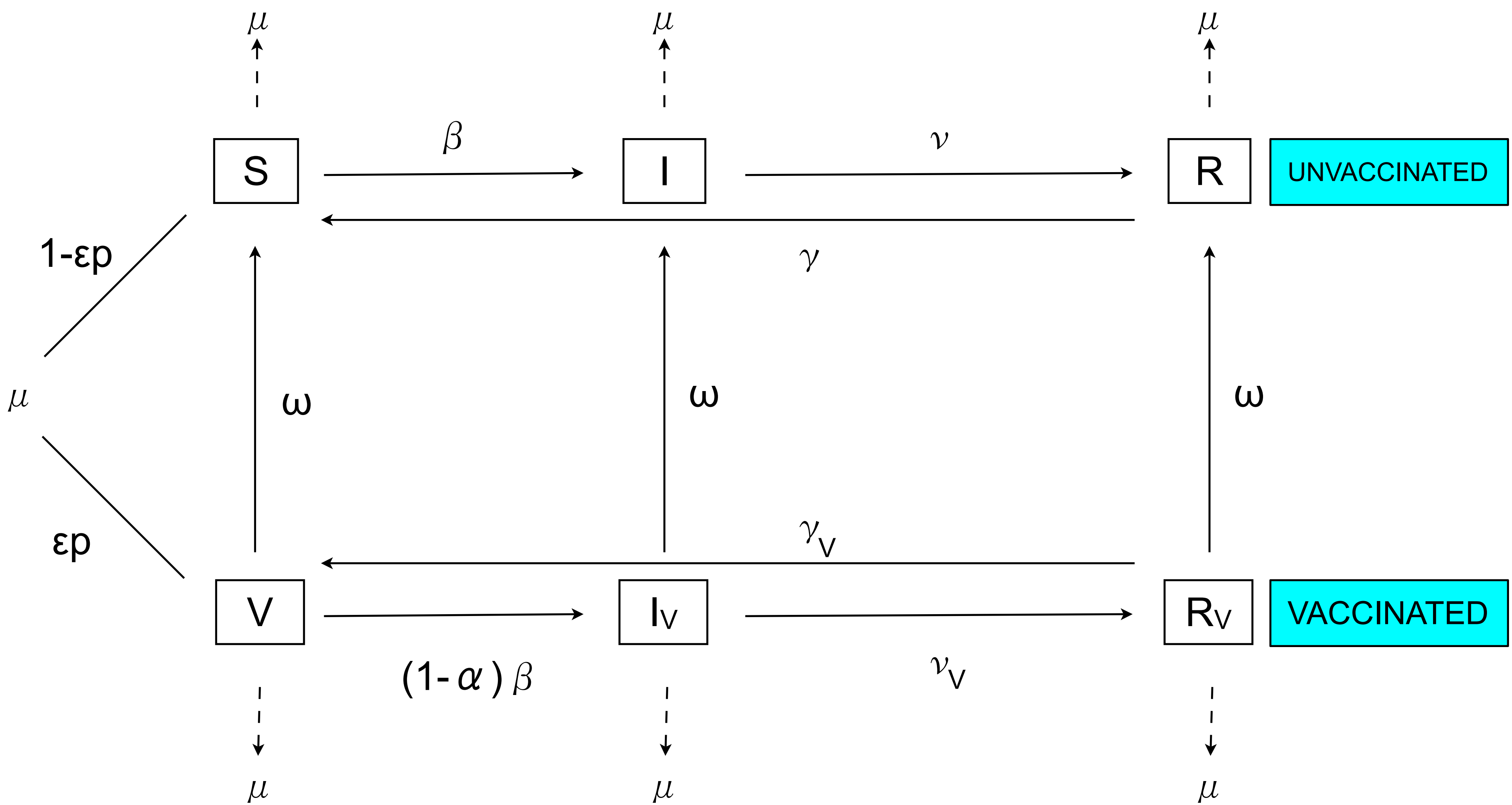

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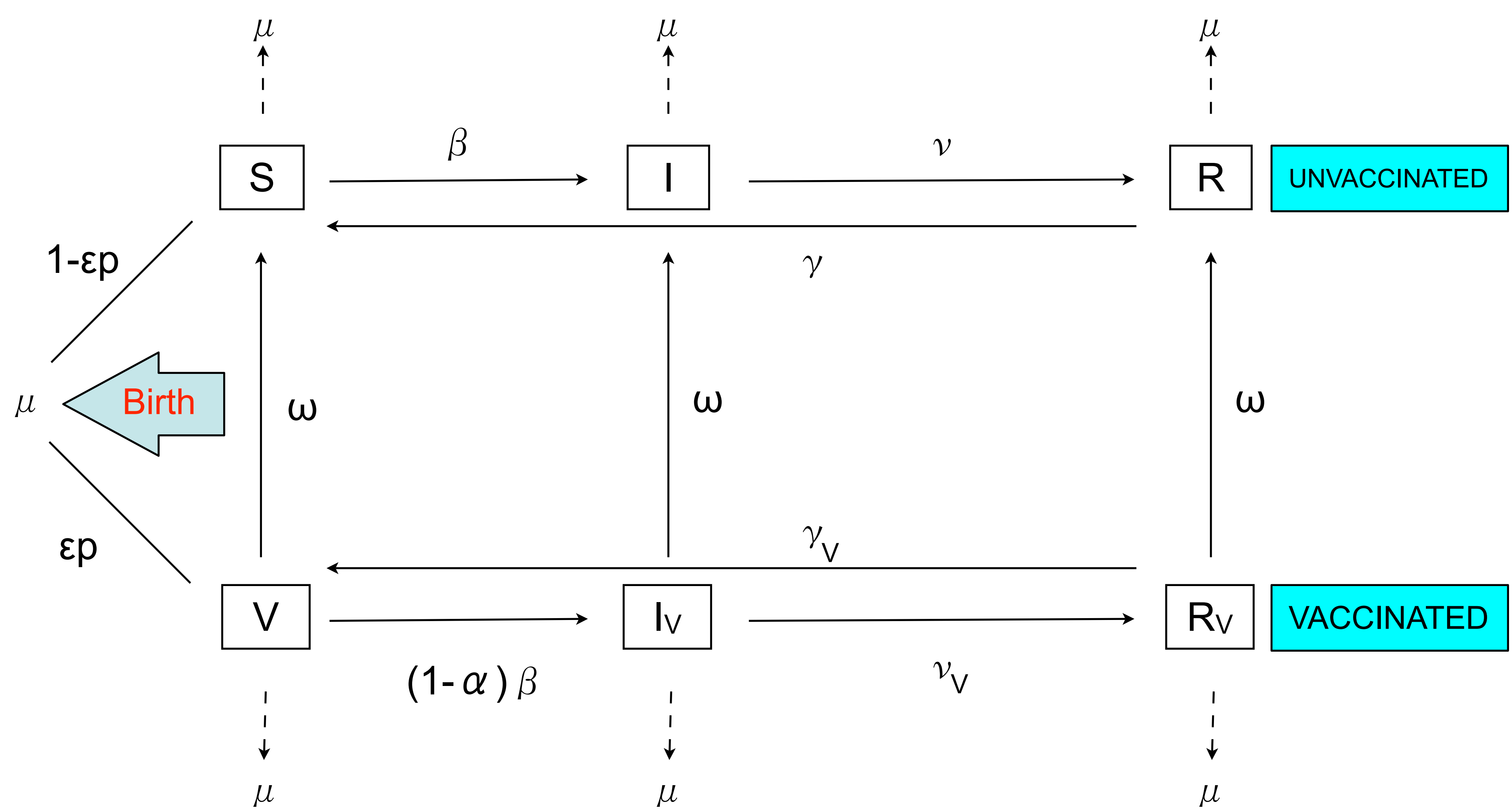

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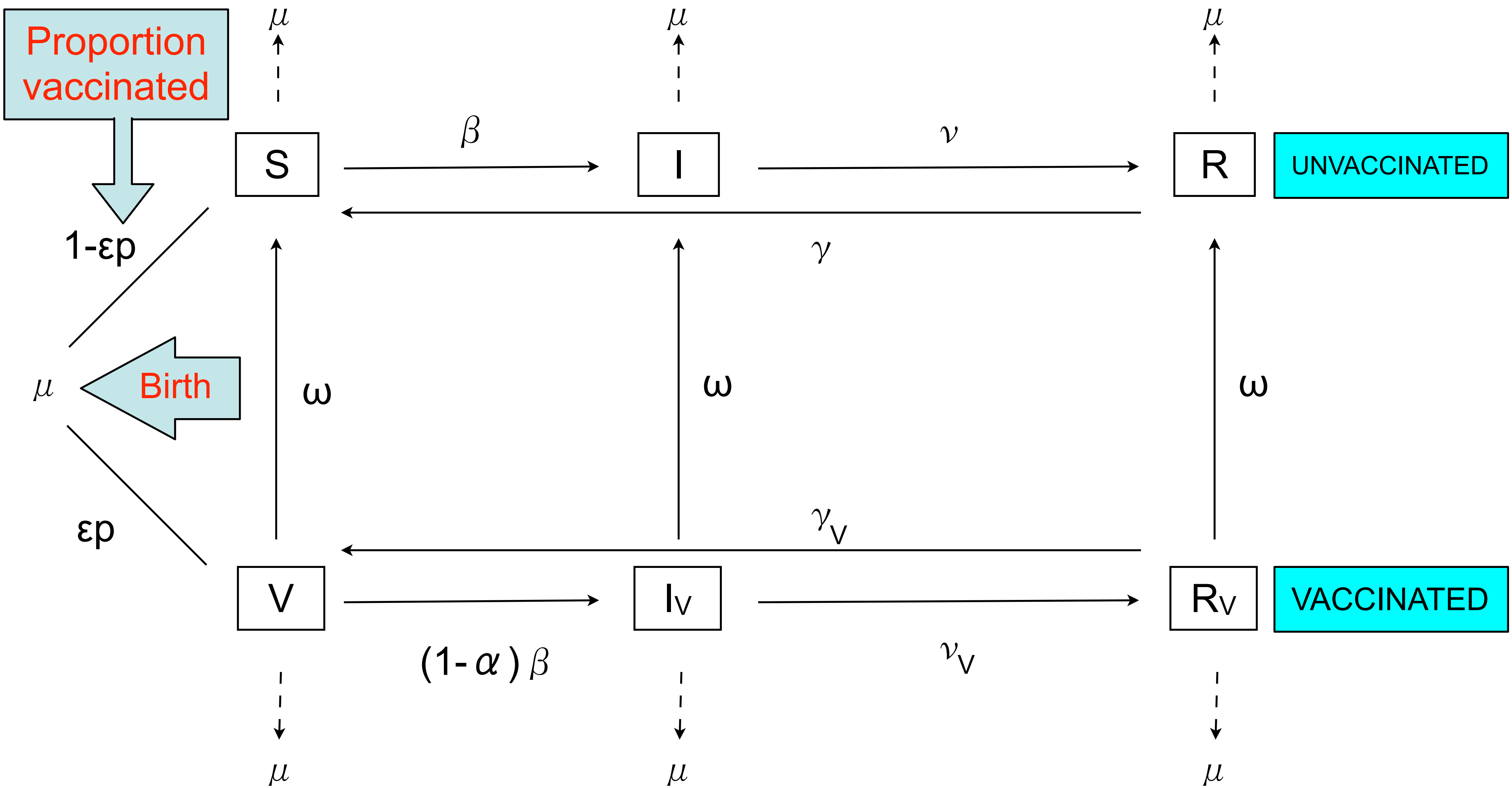

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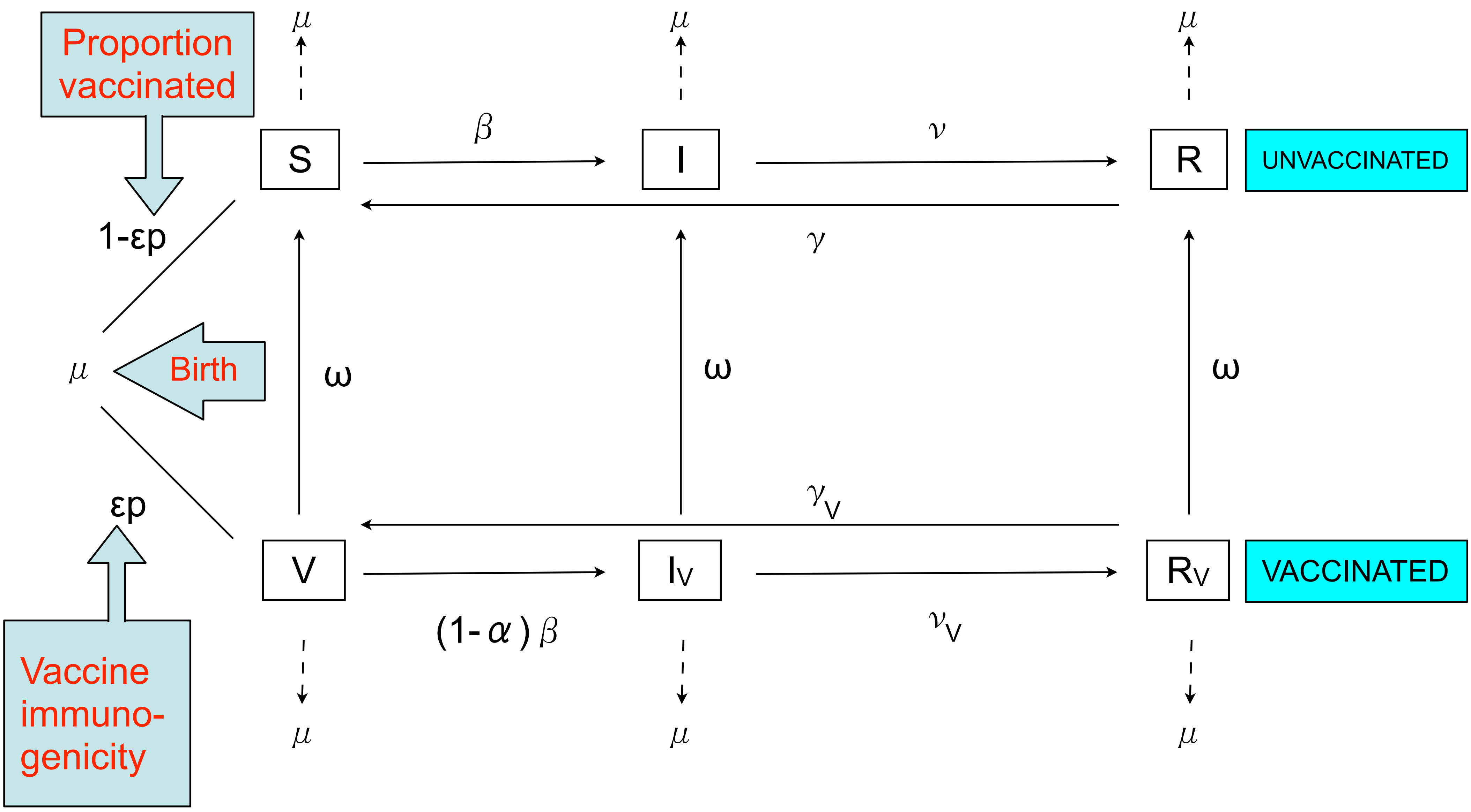

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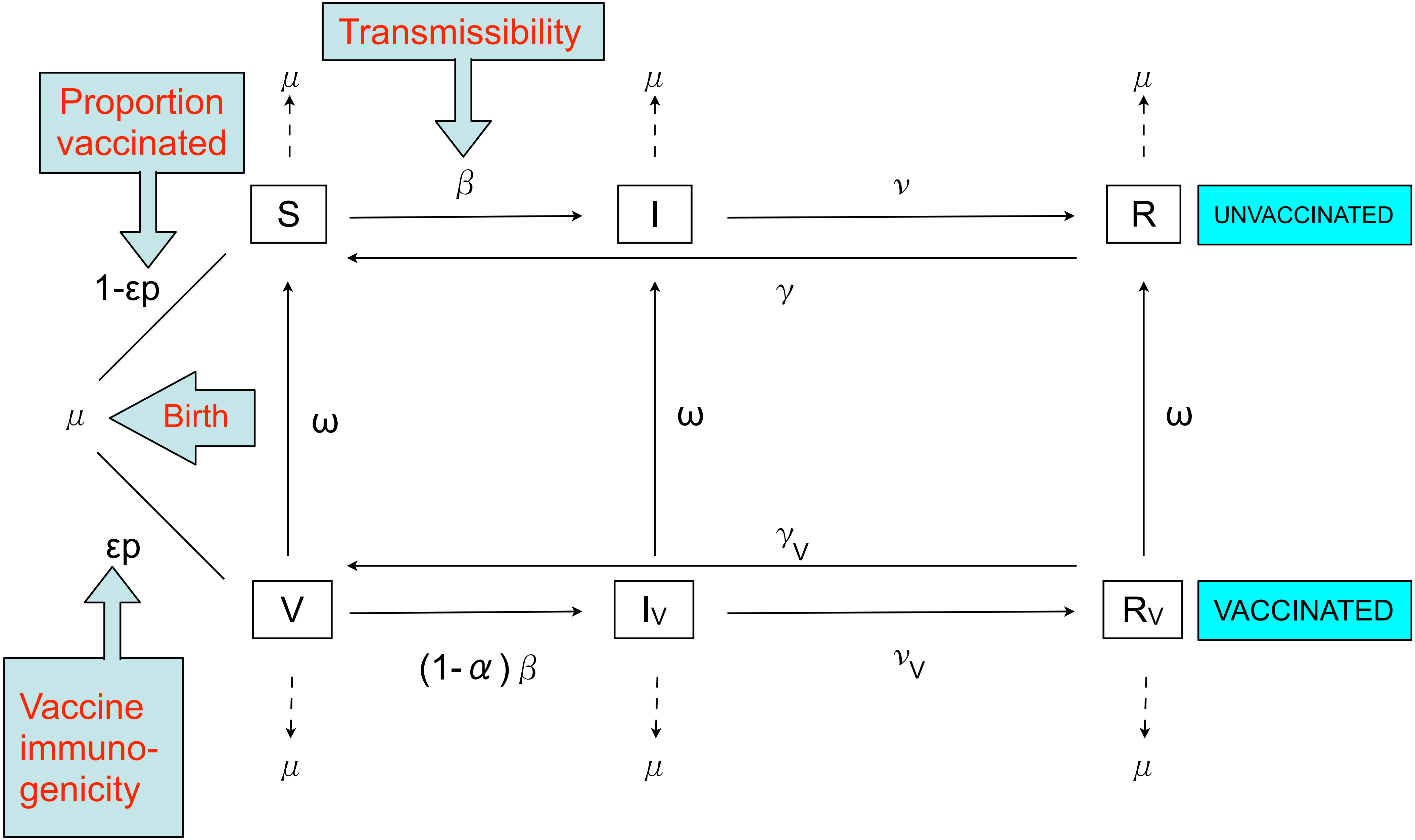

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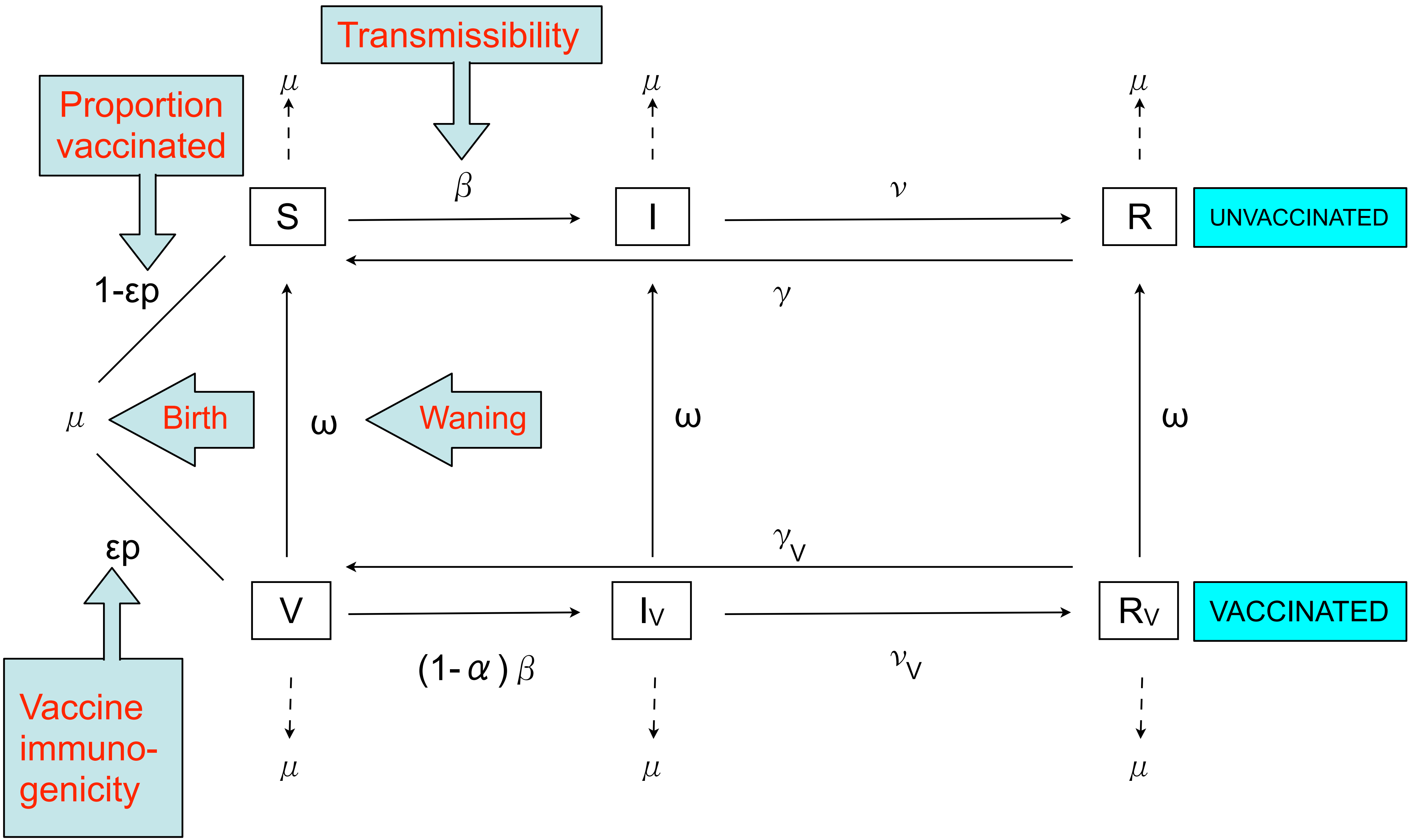

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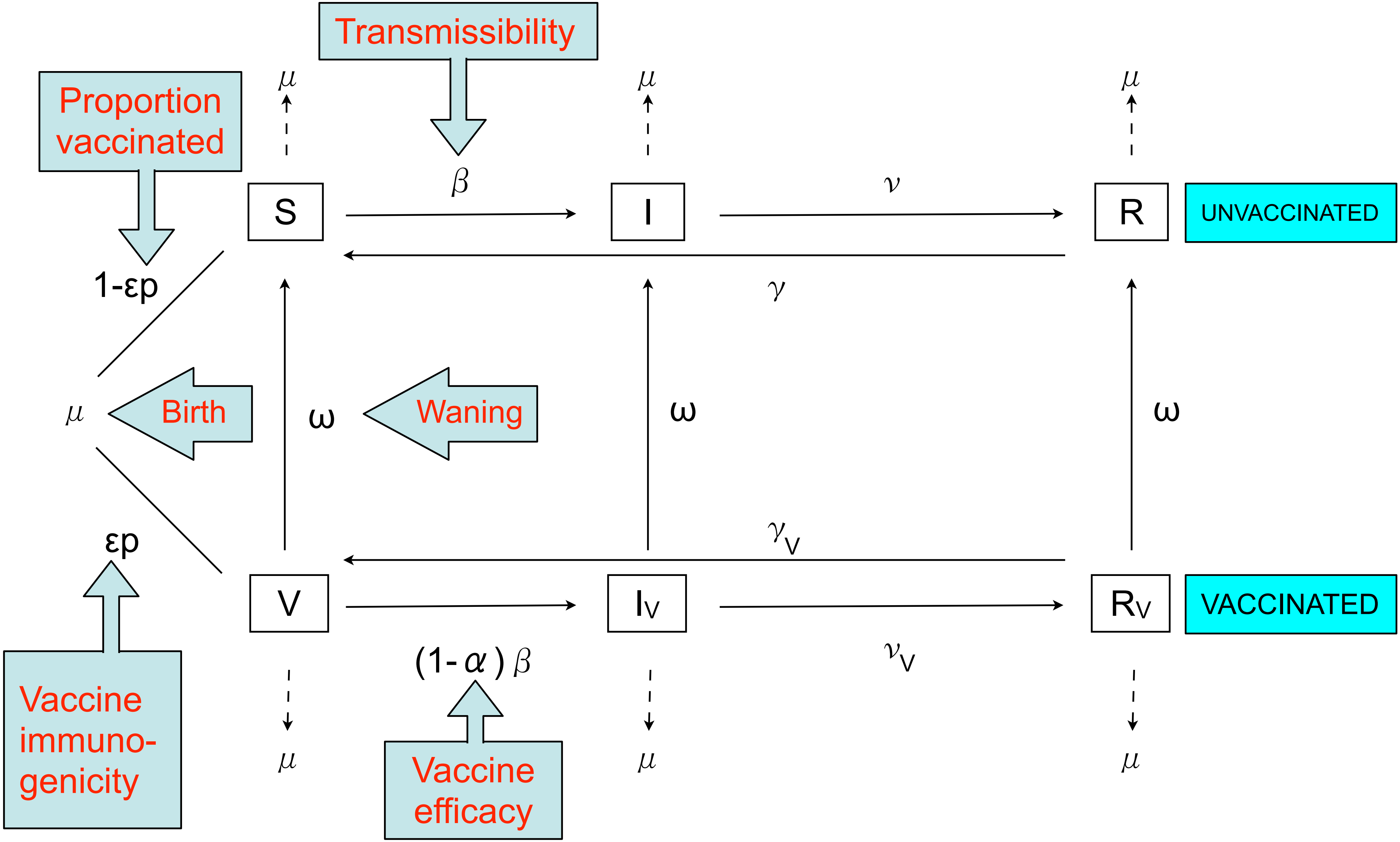

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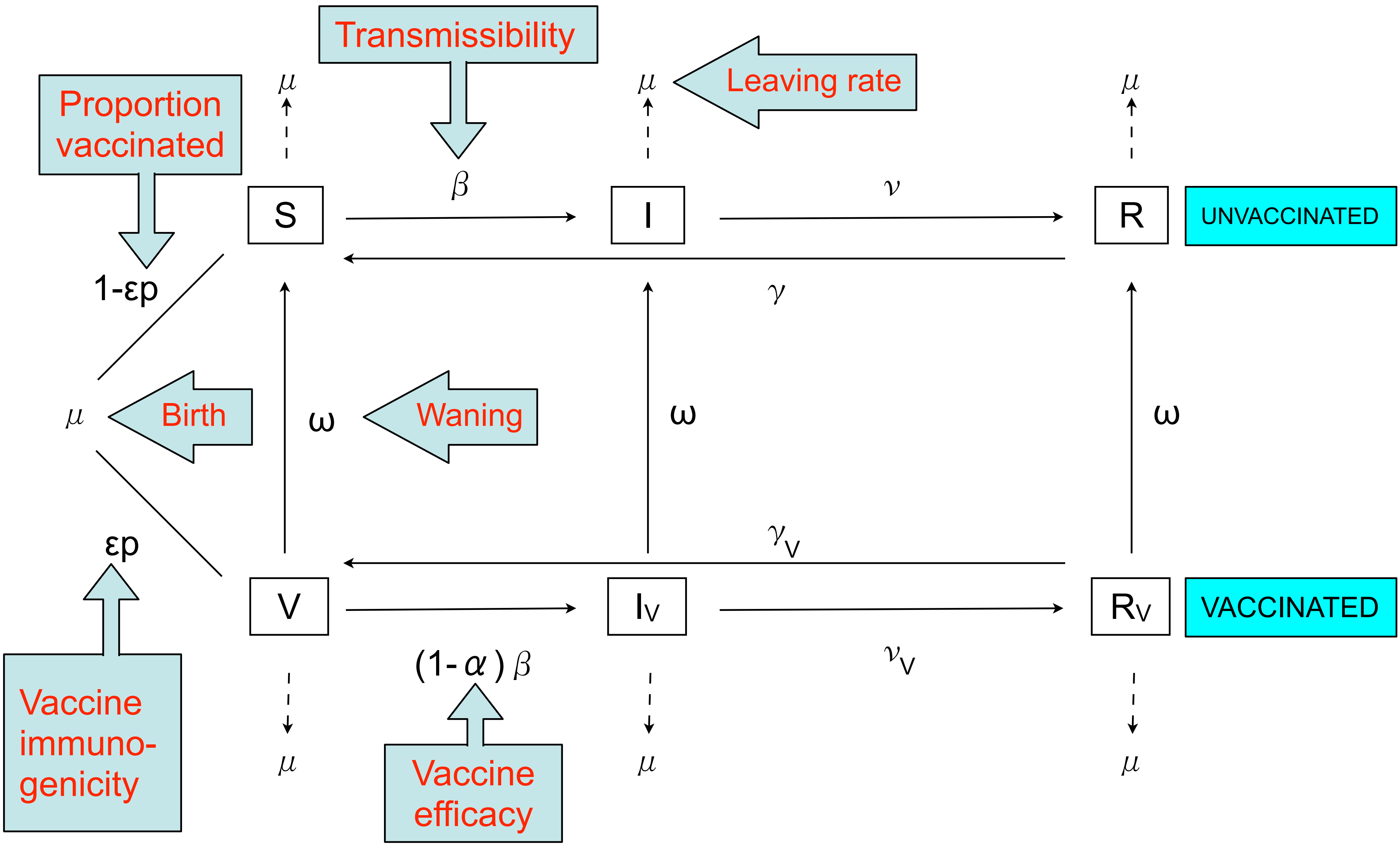

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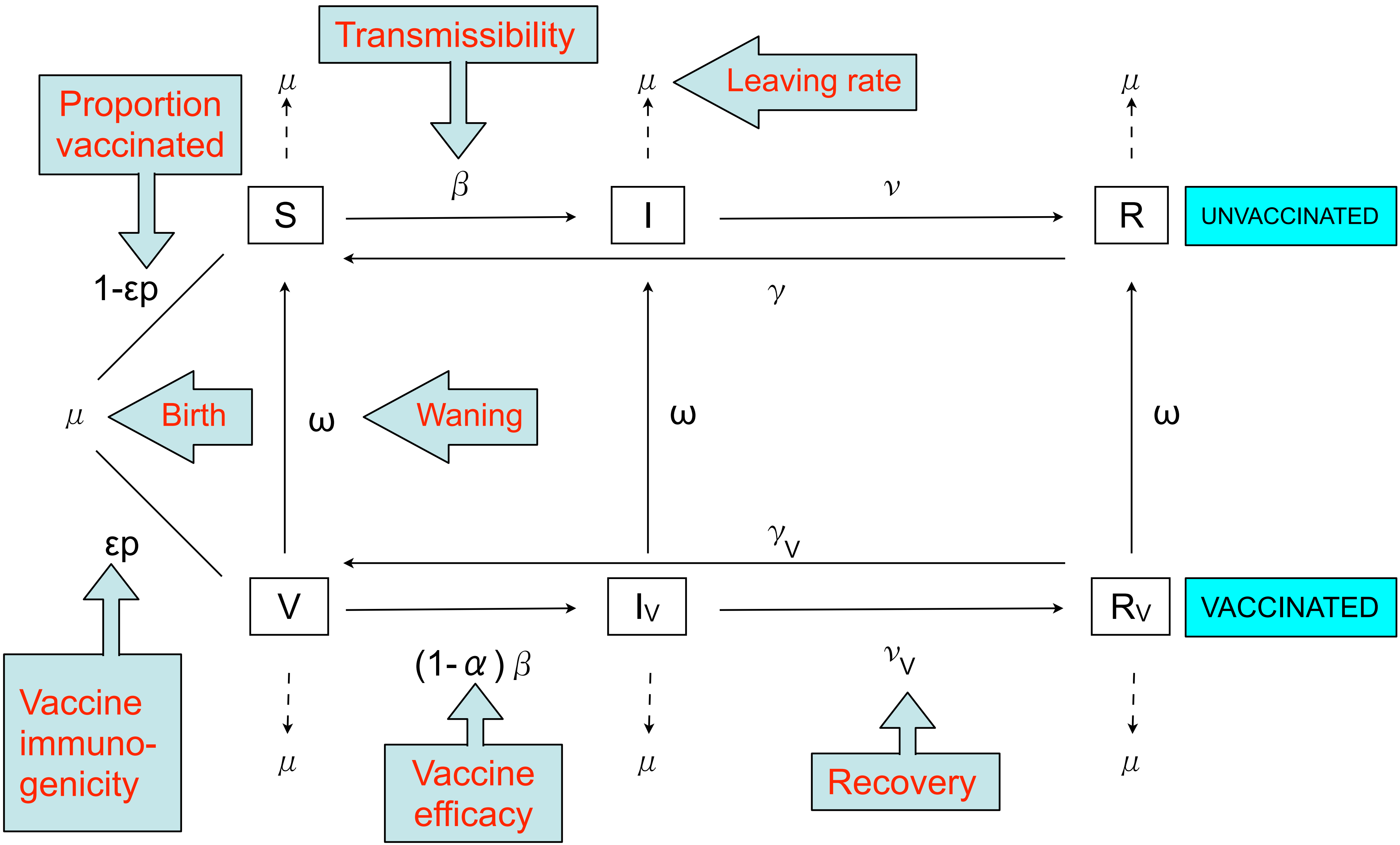

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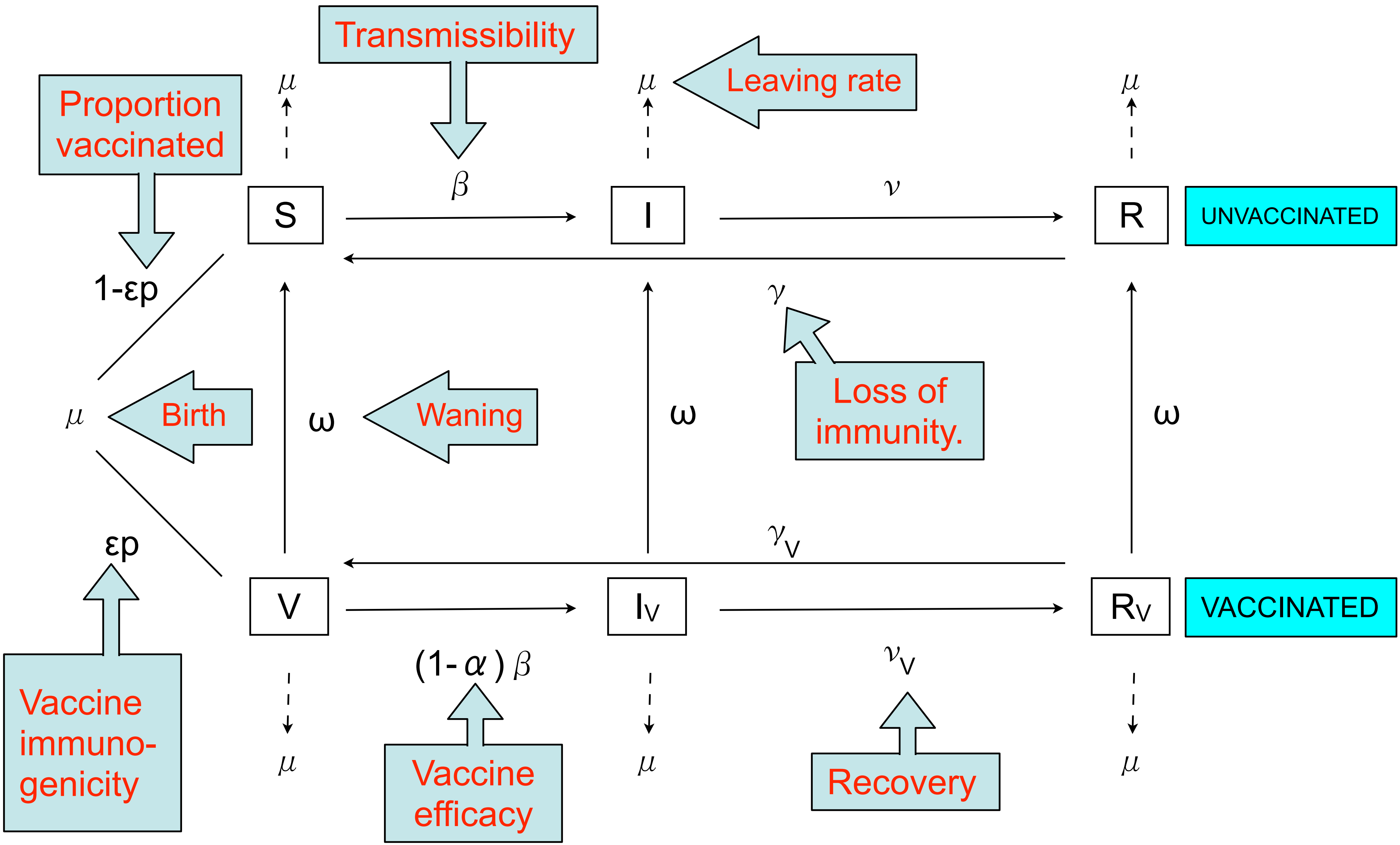

The continuous model

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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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(α may possibly be negative).

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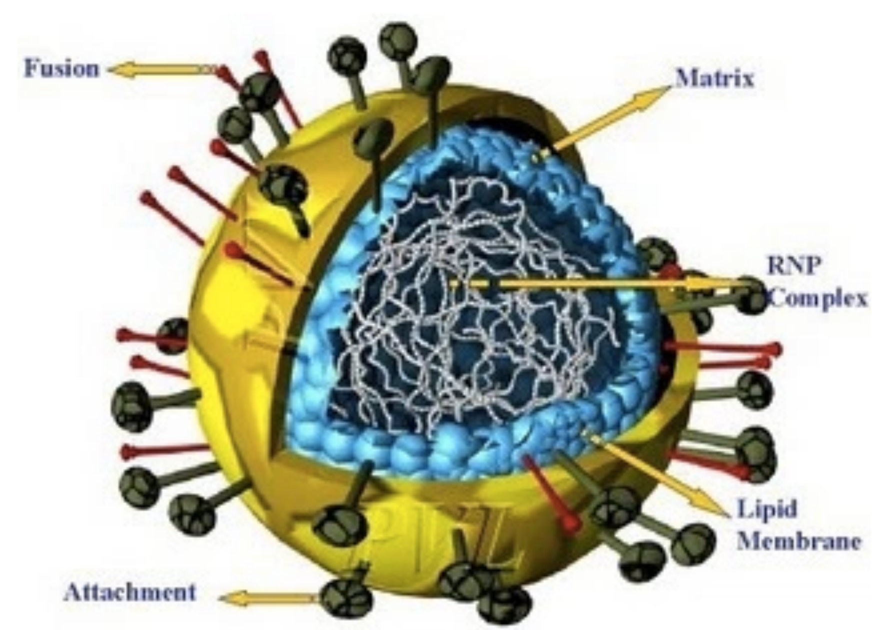

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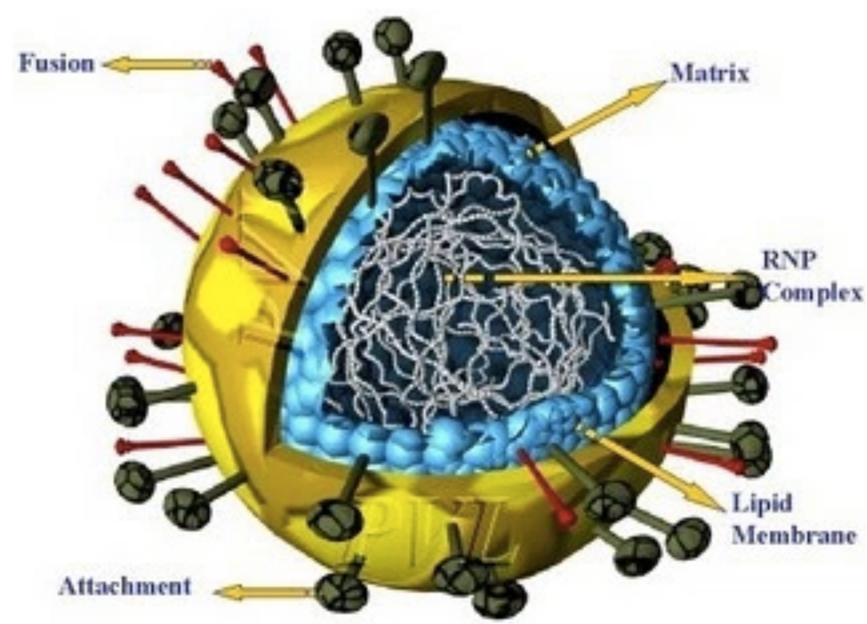

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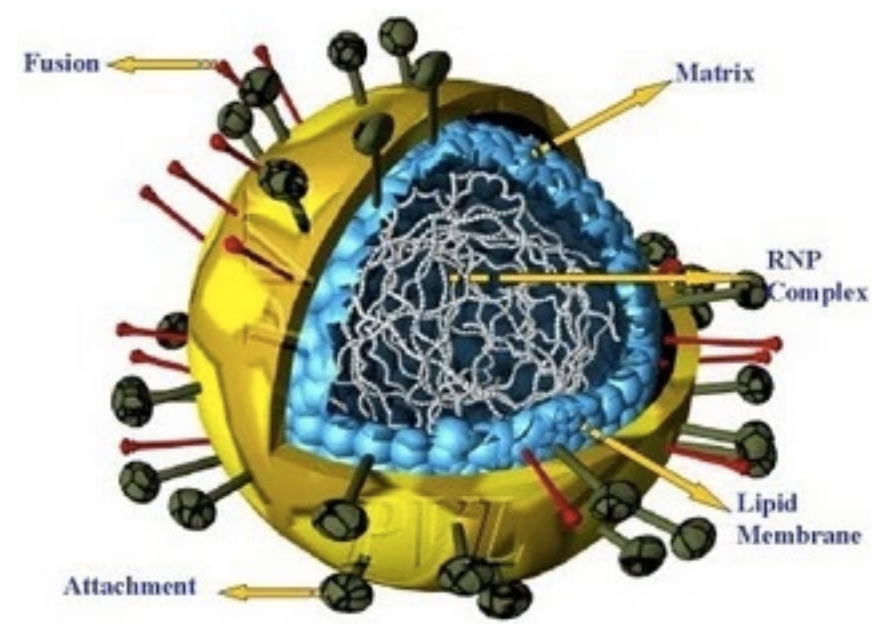

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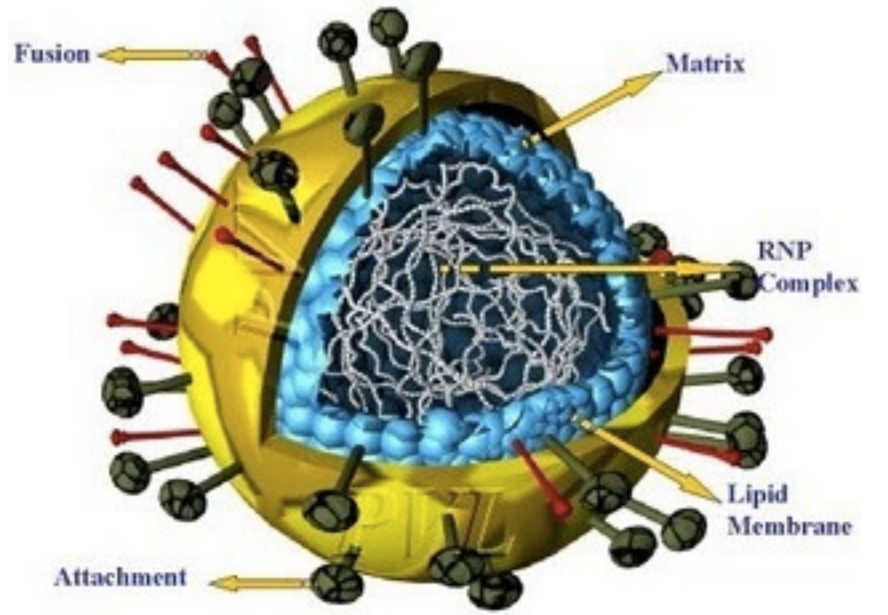

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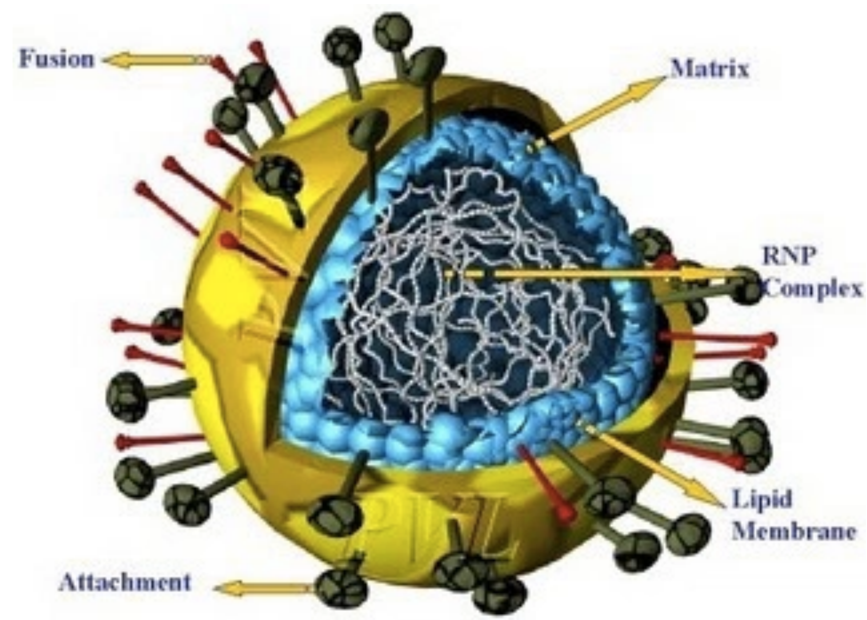

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$$\begin{aligned} b_1 &= -\beta \bar{S} + \mu + \nu - \beta_V \bar{V} + \nu_V + \mu + \omega \\ c_1 &= (\beta \bar{S} - \mu - \nu)(\beta_V \bar{V} - \nu_V - \mu - \omega) - \beta_V \bar{V}(\beta \bar{S} + \omega) \\ &= \beta \bar{S}(-\nu_V - \mu -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

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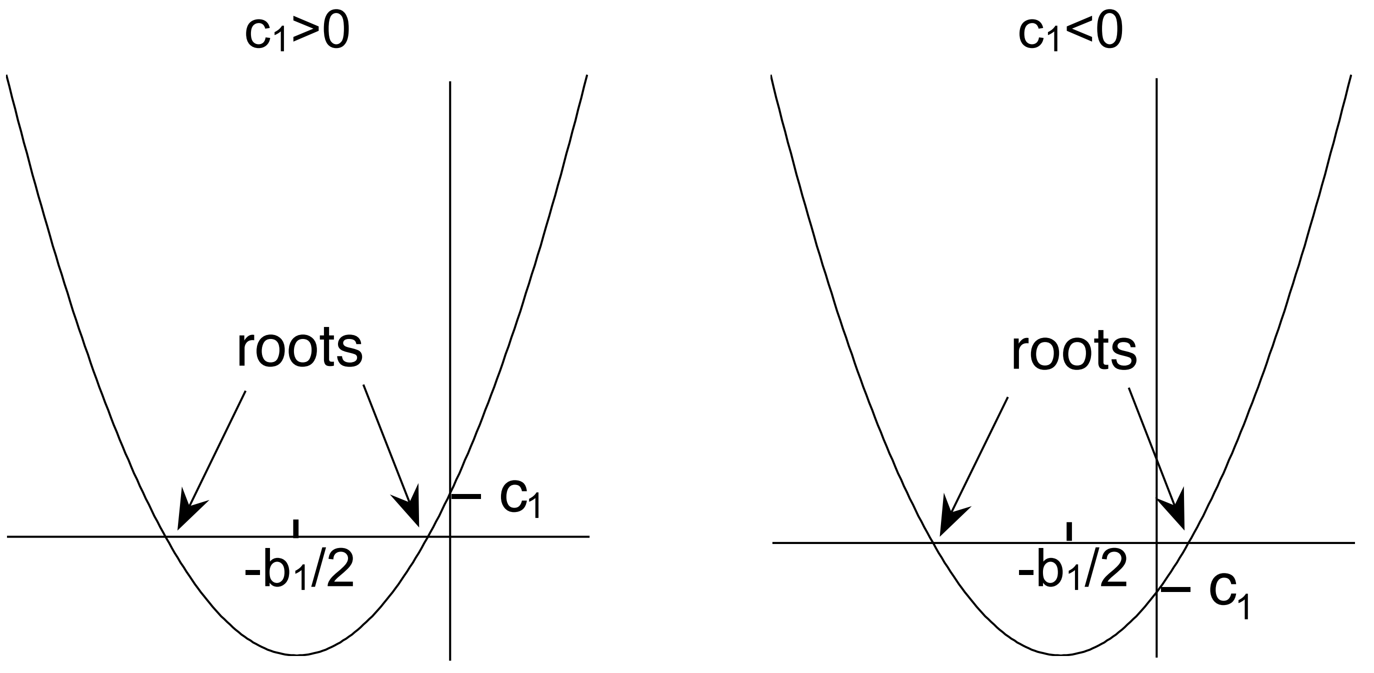
Stability of eigenvalues



b_1=vertex
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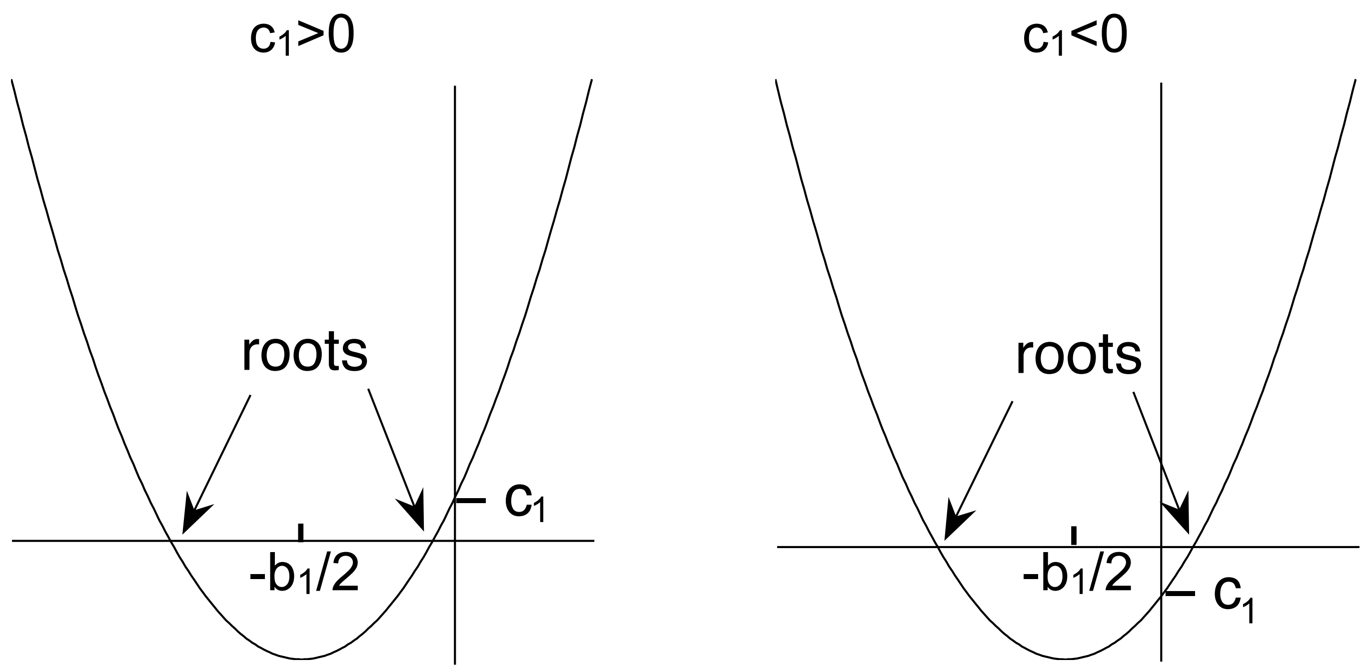

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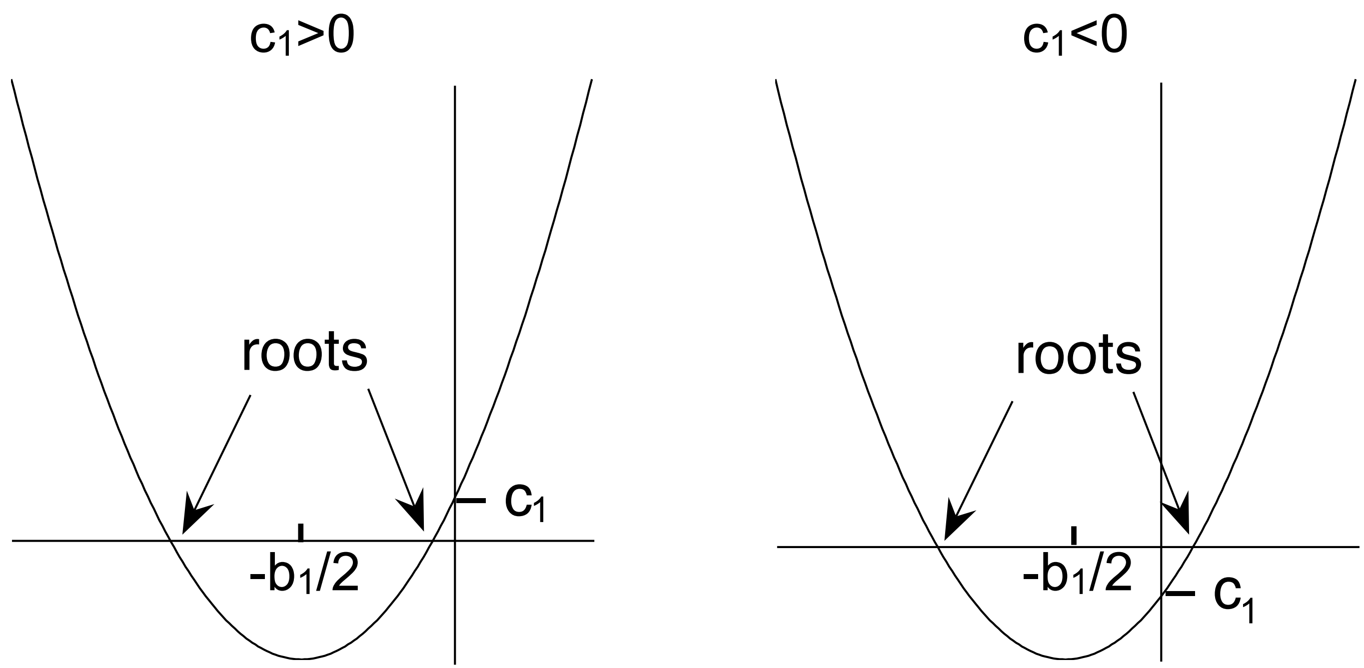

- If $b_1>0$, then c_1 is a proxy for the eigenvalues
- If $b_1<0$, then the DFE is unstable and c_1 is not a threshold.

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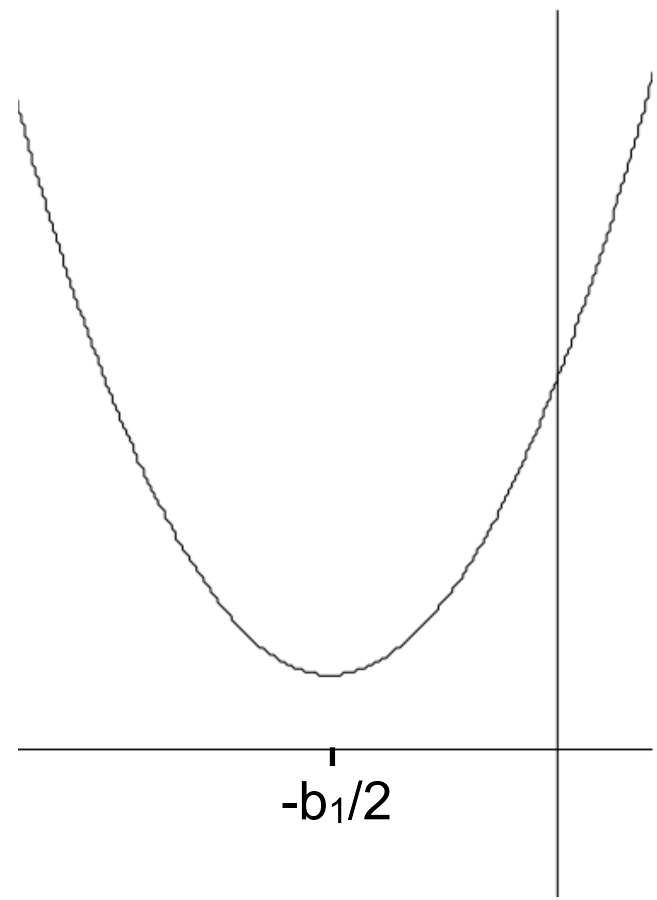
Complex eigenvalues?

- If the roots are complex, then



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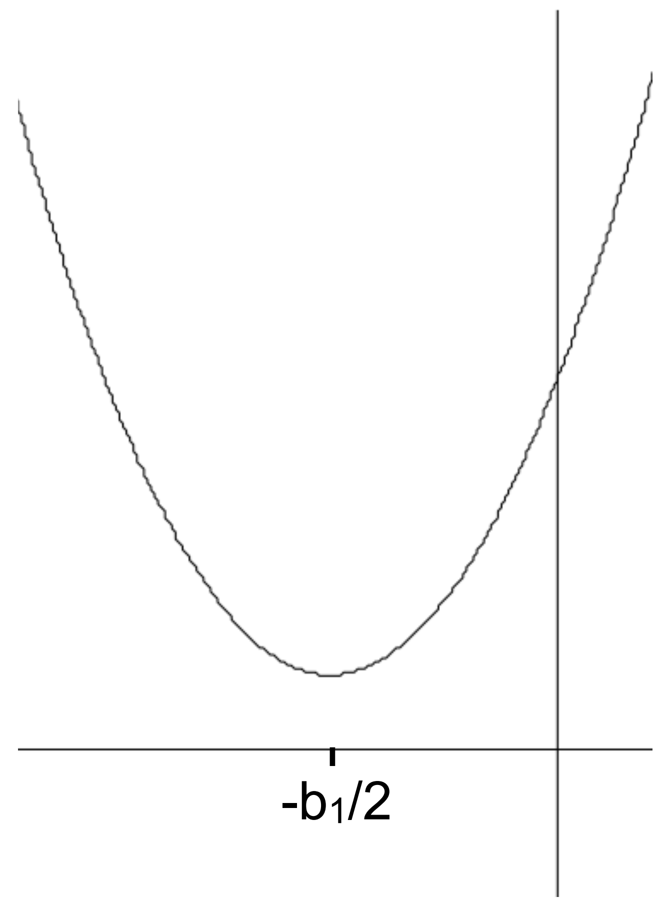
- If the roots are complex, then

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



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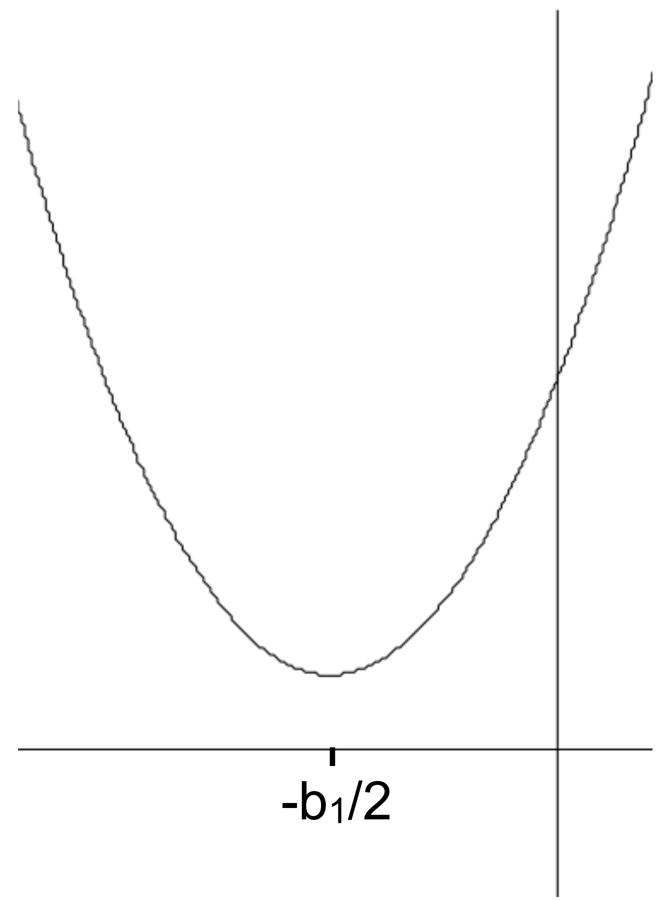

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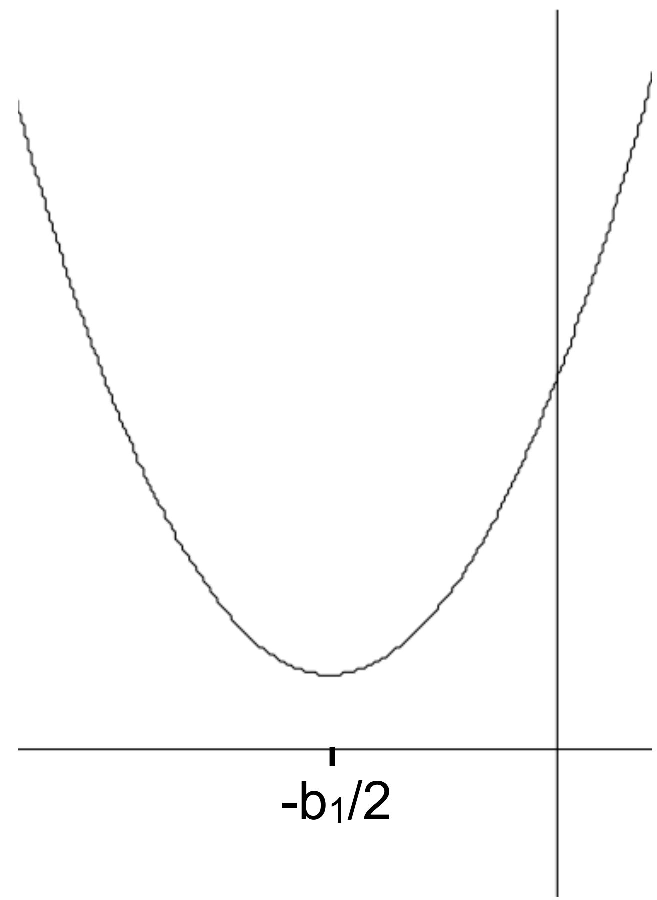

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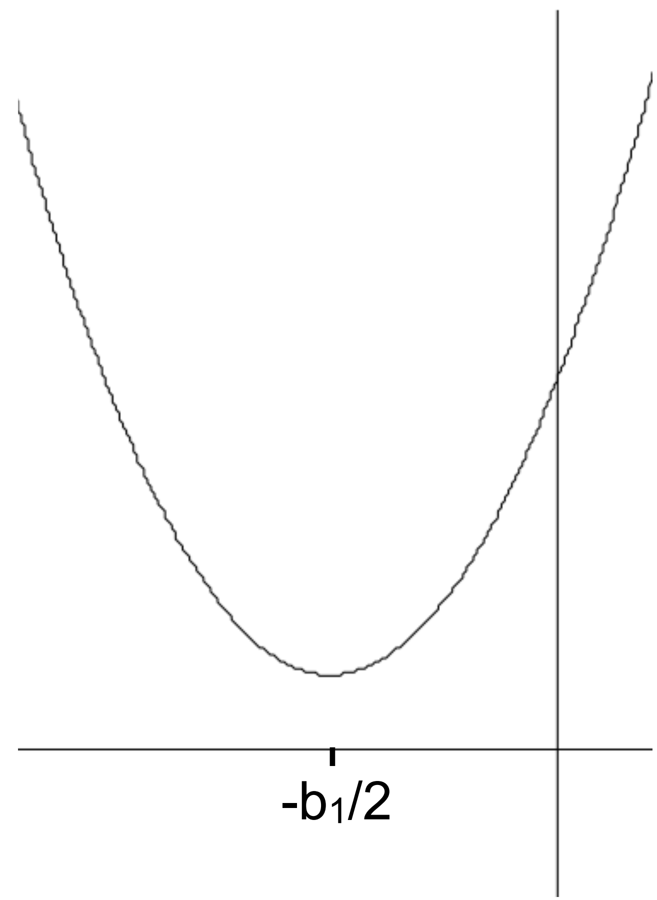
- It follows that stability in this case occurs if and only if $b_1>0$.



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- In this case, R_0 is not a threshold, and the disease can persist if $R_0<1$.

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Positive vertex

- When c_1=0, we have

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- However, we expect that vaccinated individuals will recover faster than unvaccinated individuals
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- It follows that b_1 could be negative.

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A possible turning point?

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

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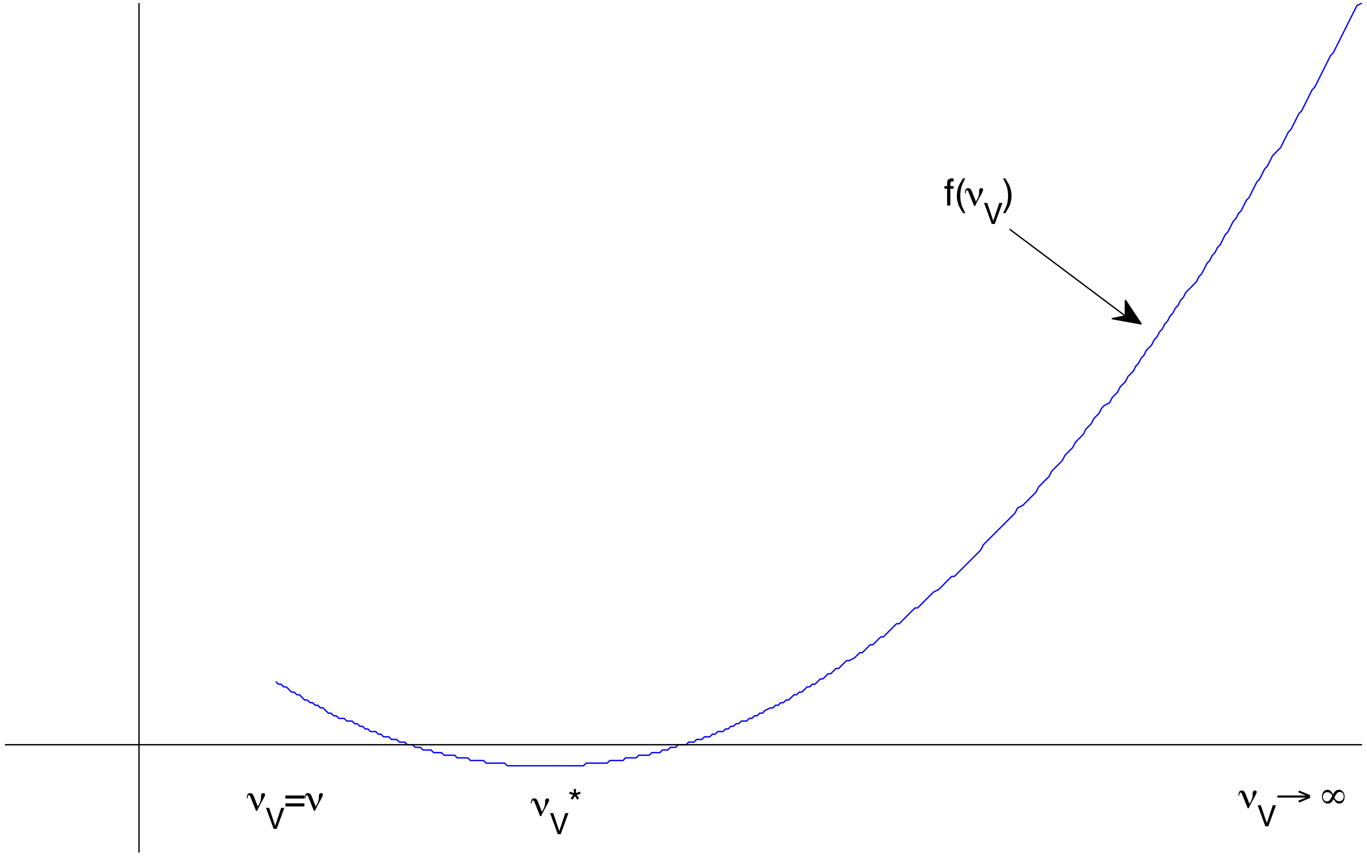
Potential form of f(ν_V)



f=vertex
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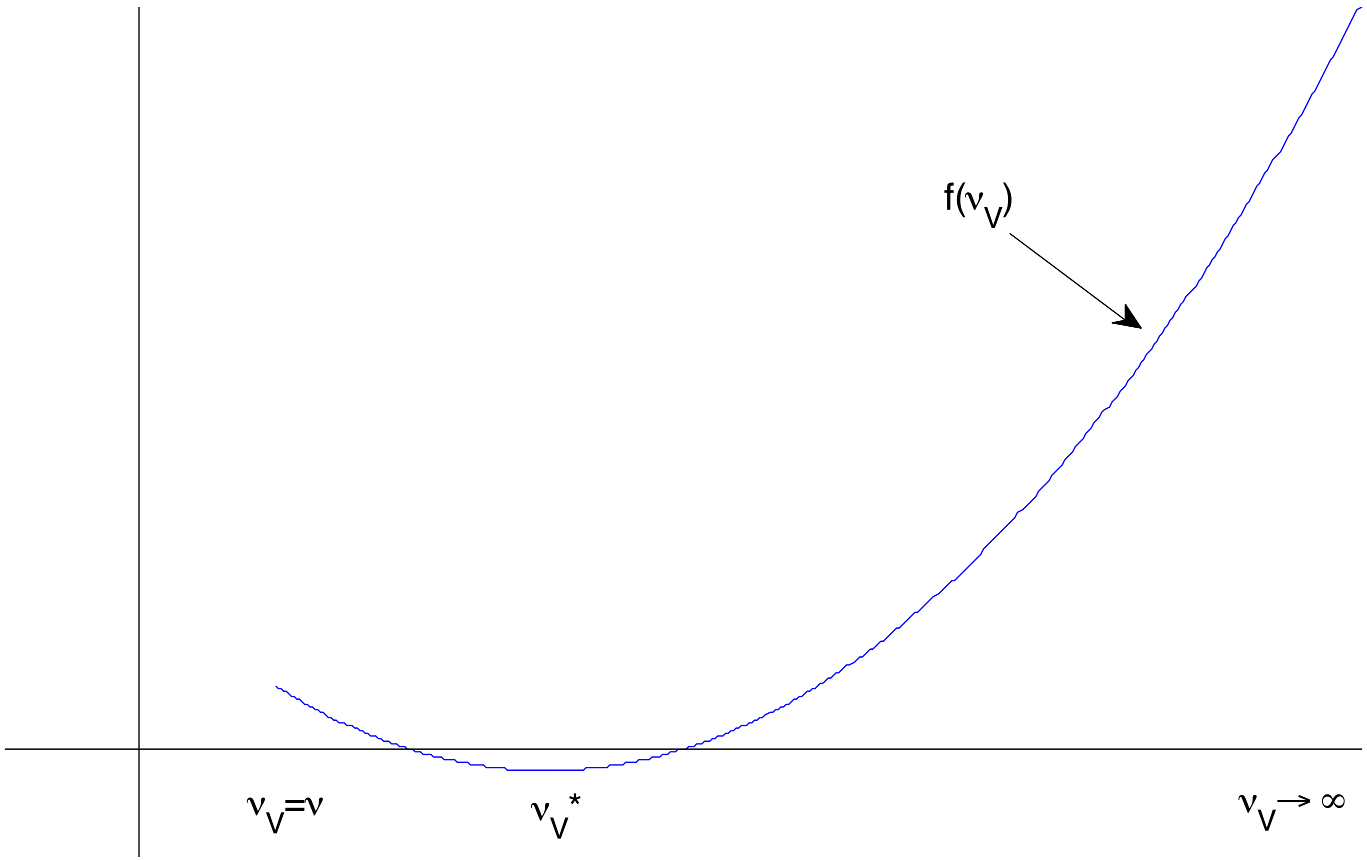
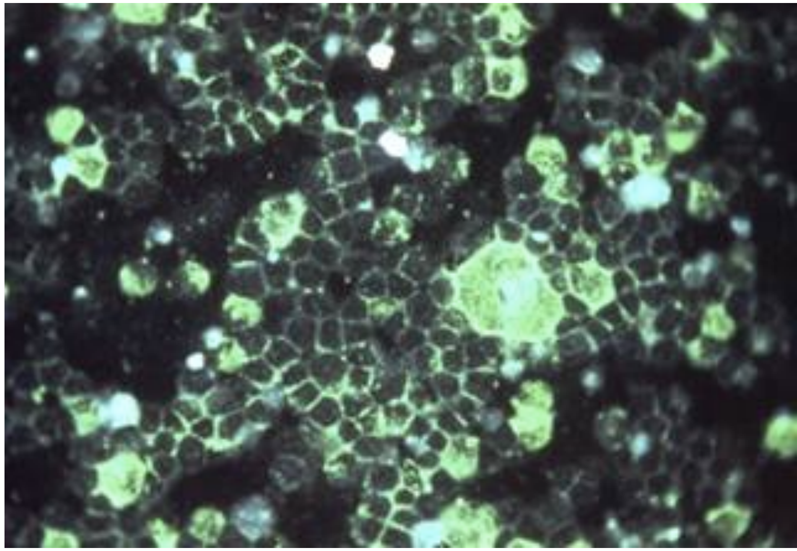


- We can prove that the turning point is a local minimum whenever it exists.

f=vertex
v,vV=recovery

Regular vaccinations

- We now refine the continuous model



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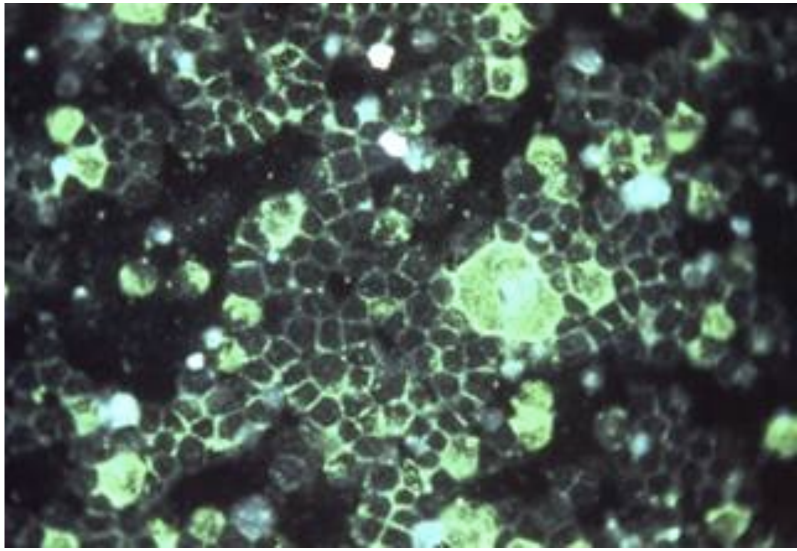

Regular vaccinations

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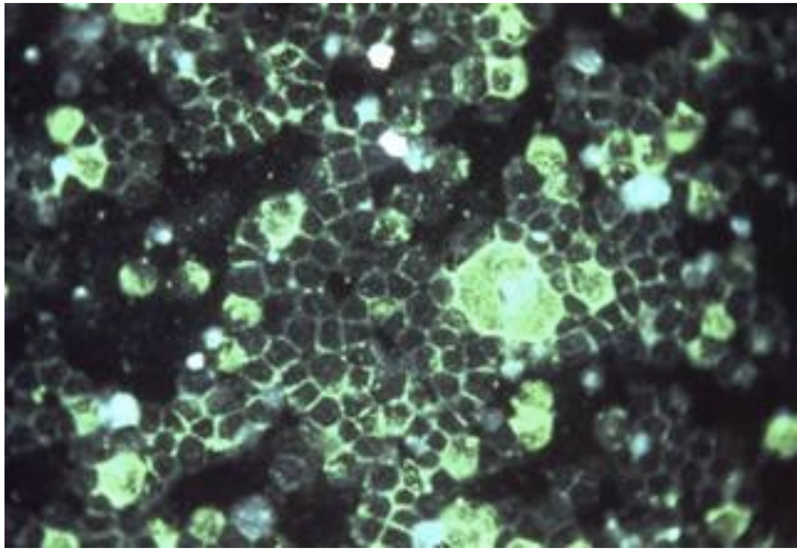
- It may also be administered at regular times



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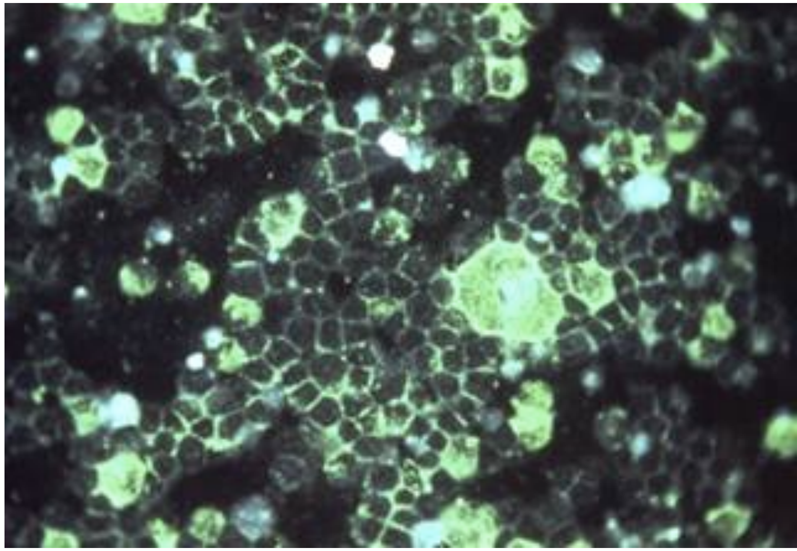

r=coverage

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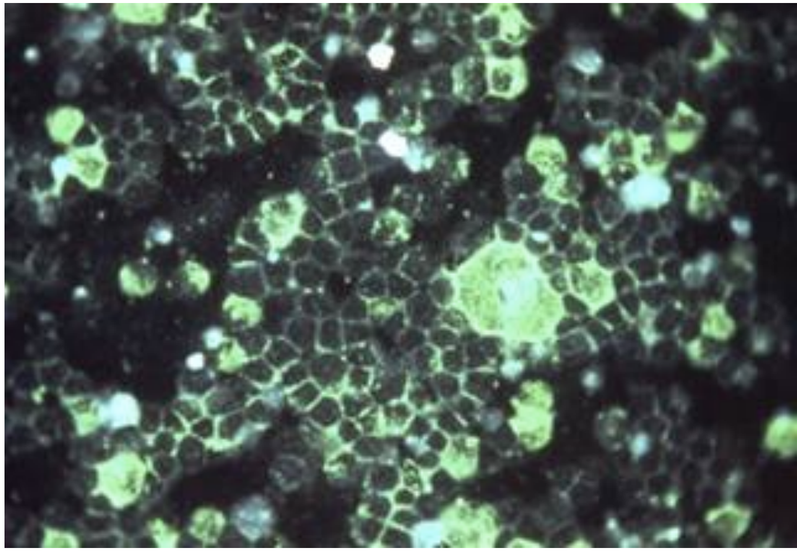
- We model a vaccine that reduces the susceptible population by a fixed proportion r



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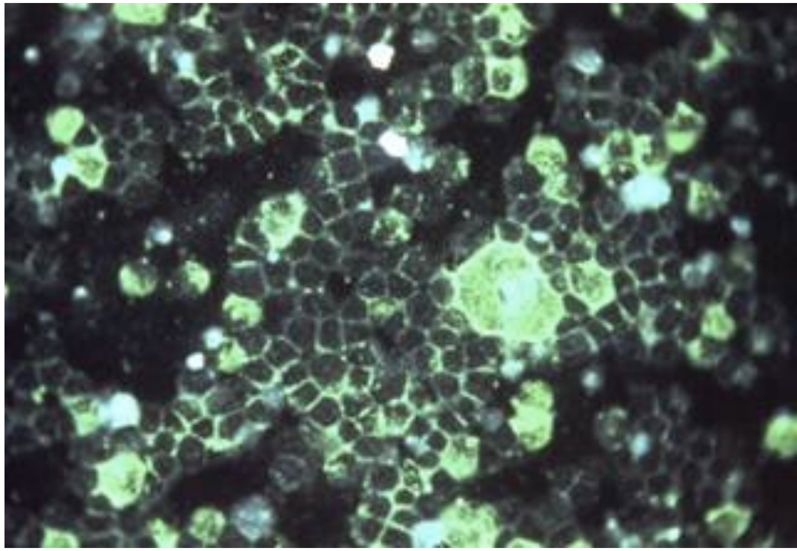

- This is described by a series of non-autonomous impulsive differential equations.

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}
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S=susceptible I,I_V=infected
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where r is the coverage and t_k are the vaccination times.

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Susceptible individuals

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

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

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

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

Susceptible individuals

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

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- Note in particular that $\lim_{\tau\to 0} S_\infty^- = 0.$

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

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

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- From the condition $T_0=1$, we can define the maximal period as

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- 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 ν=recovery
r=coverage τ=period

Summary of theoretical results

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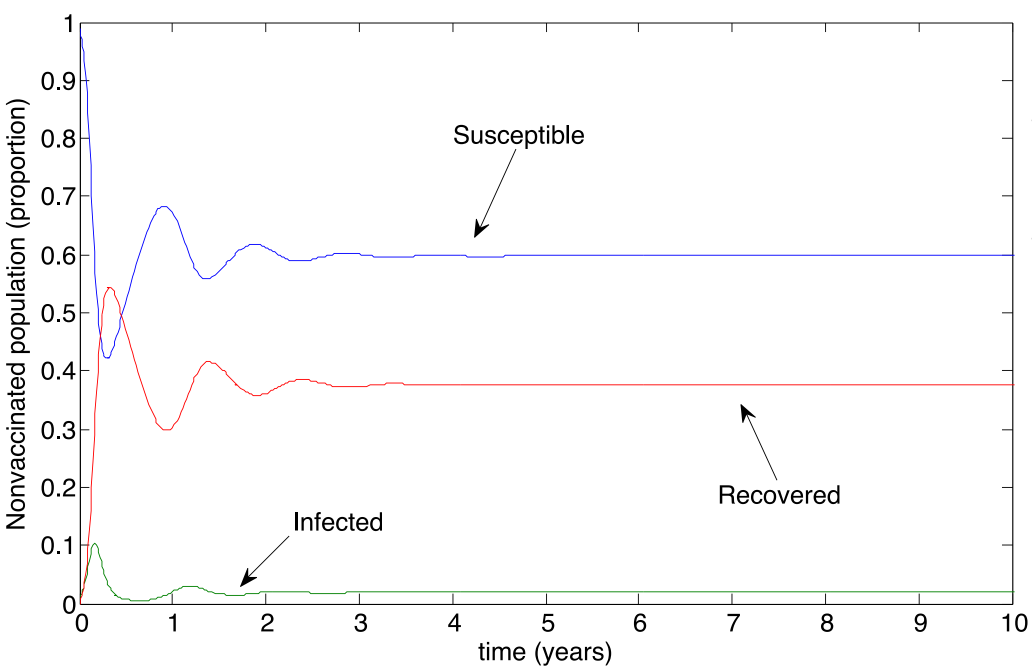
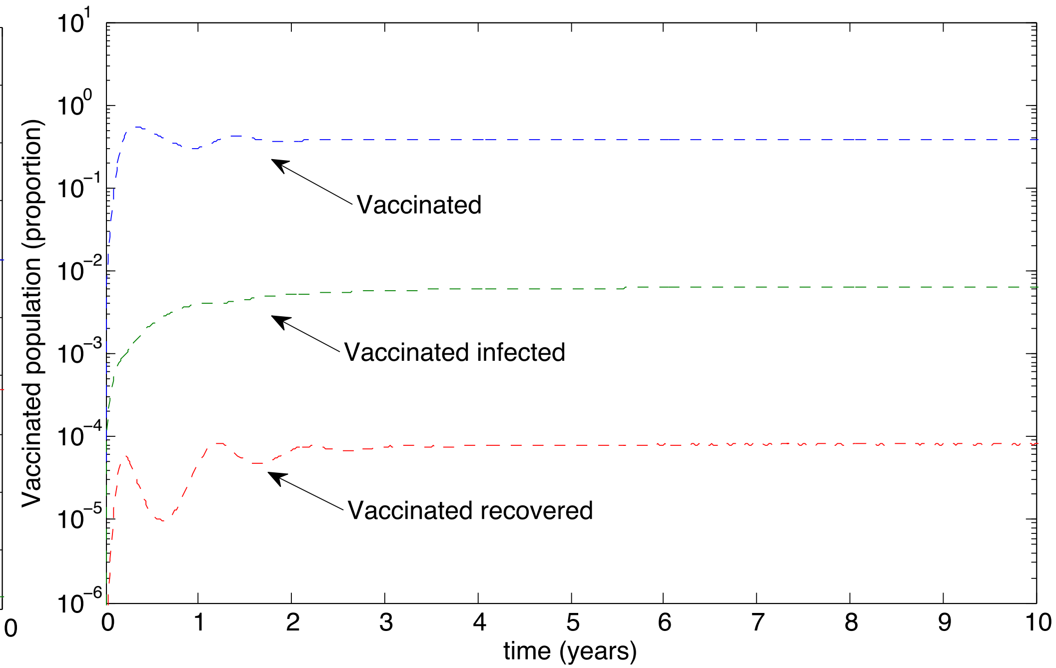
- If coverage is limited, then sufficiently frequent vaccinations can also achieve control
- Note that the impulsive reproduction number is conditional.

Continuous model, constant transmission





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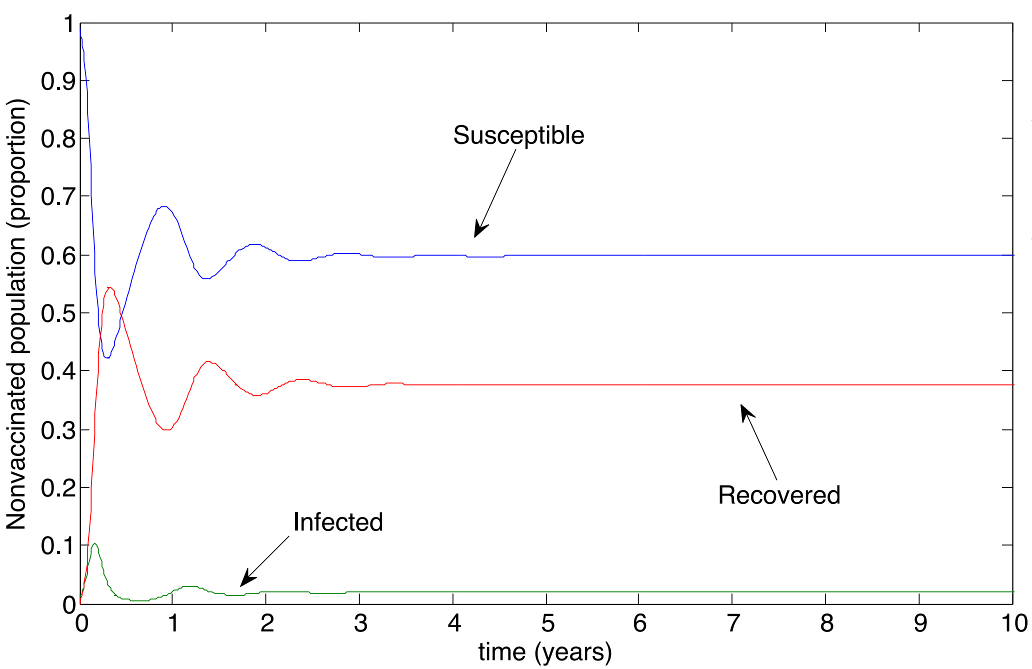
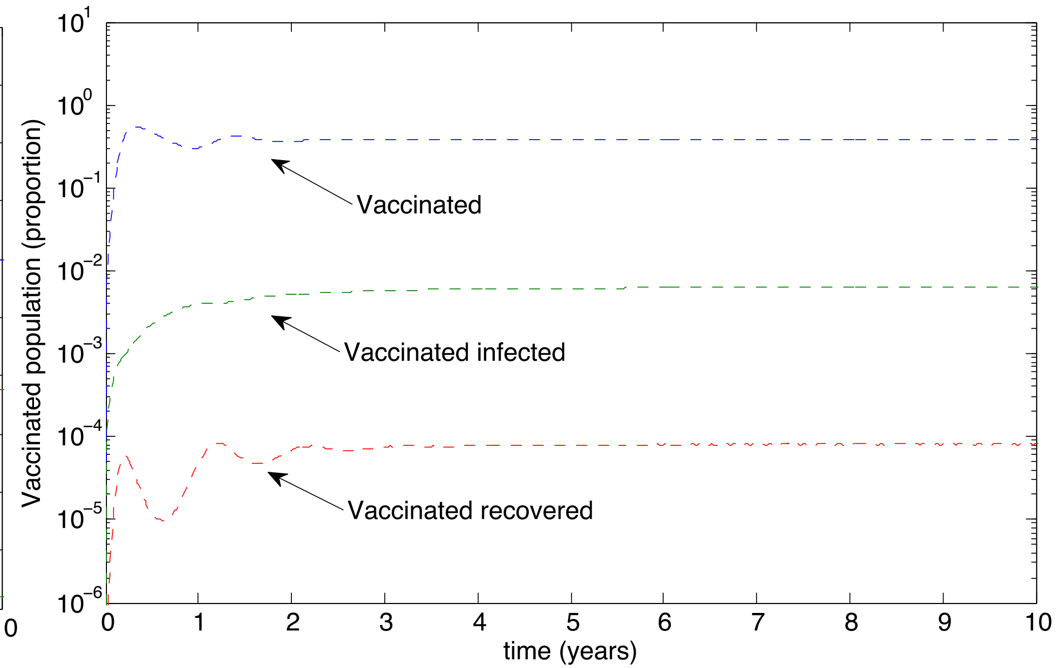
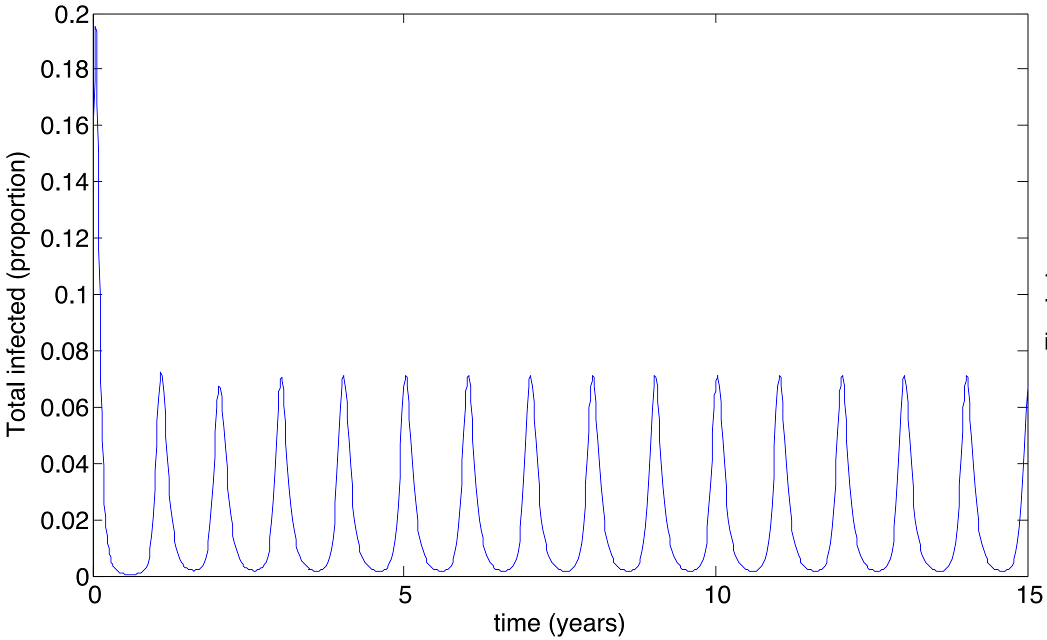


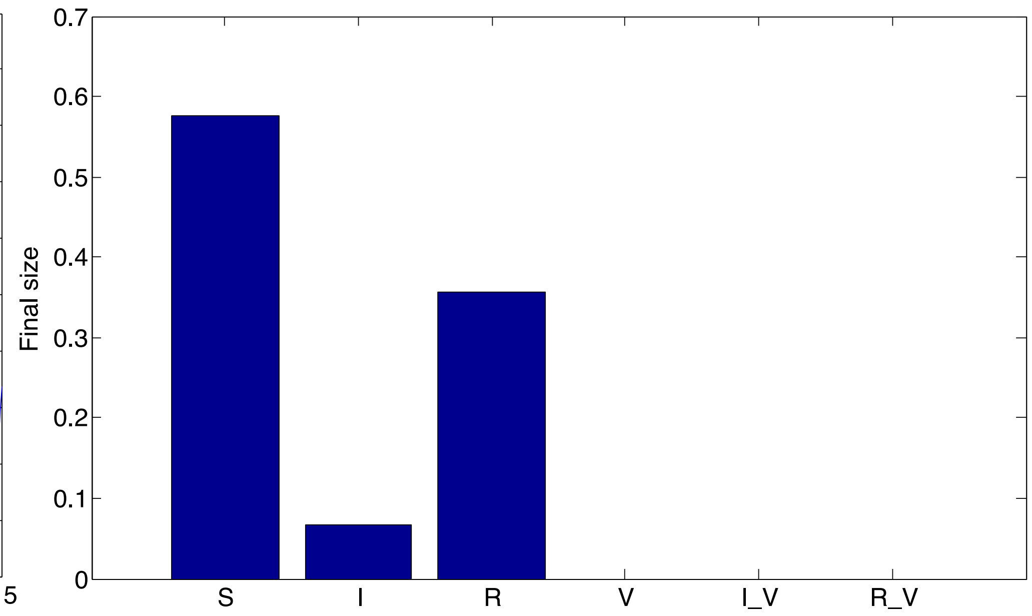


μ=1/70, ω=0.1, β=50, β_V=0.5β, ε=0.9, p=0.5, ν=36, ν_V=1.2ν, γ=1.8, γ_V=0.8γ.

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

Impulsive model, no vaccine





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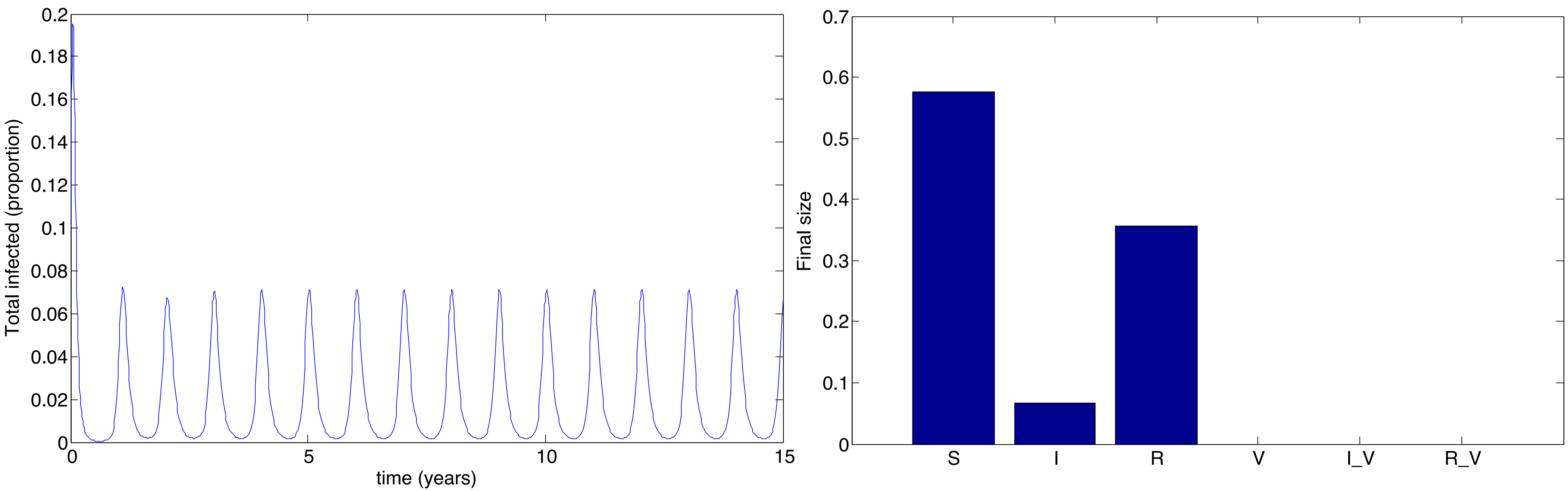
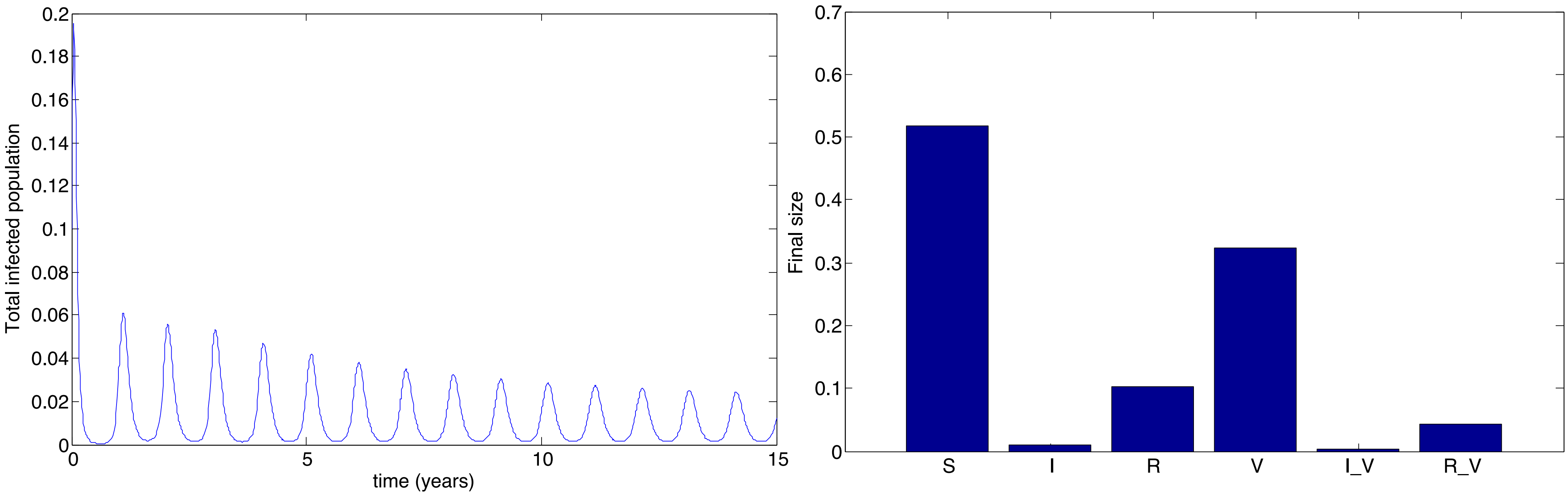


$\mu=1/70$, $\omega=0.1$, $b_0=60$, $b_1=0.16$, $\varphi=0.15$, $\beta_V=0.5\beta$, $\nu=36$, $\nu_V=1.2\nu$, $\gamma=1.8$, $\gamma_V=0.8\gamma$, $r=0$.

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



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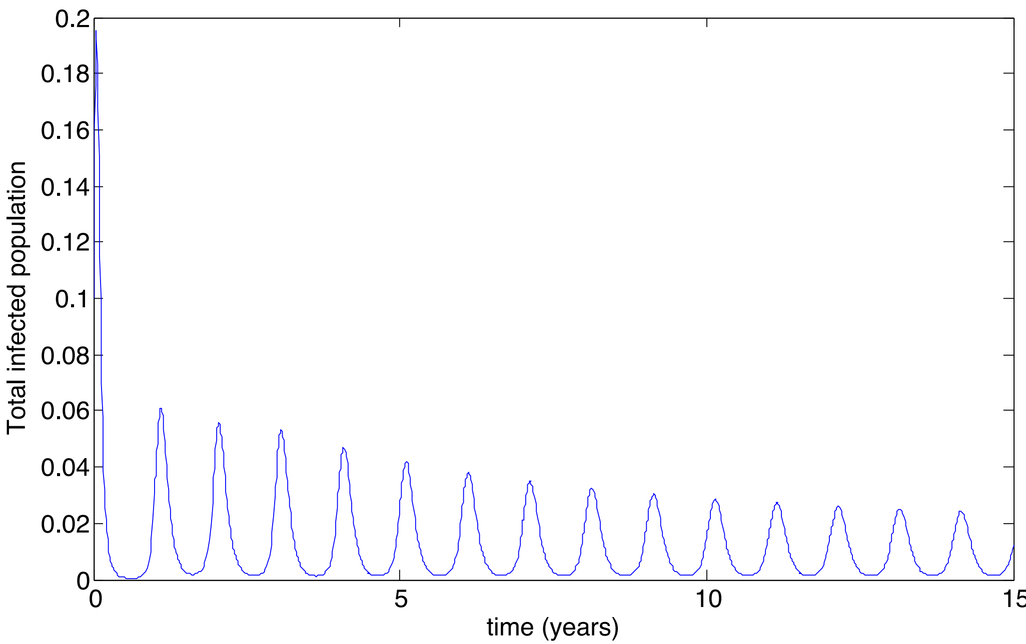

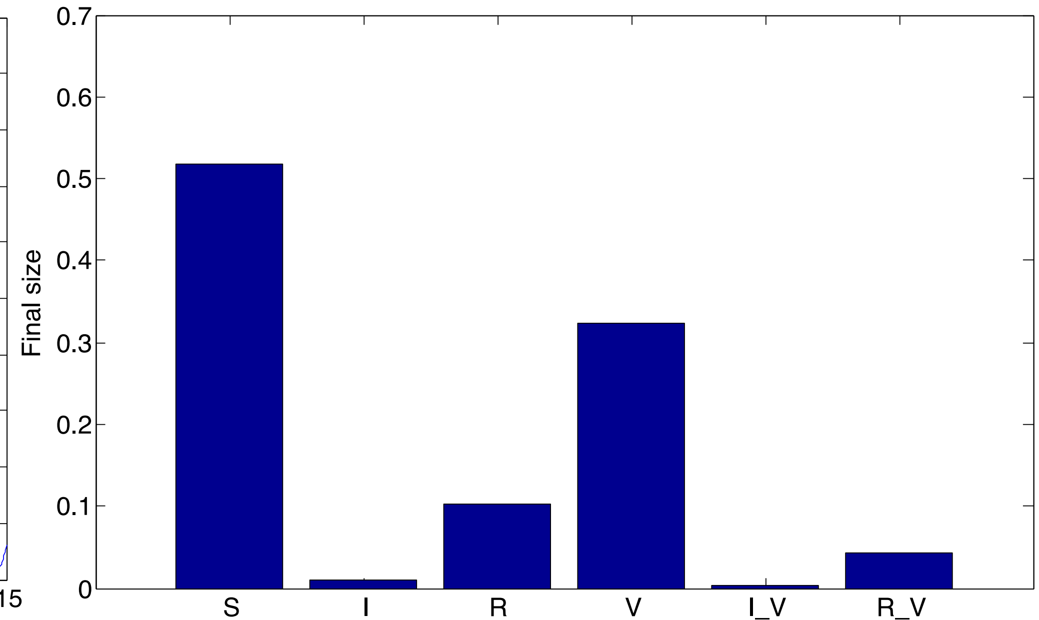

$\mu=1/70$, $\omega=0.1$, $b_0=60$, $b_1=0.16$, $\varphi=0.15$, $\beta_V=0.5\beta$, $\nu=36$, $\nu_V=1.2\nu$, $\gamma=1.8$, $\gamma_V=0.8\gamma$, $r=0.1$.

μ=background death ω=waning
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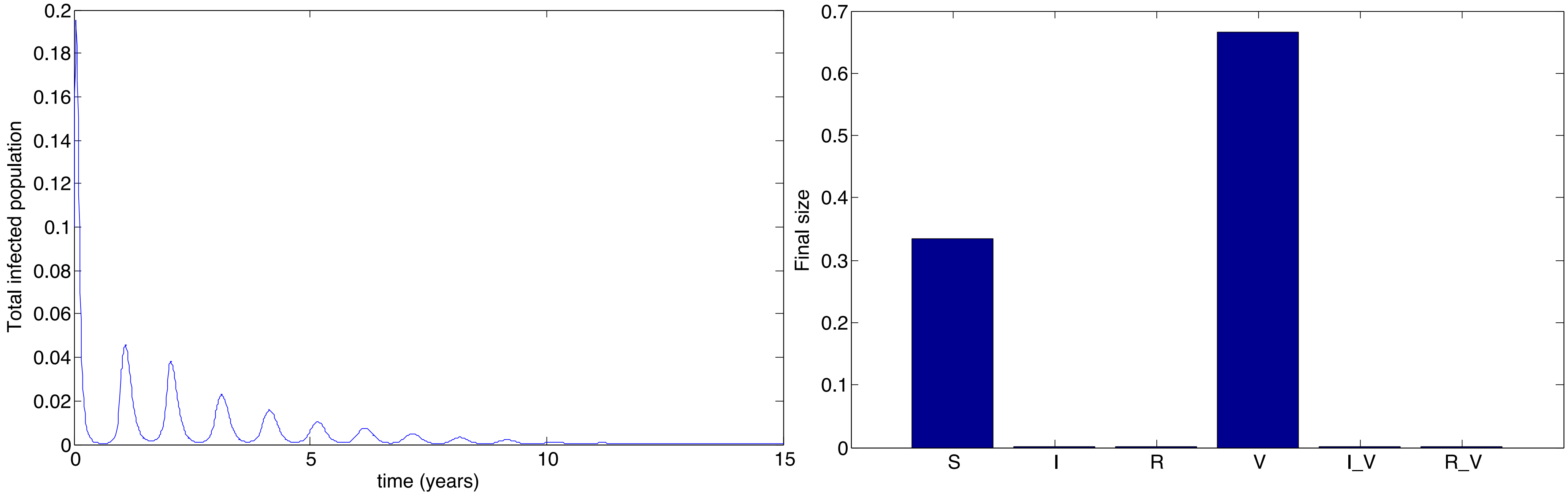
Impulsive model, 25% vaccination



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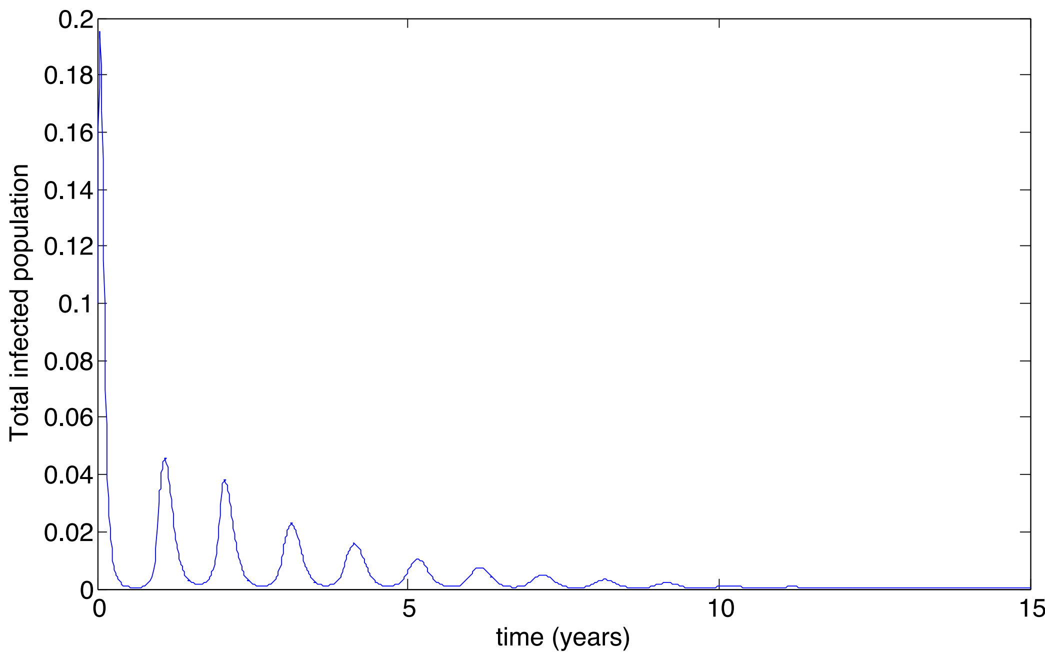

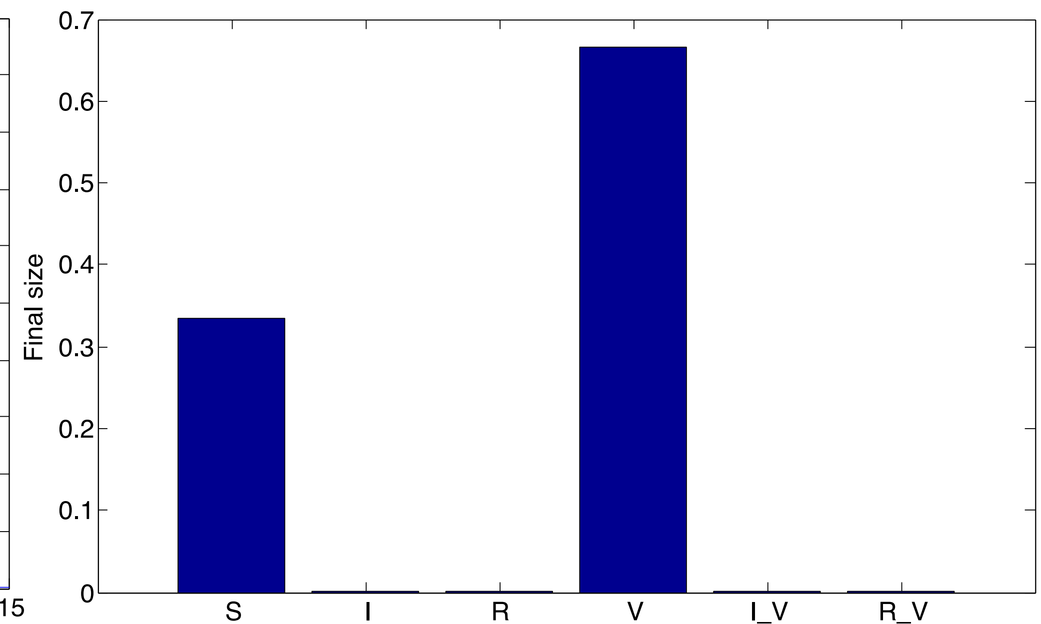

$\mu=1/70$, $\omega=0.1$, $b_0=60$, $b_1=0.16$, $\varphi=0.15$, $\beta_V=0.5\beta$, $\nu=36$, $\nu_V=1.2\nu$, $\gamma=1.8$, $\gamma_V=0.8\gamma$, $r=0.25$.

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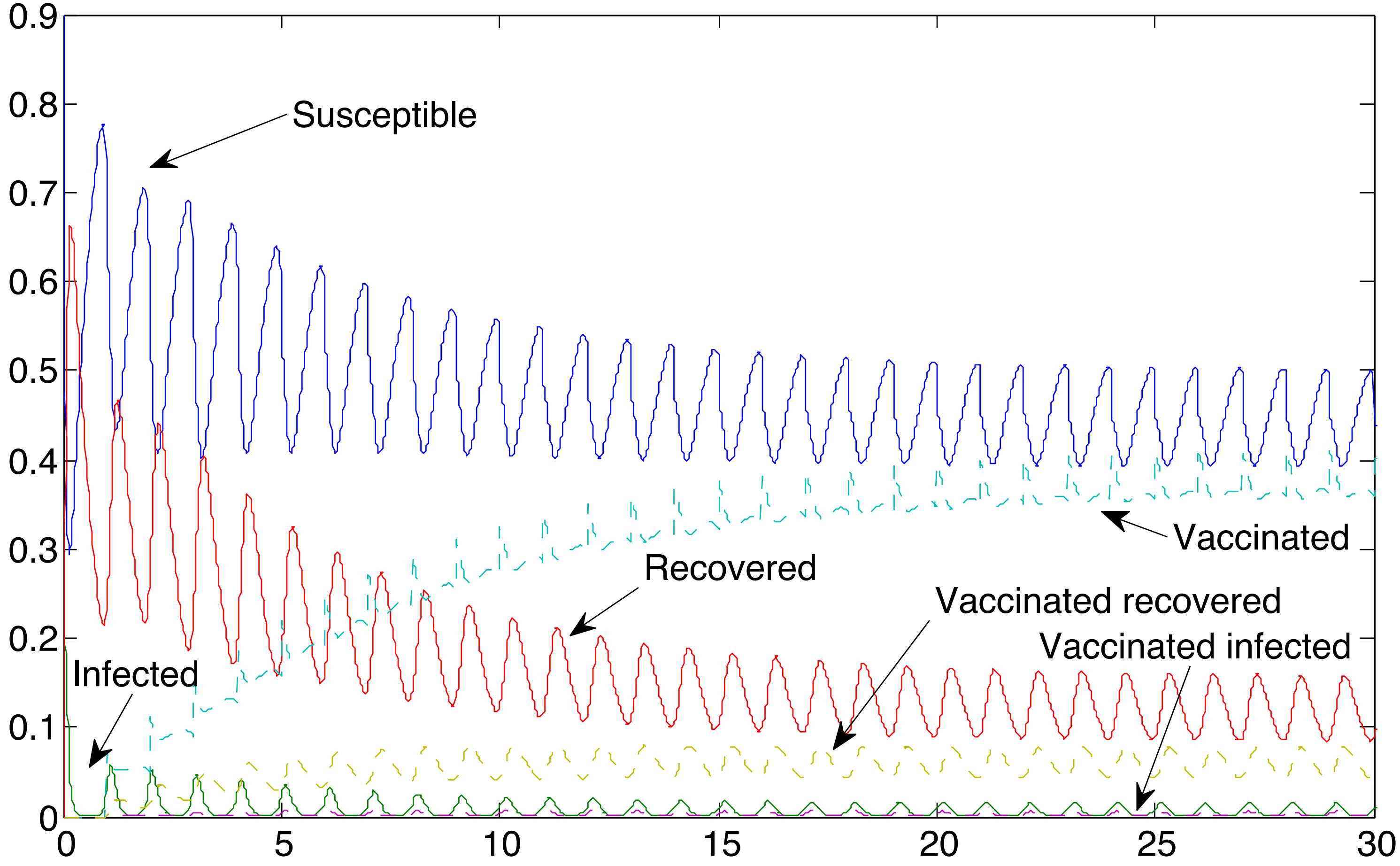
Population dynamics



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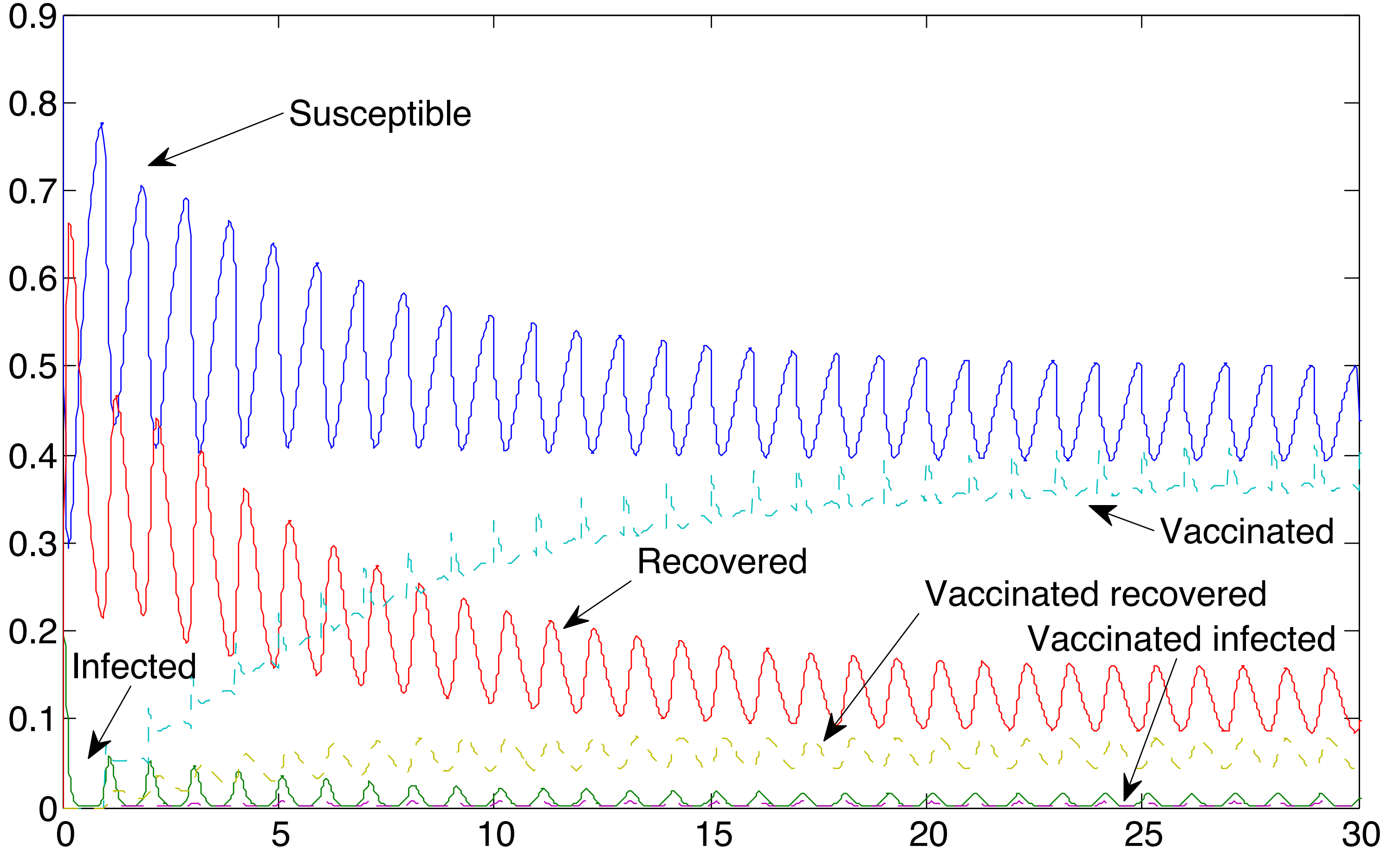
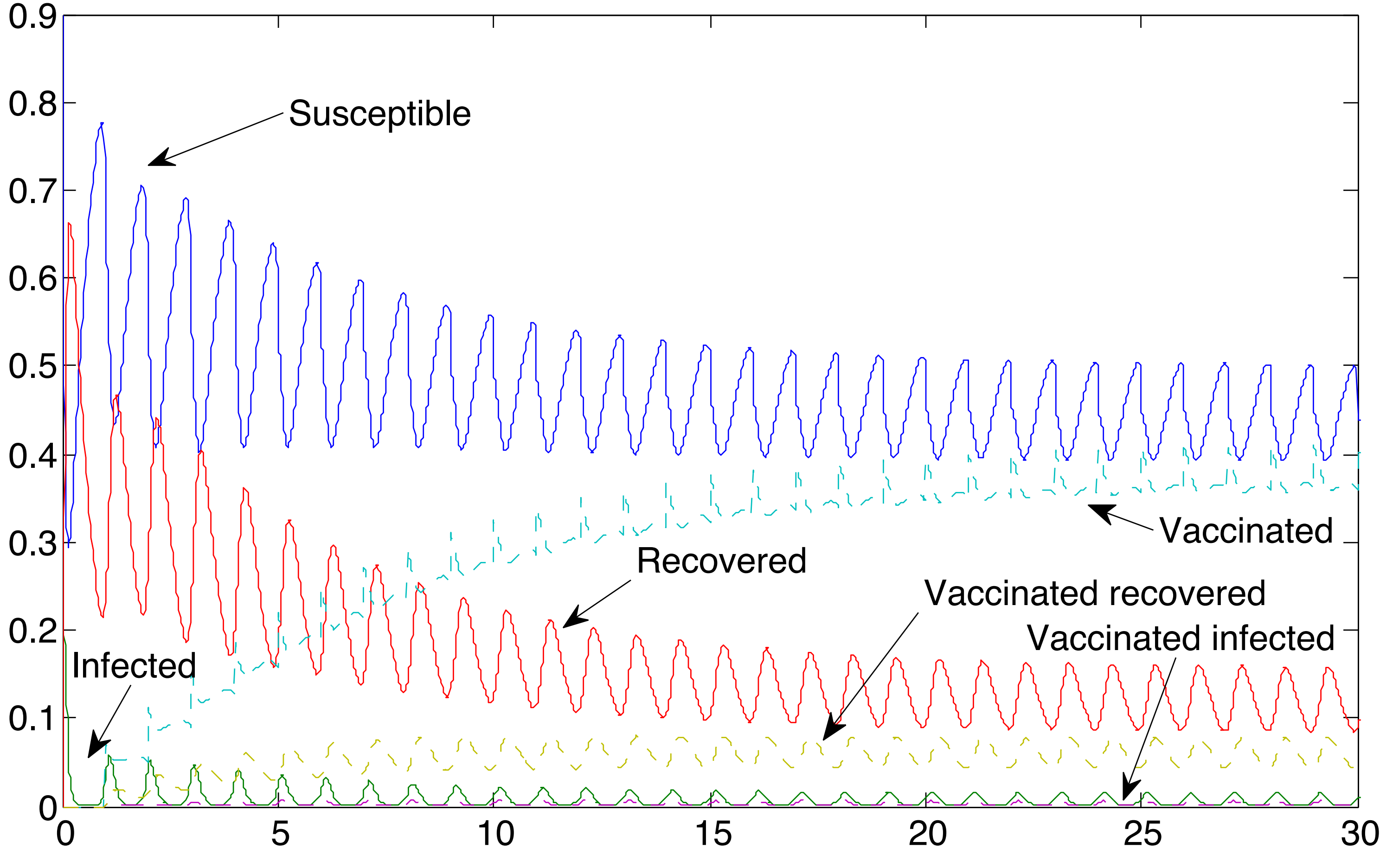


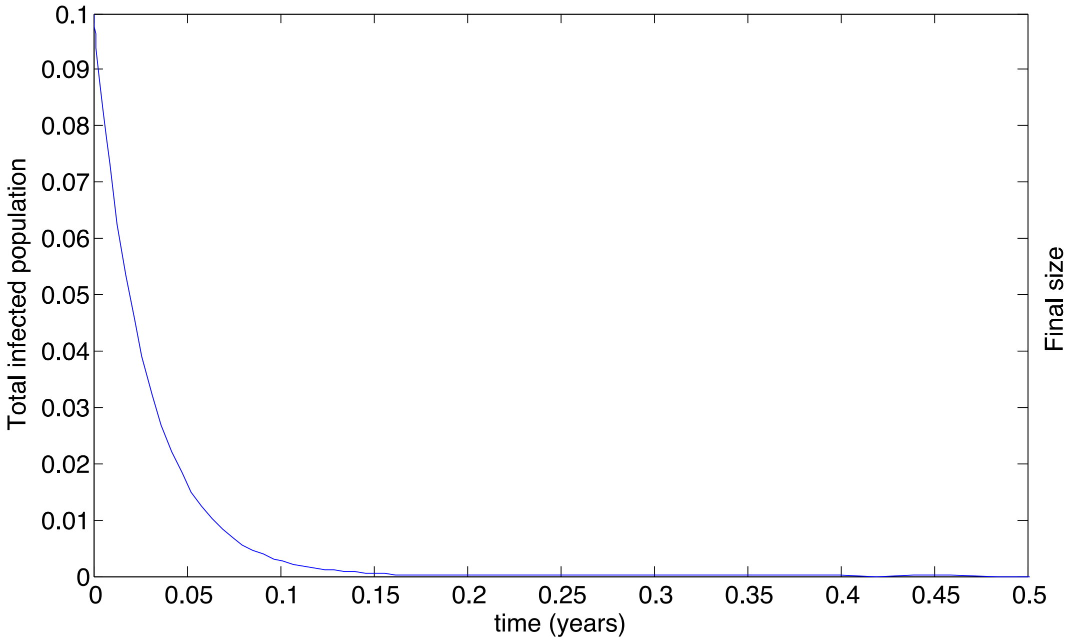
- 10% vaccination

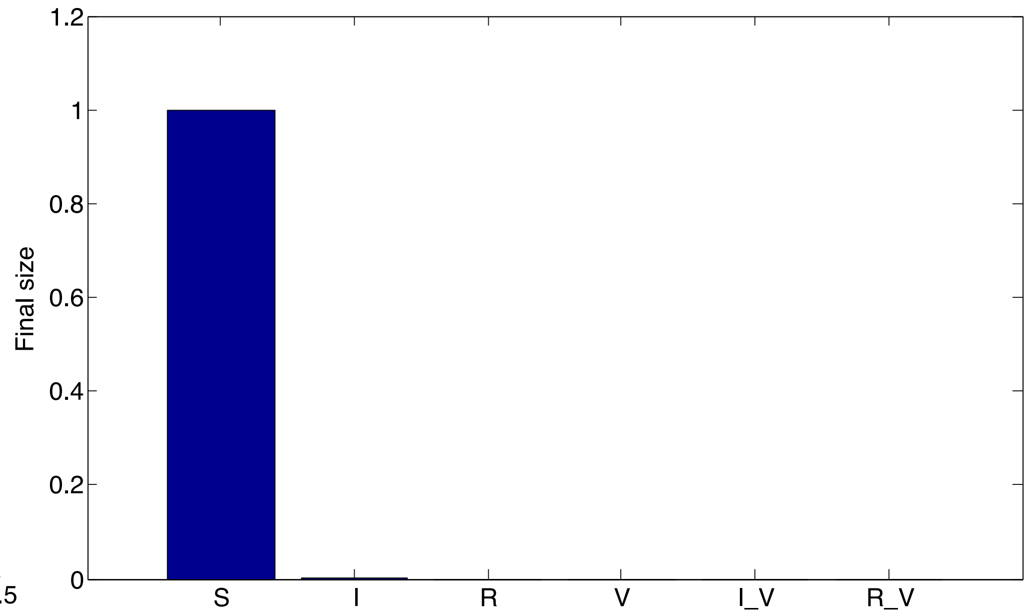
Population dynamics



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

Extreme parameters, no vaccine





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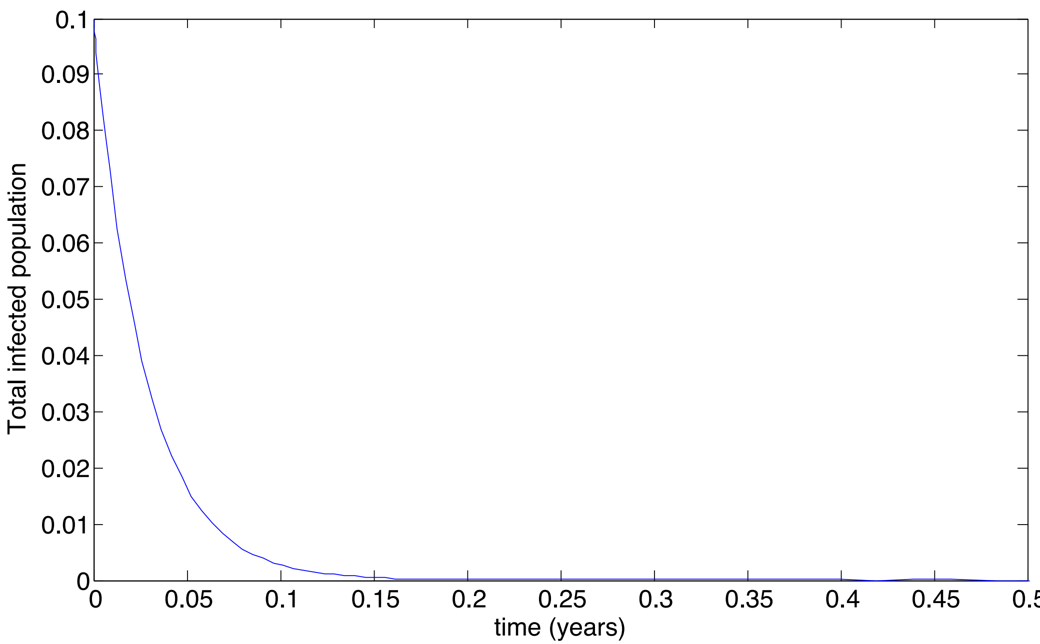

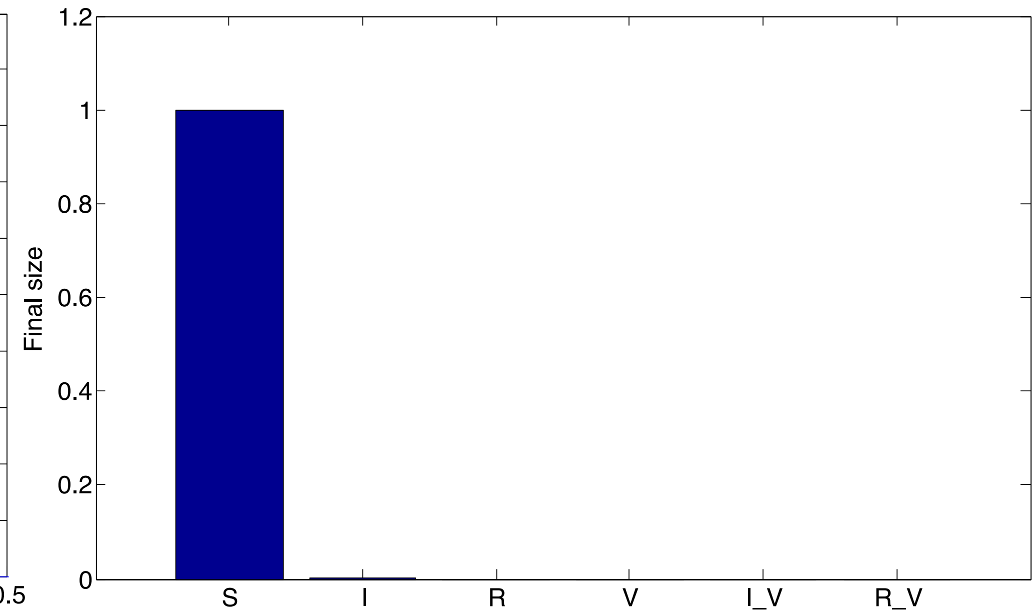

μ=1/70, ω=0.1, β=0.03, β_V=300, ν=36, ν_V=177, γ=1.8, γ_V=0.8γ, r=0.

μ=background death ω=waning
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β_V=transmissibility ν,ν_V=recovery
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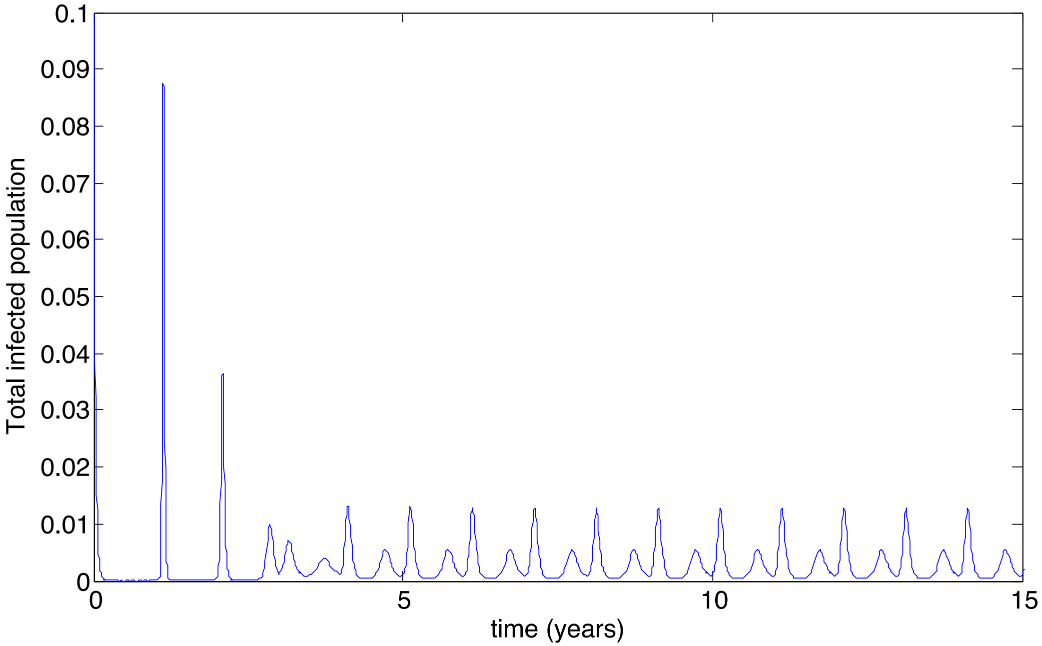
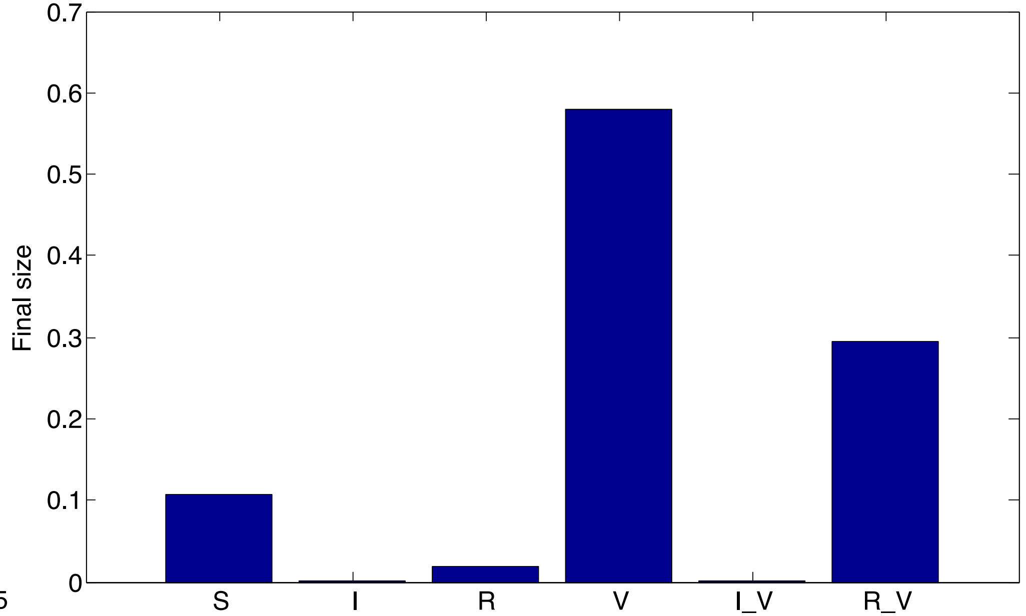
Extreme parameters, 100% vaccination





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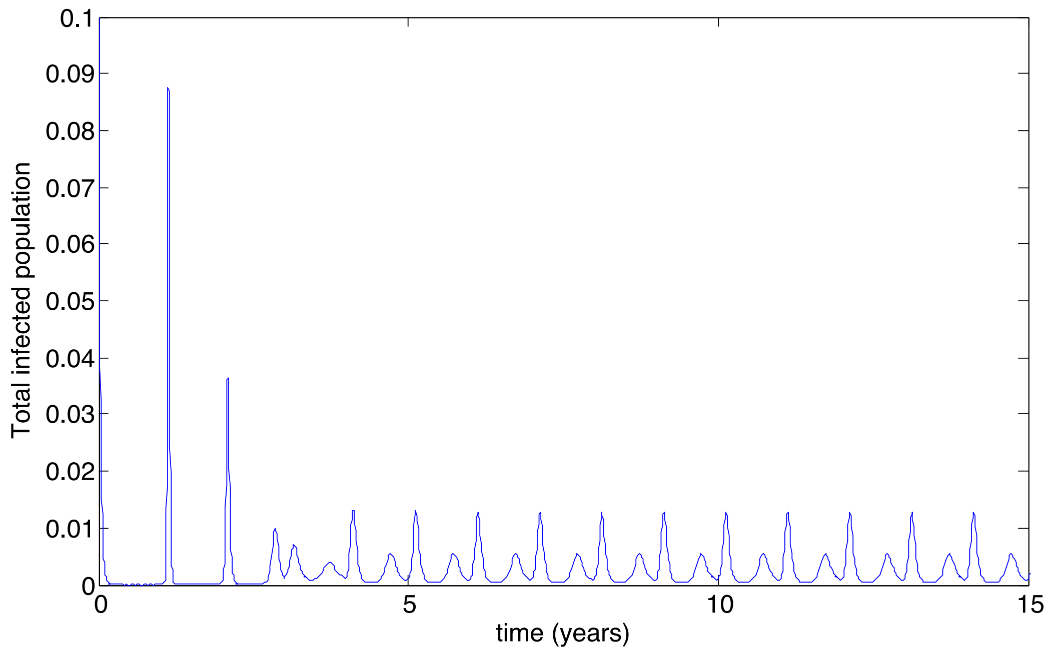

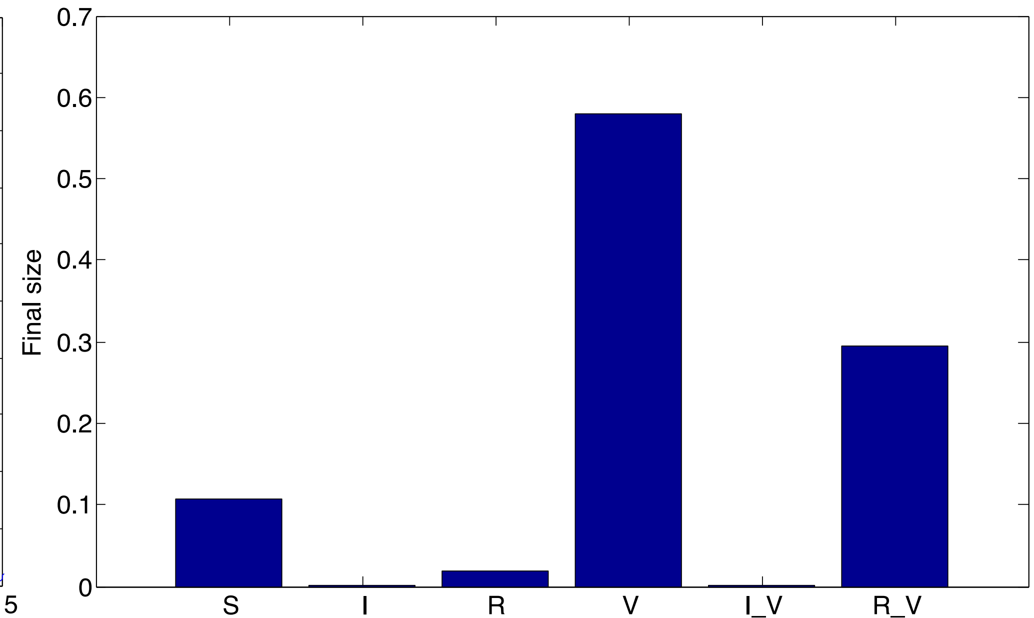

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- But recovery was fast
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- Note that this is not a backward bifurcation
- Rather, it is a destabilisation of the DFE.

Summary

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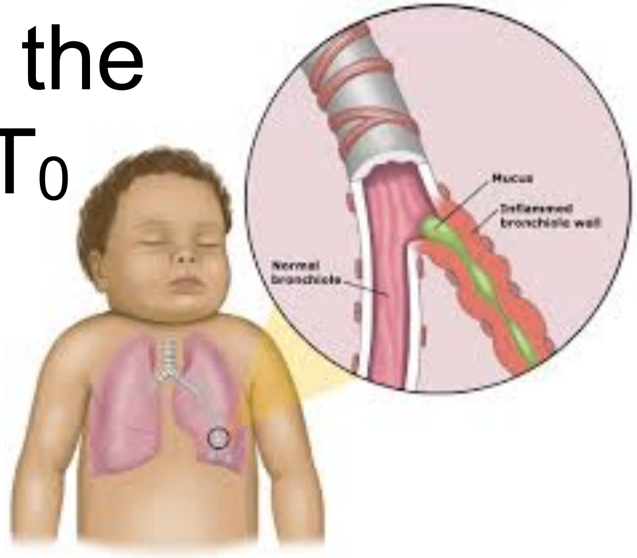
Summary

- 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



T_0=*impulsive reproduction number*

Impulsive reproduction number

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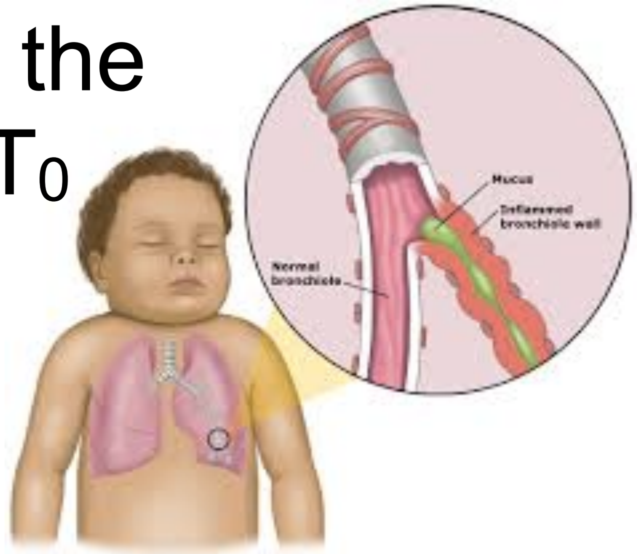
- This is a sufficient (but not necessary) condition that ensures eradication if $T_0<1$



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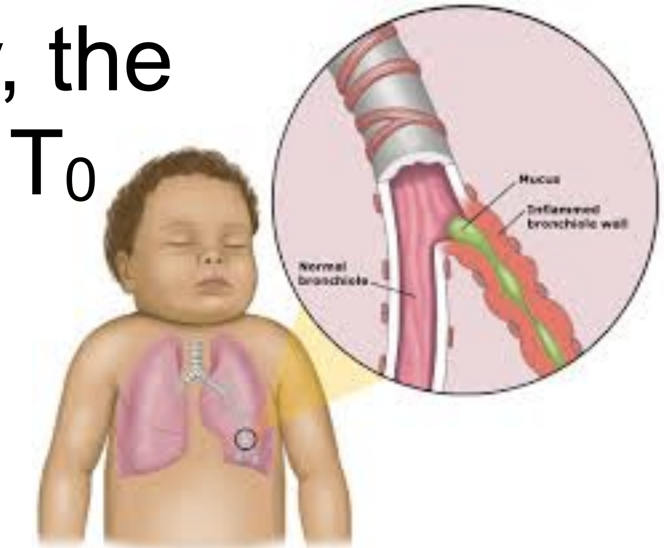

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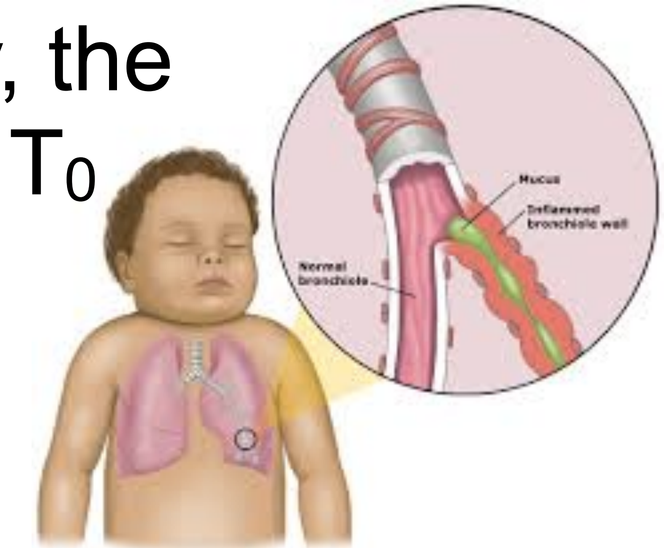
- The result is eventual eradication of the infection.



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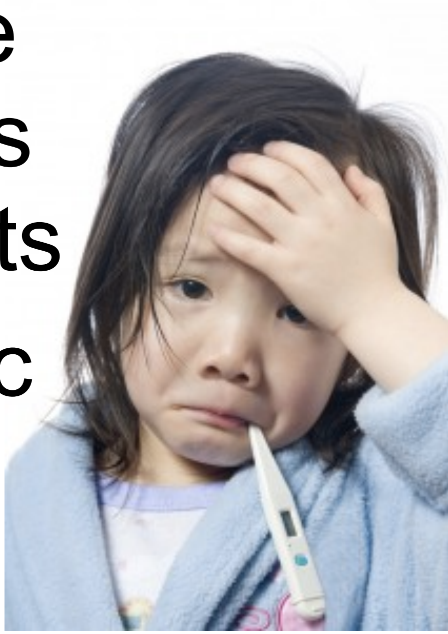
- In particular, if the strength of periodic vaccination r is sufficiently high, the disease will be controlled



r=coverage

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

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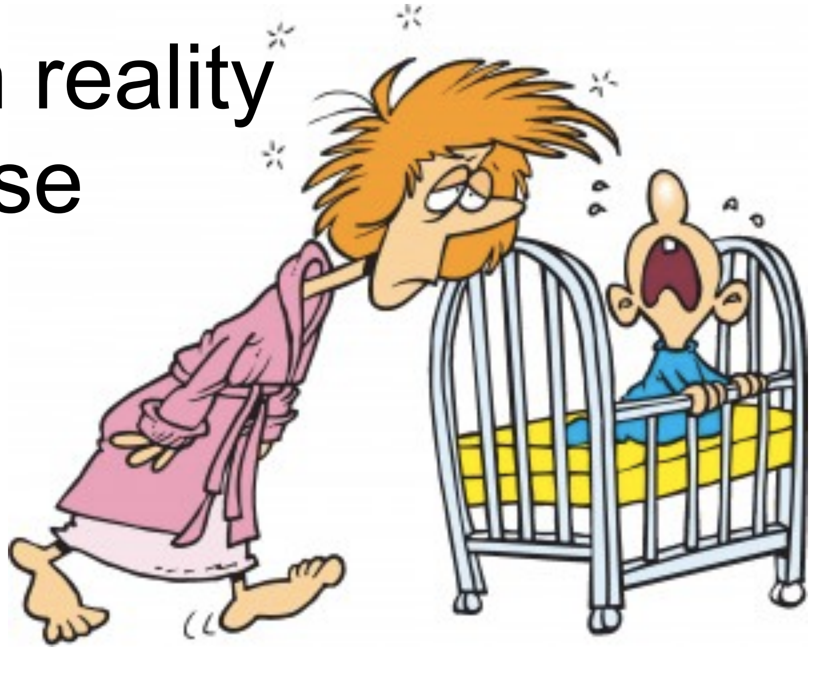

Infection spikes

- 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.

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- Constant birth and death
- Maternal vaccination in the first model.

Conclusions

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- 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