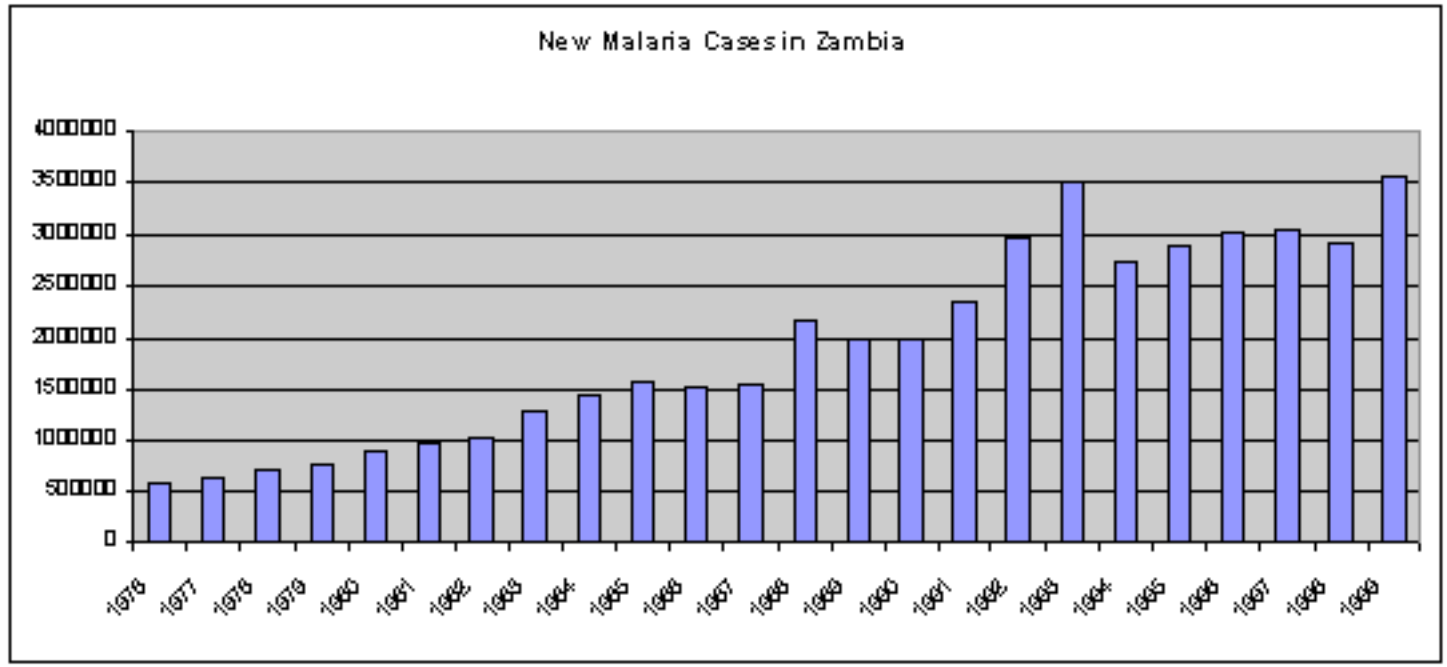
Could low-efficacy malaria vaccines increase secondary infections in endemic areas?

Robert Smith?

The University of Ottawa

Malaria

- One of the most important human diseases throughout the tropical and sub-tropical regions of the world



Source: NMCC Central Board of Health, 2000

Malaria

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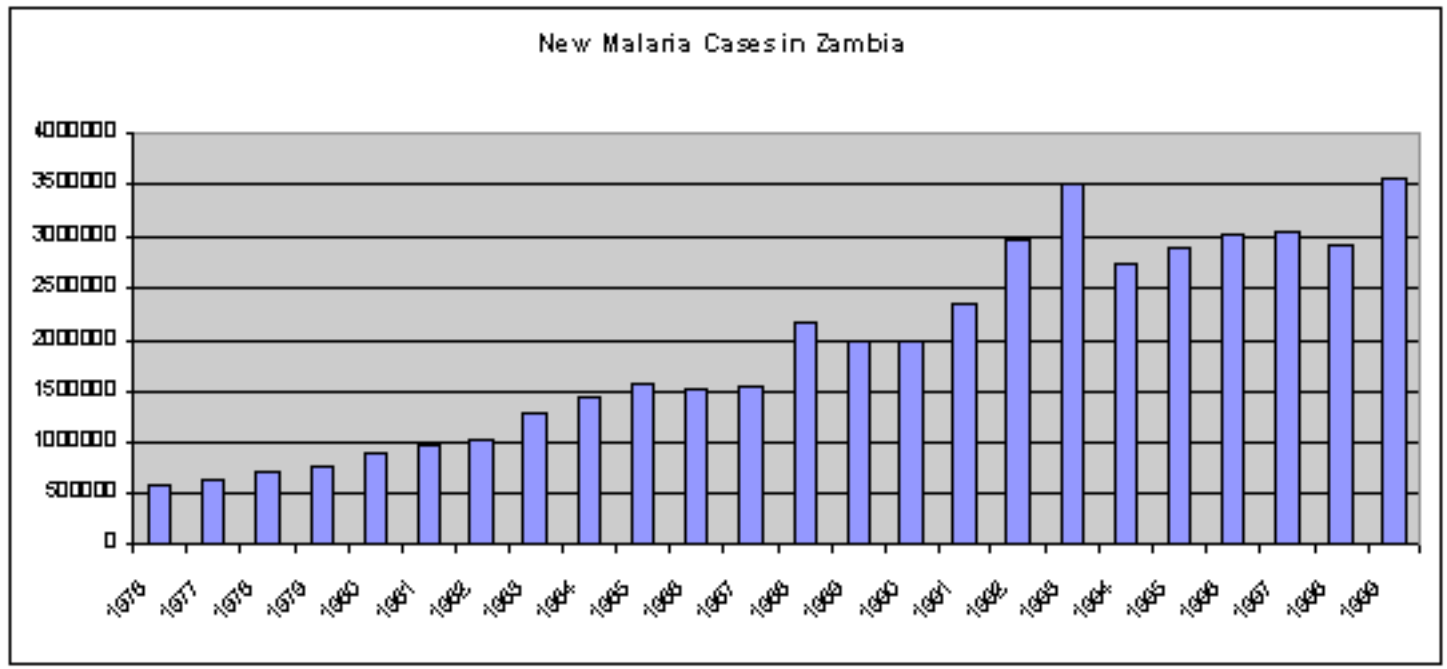
- More than 300 million acute illnesses each year



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Malaria

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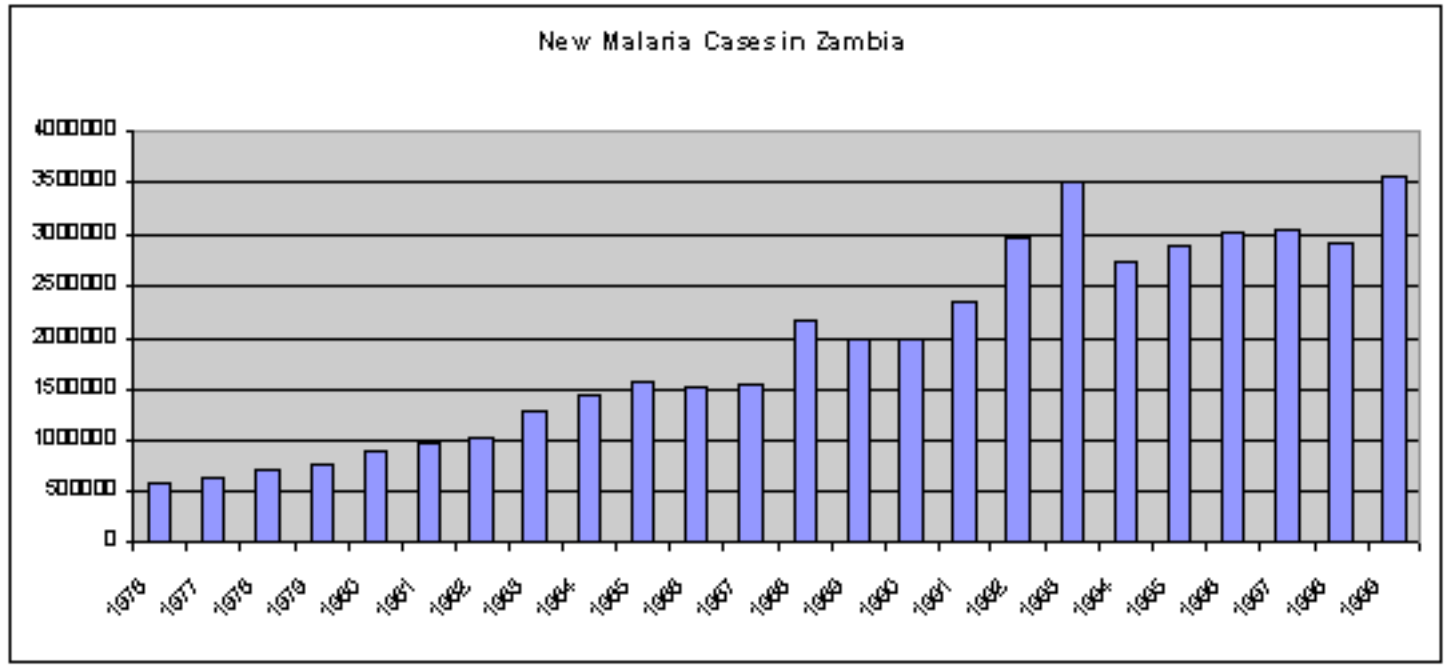
- More than 300 million acute illnesses each year
- 1,000,000 deaths annually.



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Symptoms

- Repeated episodes of fever

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- Death.

Endemic areas

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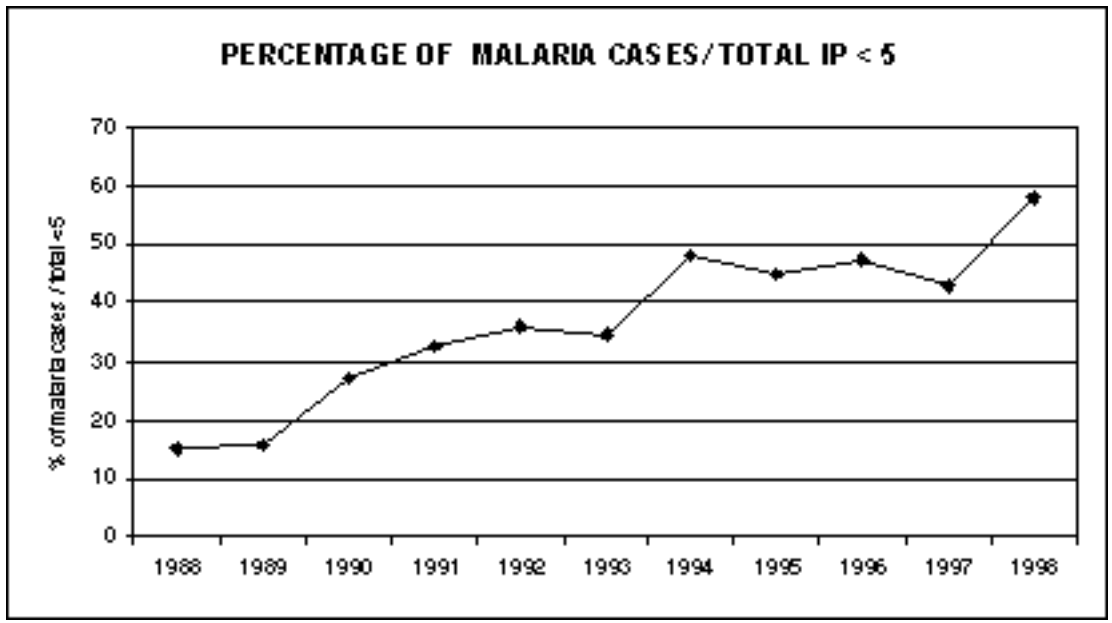
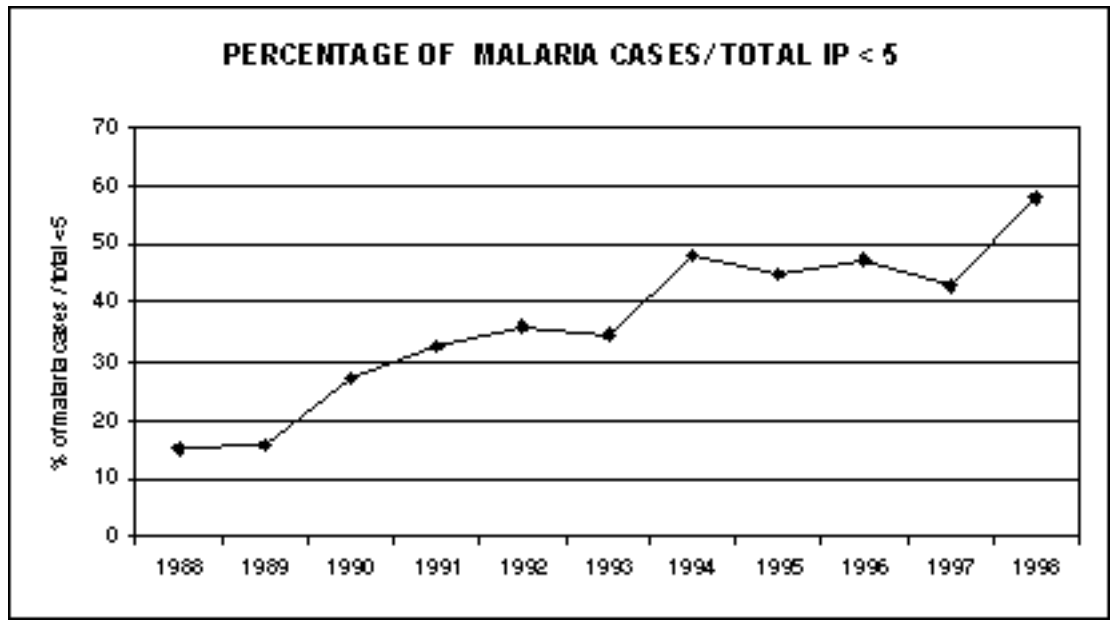


Admissions to St. Kitzo-Matany hospital, Uganda

Endemic areas

- 90% of malaria deaths occur in sub-Saharan Africa
- Mostly among young children
- Even when it doesn't kill, acute illness can devastate economies in the developing world.



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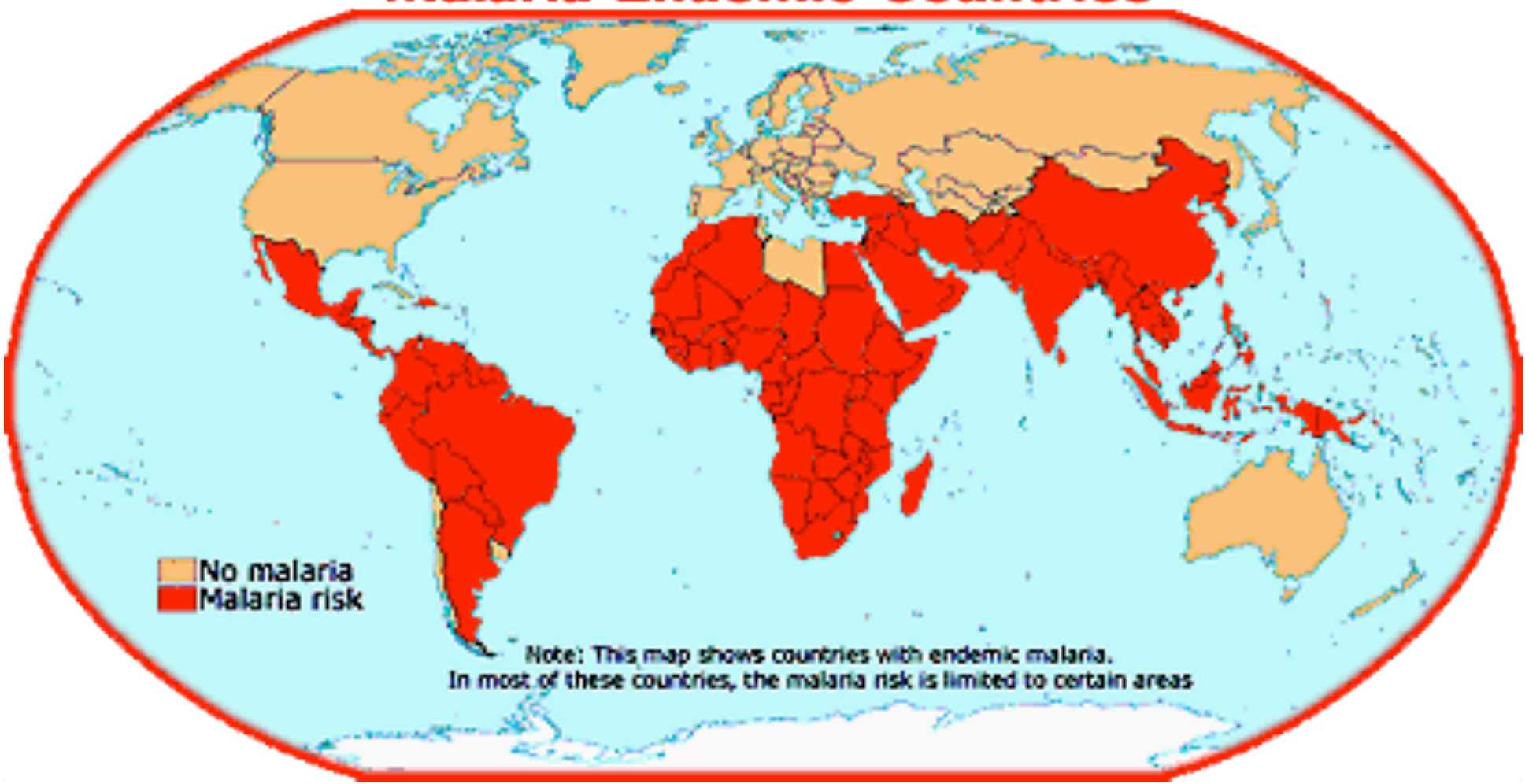
Malaria Endemic Countries



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- Recently, a candidate vaccine (RTS,S/AS01) completed Phase III trials
- It cut the risk of developing severe malaria by 26%
- The efficacy in infants was only 31%.

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RTS,S/AS01 vaccine (Mosquirix)

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- Phase III trial completed in 2012
- Currently in development commercially
- Not expected on the market for a few years.

The downside

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- Such vaccines hold great hope for containing the spread of the disease
- However, they are likely to have poor efficacy, at least initially
- This may result in a net increase in infections.

Candidate vaccines

- Such vaccines permit infection but reduce parasite burden

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- We call these "disease-modifying" vaccines.

Disease-modifying vaccines

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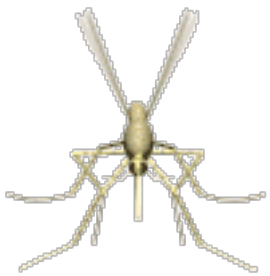
Potential effects

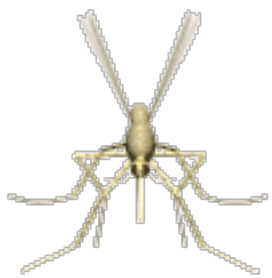
Potential effects from a malaria vaccine could include:



Potential effects

Potential effects from a malaria vaccine could include:

i. increasing the recovery rate



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Potential effects from a malaria vaccine could include:

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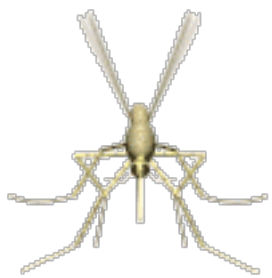
ii. increasing the acquired immunity rate



Potential effects

Potential effects from a malaria vaccine could include:

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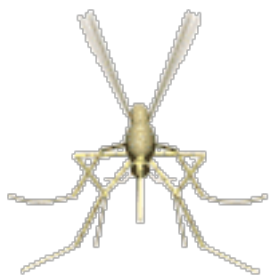
iii. reducing the rate of infection.



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ii. the vaccine may on "take" in a proportion ε of people vaccinated
iii. the vaccine may wane at rate ω
iv. the vaccine may have suboptimal efficacy ψ.

Efficacy

A disease-modifying vaccine with 35% efficacy would:

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  (so you're less likely to transmit the disease).

Four groups

For any vaccine, there are four groups:

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a) those who never received the vaccine;

Four groups

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‘Vaccinated’ individuals

- ‘Unvaccinated’ individuals = groups (a)-(c)

‘Vaccinated’ individuals

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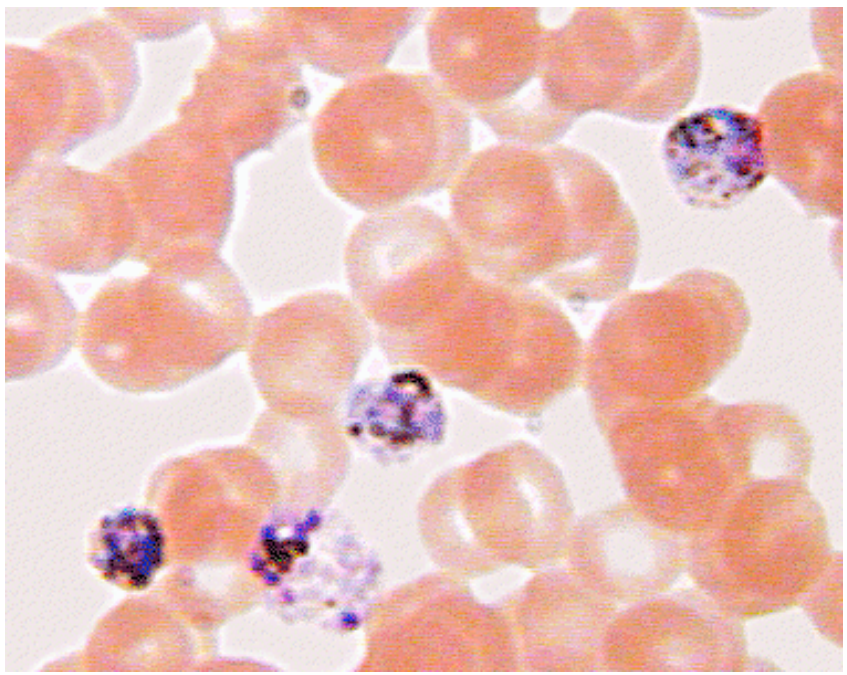
- ‘Vaccinated’ individuals = group (d).

Vaccinated individuals

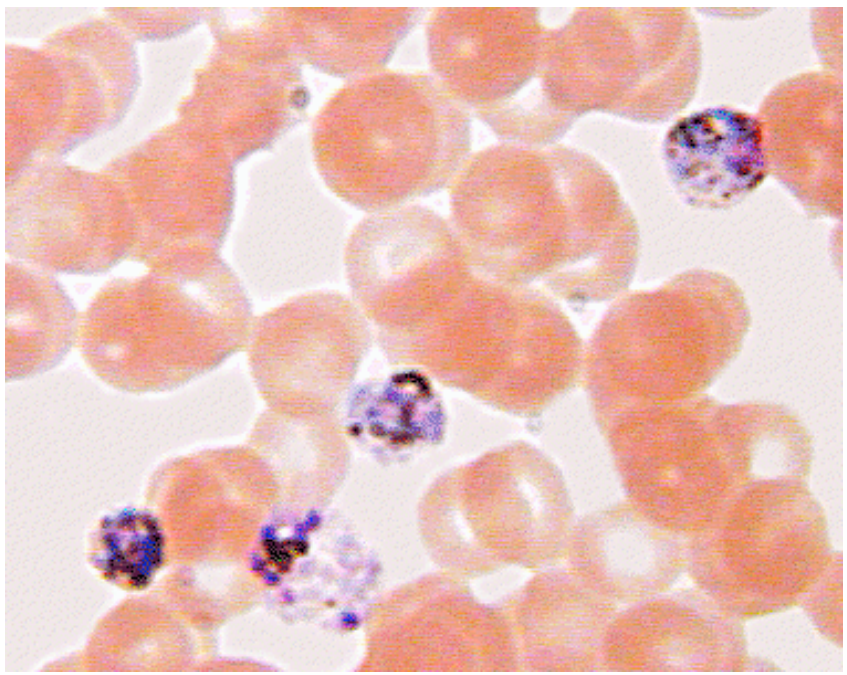
Vaccinated individuals may have



Vaccinated individuals

Vaccinated individuals may have

- a reduced rate of infection



Vaccinated individuals

Vaccinated individuals may have

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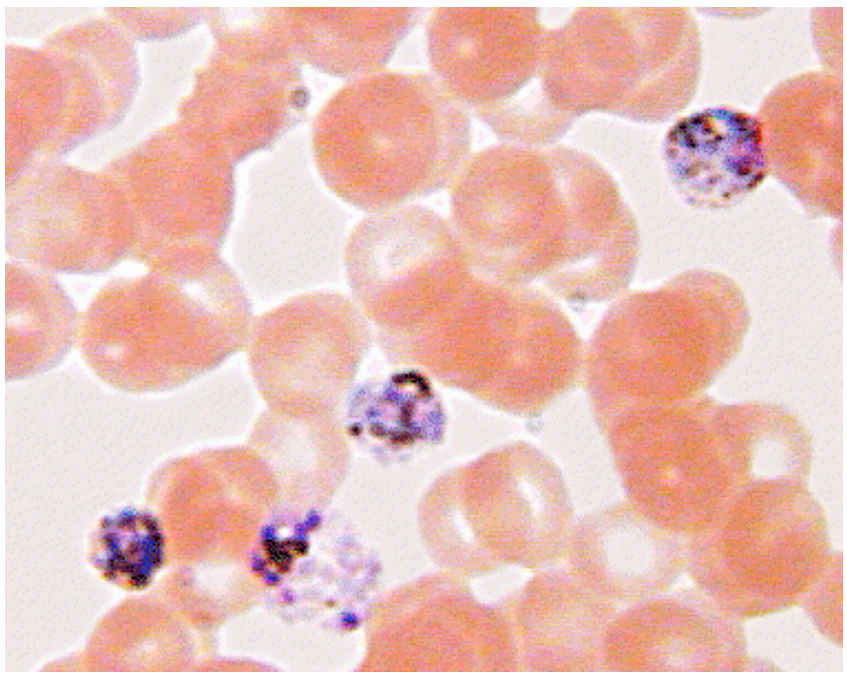
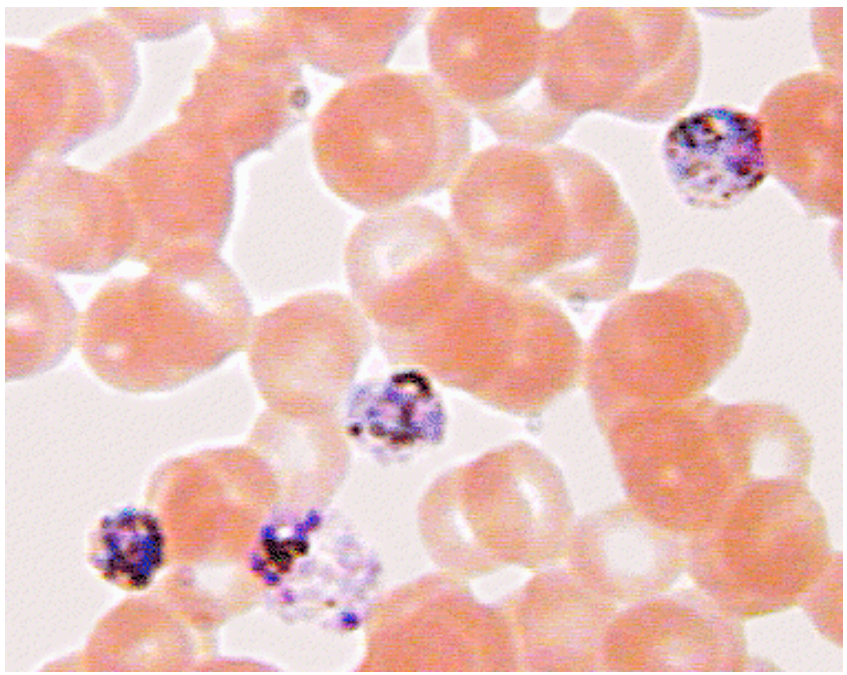


Vaccinated individuals

Vaccinated individuals may have

- a reduced rate of infection
- increased life expectancy
- faster recovery.



Duration of infection

Thus the duration of infection for ‘vaccinated’ individuals may

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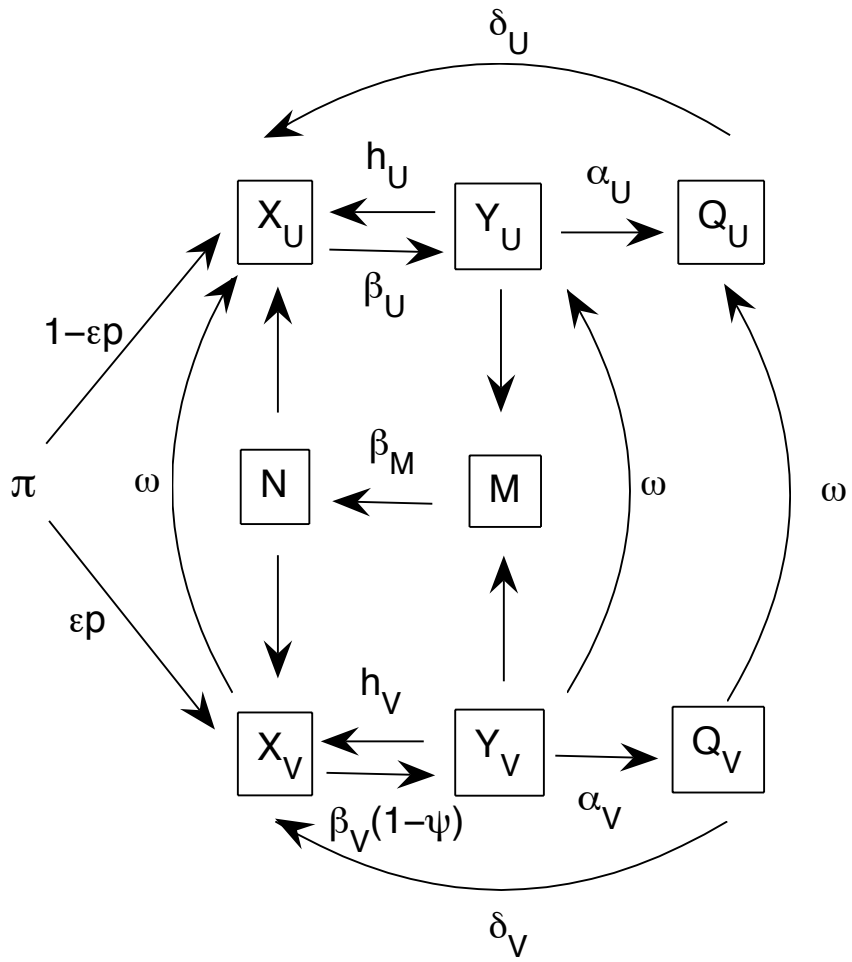
- decrease (due to higher recovery rates)

Duration of infection

Thus the duration of infection for ‘vaccinated’ individuals may

- decrease (due to higher recovery rates)
- increase (due to fewer deaths).

The model



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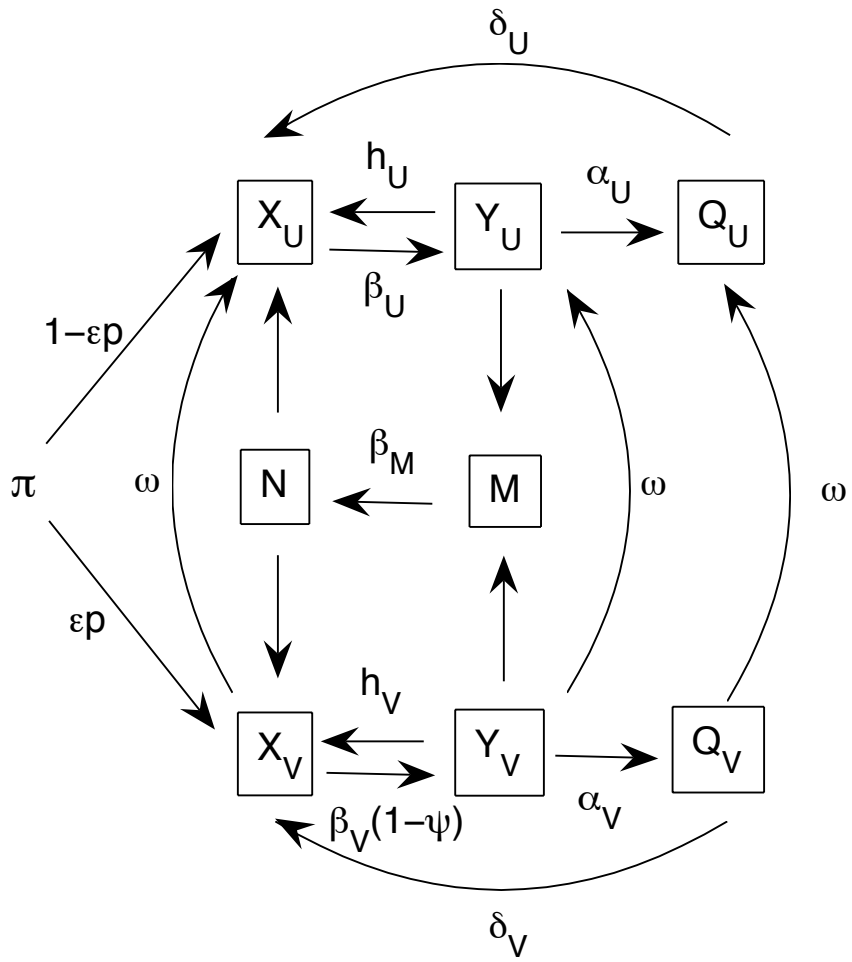
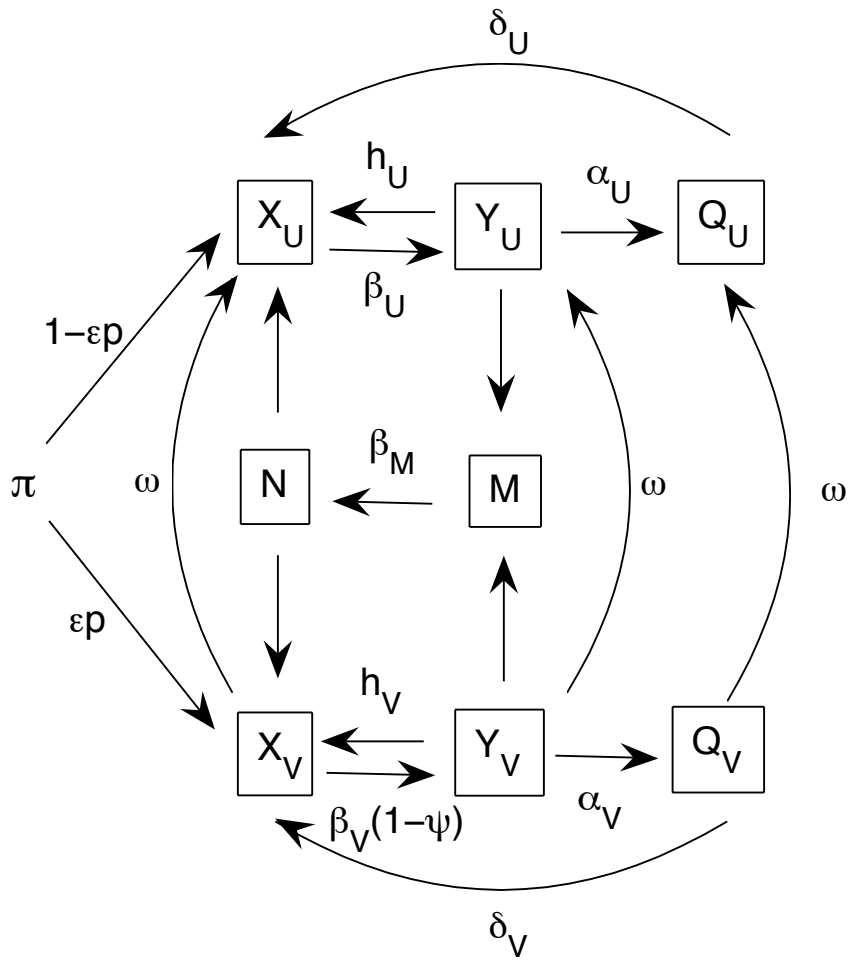


UNVACCINATED

The model



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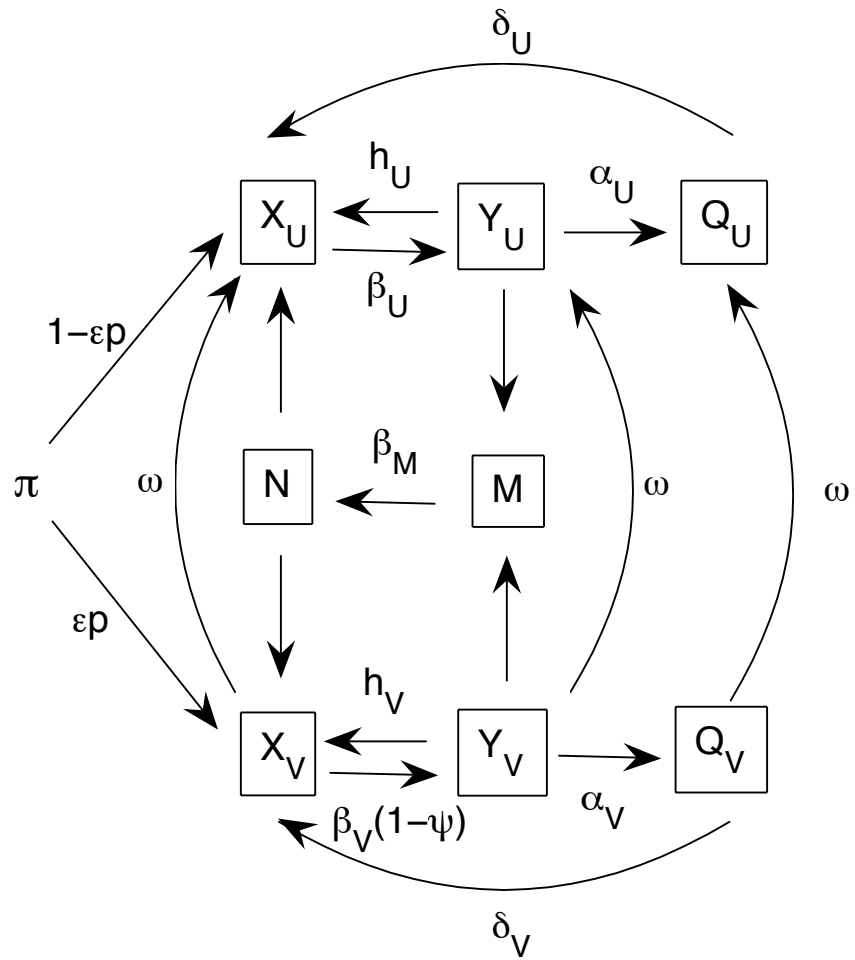

UNVACCINATED

MOSQUITOS

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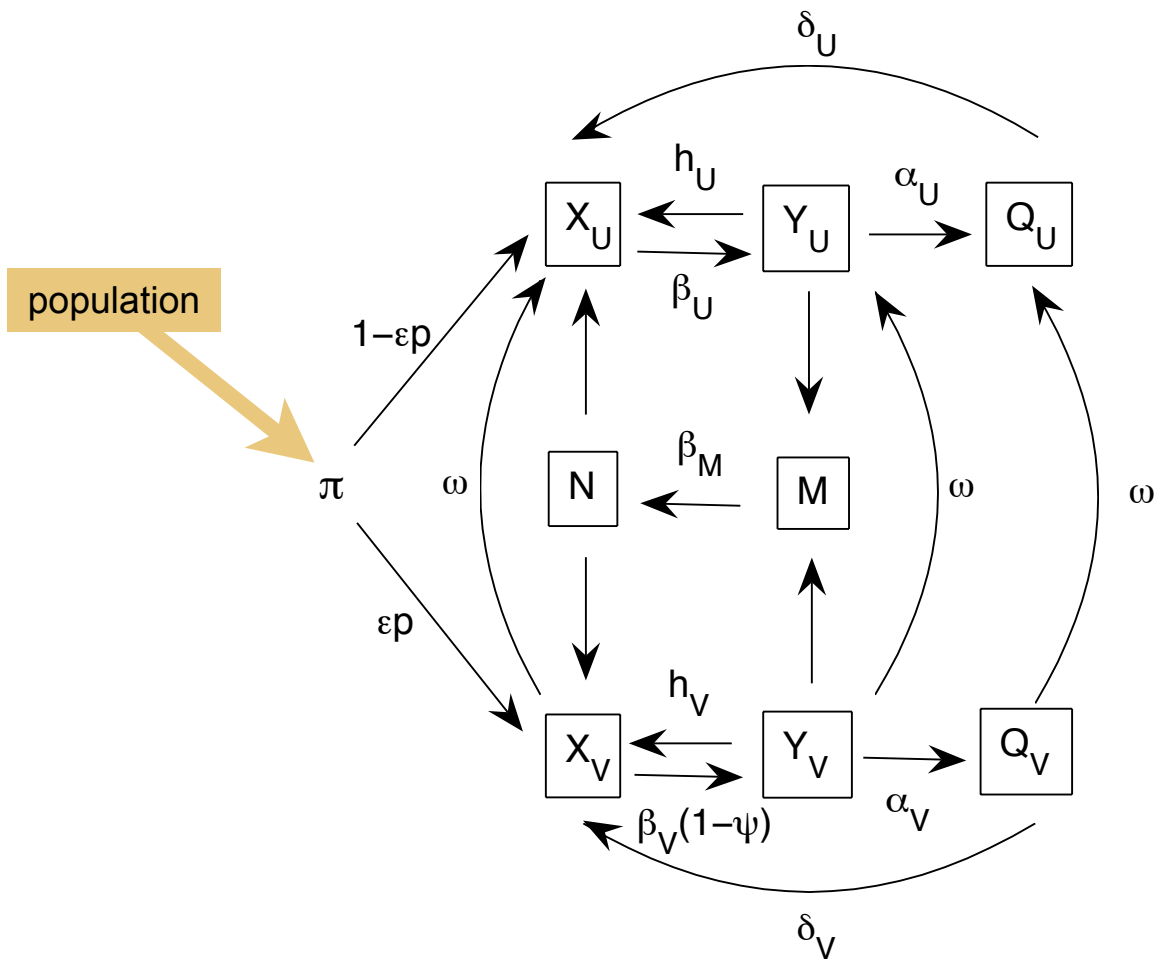

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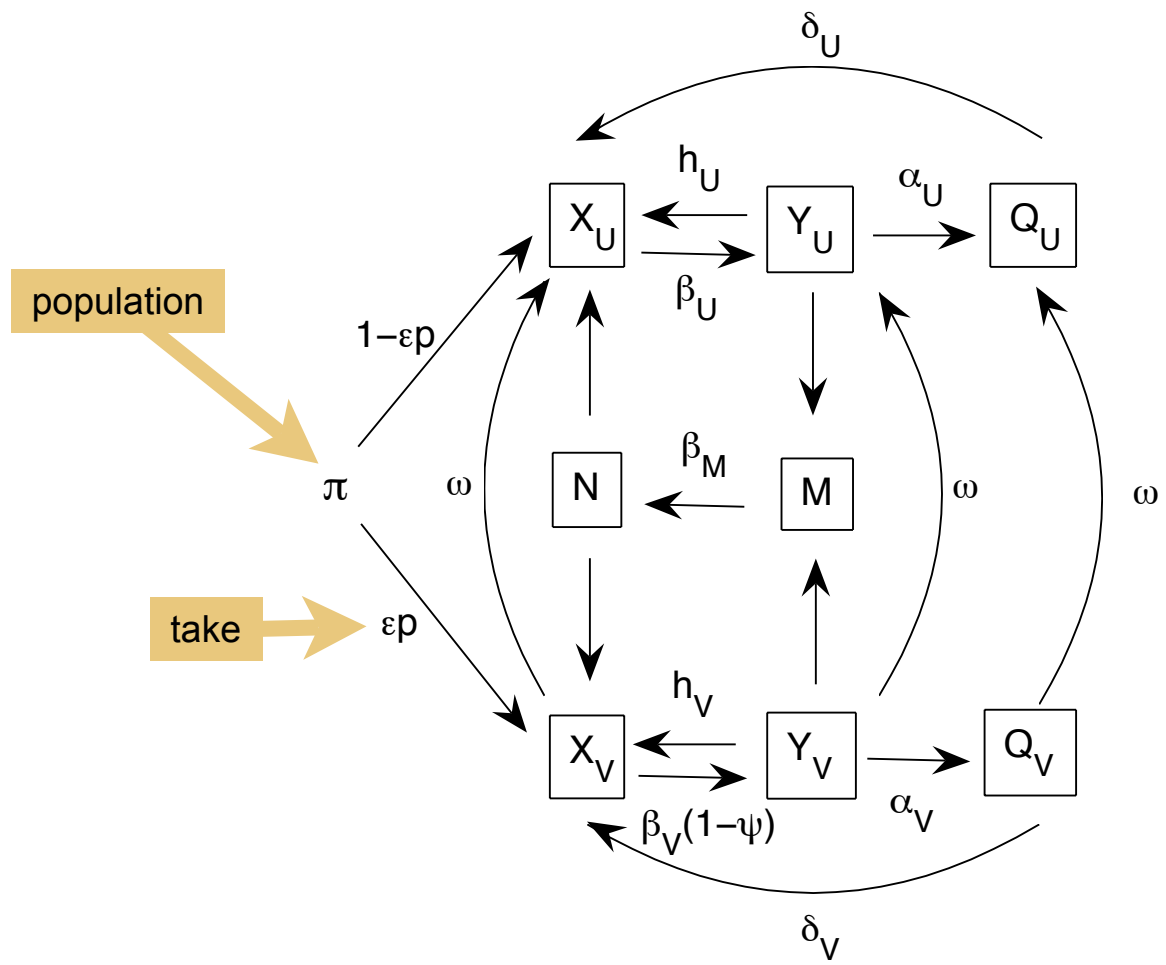

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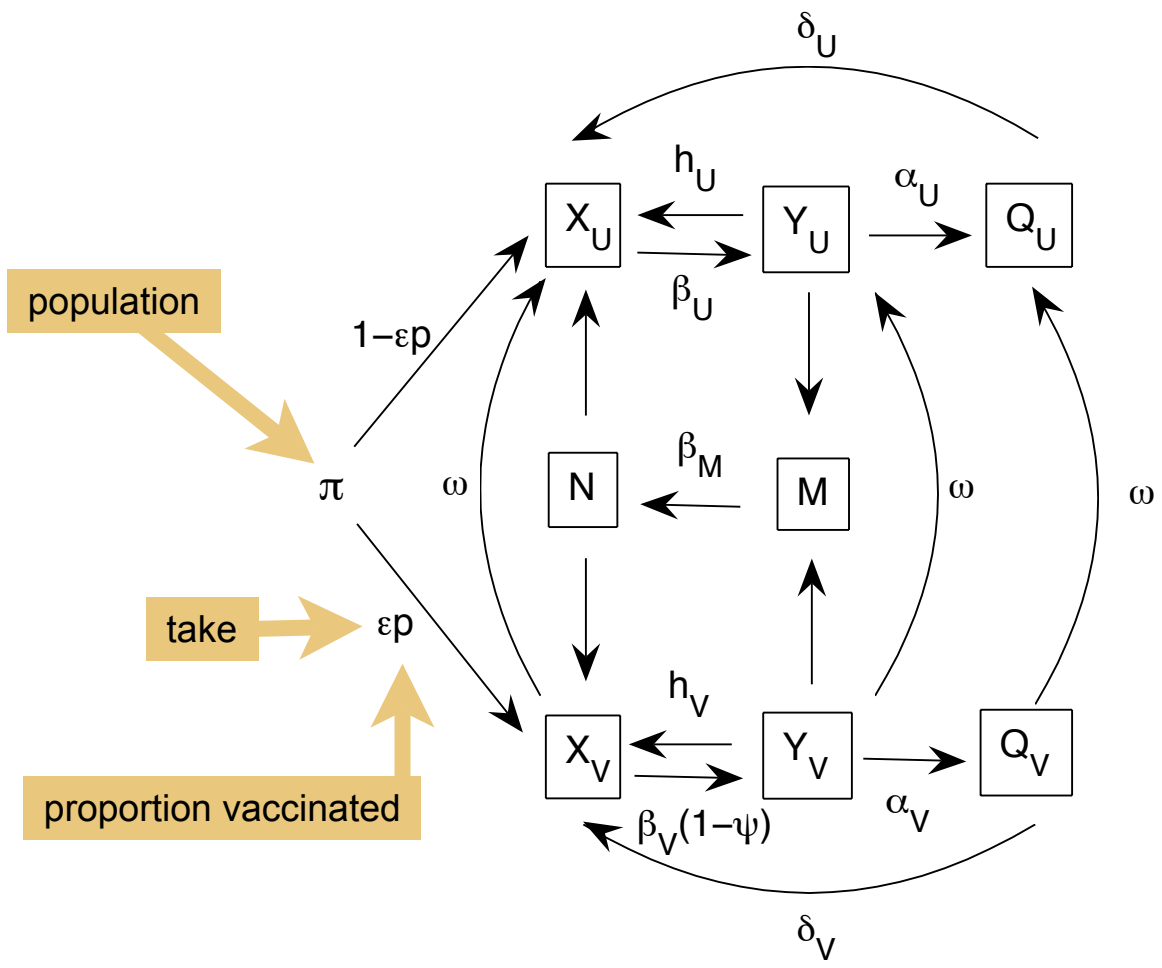

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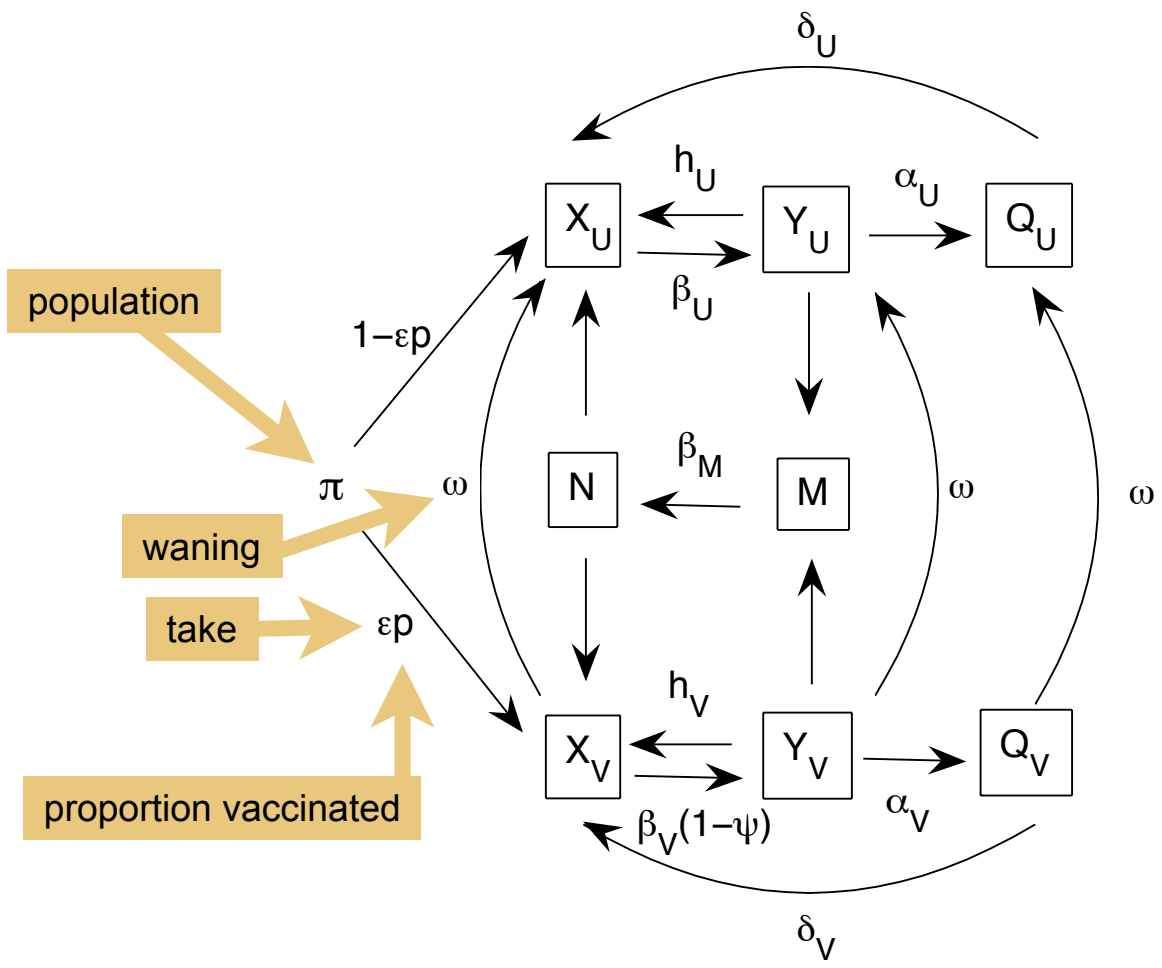

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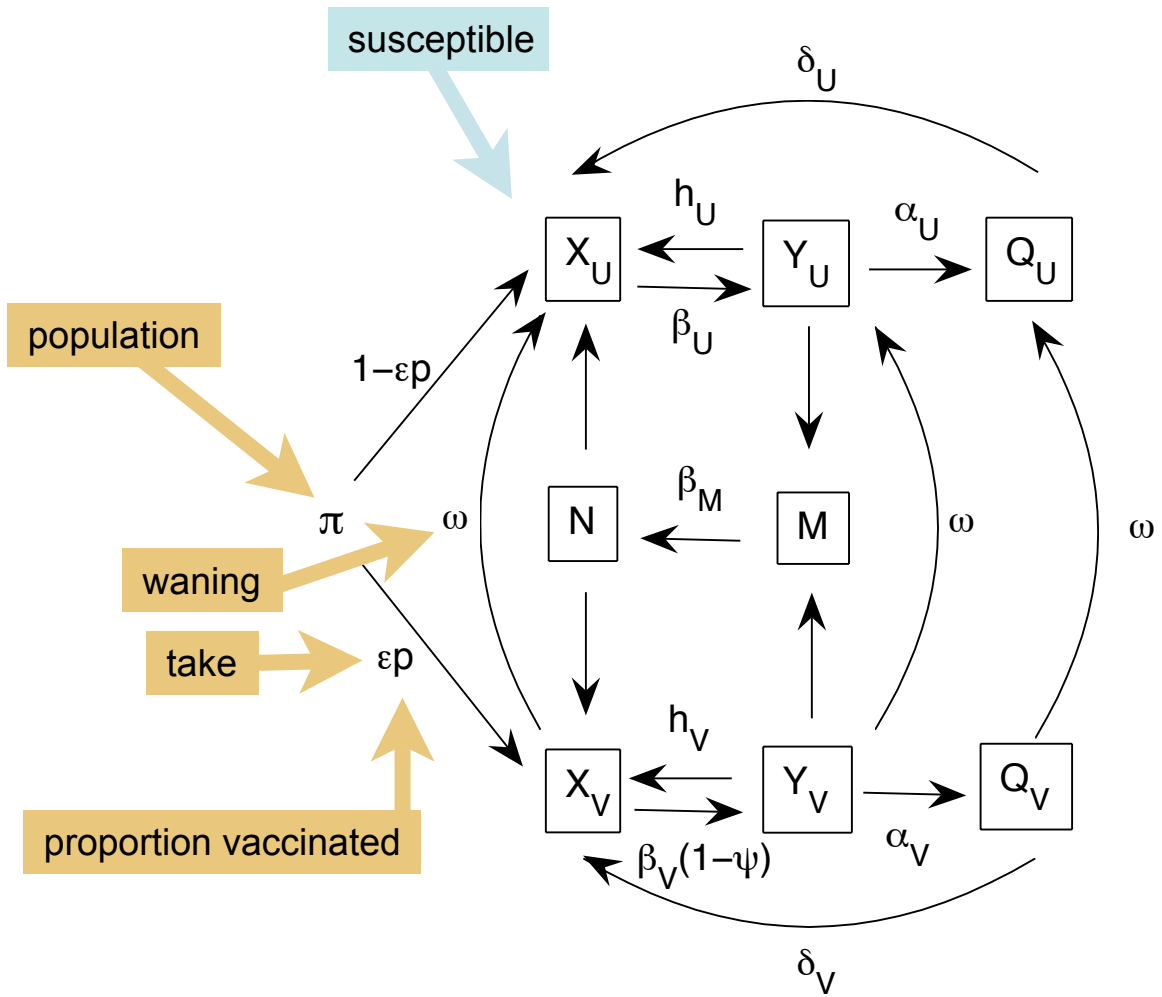

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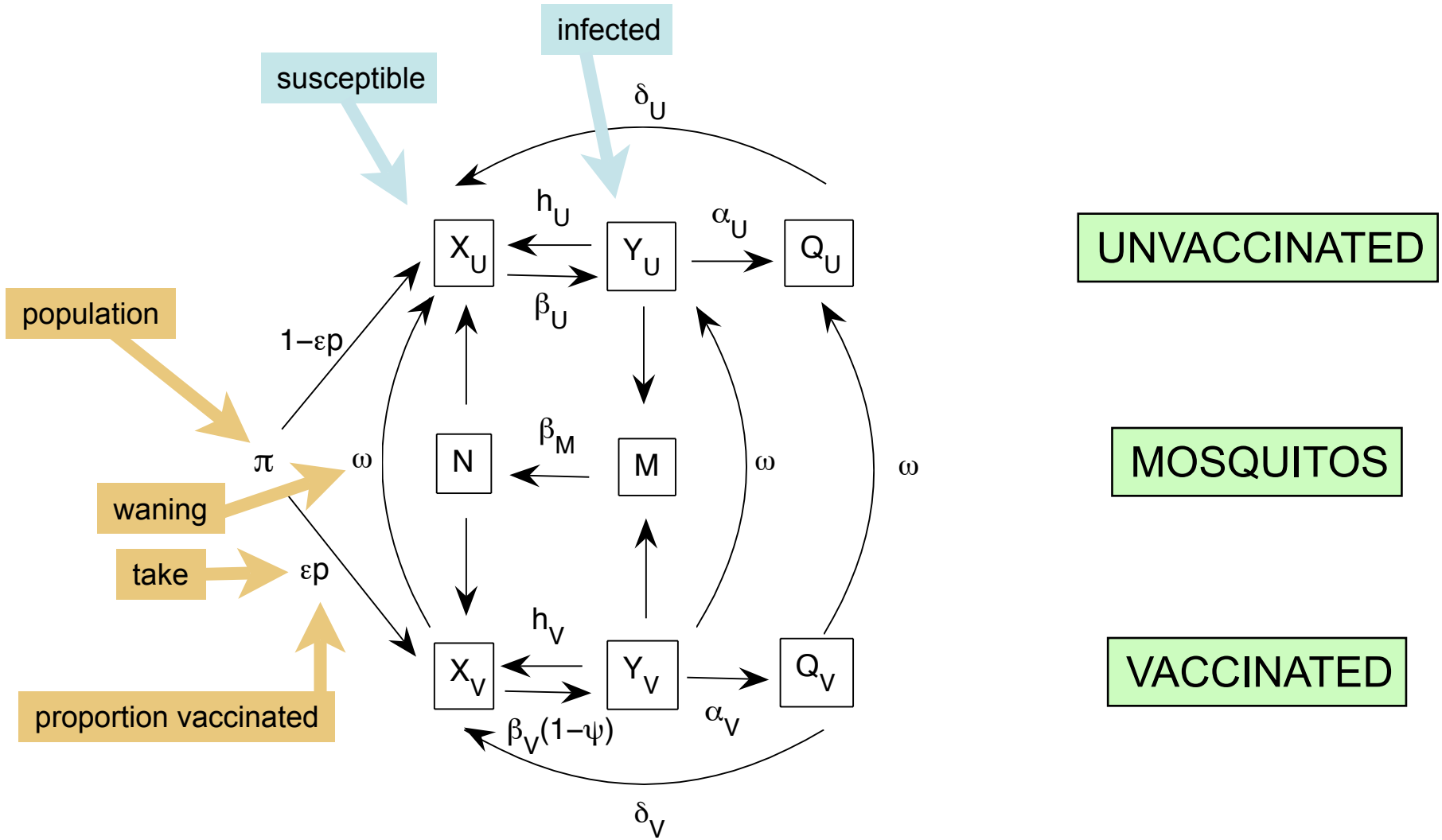
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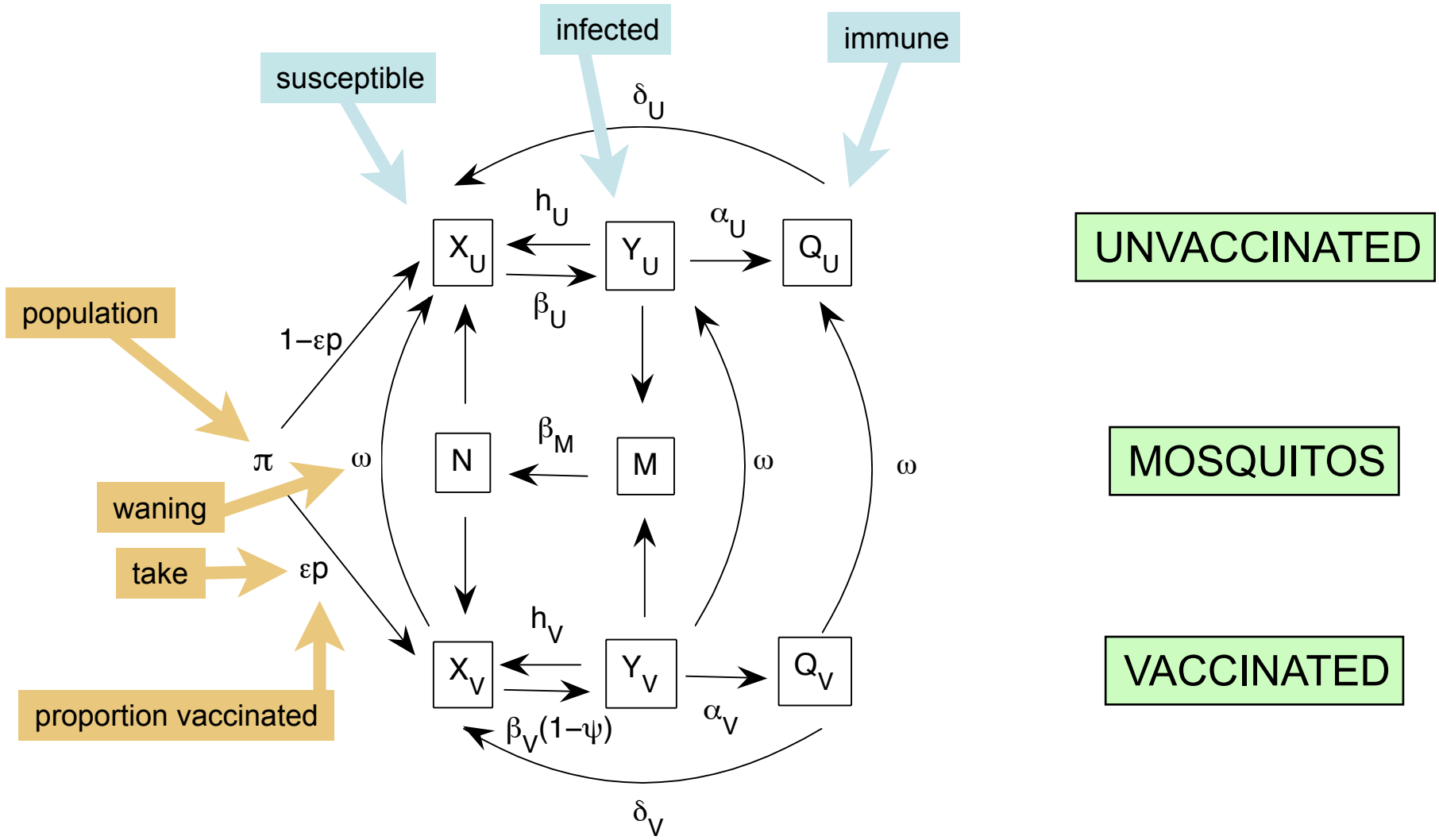
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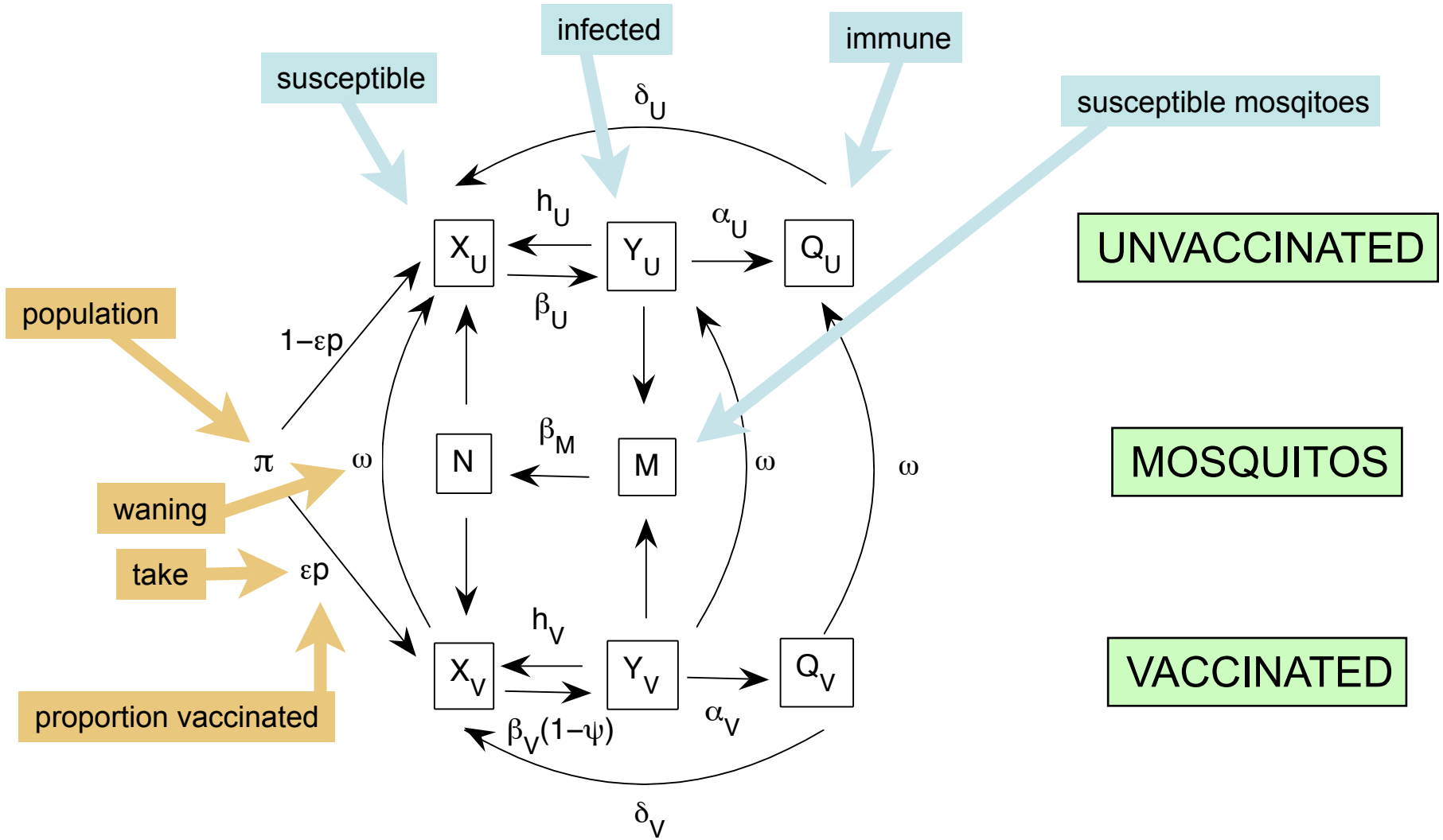
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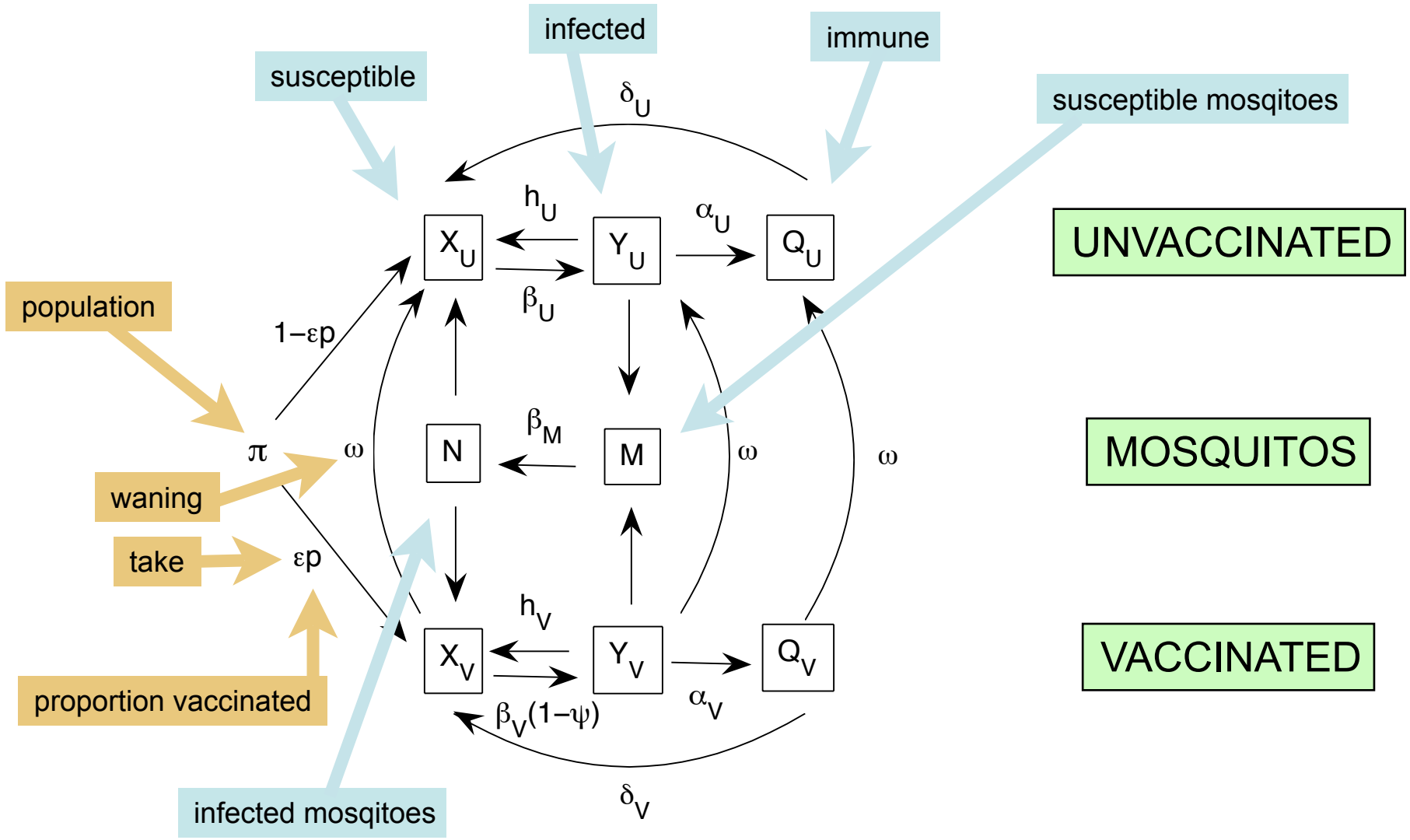
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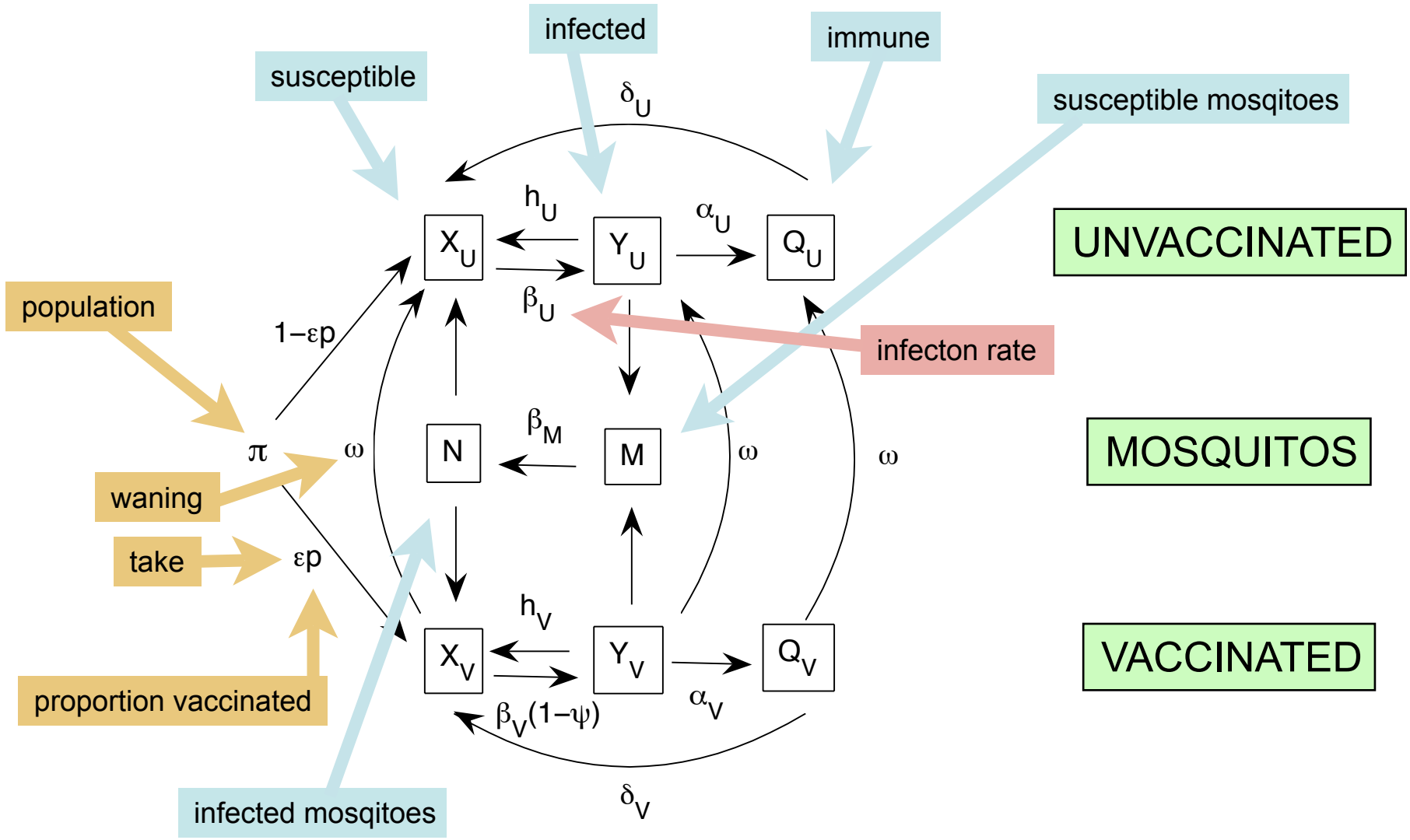
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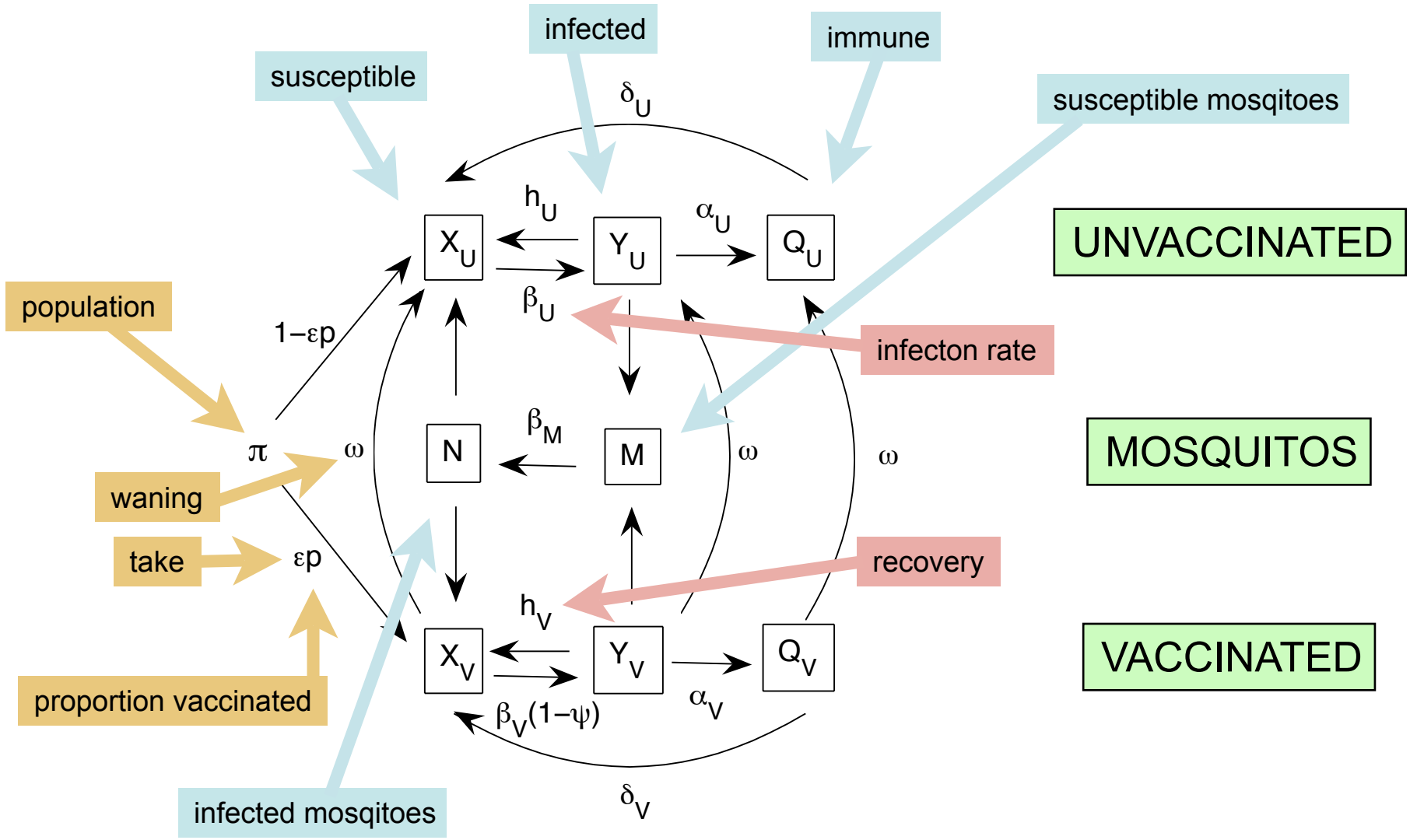
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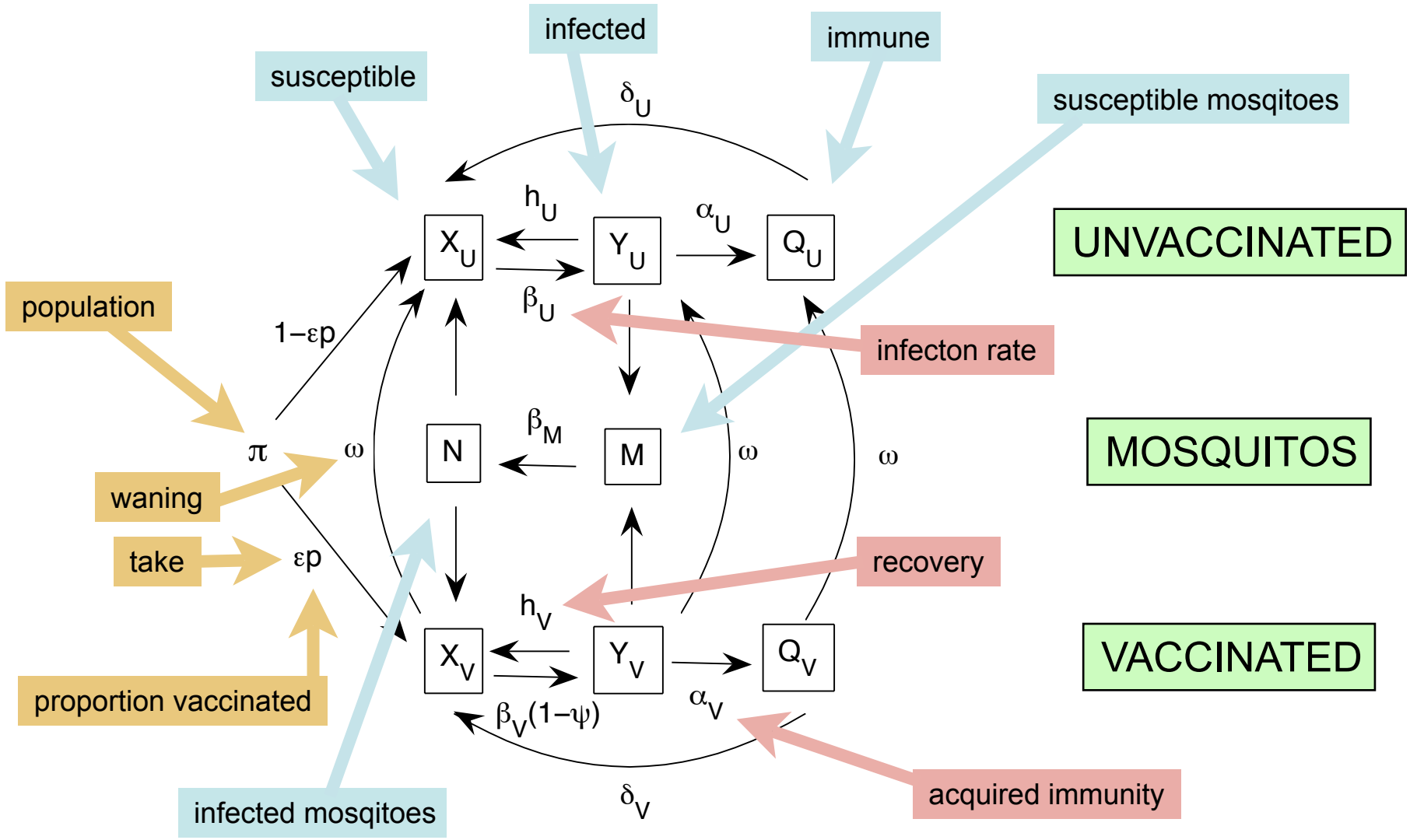
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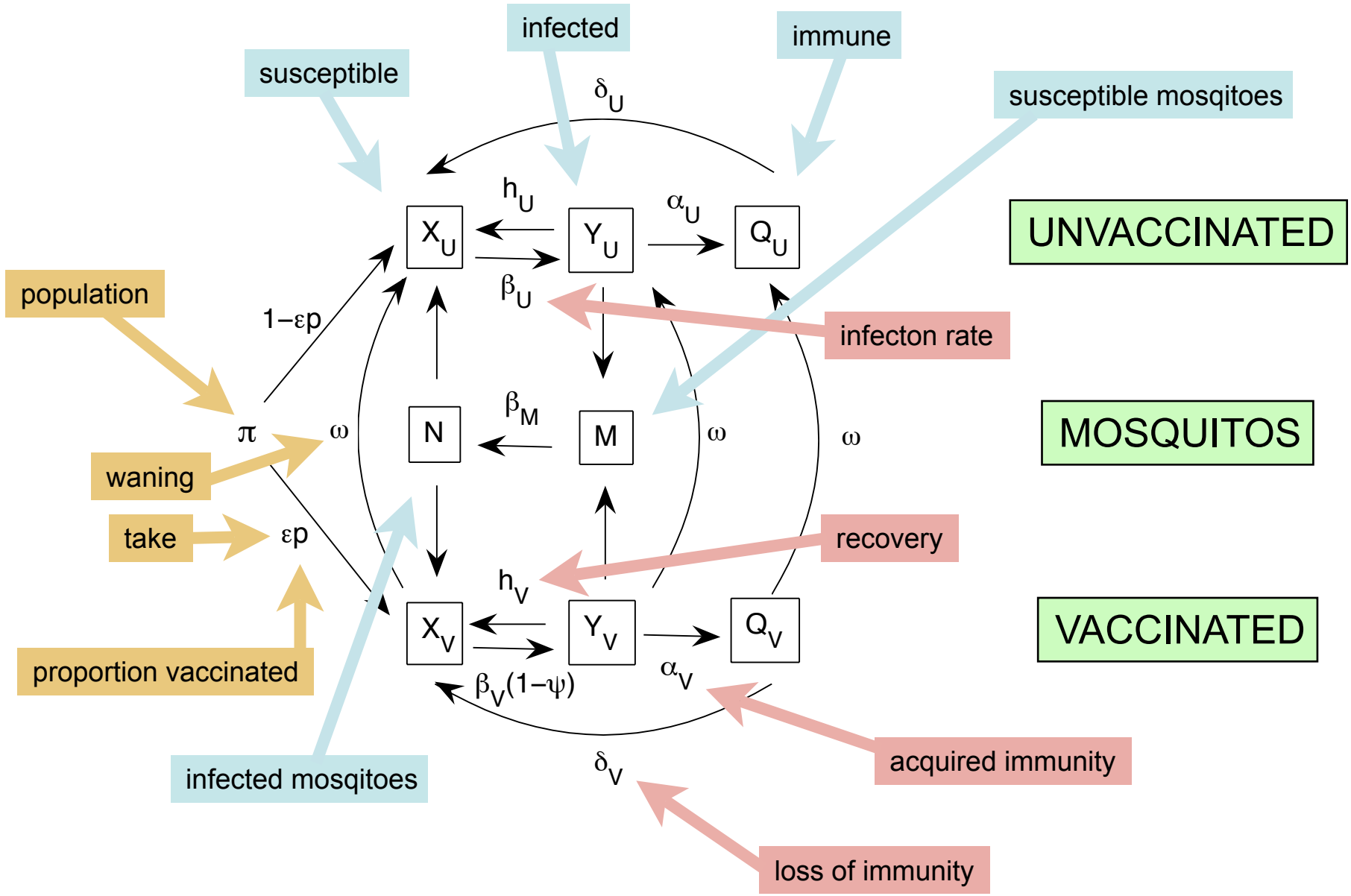
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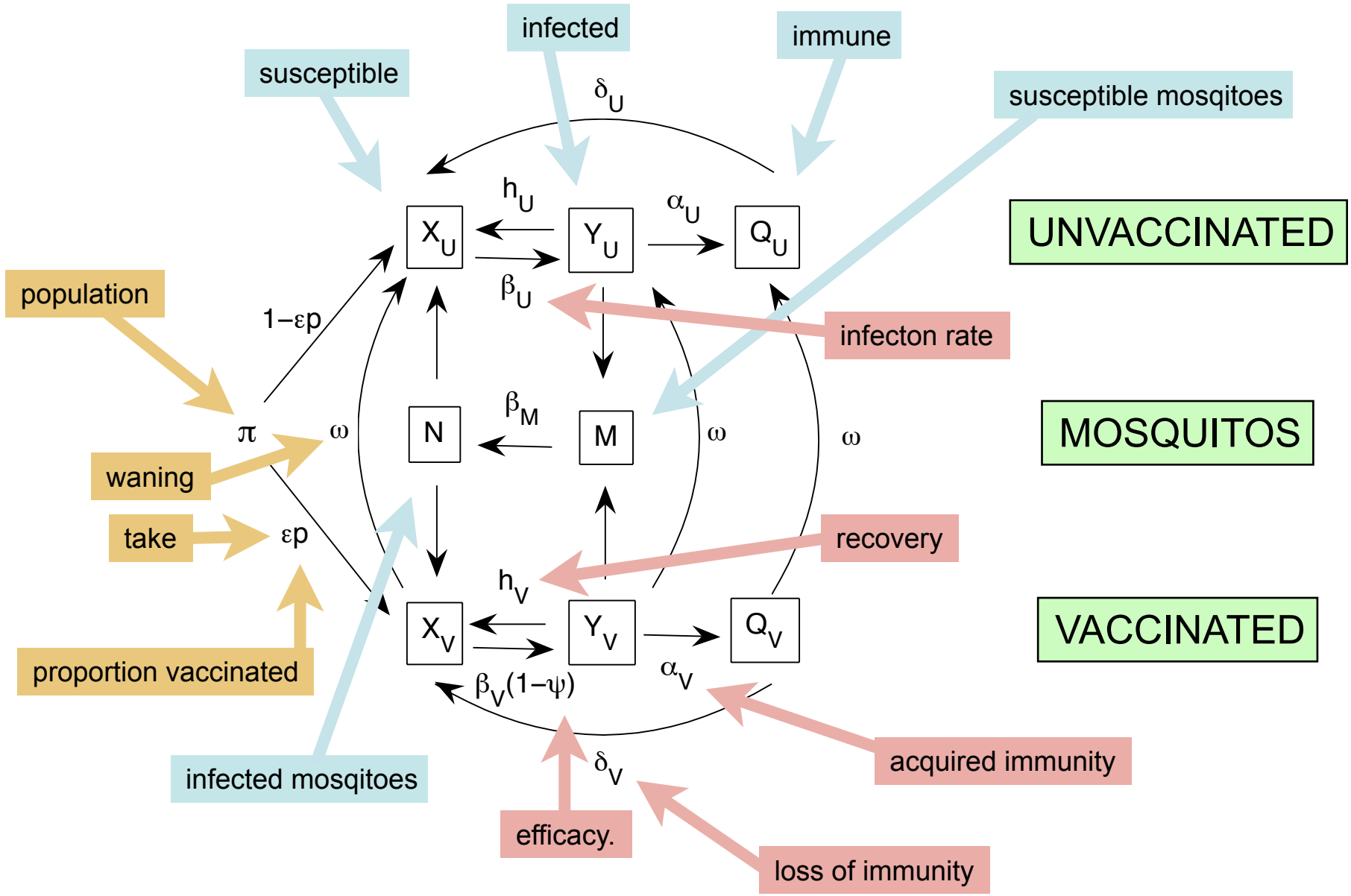
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The ODEs

$$
\begin{aligned}
\frac{\mathrm{d}M}{\mathrm{d}t} &= \Omega - \beta_M Y_U M - \beta_M Y_V M - \mu_M M \\
\frac{\mathrm{d}N}{\mathrm{d}t} &= \beta_M Y_U M + \beta_M Y_V M - \mu_M N \\
\frac{\mathrm{d}X_U}{\mathrm{d}t} &= (1-\epsilon p)\pi - \mu X_U - \beta_U N X_U + \omega X_V + h_U Y_U + \delta_U Q_U \\
\frac{\mathrm{d}X_V}{\mathrm{d}t} &= \epsilon p \pi - \mu X_V - (1-\psi)\beta_V N X_V - \omega X_V + h_V Y_V + \delta_V Q_V \\
\frac{\mathrm{d}Y_U}{\mathrm{d}t} &= \beta_U N X_U - (\mu + \gamma_U + \alpha_U + h_U) Y_U + \omega Y_V \\
\frac{\mathrm{d}Y_V}{\mathrm{d}t} &= (1-\psi)\beta_V X_V - (\mu + \gamma_V + \alpha_V + h_V) Y_V - \omega Y_V \\
\frac{\mathrm{d}Q_U}{\mathrm{d}t} &= \alpha_U Y_U - (\mu + \delta_U) Q_U + \omega Q_V \\
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- S = proportion "successfully" vaccinated.

R_0=reproductive number (unvaccinated)
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Vaccine coverage level

- When $R_p = 1$, $SR_V + (1-S)R_0 = 1$

R_j=reproductive numbers (pop, vacc, unvacc) ω=waning ε=take
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is the threshold vaccine coverage level.

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- However, this may not be achievable in real terms.

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- This may occur if many more people survive to become infected later.

Increasing secondary infections

- The number of secondary infections will increase if $R_p > R_0$

R_j=reproductive numbers (pop, vacc, unvacc) Ψ=efficacy
S=proportion vaccinated β_j=rate of infection ξ_j=duration

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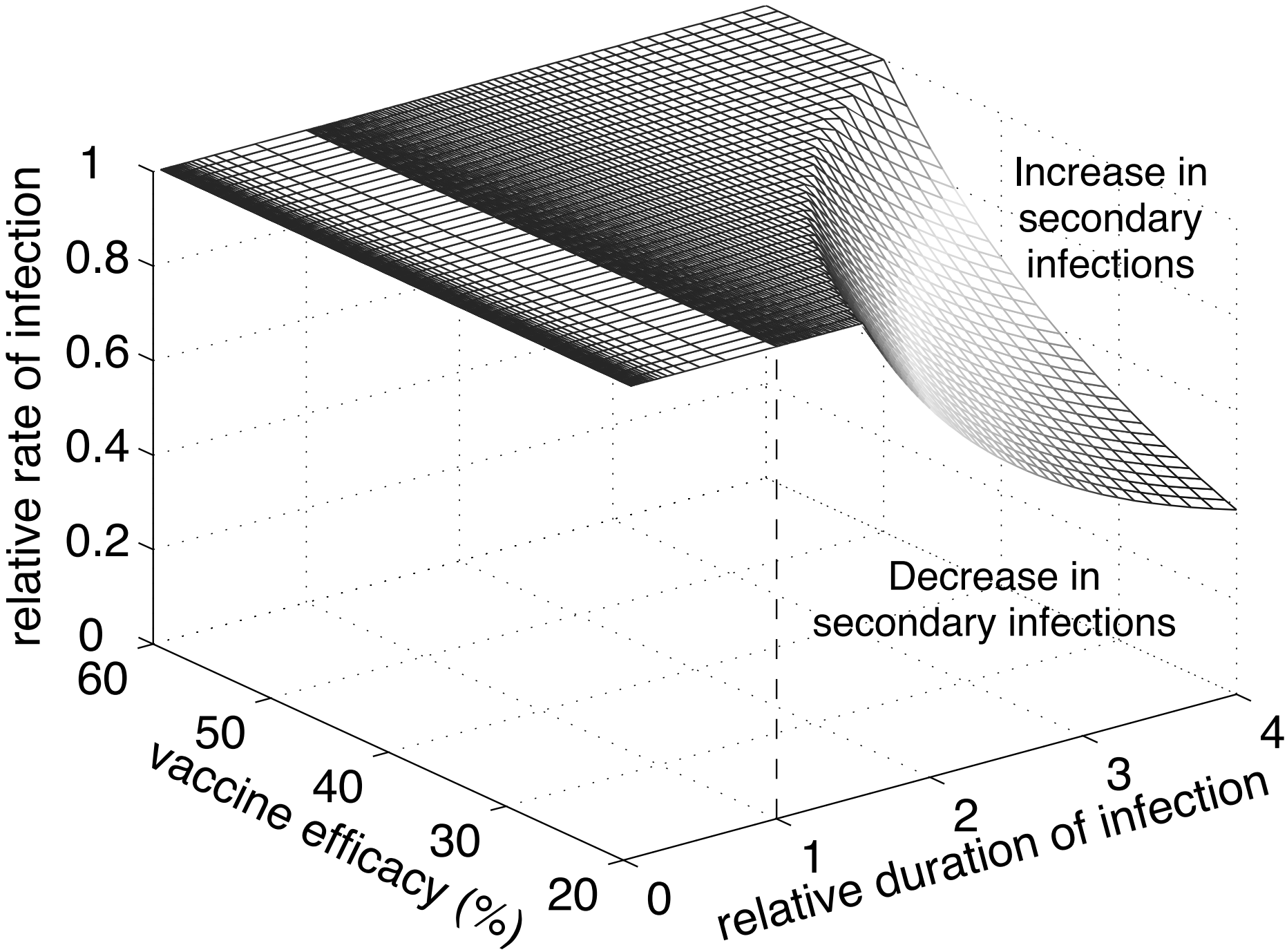
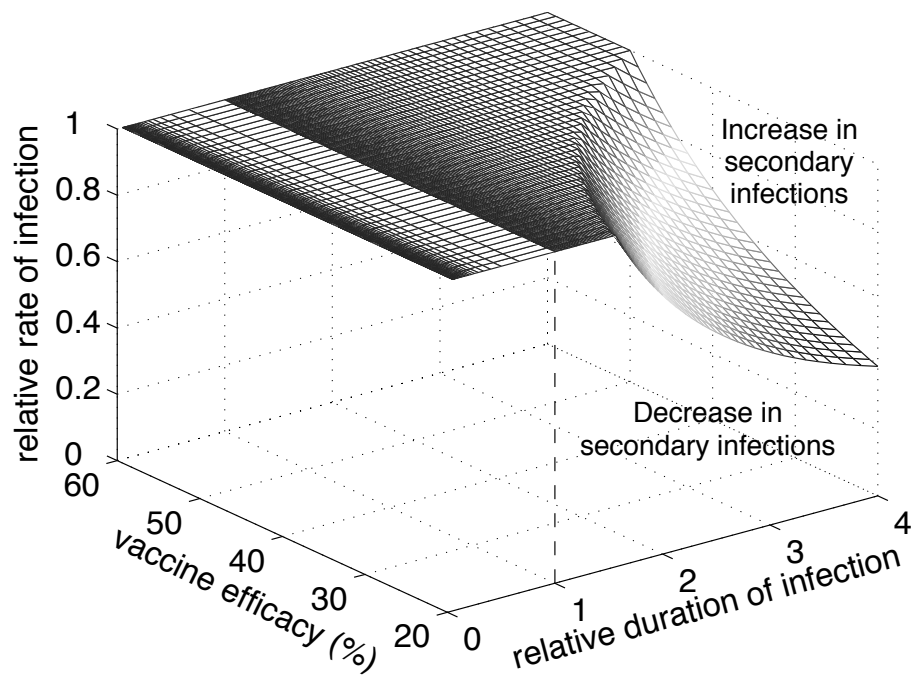

relative rate of infection
1
0.8
0.6
0.4
0.2
0
60
50
40
30
20
vaccine efficacy (%)
0
1
2
3
4
relative duration of infection
Increase in secondary infections
Decrease in secondary infections

Decreasing rate and duration

- If the rate and duration of infection both decrease, the number of secondary infections will always decrease



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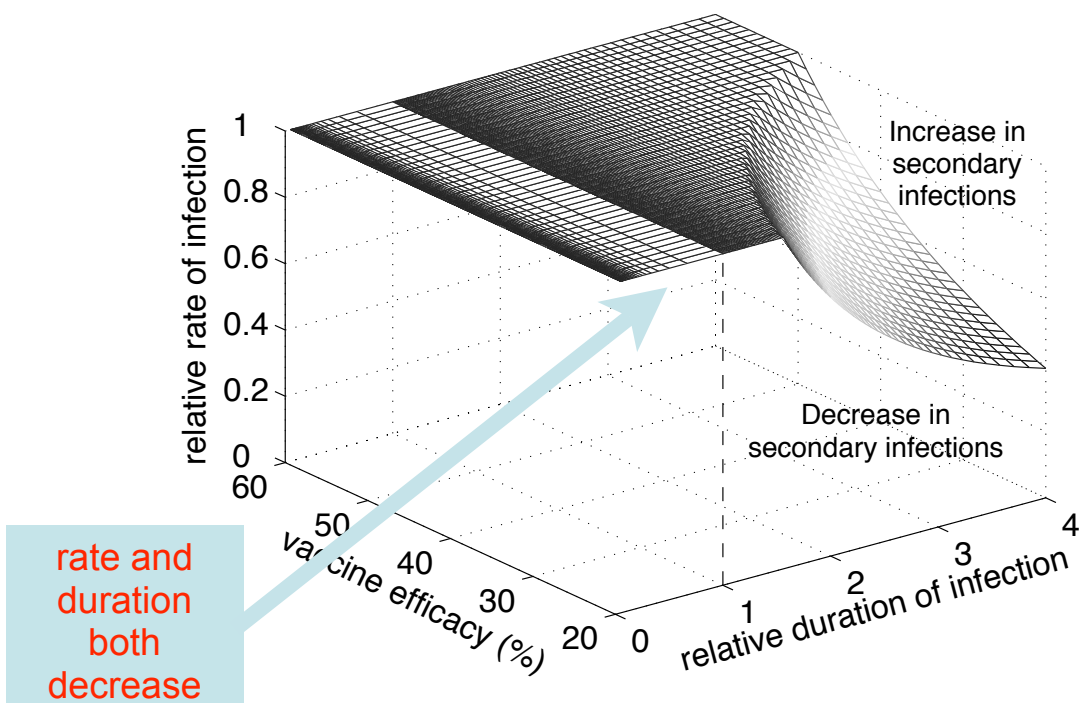
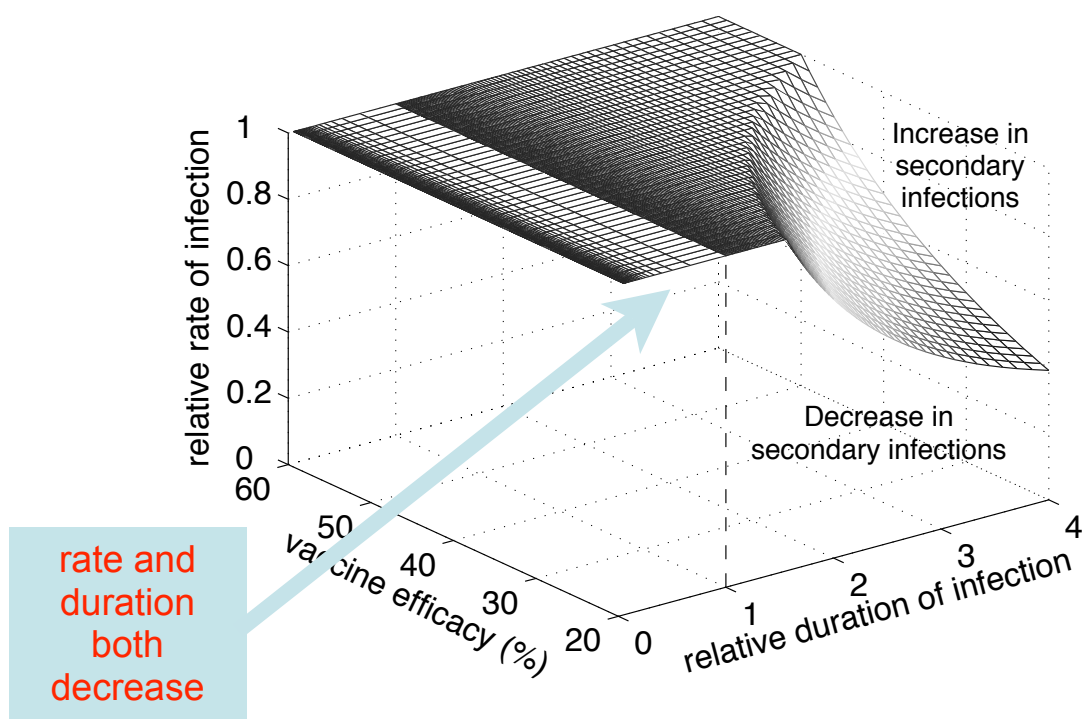


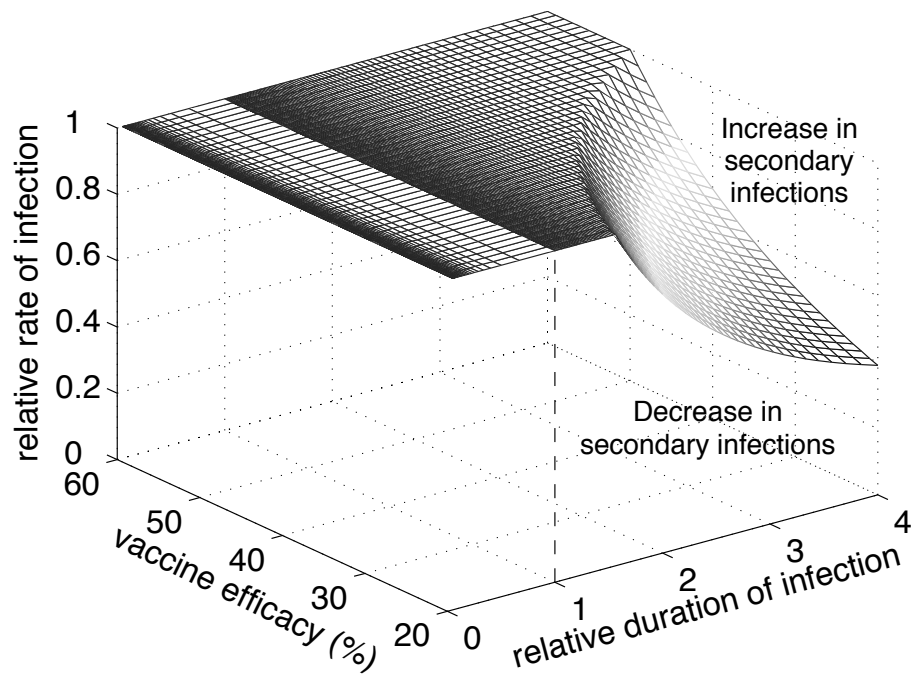
Decreasing rate and duration

- If the rate and duration of infection both decrease, the number of secondary infections will always decrease
- (Not terribly surprising.)



A duration “shoulder”

- For a given vaccine efficacy, there is a duration “shoulder”



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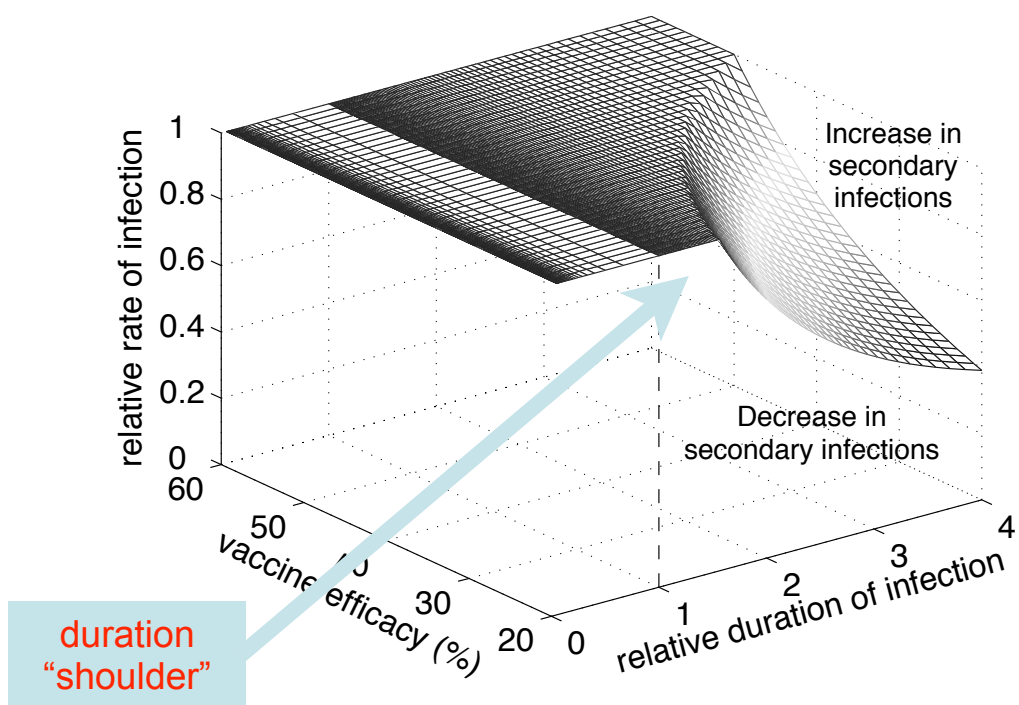

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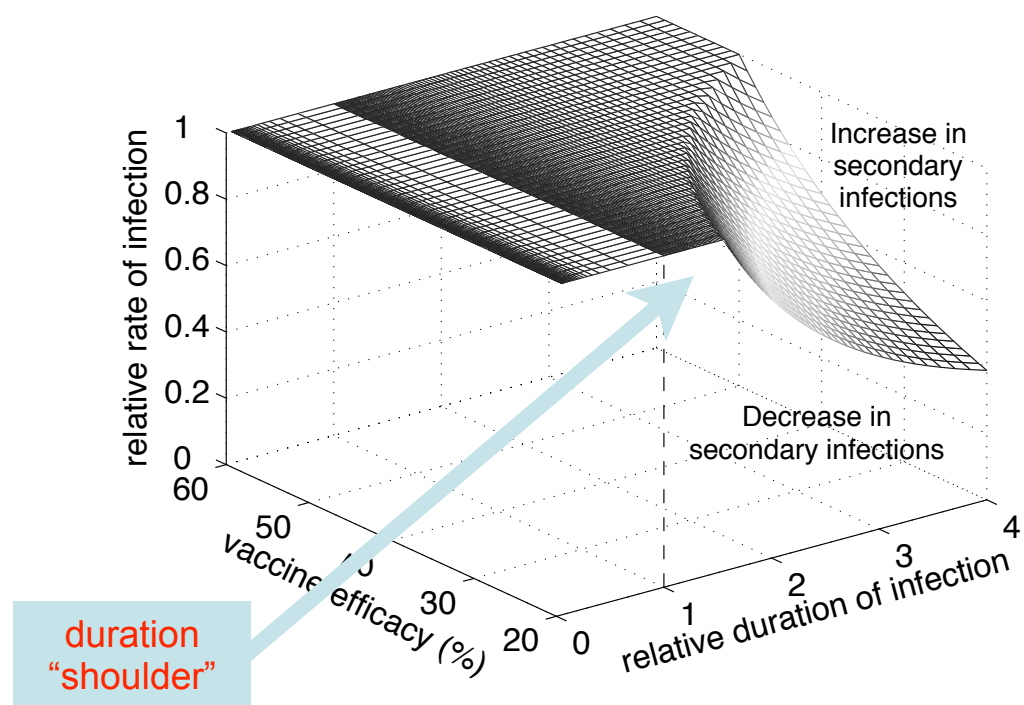
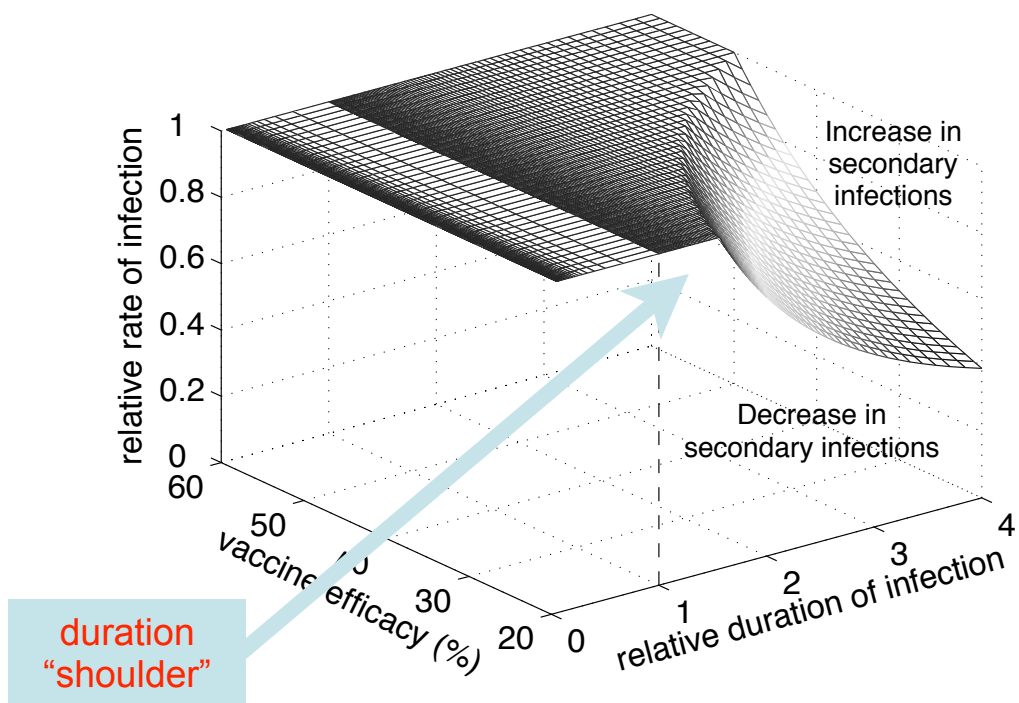
- For a given vaccine efficacy, there is a duration “shoulder”
- A small increase in the duration of infection will still decrease the number of secondary infections



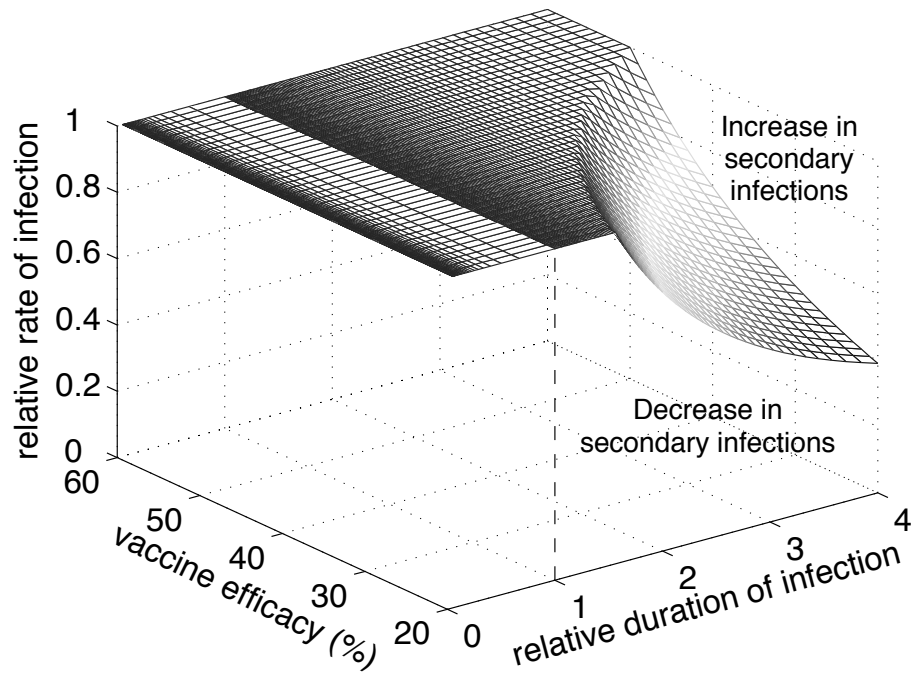
A duration “shoulder”

- For a given vaccine efficacy, there is a duration “shoulder”
- A small increase in the duration of infection will still decrease the number of secondary infections
- This is true even if the rate of infection is unchanged.



Beyond the “shoulder”

- If the duration of infection is significantly increased, then it is crucial that the rate of infection be decreased accordingly



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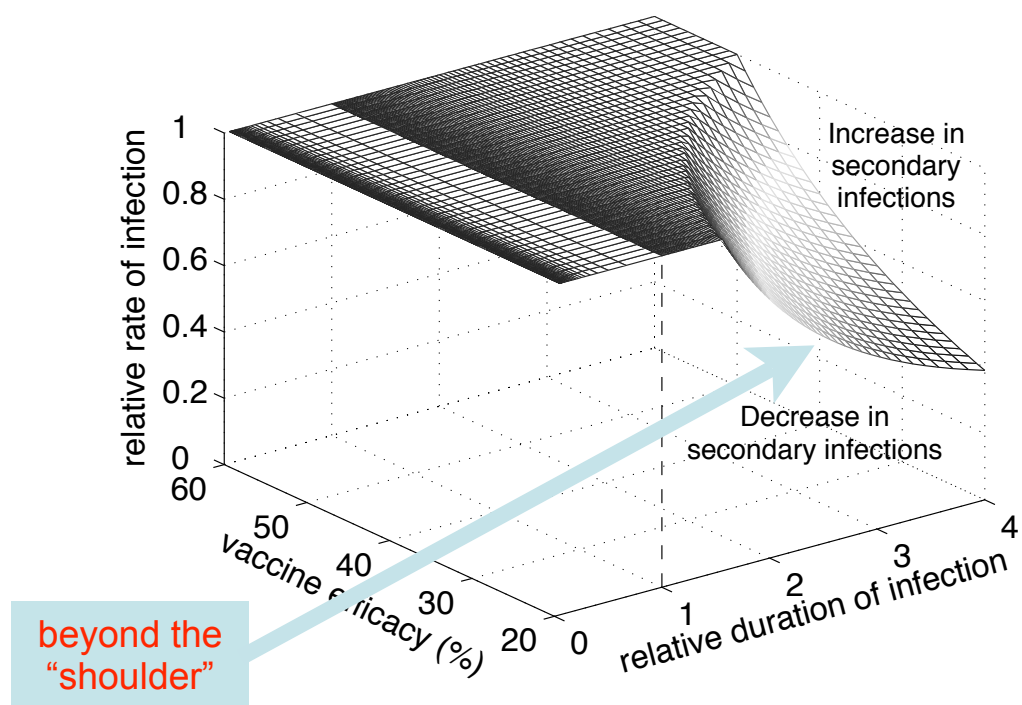
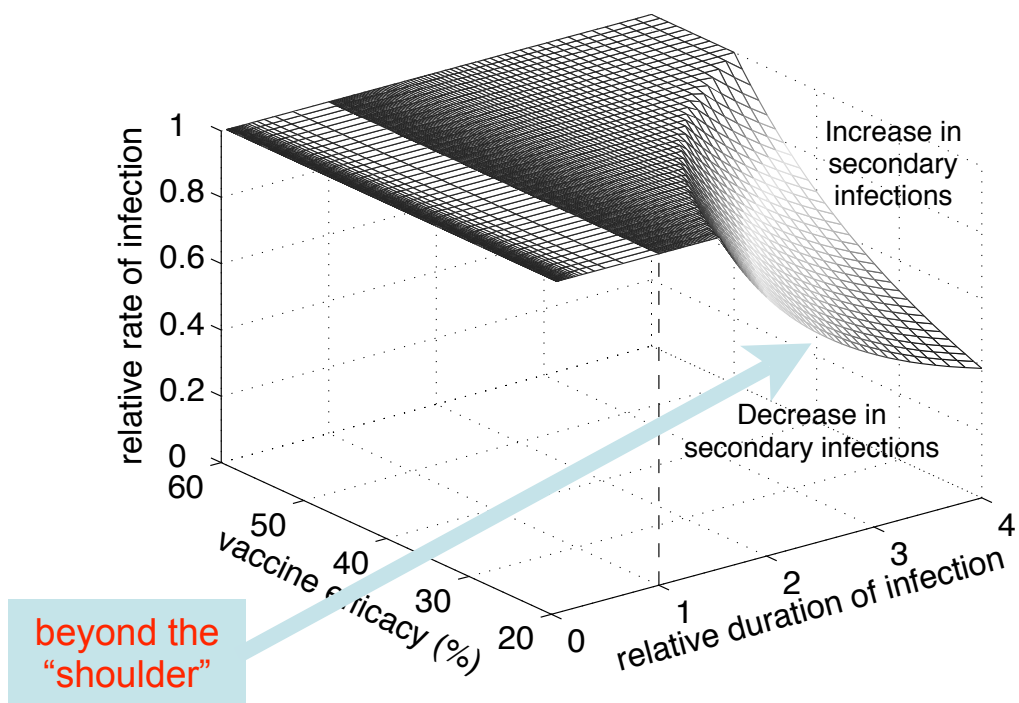


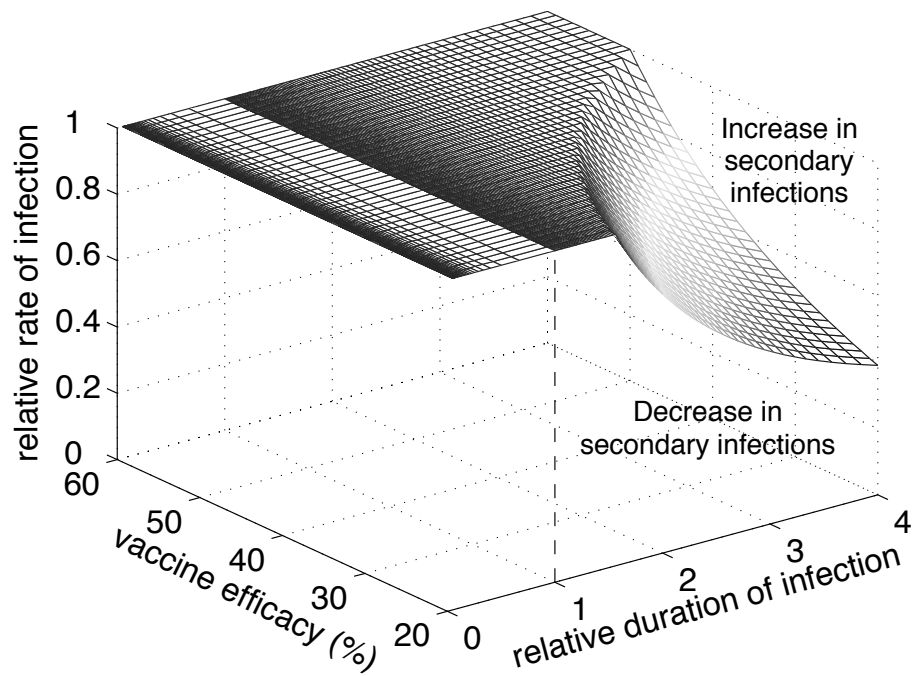
Beyond the “shoulder”

- If the duration of infection is significantly increased, then it is crucial that the rate of infection be decreased accordingly
- Thus is crucial for low-efficacy vaccines.



An example

- A 20% efficacious vaccine could accomodate an increase in the duration of infection by as much as 1.56 times thhe current duration of infection



An example

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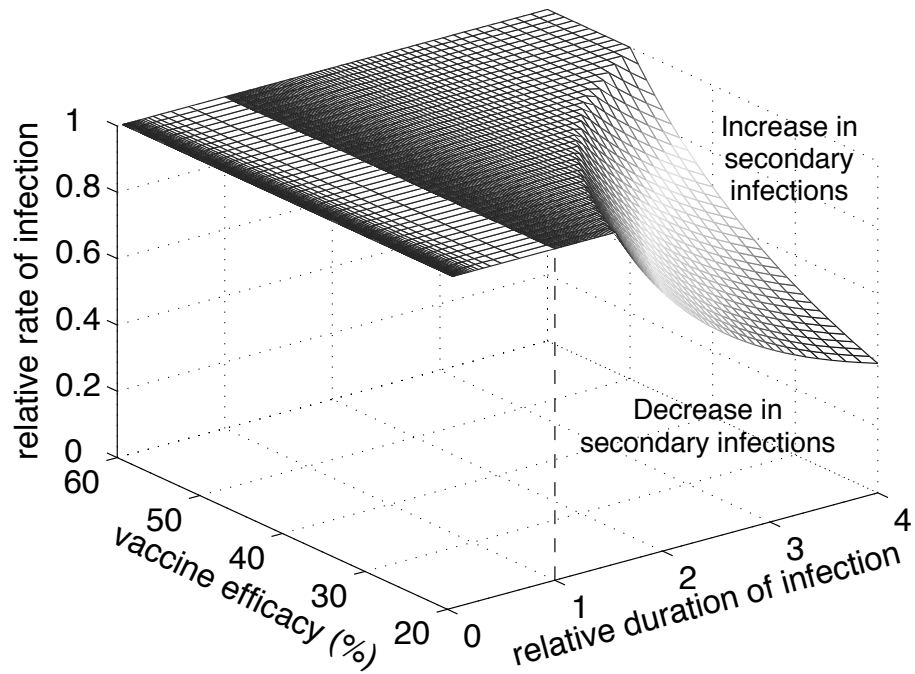
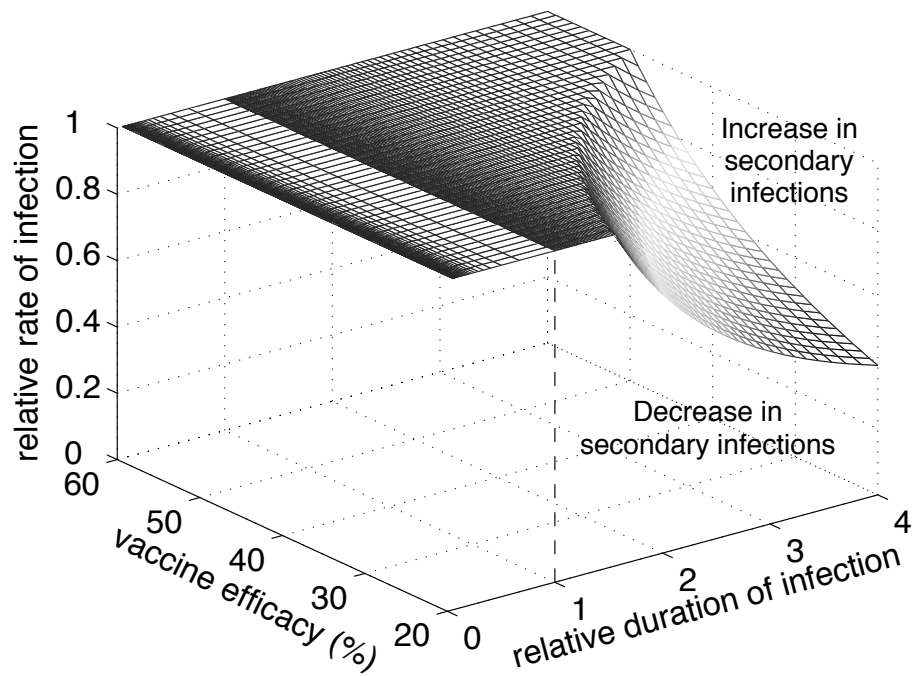
- Even if there is no reduction in the rate of infection, the net result will still be a decrease in secondary infections.



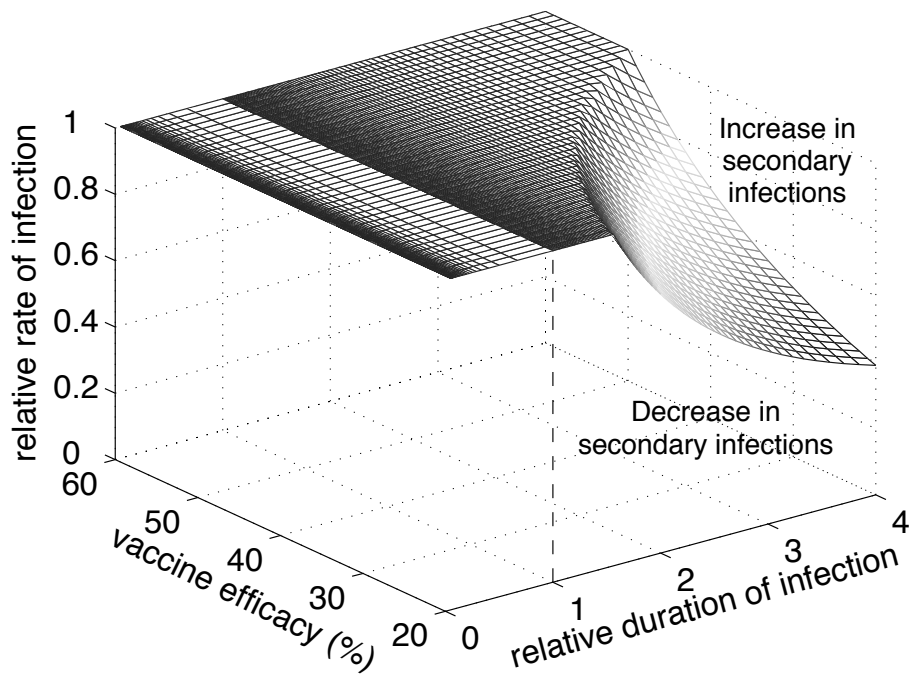
Reducing the infection rate

- However, a 20% efficacious vaccine that increased the duration of infection by a factor of 4 would lead to an increase in secondary infections...



Reducing the infection rate

- However, a 20% efficacious vaccine that increased the duration of infection by a factor of 4 would lead to an increase in secondary infections...
- ...unless the rate of infection for the vaccinated population were reduced to 40% of the current rate of infection.



Conclusions

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Conclusions

- An imperfect malaria vaccine can eradicate the disease, if the coverage levels are sufficiently high
- Duration of infection decreases ⇒ secondary infections always decrease
- Small increases in the duration of infection can be tolerated, but larger increases must be accompanied by a reduction in the rate of infection
- This is critical for low-efficacy vaccines.

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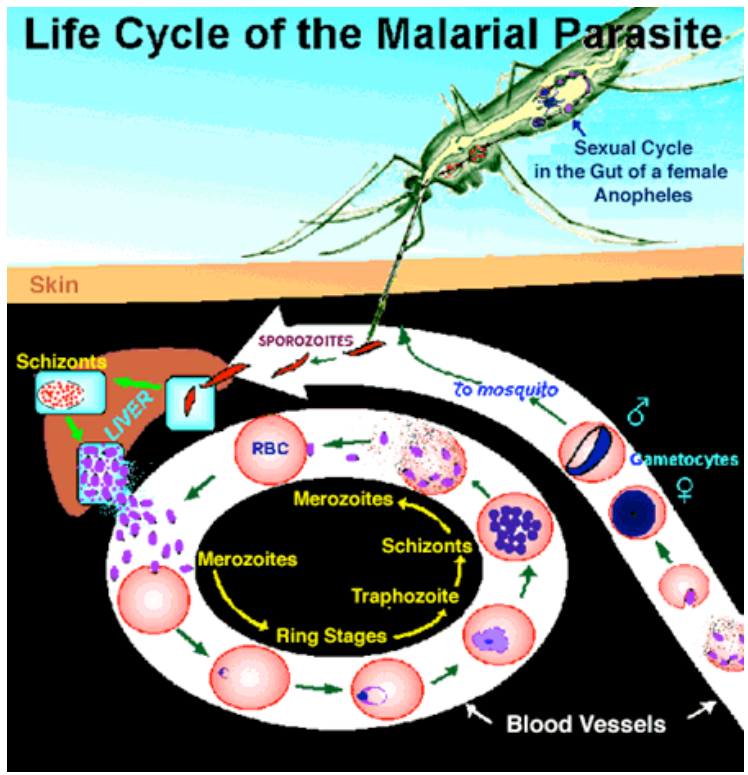
- A disease-modifying malaria vaccine with a high duration of infection...

  (for example, one which reduced mortality, but had no effect on the recovery rates)
- ...might be quite desirable for the developed world, if the prospect of reinfection is negligible.

Recommendation

Low-efficacy vaccines that result in high durations of infection must significantly lower the rate of infection if they are to be used in endemic areas.



Key reference

- R.J. Smith?, Could low-efficacy malaria vaccines increase secondary infections in endemic areas? (*Mathematical Modeling of Biological Systems, Volume II (2007). A. Deutsch, R. Bravo de la Parra, R. de Boer, O. Diekmann, P. Jagers, E. Kisdi, M. Kretzschmar, P. Lansky and H. Metz (eds). Birkhäuser, Boston, 3-10*)