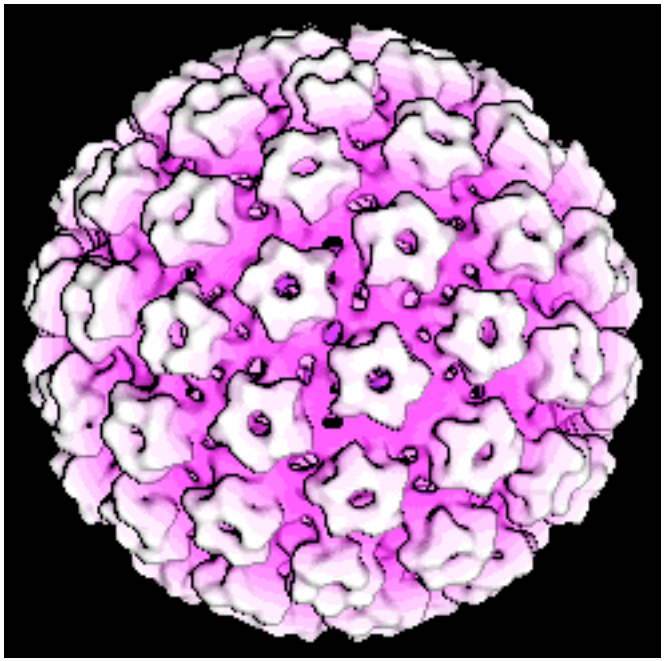
Evaluating HPV vaccination for children vs. adults

Robert Smith?

Departments of Mathematics and Faculty of Medicine
The University of Ottawa

Outline

- Epidemiology of HPV



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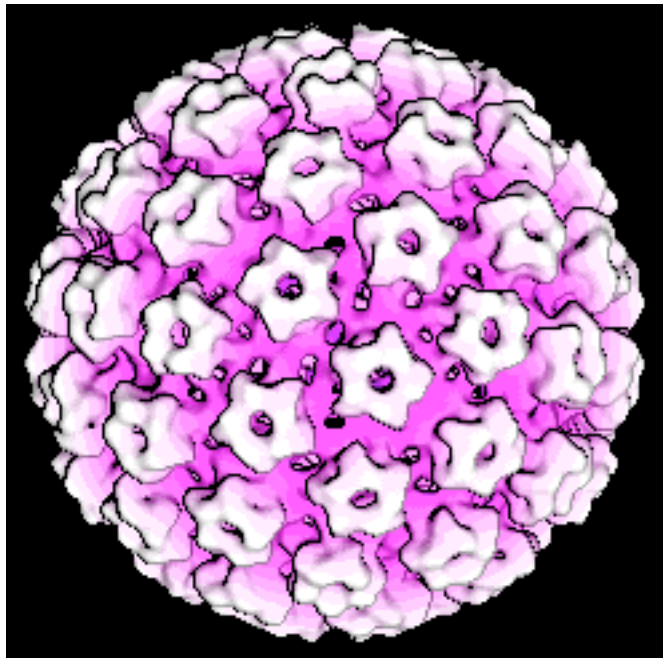

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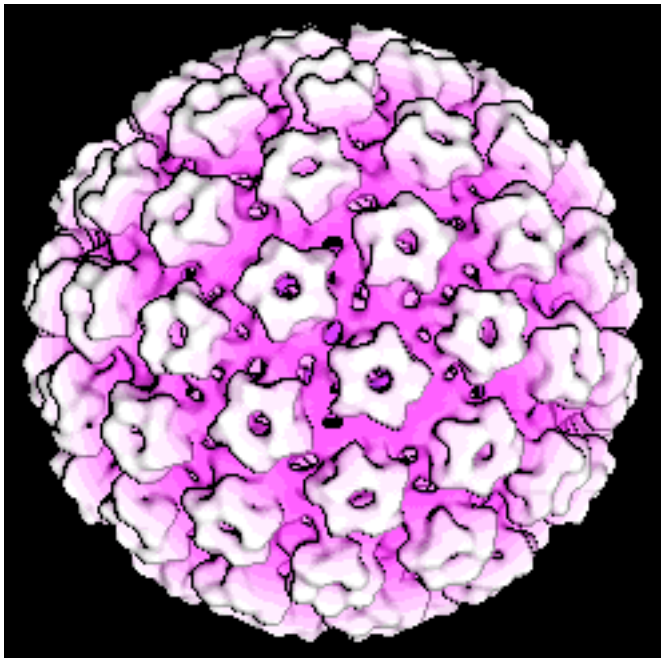

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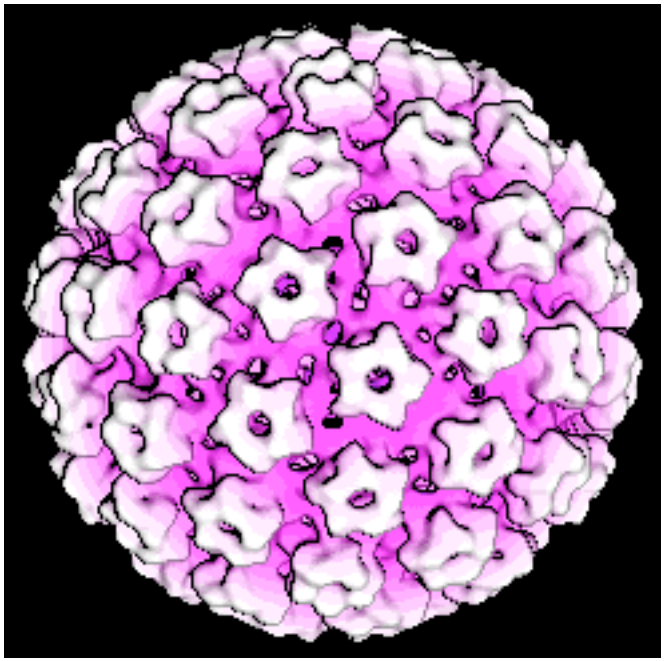
- The mathematical model



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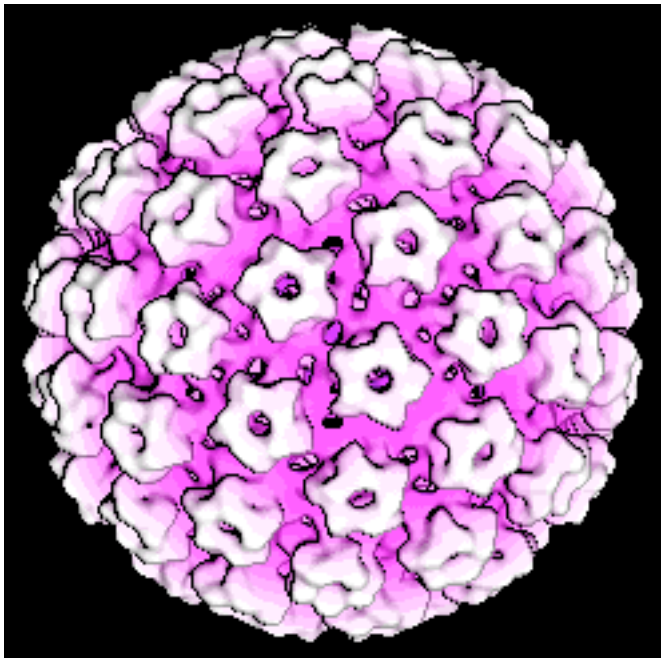

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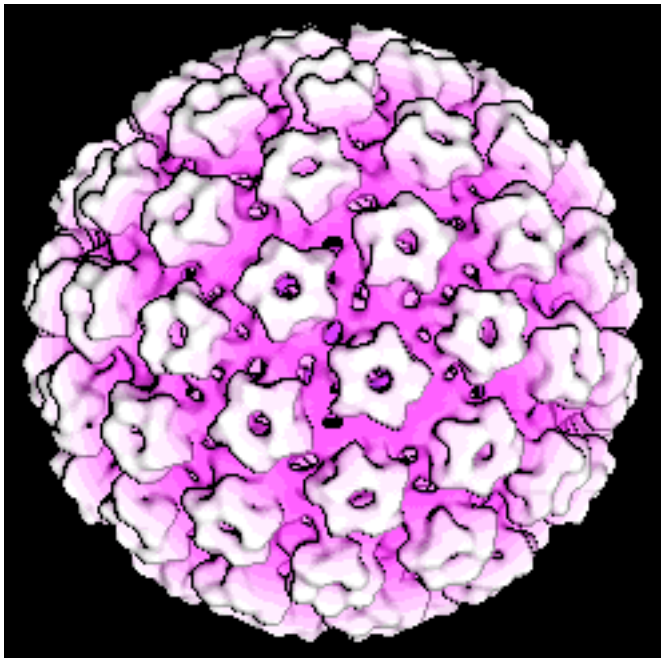

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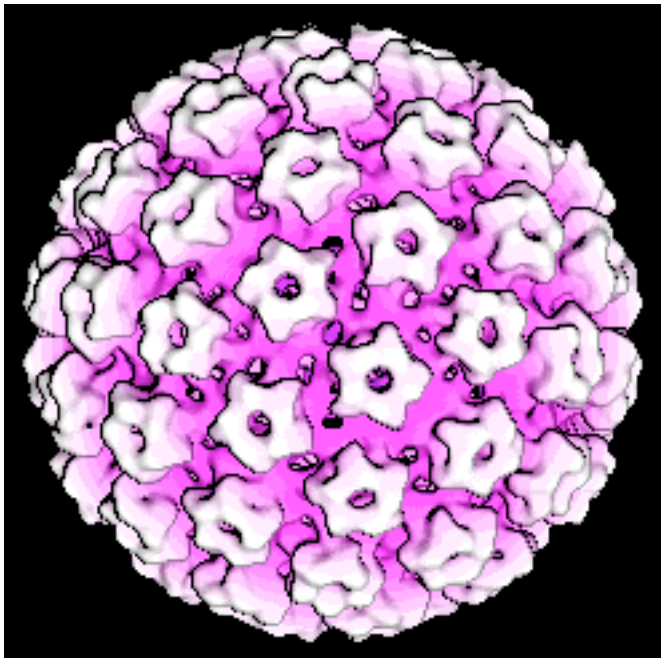

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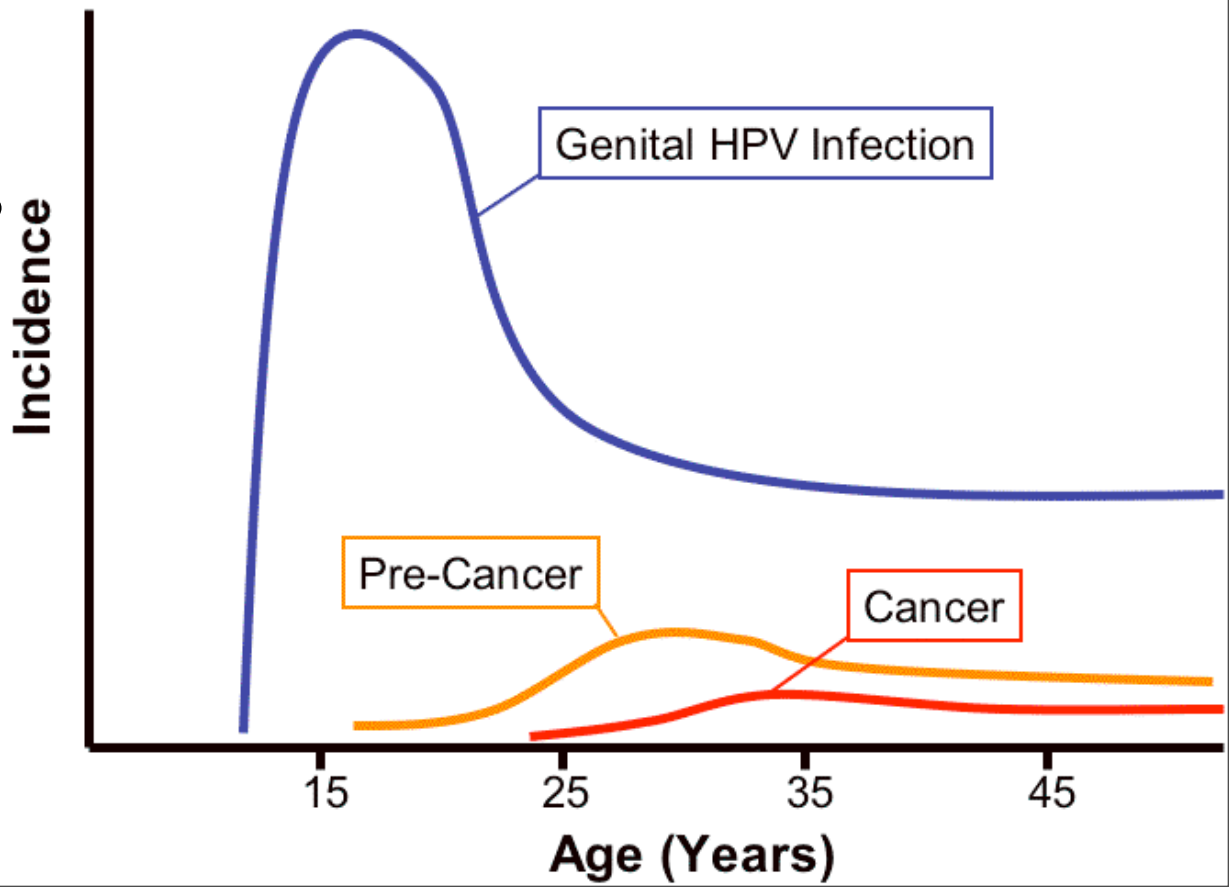

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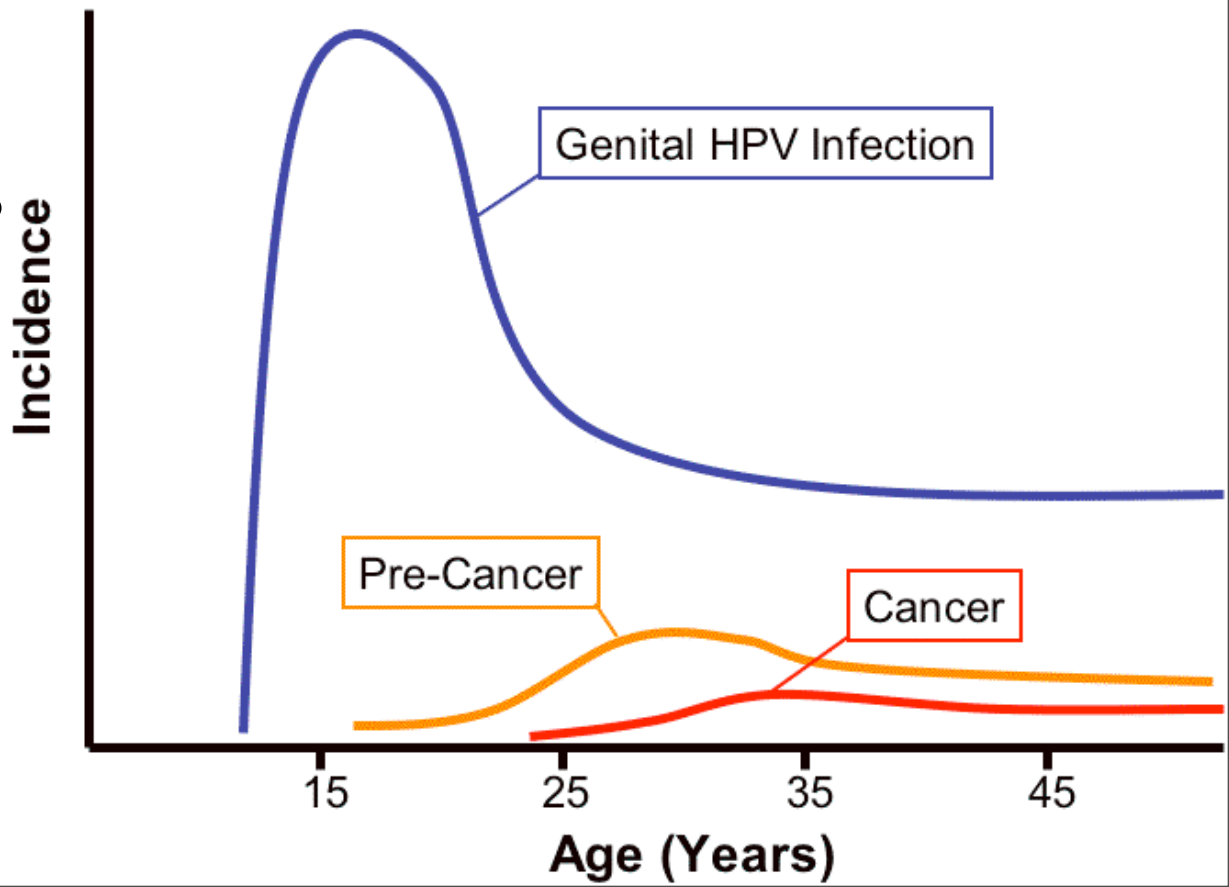

HPV infections

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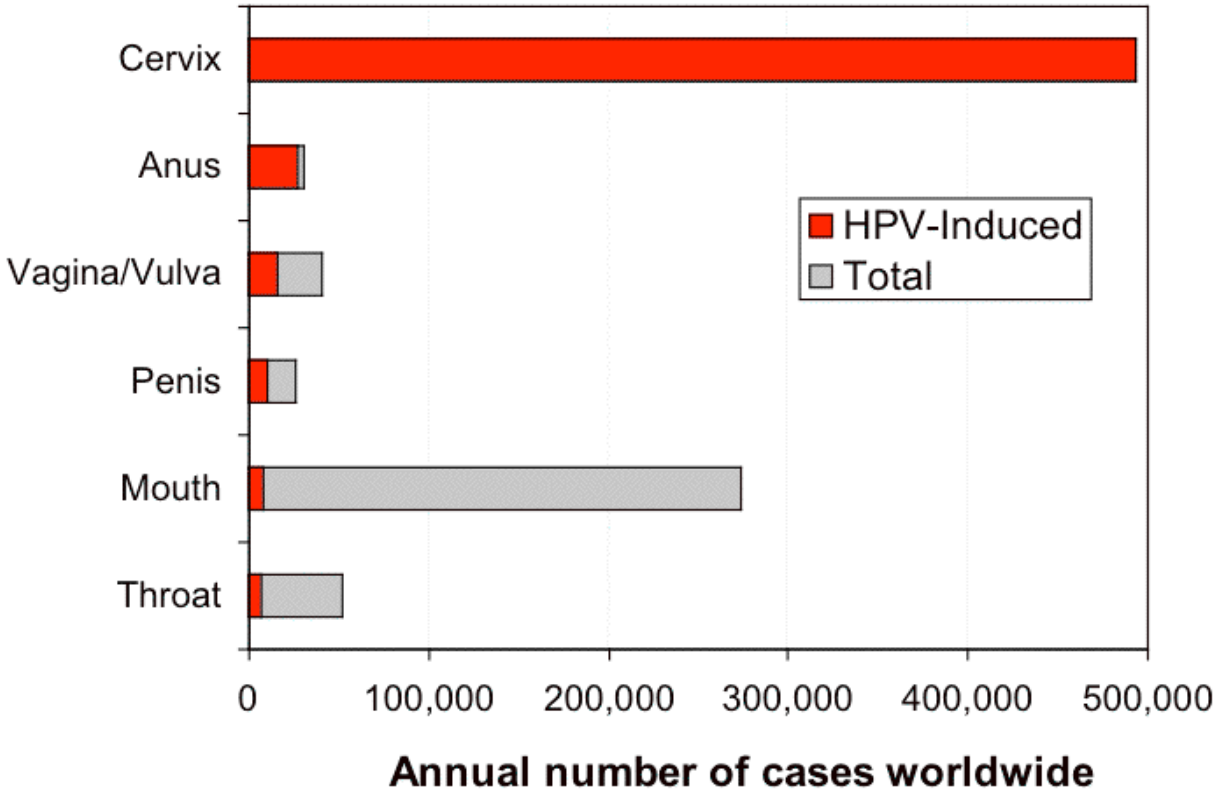

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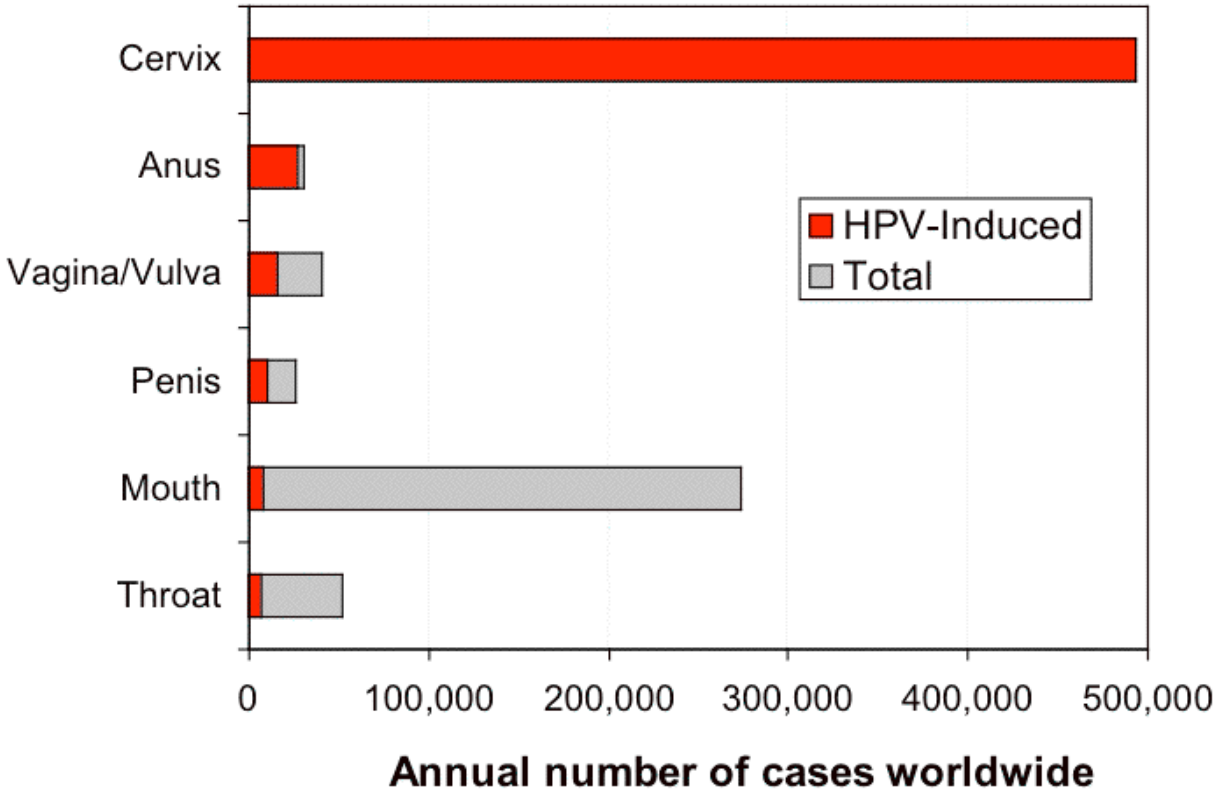

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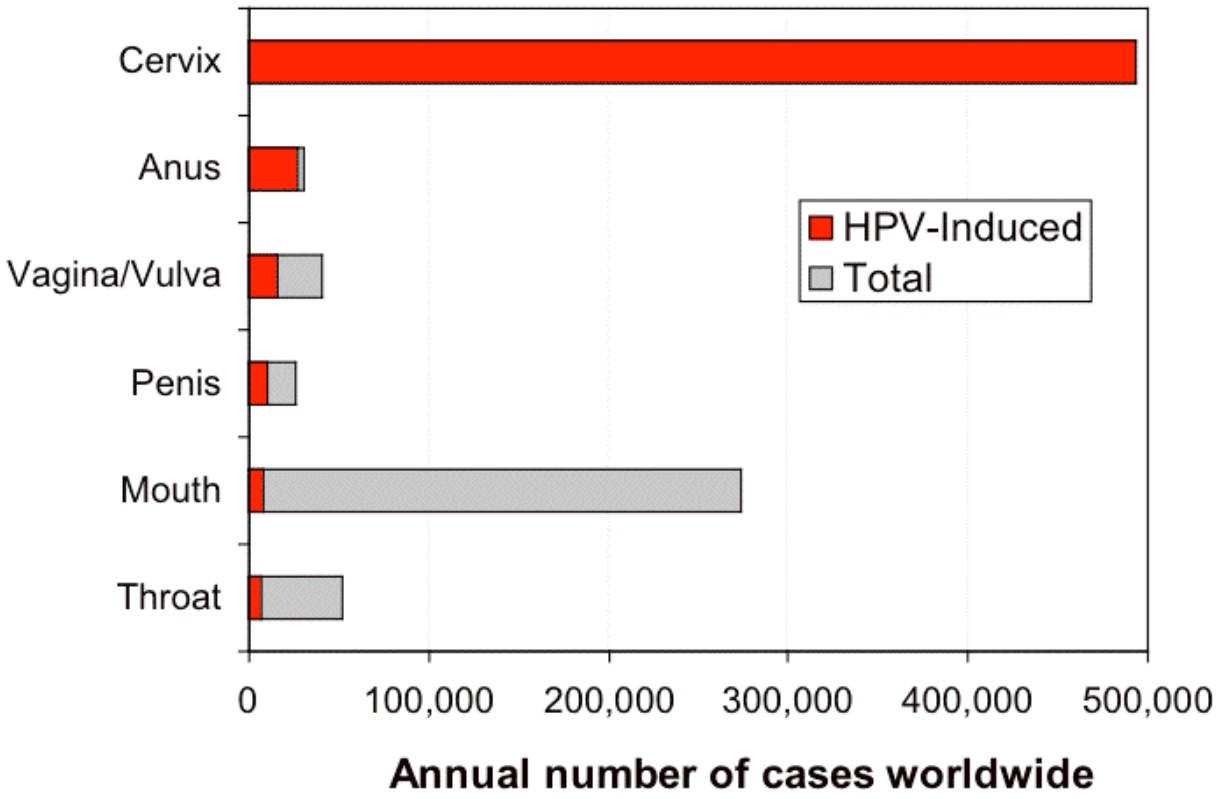

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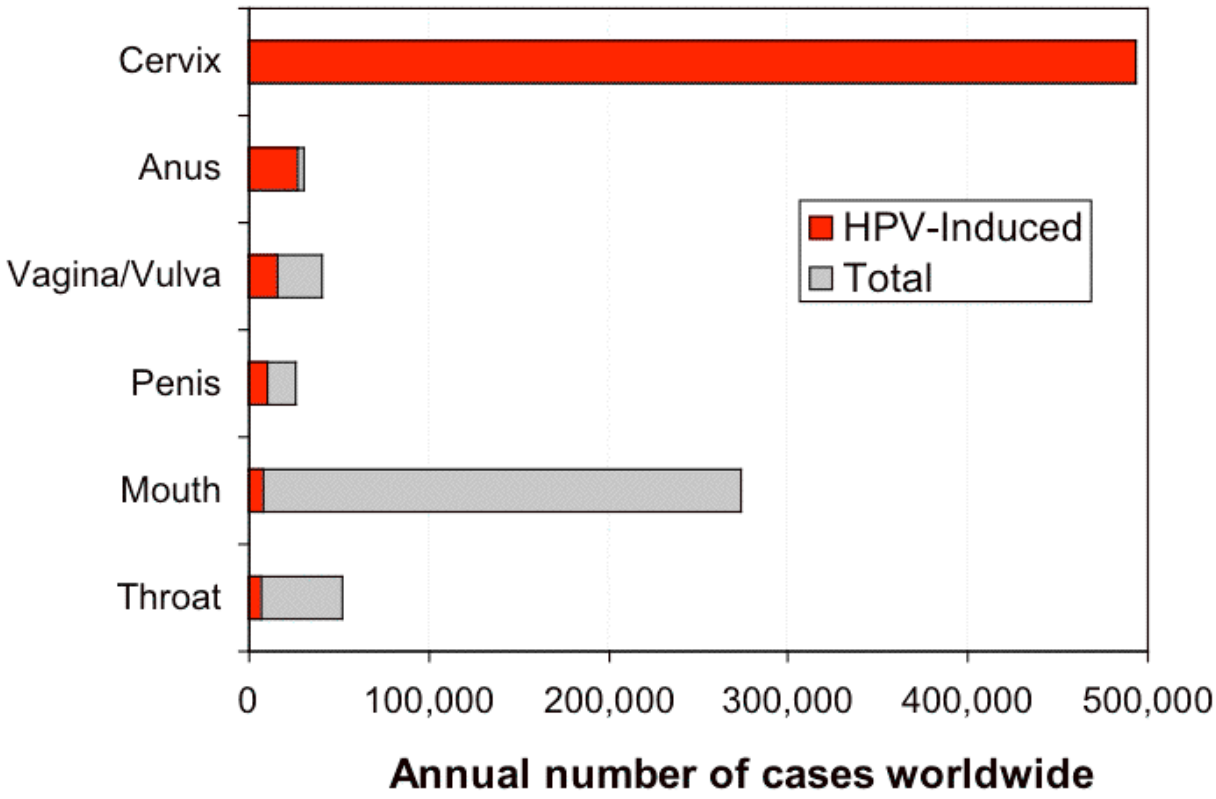

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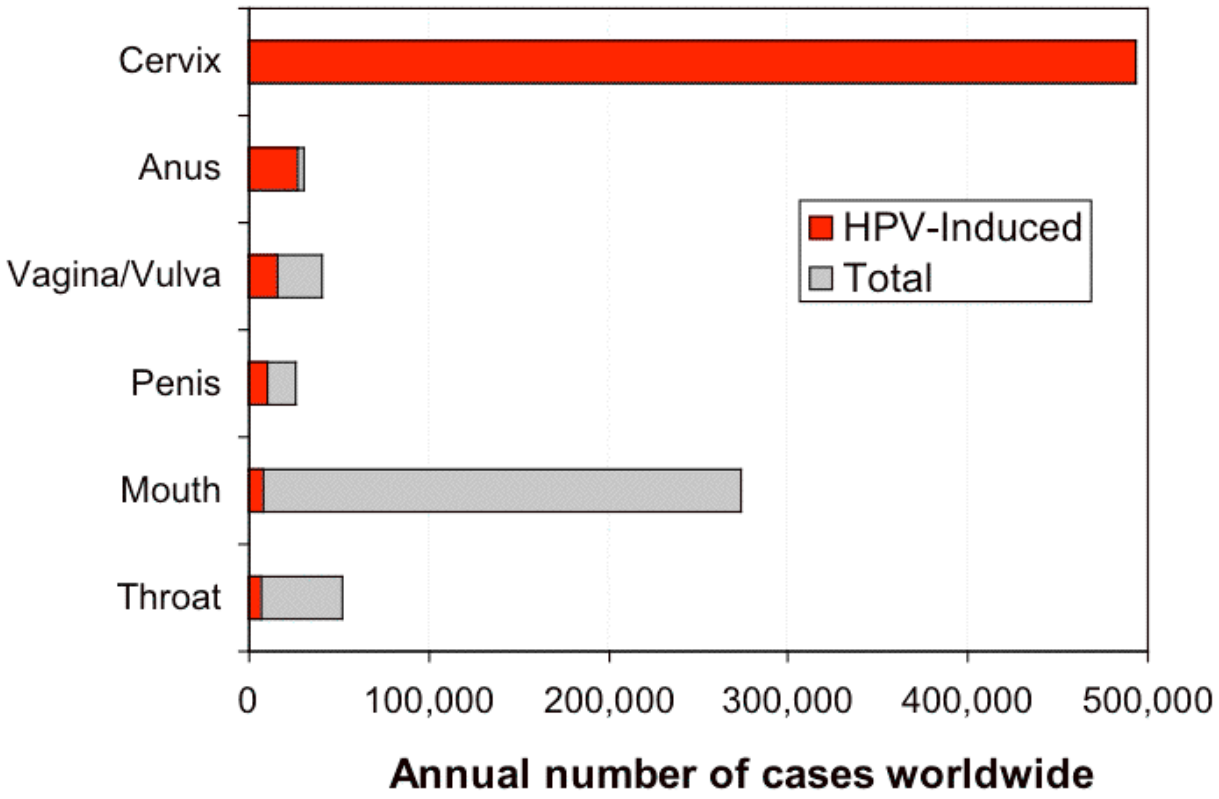

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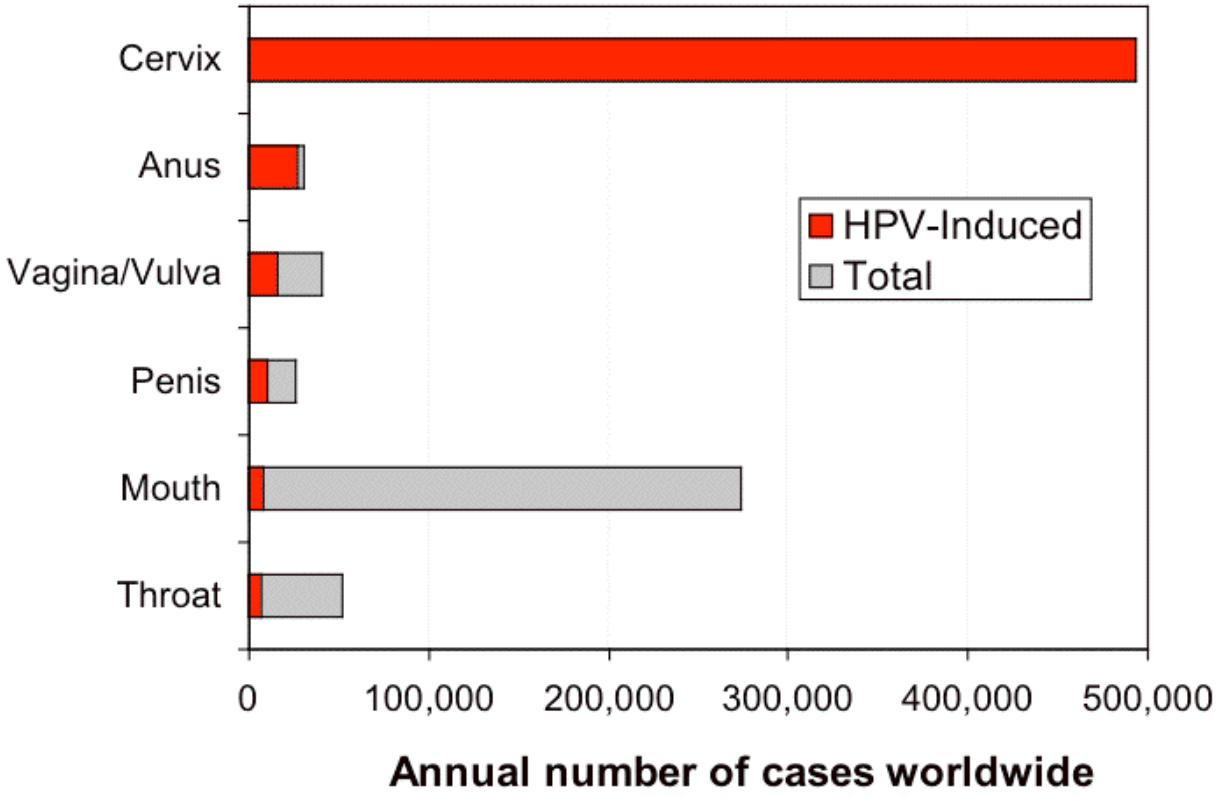

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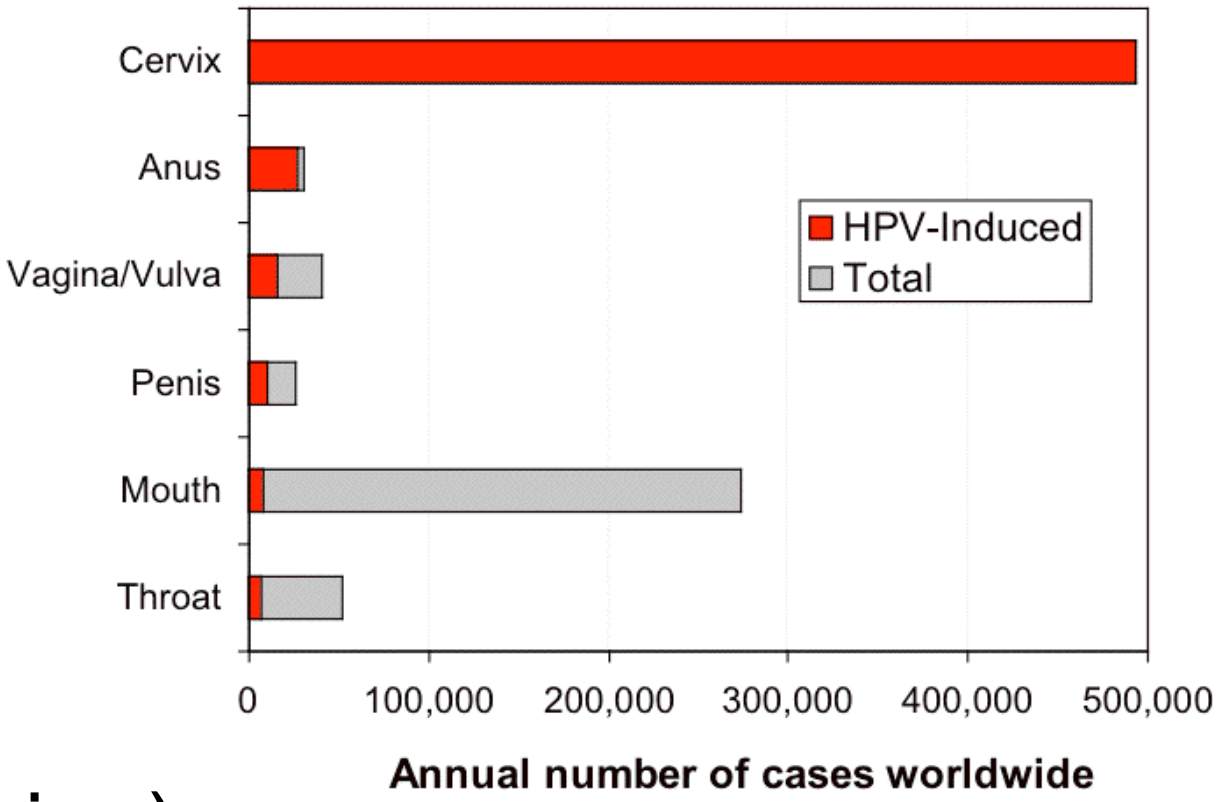

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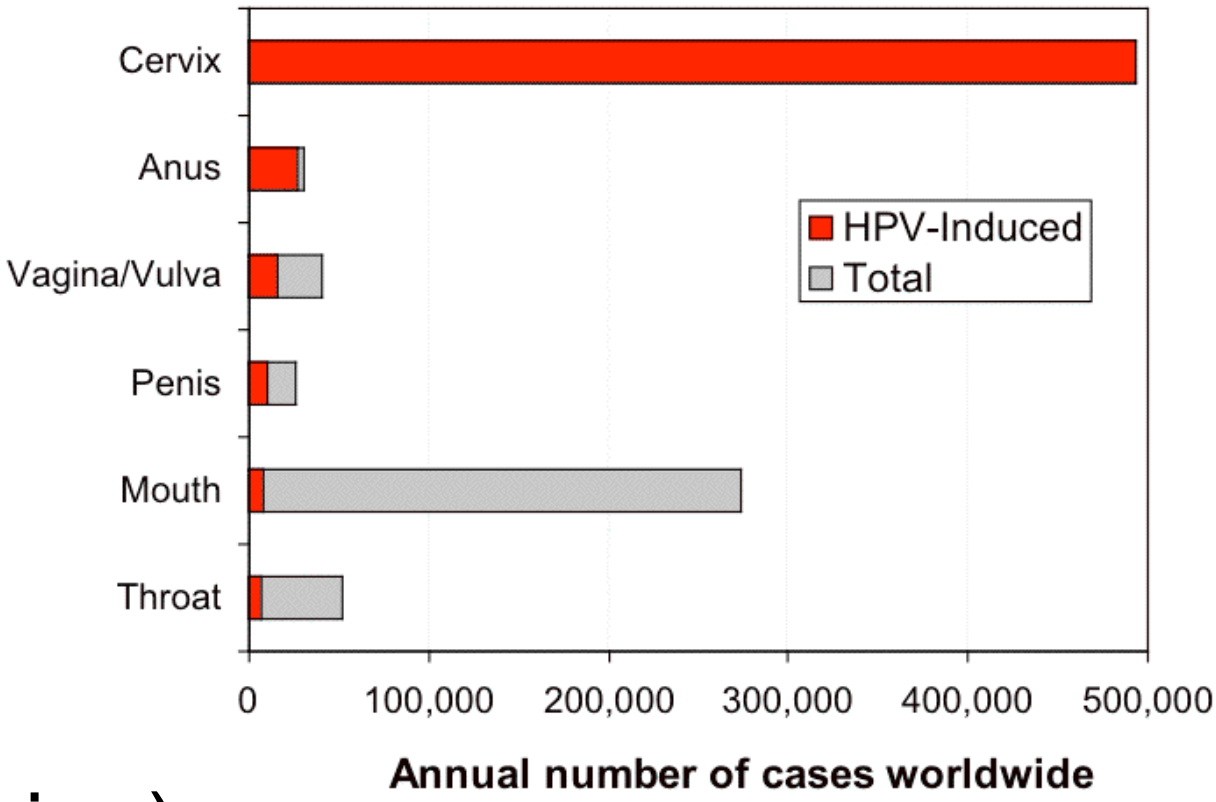

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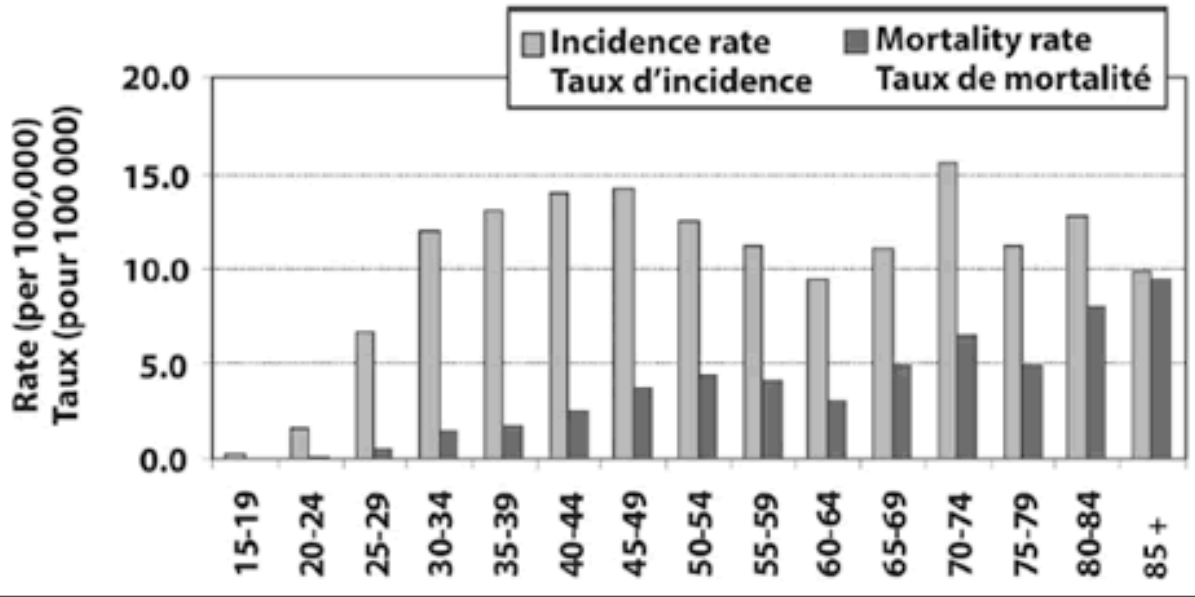
- Cervical cancer is the second most common cause of death from cancer in women.

Infections in the US

- 6,200,000 infections per year



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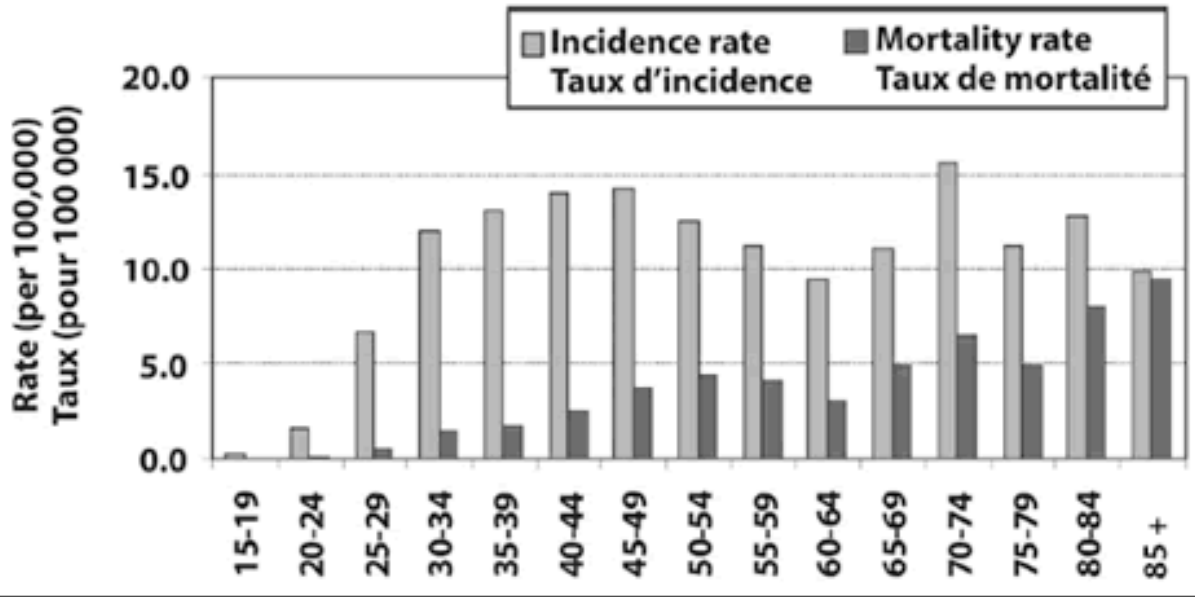

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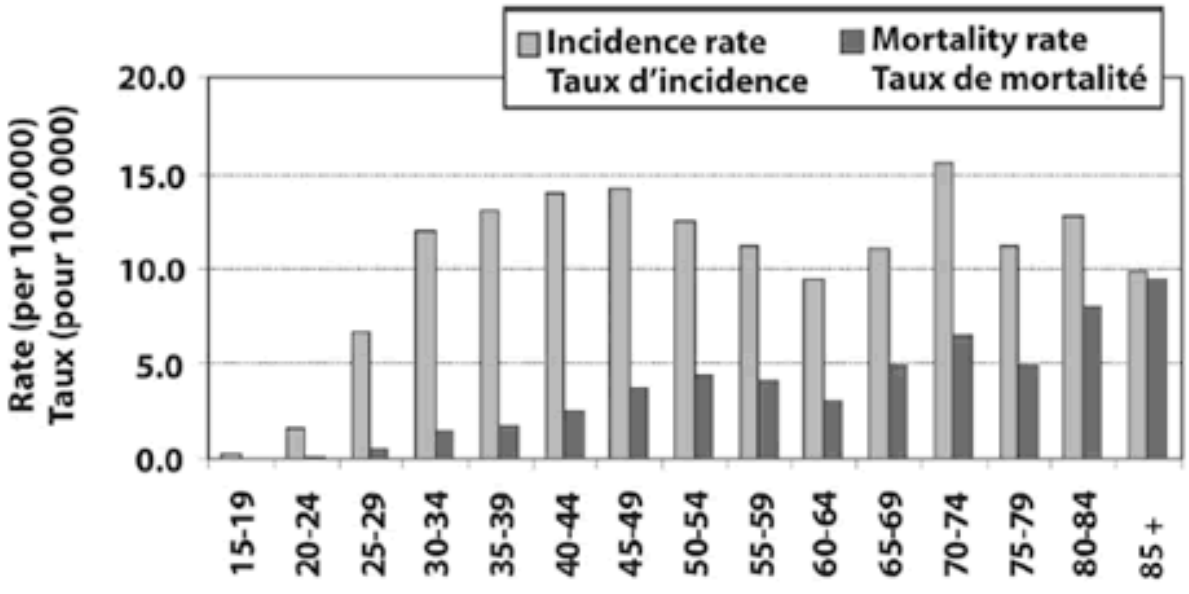

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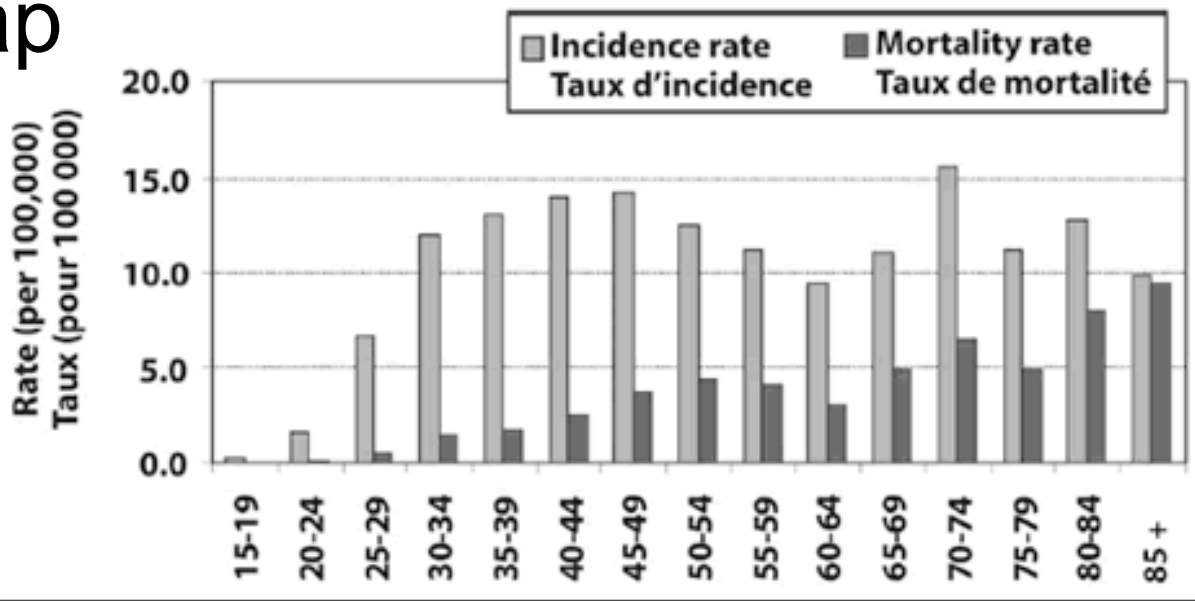
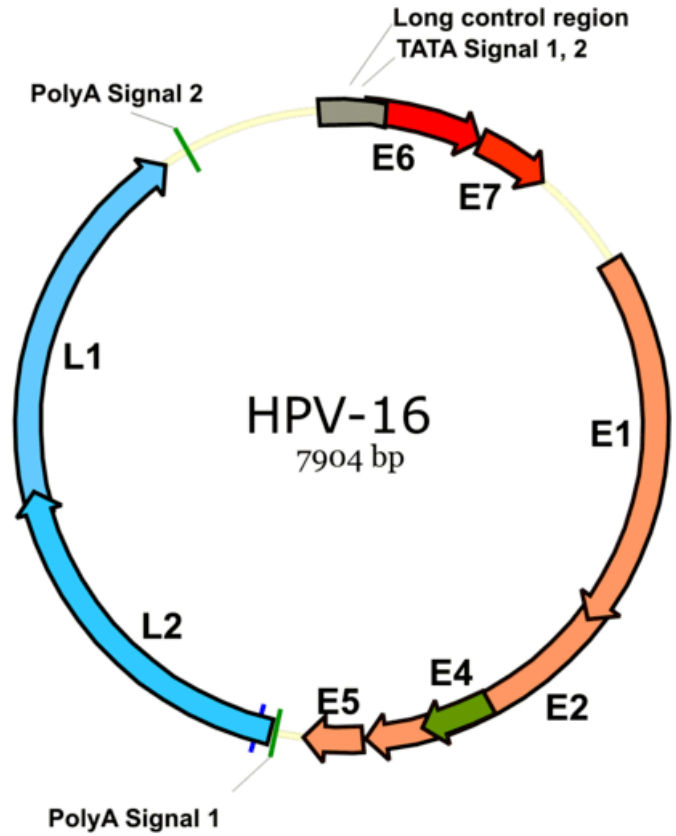
(many fewer than would be caused by HPV, due to effective pap smear screening and precancer treatments).



HPV strains of interest

- Types 6 and 11 account for 90% of genital wart infections



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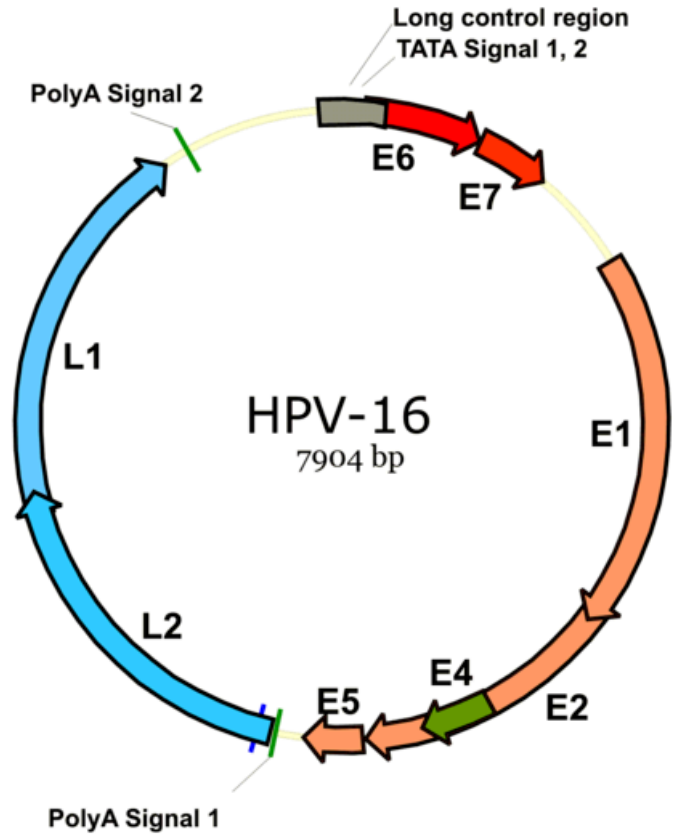

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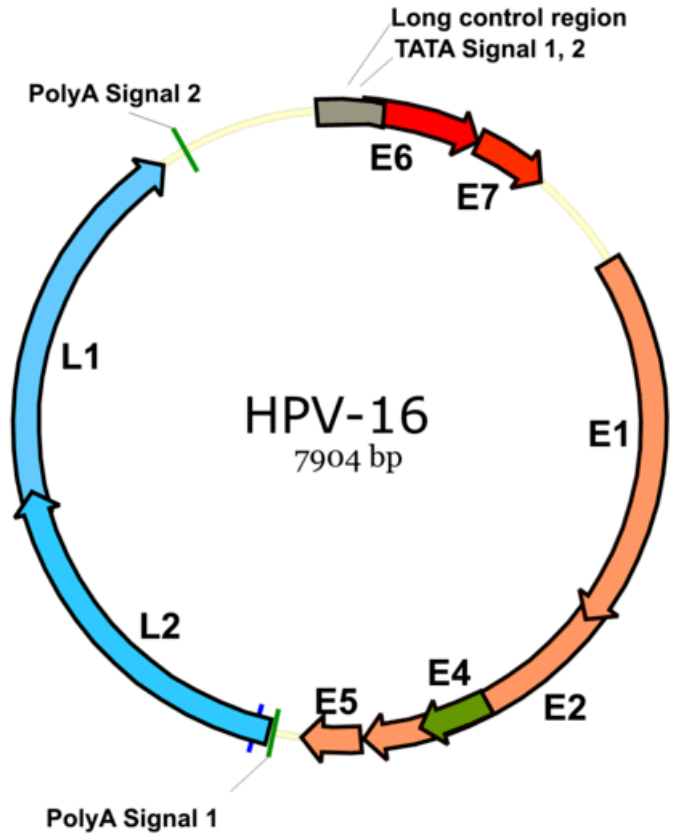

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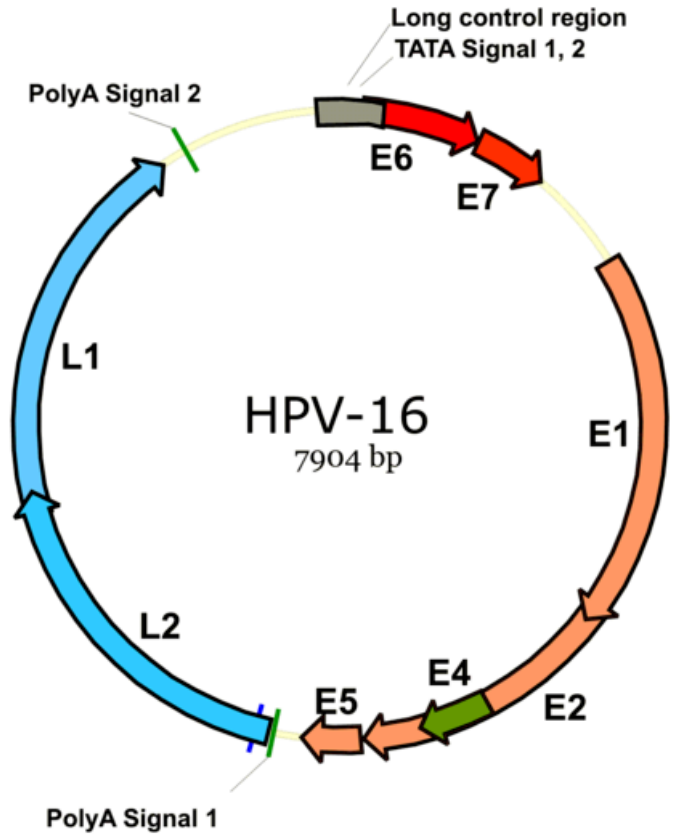
- Types 16 and 18 are responsible for 65% of cervical cancer cases.



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- Vaccines are estimated at 90-100% efficacy.

The vaccines

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- Some evidence of cross-protection against strains 31 and 45 (the other cancer strains).

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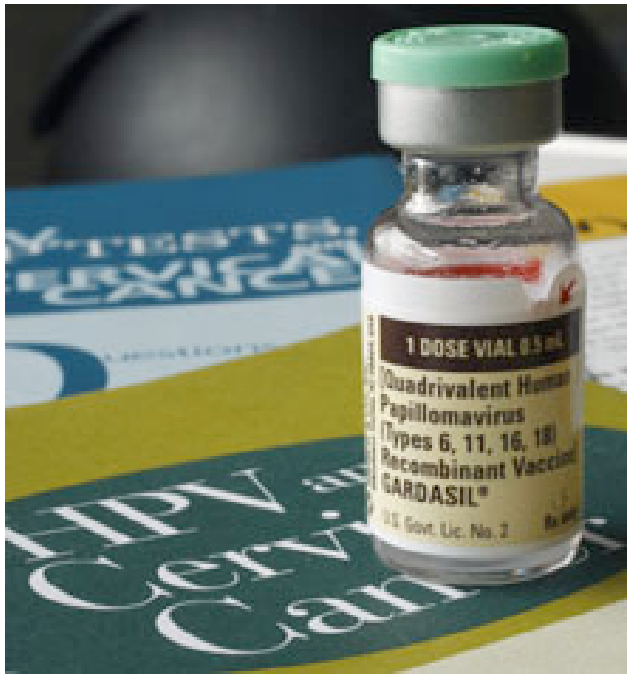

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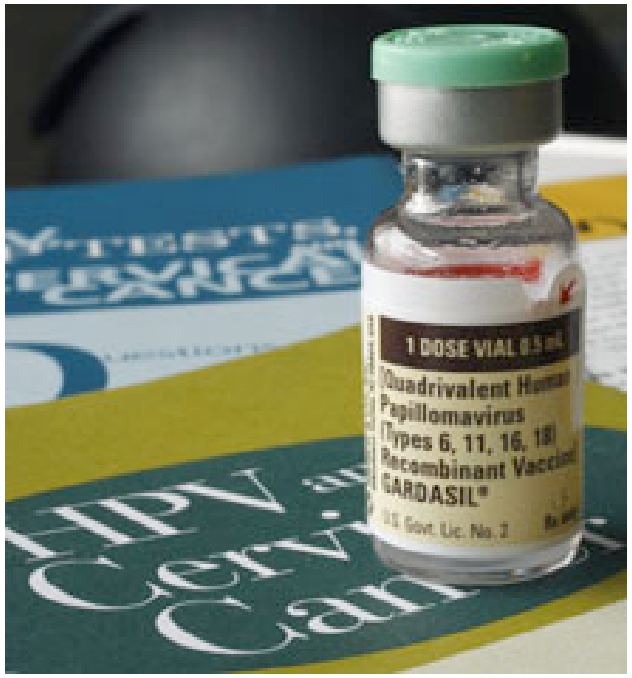

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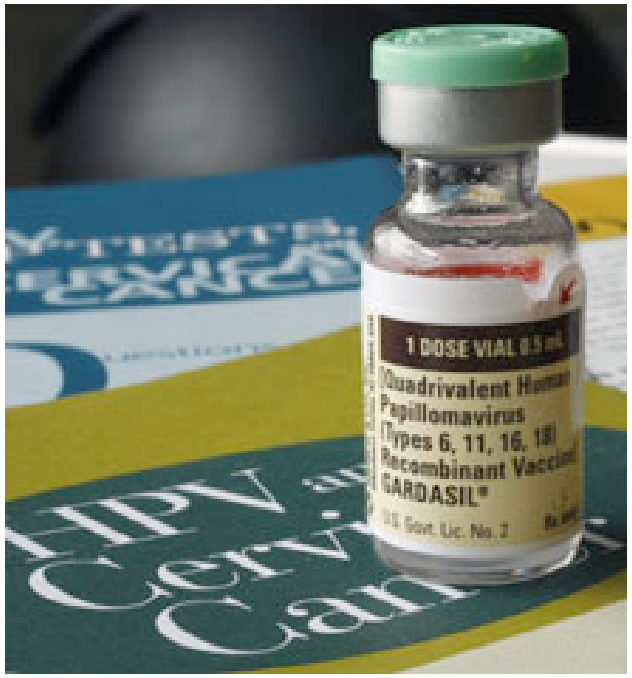

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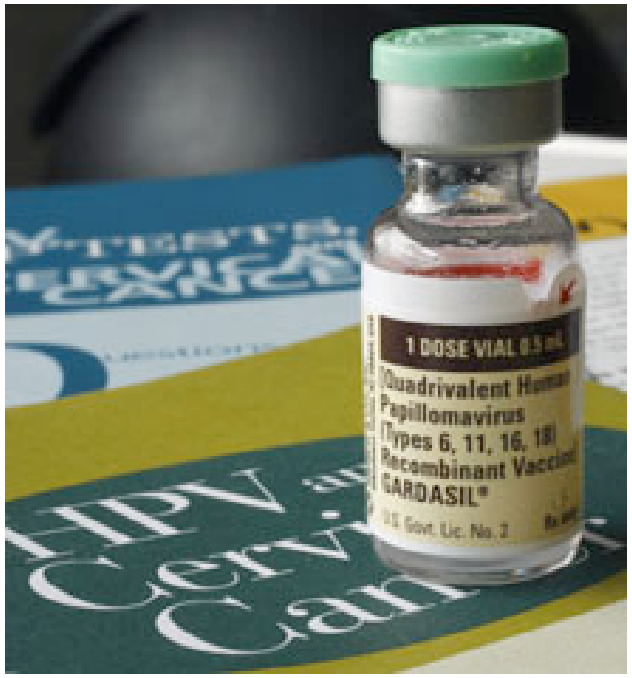

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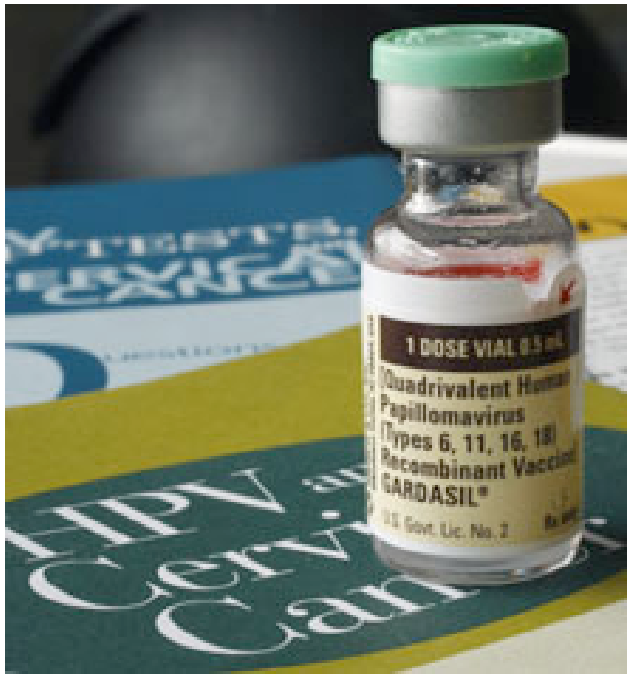

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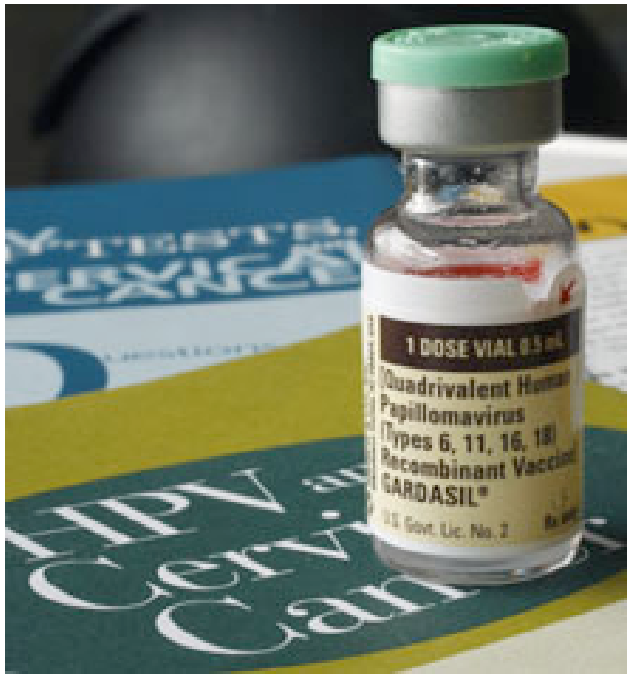

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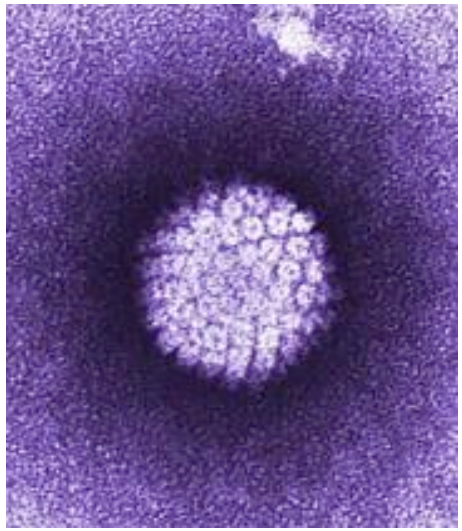

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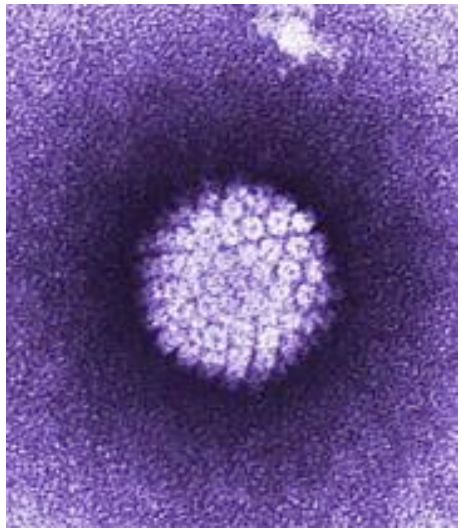

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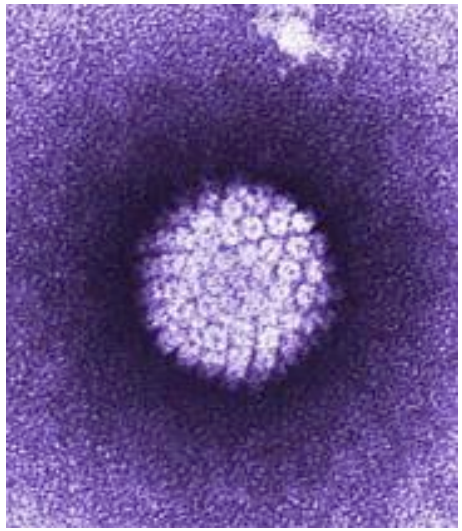
- However, uptake rates are low
- Thus, we'll assume vaccinated men have a negligible effect on the outcome.



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- The vaccine is available to women aged 14-26, but is not covered by Canadian health plans.

Coverage levels

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- In the first year, Ontario reported only 53% vaccination coverage.

Research questions

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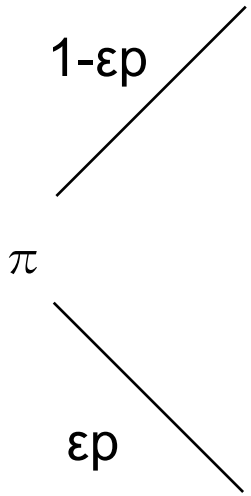
The model



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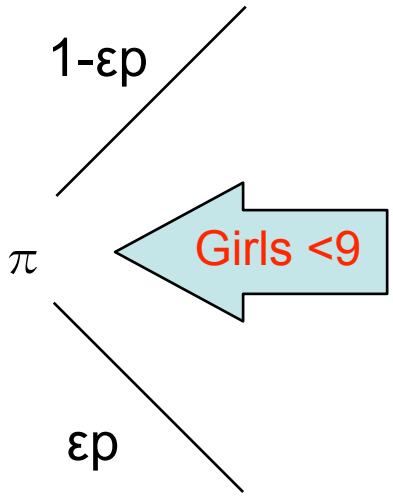

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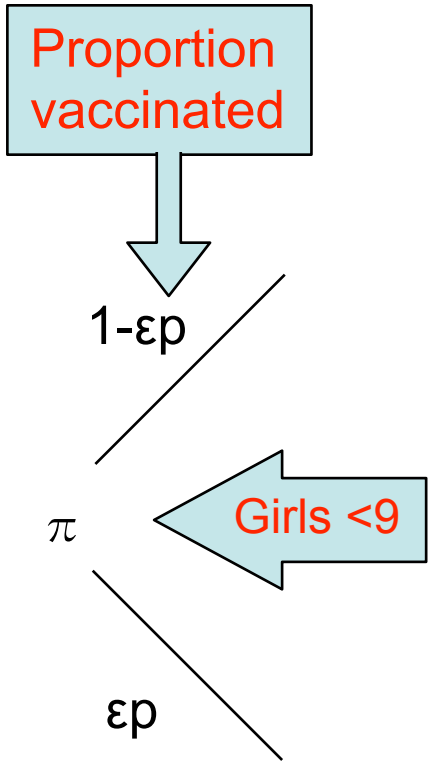

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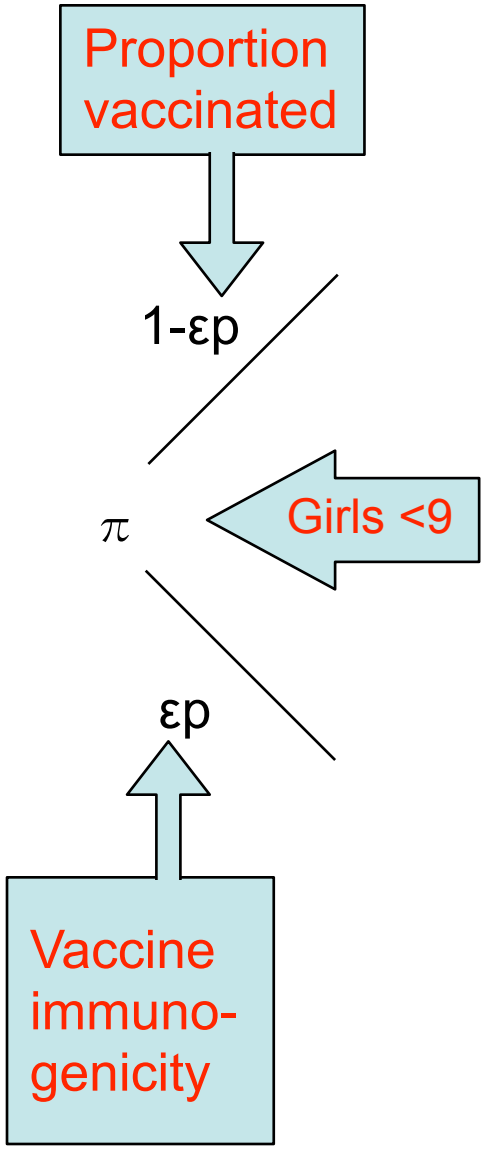
Proportion vaccinated
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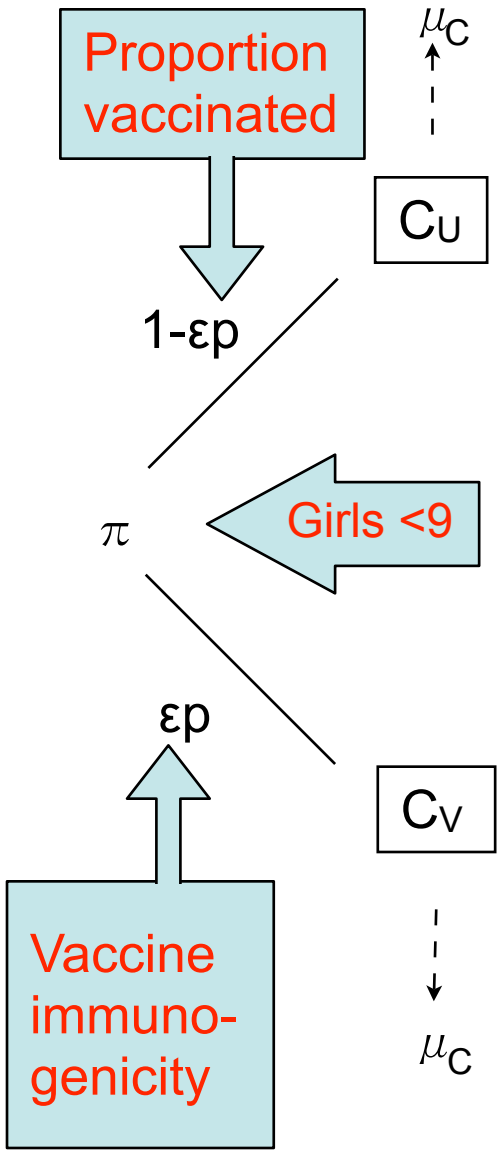
π
Girls <9
εp
Vaccine immuno-genicity

The model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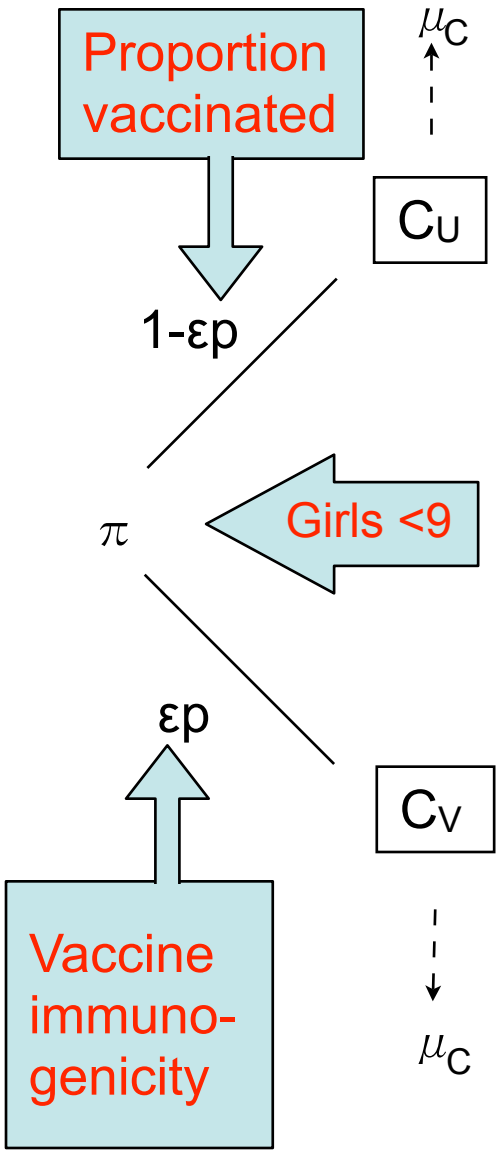

UNVACCINATED

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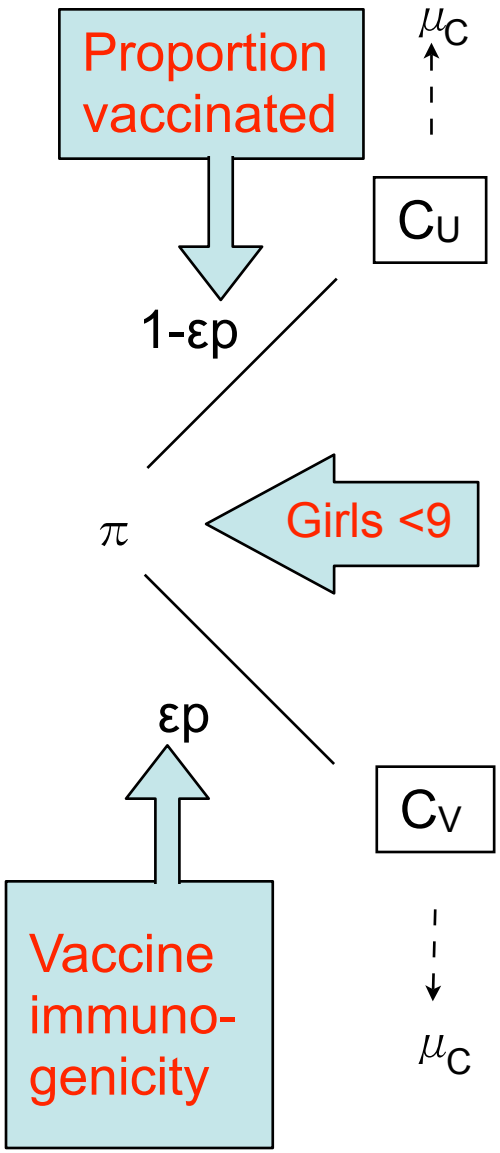

UNVACCINATED

VACCINATED

The model


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C_V
VACCINATED
Vaccine immuno-genicity
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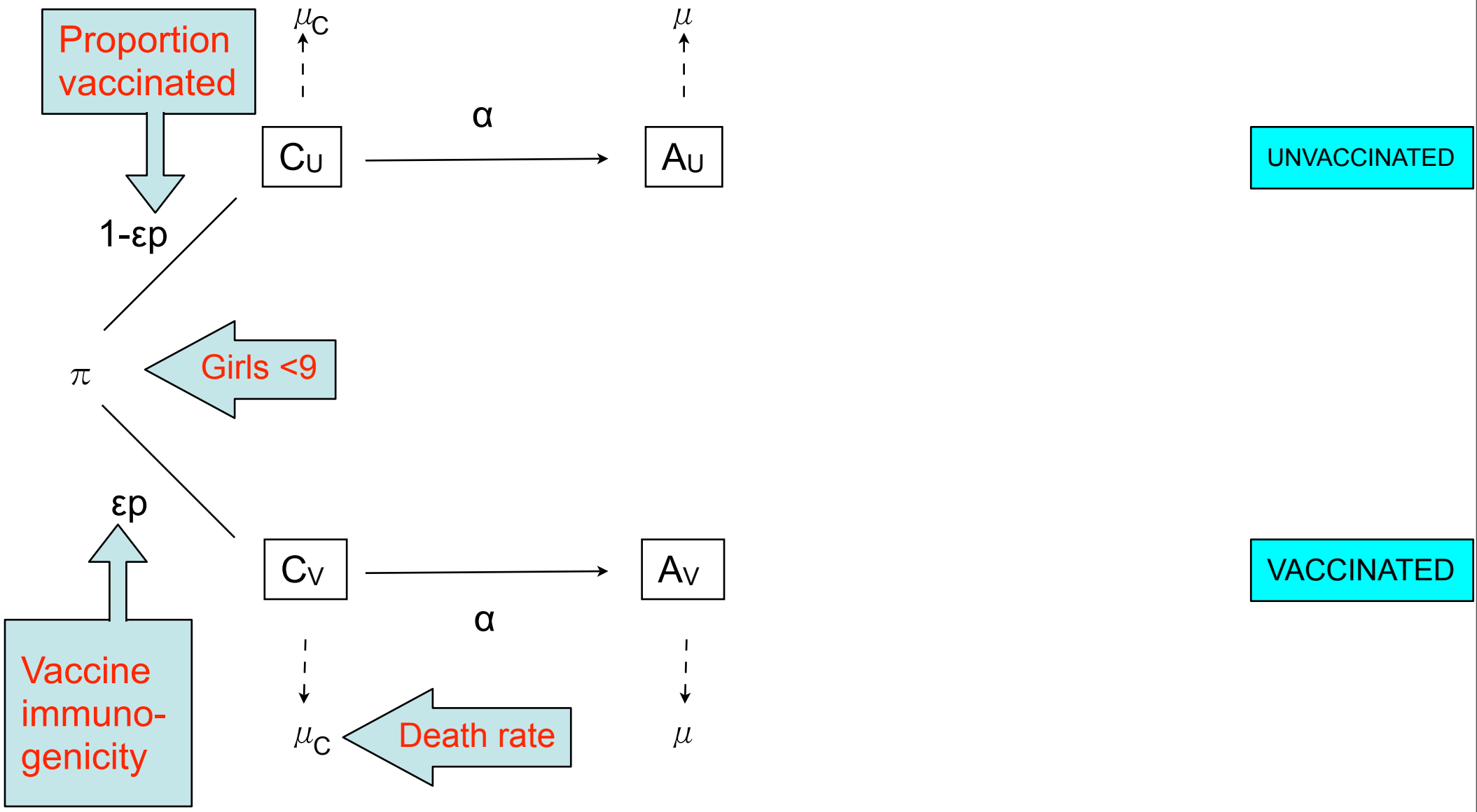
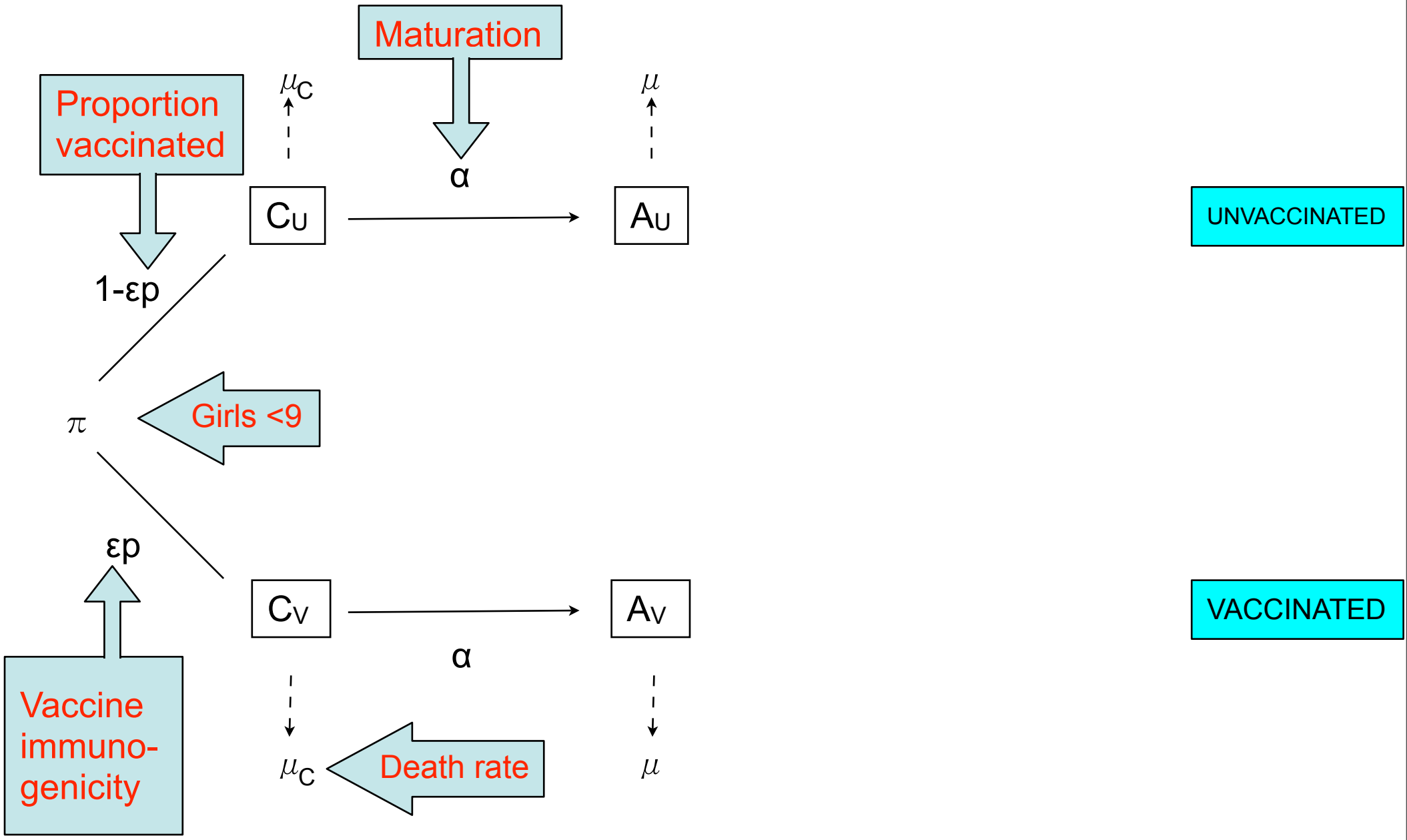
Death rate

The model


Proportion vaccinated
μ_C
μ
α
C_U
A_U
UNVACCINATED
1-εp
π
Girls <9
εp
C_V
A_V
VACCINATED
α
Vaccine immuno-genicity
μ_C
Death rate
μ

The model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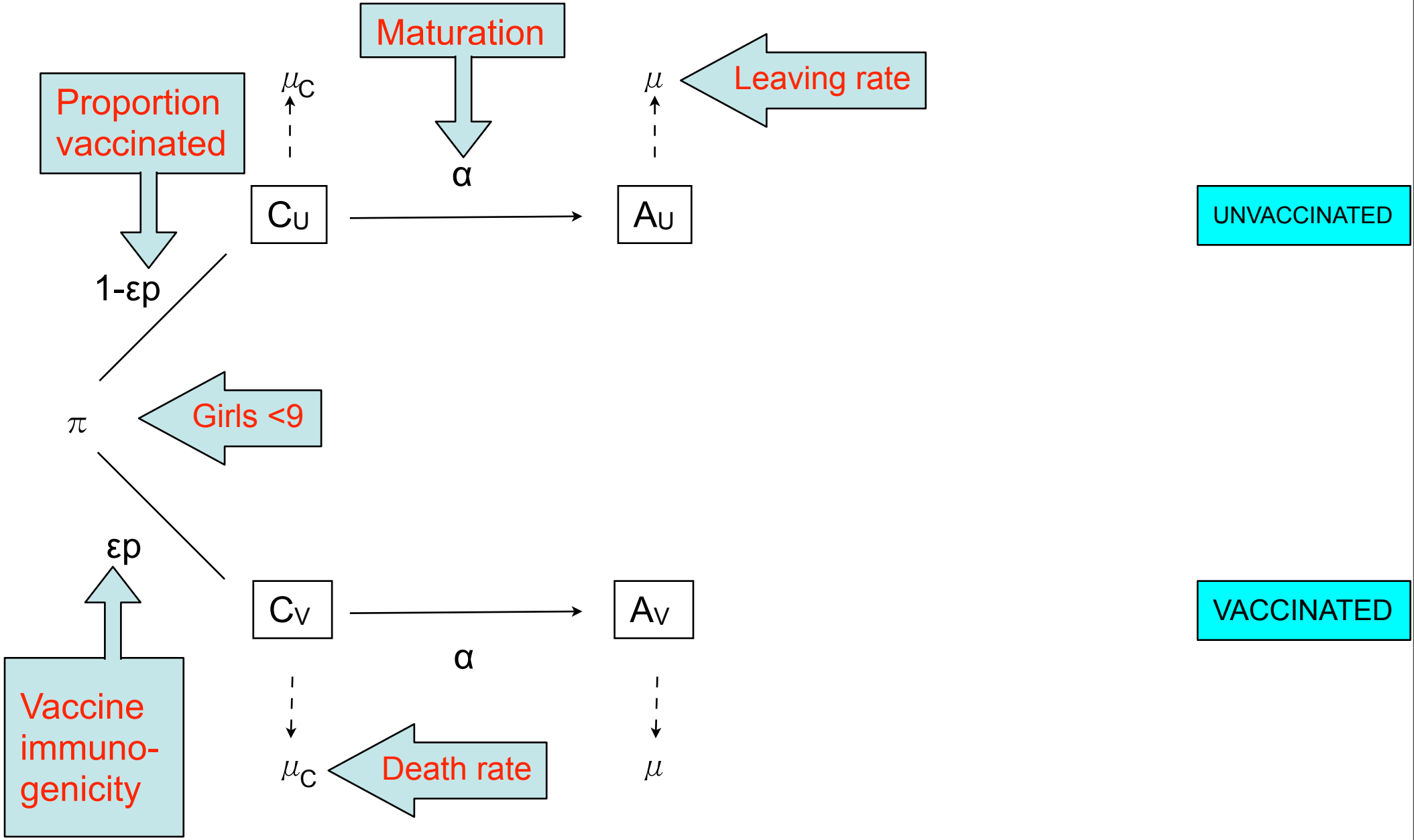
Maturation
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Leaving rate
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Vaccine immuno-genicity
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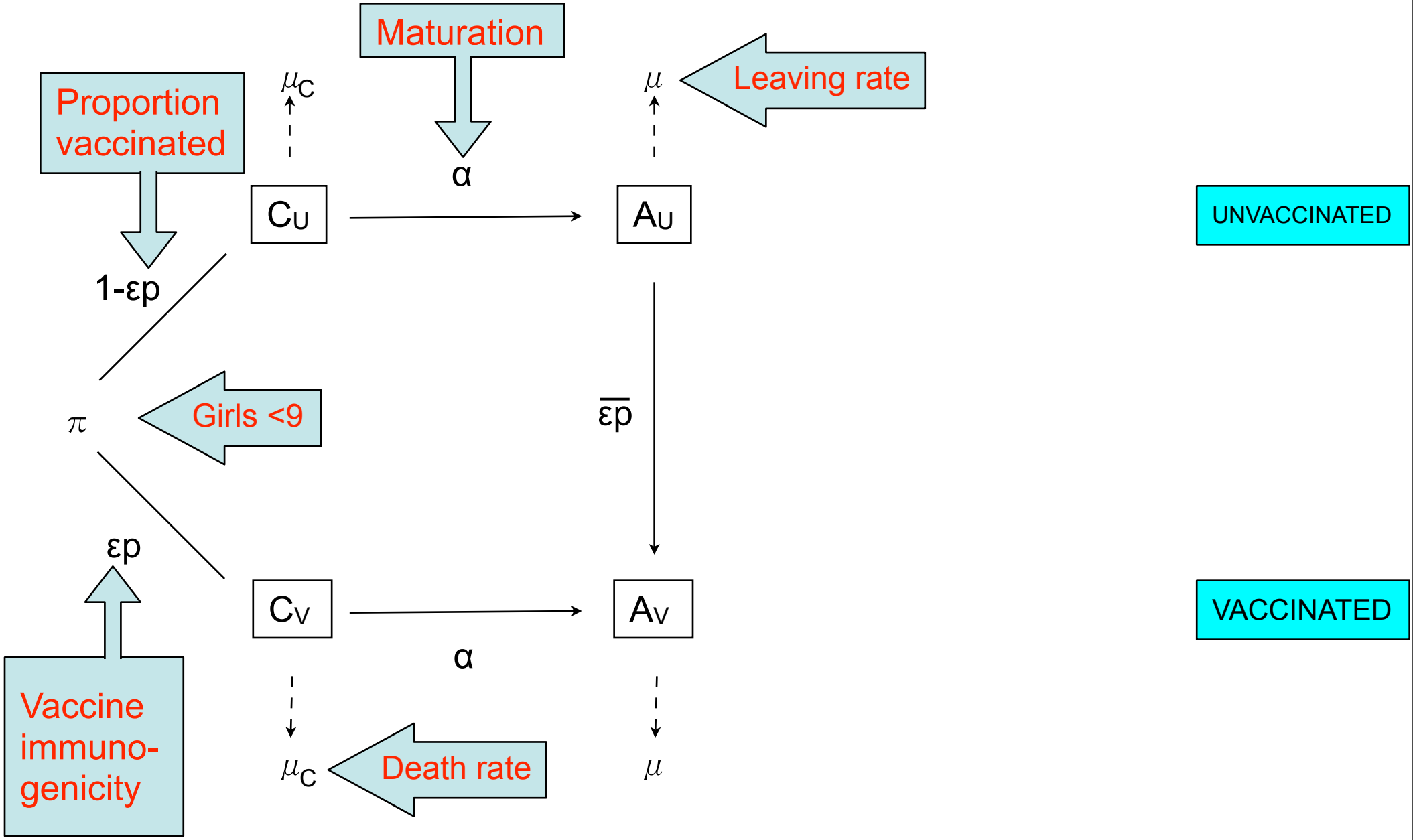
The model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$\overline{\varepsilon p}$
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Vaccine immuno-genicity
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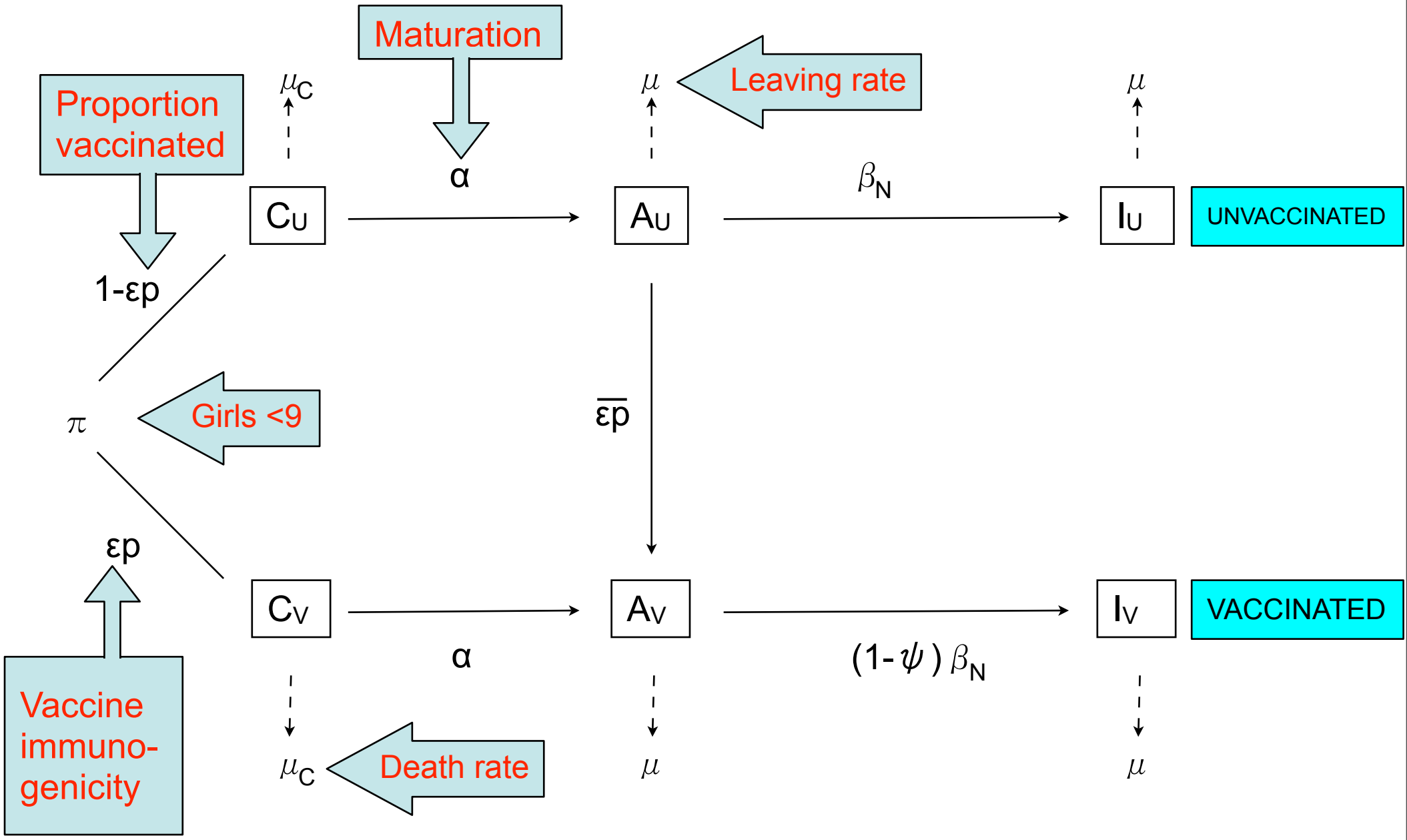
The model


Maturation
Proportion vaccinated
μ_C
μ
Leaving rate
μ
α
β_N
C_U
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1-εp
π
Girls <9
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εp
C_V
A_V
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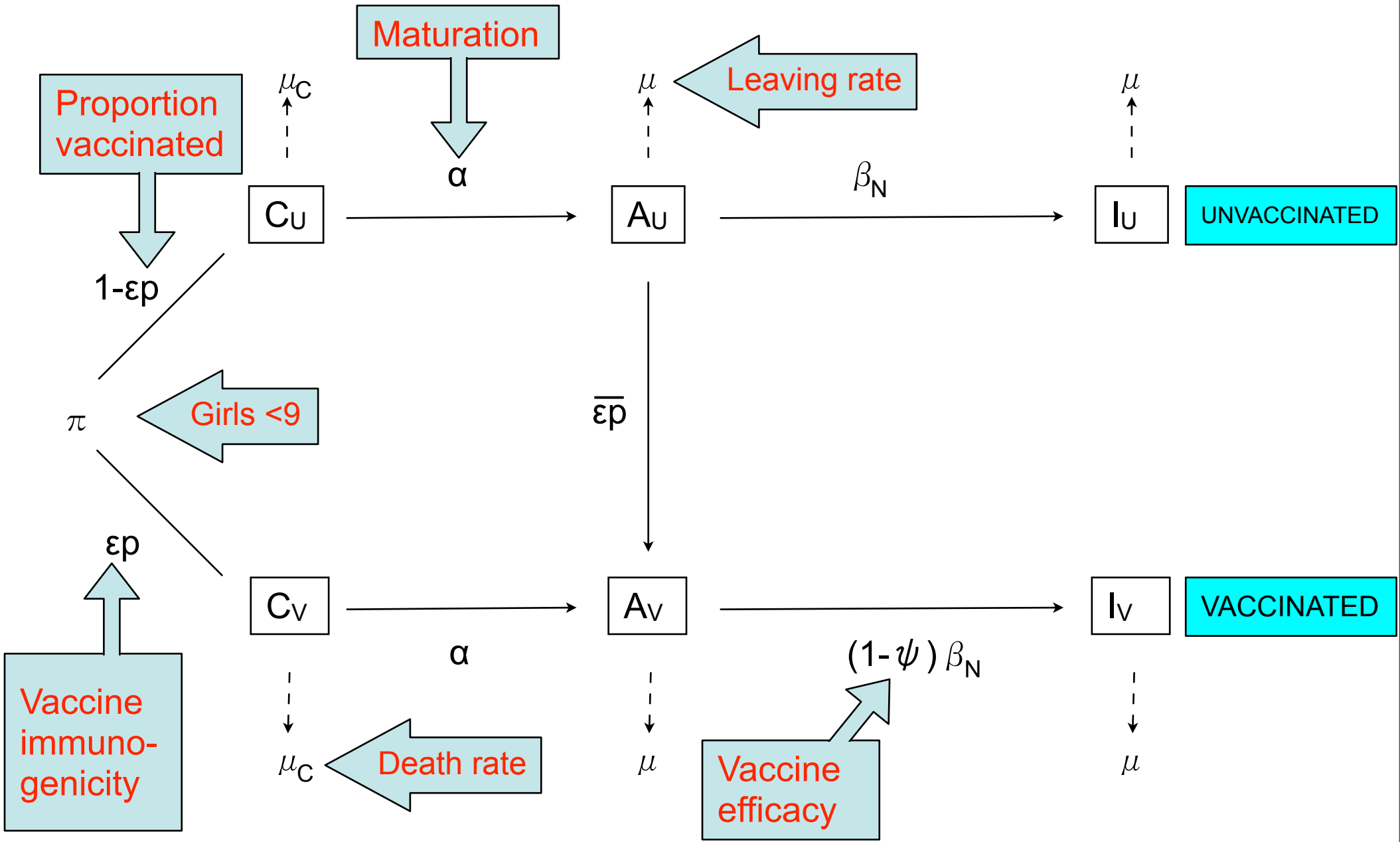
VACCINATED
α
$(1-\psi)\,\beta_N$
Vaccine immuno-genicity
μ_C
Death rate
μ
μ

The model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C_V
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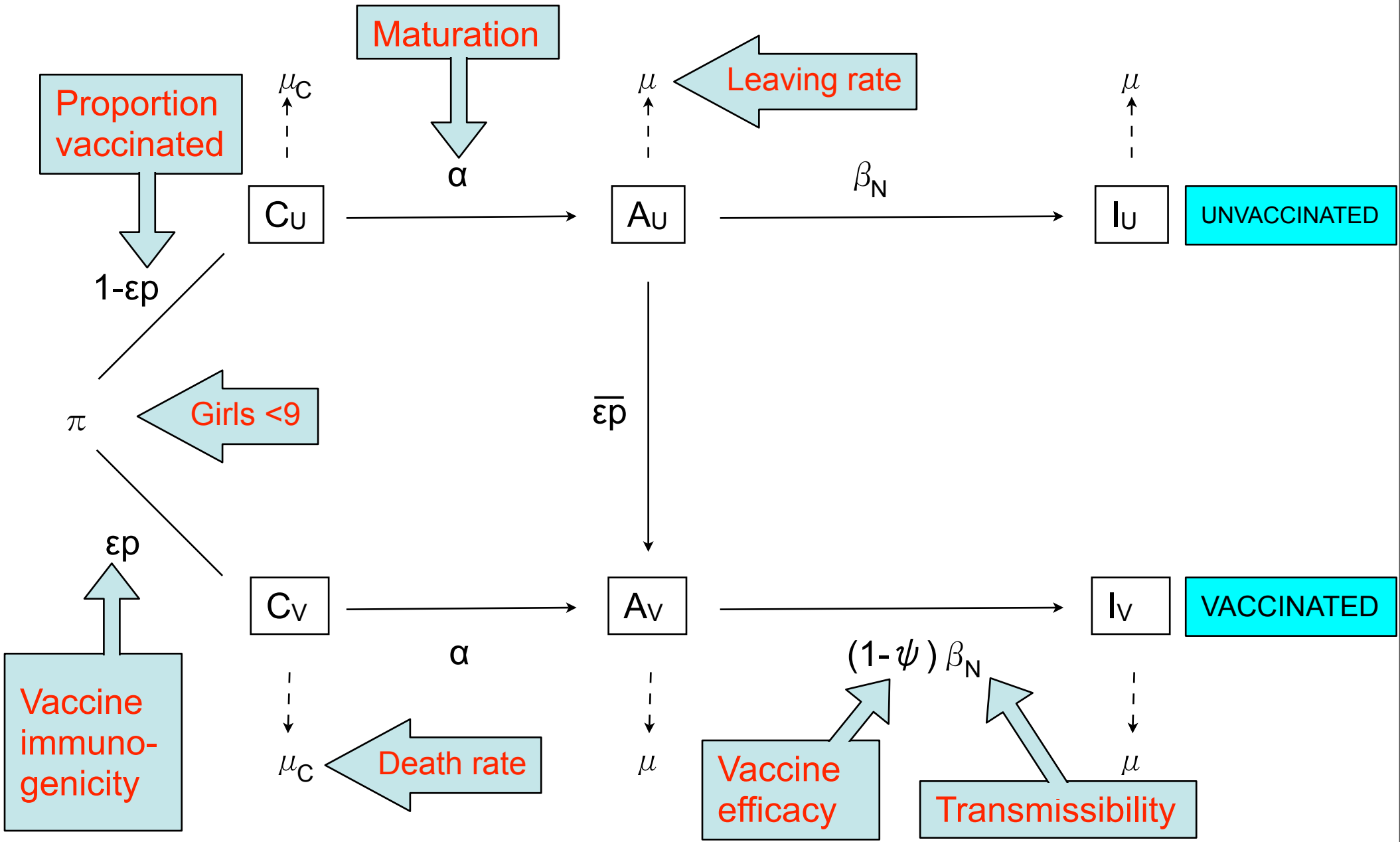
α
$(1-\psi)\,\beta_N$
Vaccine immuno-genicity
μ_C
Death rate
μ
Vaccine efficacy
μ

The model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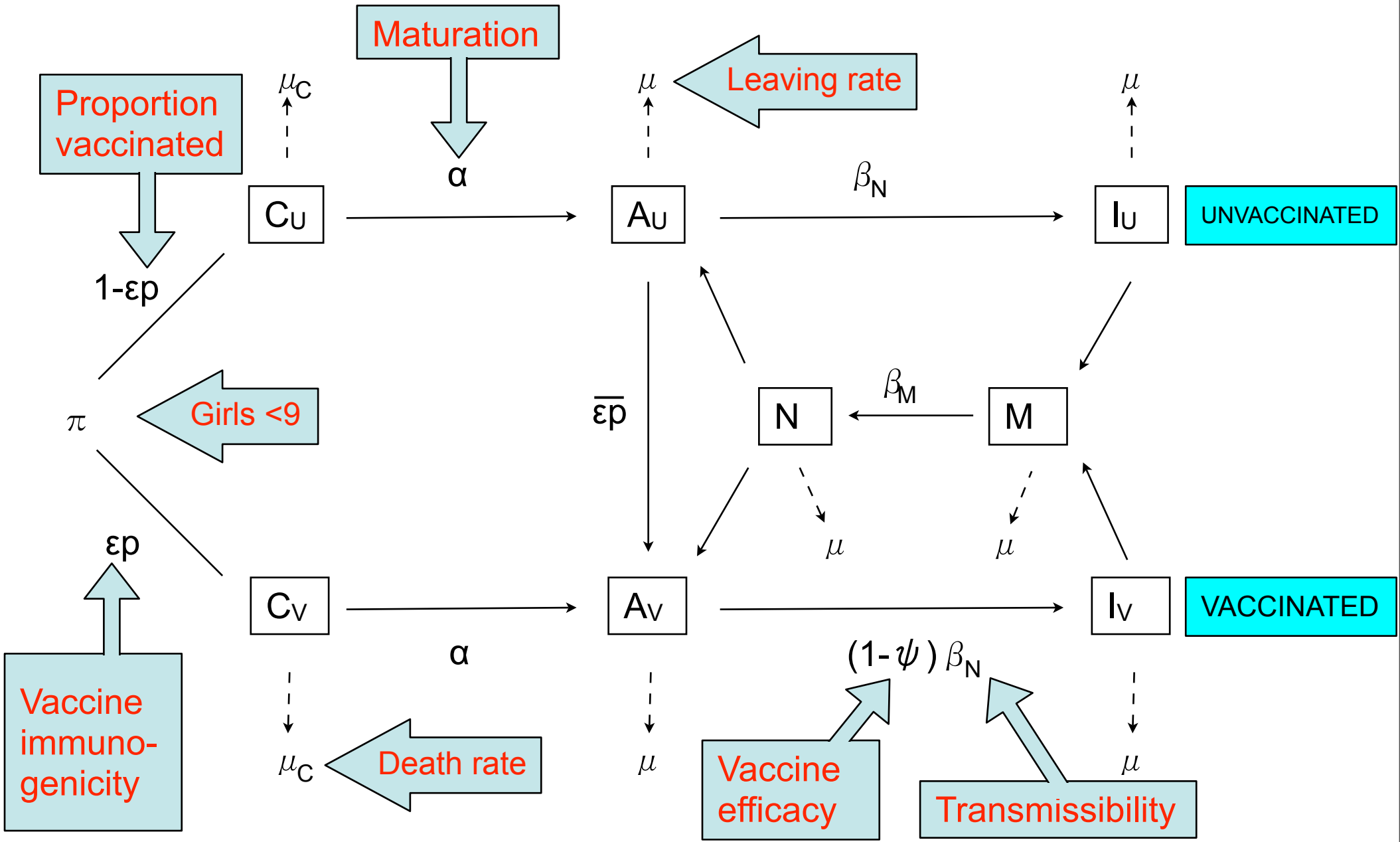
Vaccine immuno-genicity
μ_C
Death rate
μ
Vaccine efficacy
Transmissibility
μ

The model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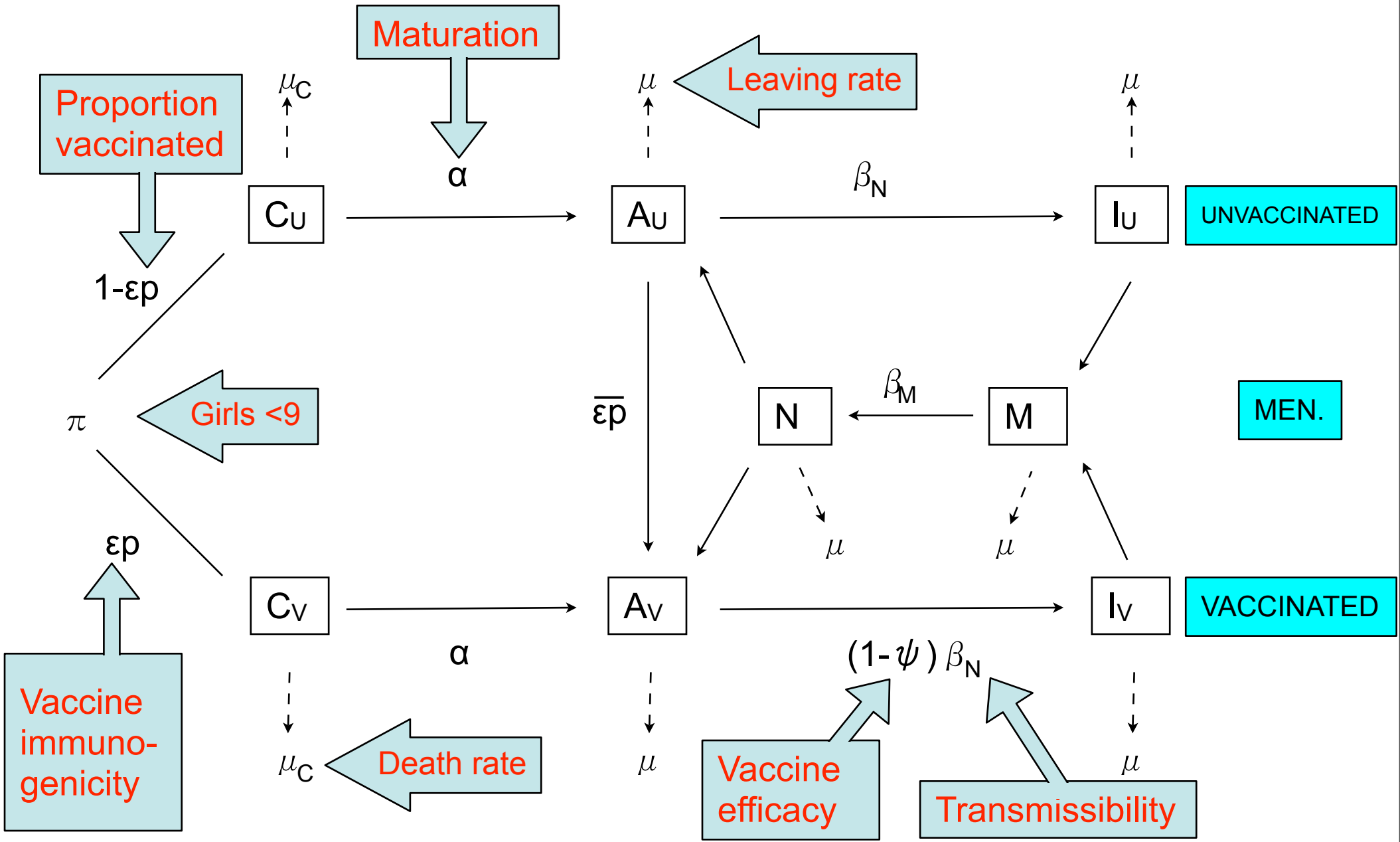
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β_M
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MEN.
μ
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εp
C_V
A_V
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VACCINATED
α
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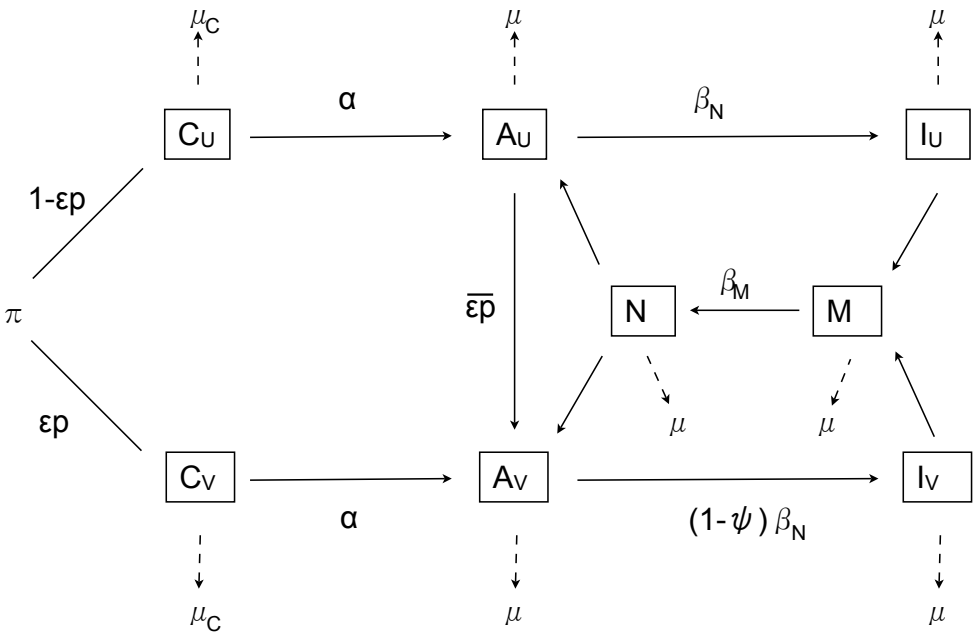
Vaccine immuno-genicity
μ_C
Death rate
μ
Vaccine efficacy
μ
Transmissibility

The ODEs


μ_C
μ
μ
α
β_N
C_U
A_U
I_U
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β_M
π
N
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εp
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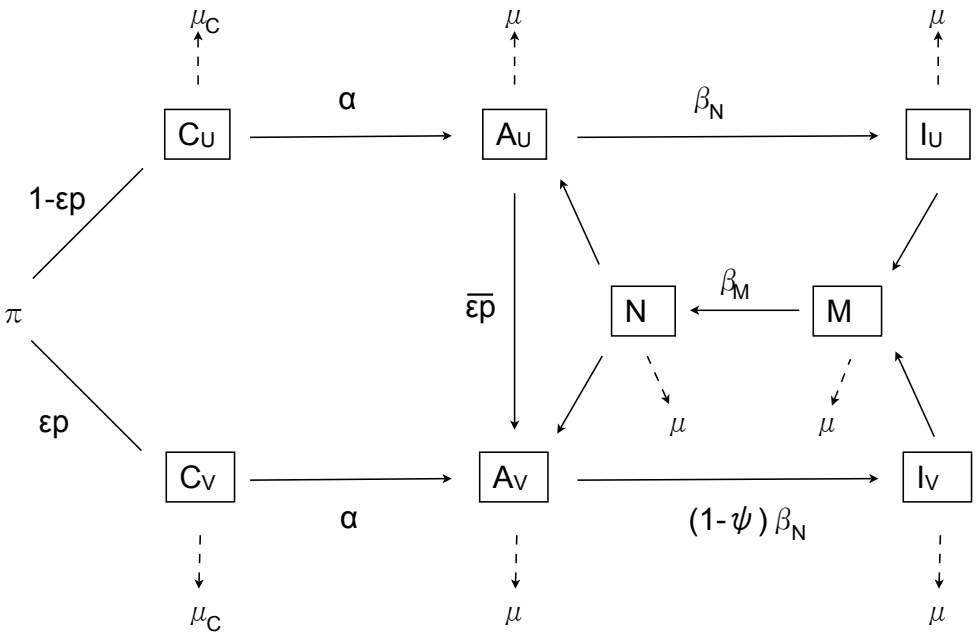
μ
C_V
A_V
I_V
α
$(1-\psi)\,\beta_N$
μ_C
μ
μ

The ODEs



$$
\begin{aligned}
\frac{dC_U}{dt} &= \pi_W(1-\epsilon p) - \alpha C_U - \mu_C C_U \\
\frac{dC_V}{dt} &= \pi_W \epsilon p - \alpha C_V - \mu_C C_V \\
\frac{dA_U}{dt} &= \alpha C_U - f(\bar{\epsilon}\bar{p})A_U - \mu A_U - \beta_N A_U N \\
\frac{dA_V}{dt} &= \alpha C_V + f(\bar{\epsilon}\bar{p})A_U - \mu A_V - (1-\psi)\beta_N A_V N \\
\frac{dI_U}{dt} &= \beta_N A_U N - \mu I_U \\
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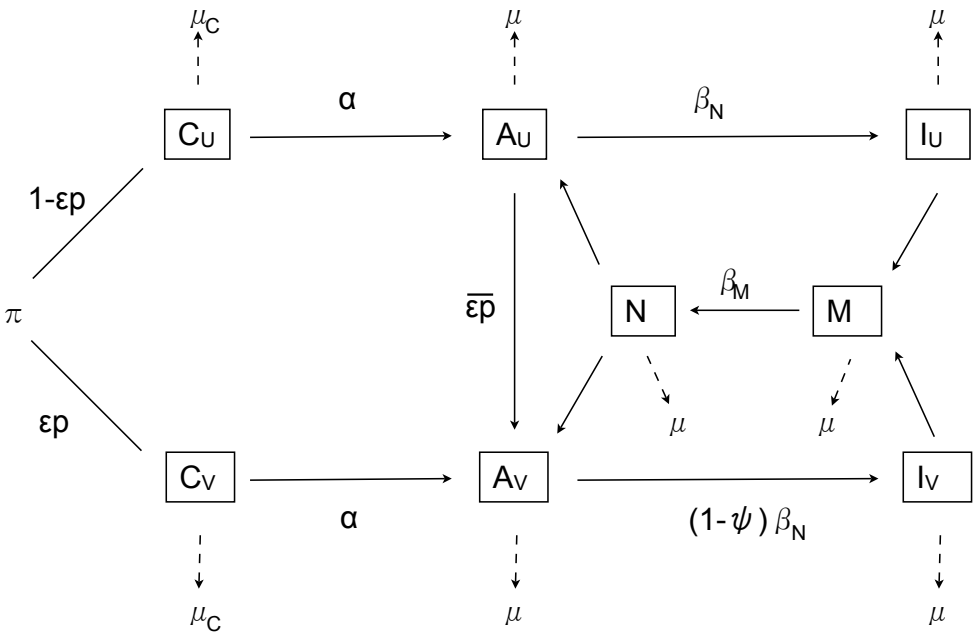
\frac{dM}{dt} &= \pi_M - \beta_M I_U M - \mu M - \beta_M I_V M \\
\frac{dN}{dt} &= \beta_M I_U M - \mu N + \beta_M I_V M \,.
\end{aligned}
$$

The ODEs



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$$

Adult vaccination rate

- The rate of vaccination of adults is

$$f(\bar{\epsilon}\bar{p}) = \frac{c\bar{\epsilon}\bar{p}}{1 - \bar{\epsilon}\bar{p} + \gamma}$$

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  where c/γ is the maximum possible rate of vaccination, assuming perfect efficacy and immunogenicity
- This rate is zero if nobody is vaccinated and high (but not infinite) if everybody is.

ε=*immunogenicity (adults)*
p=coverage (adults)

Model assumptions

- Men do not get vaccinated

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- Children progress to the sexually active pool after 3 years

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- Overall prevalence matched the Canadian average (24%).

Disease-free equilibrium

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C_j=children A_j=uninfected women
I_j=infected adults M=uninfected men
N=infected men π_M=boys π_W=girls
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α=maturation rate f=adult vaccination
μ=leaving rate μ_C= childhood mortality

Disease-free equilibrium

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$$\bar{C}_U = \frac{\pi_W(1-\epsilon p)}{\alpha+\mu_C} \qquad \bar{C}_V = \frac{\pi_W \epsilon p}{\alpha+\mu_C}$$

$$\bar{A}_U = \frac{\alpha C_U}{f+\mu} \qquad \bar{A}_V = \frac{\alpha C_V + f A_U}{\mu}$$

$$\bar{I}_U = 0 \qquad \bar{I}_V = 0$$

$$\bar{M} = \frac{\pi_M}{\mu} \qquad \bar{N} = 0$$

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Jacobian

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$$J = \begin{bmatrix} -\mu_C - \alpha & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -\mu_C - \alpha & 0 & 0 & 0 & 0 & 0 & 0 \\ \alpha & 0 & -f - \mu & 0 & 0 & 0 & 0 & -\beta_N A_U \\ 0 & \alpha & f & -\mu & 0 & 0 & 0 & -(1-\psi)\beta_N A_V \\ 0 & 0 & 0 & 0 & -\mu & 0 & 0 & \beta_N A_U \\ 0 & 0 & 0 & 0 & 0 & -\mu & 0 & (1-\psi)\beta_N A_V \\ 0 & 0 & 0 & 0 & -\beta_M M & -\beta_M M & -\mu & 0 \\ 0 & 0 & 0 & 0 & \beta_M M & \beta_M M & 0 & -\mu \end{bmatrix}$$

A_j=uninfected women M=uninfected men
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Critical coverage threshold

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$$\epsilon p \quad = \quad \frac{1}{\psi\mu}\left[\mu + f(\bar{\epsilon}\bar{p})(1-\psi) - \frac{\mu^4(\mu + f(\bar{\epsilon}\bar{p}))(\alpha+\mu_C)}{\beta_M\beta_N\pi_M\pi_W\alpha}\right]$$

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- If coverage exceeds this level, then we have eradication.

π_M=boys π_W=girls ε=immunogenicity
p=coverage β_j=transmission rate
ψ=vaccine efficacy α=maturation rate
f=adult vaccination μ=leaving rate
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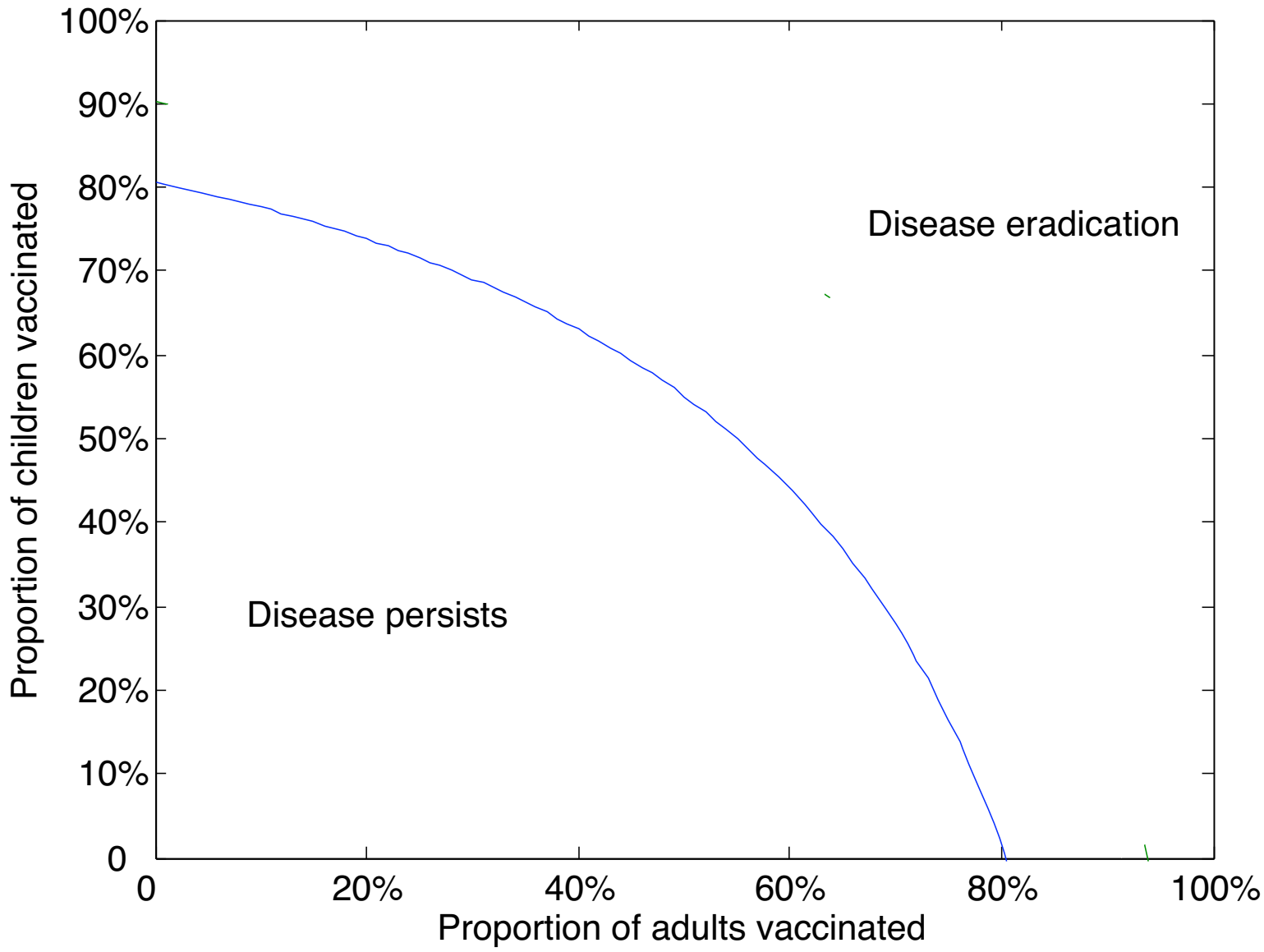
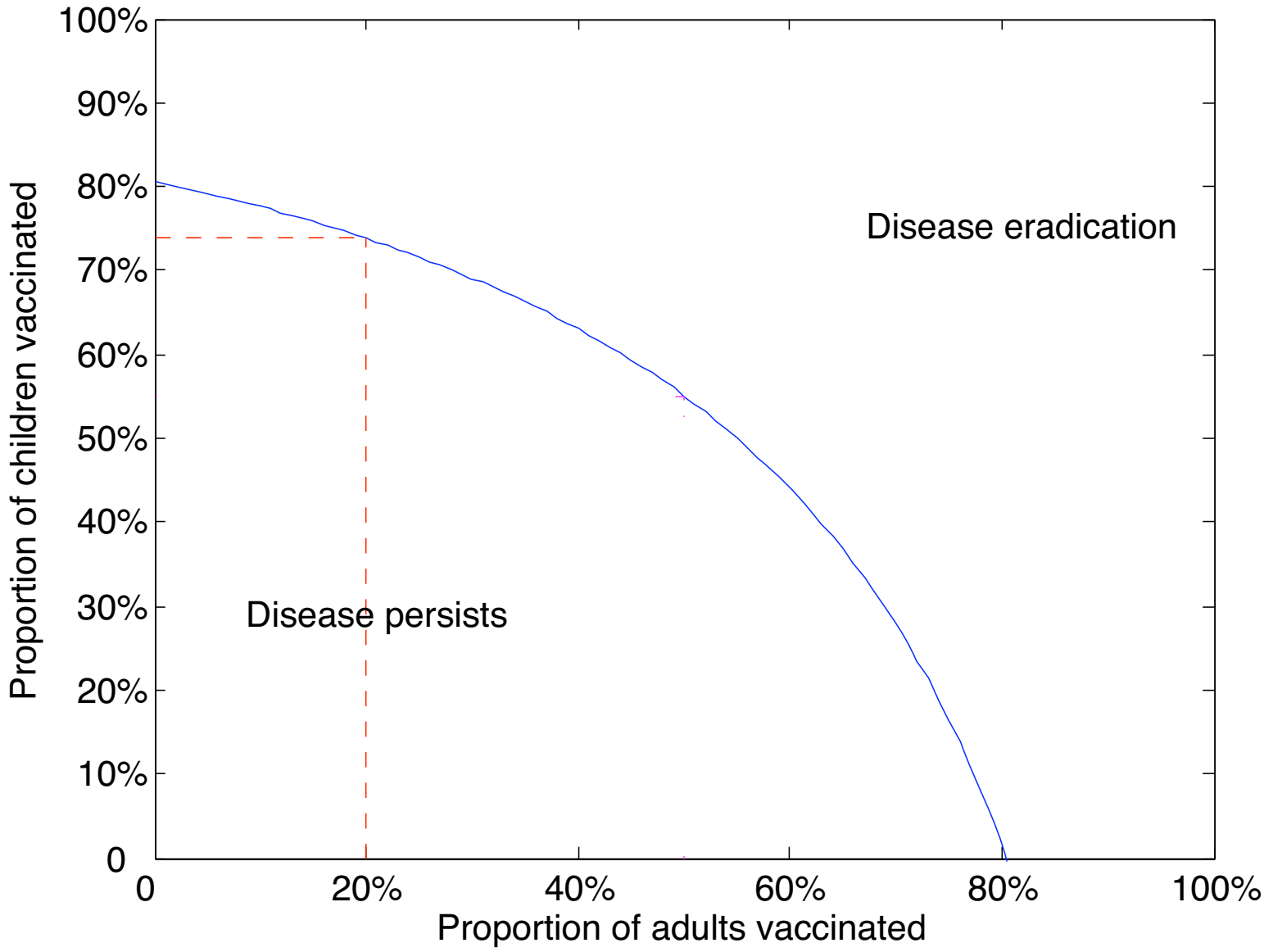
Results


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0
Proportion of children vaccinated
Disease eradication
Disease persists
0
20%
40%
60%
80%
100%
Proportion of adults vaccinated

Results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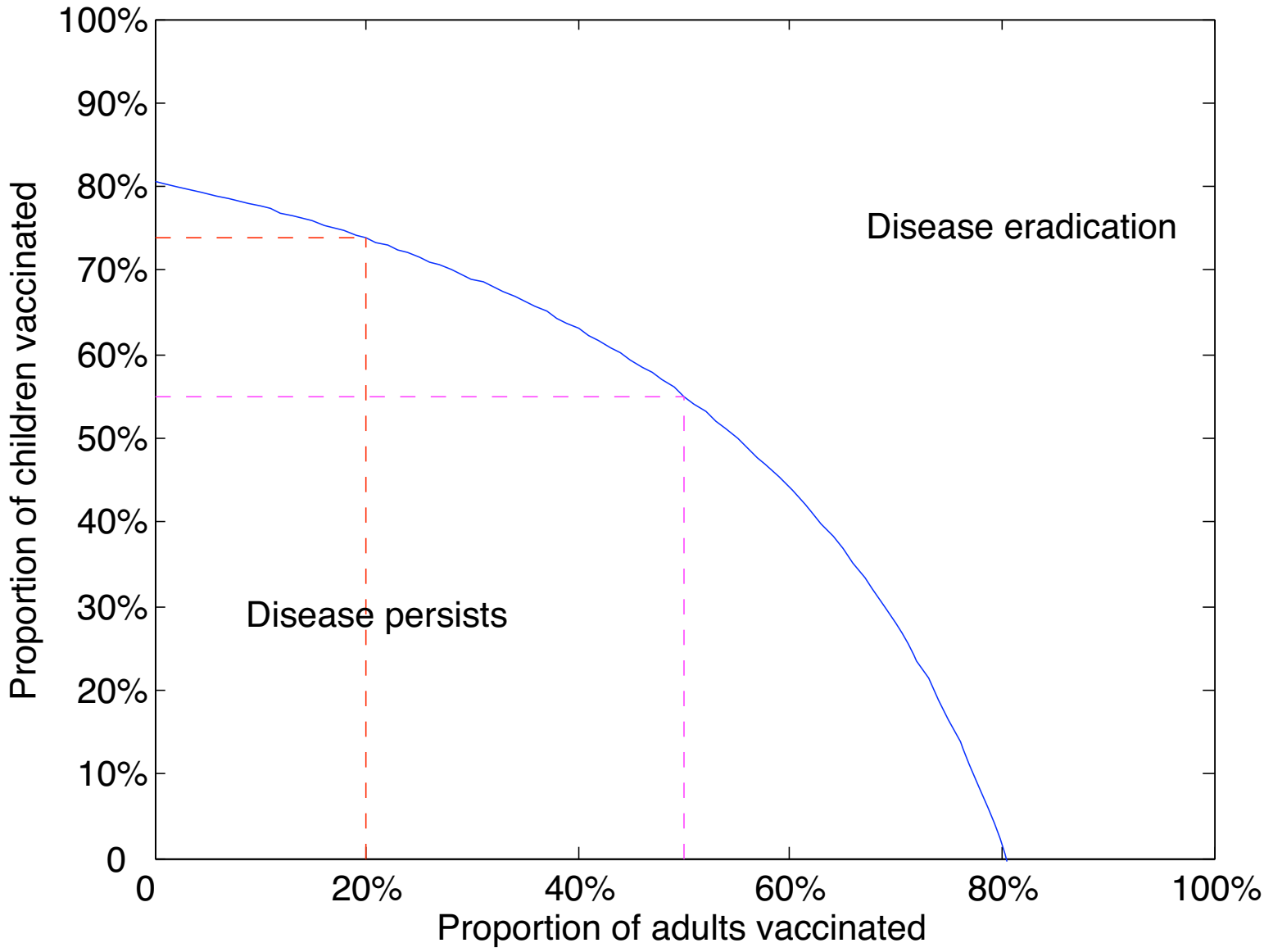
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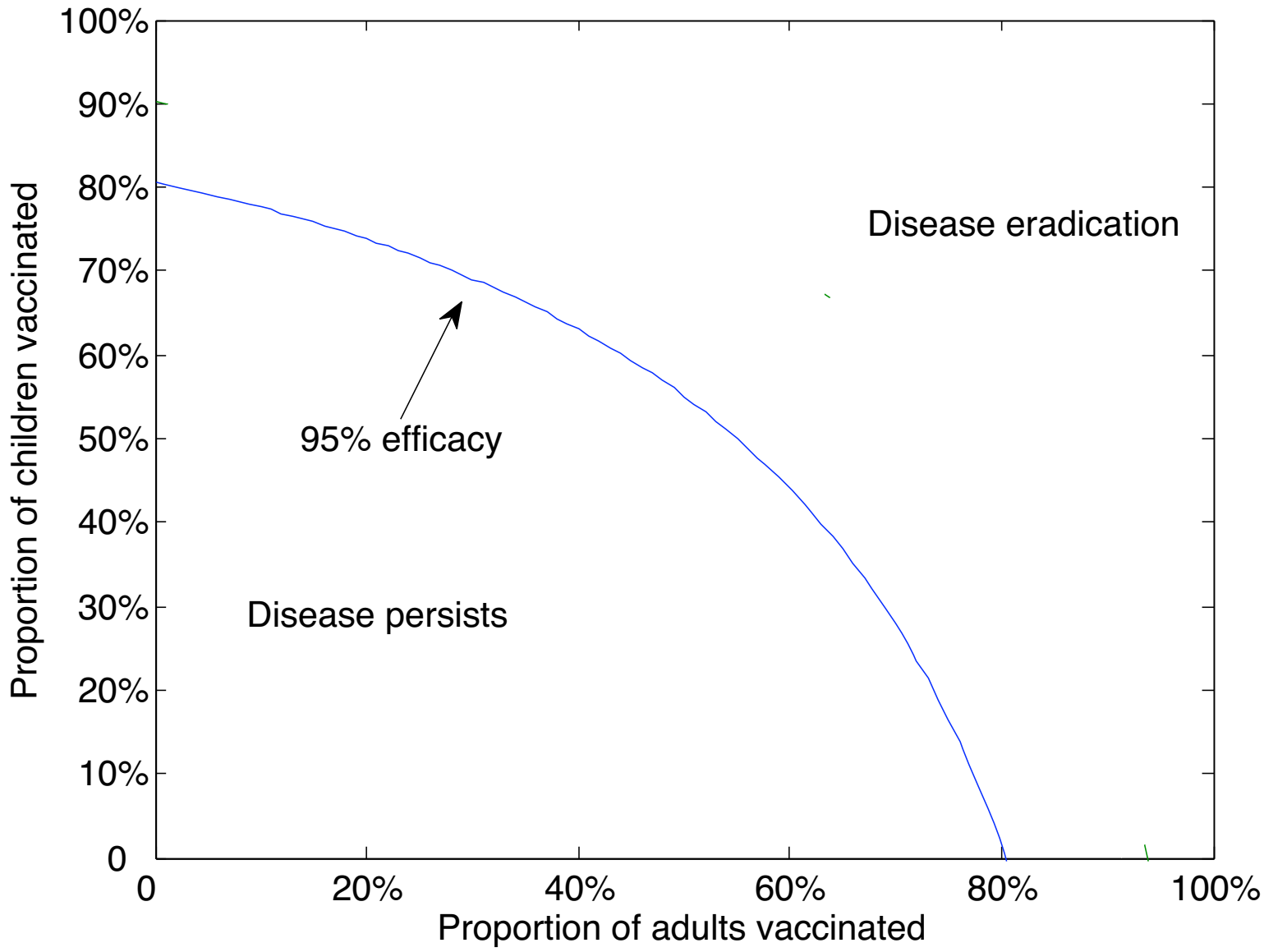
What happens as the efficacy decreases?



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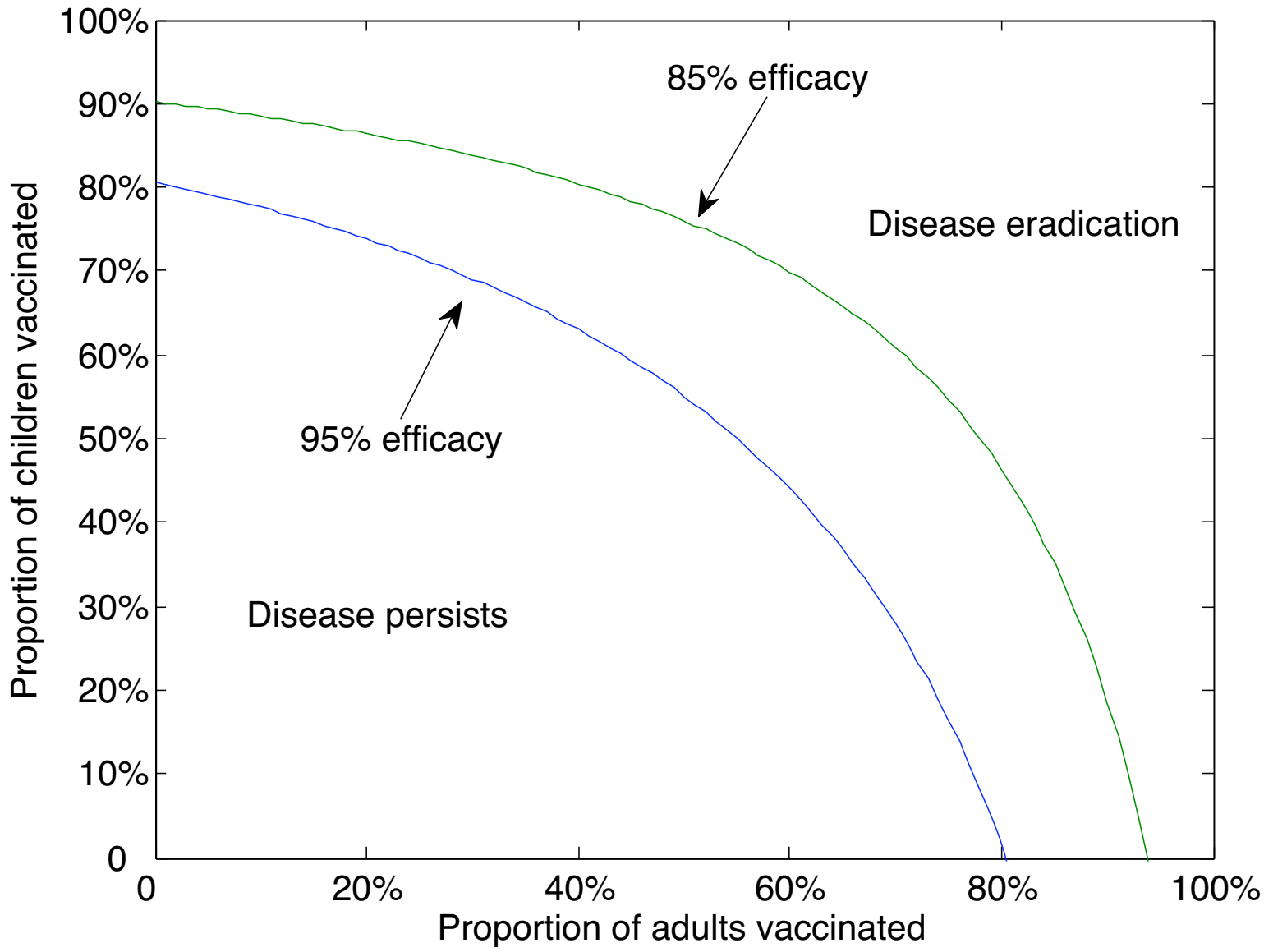
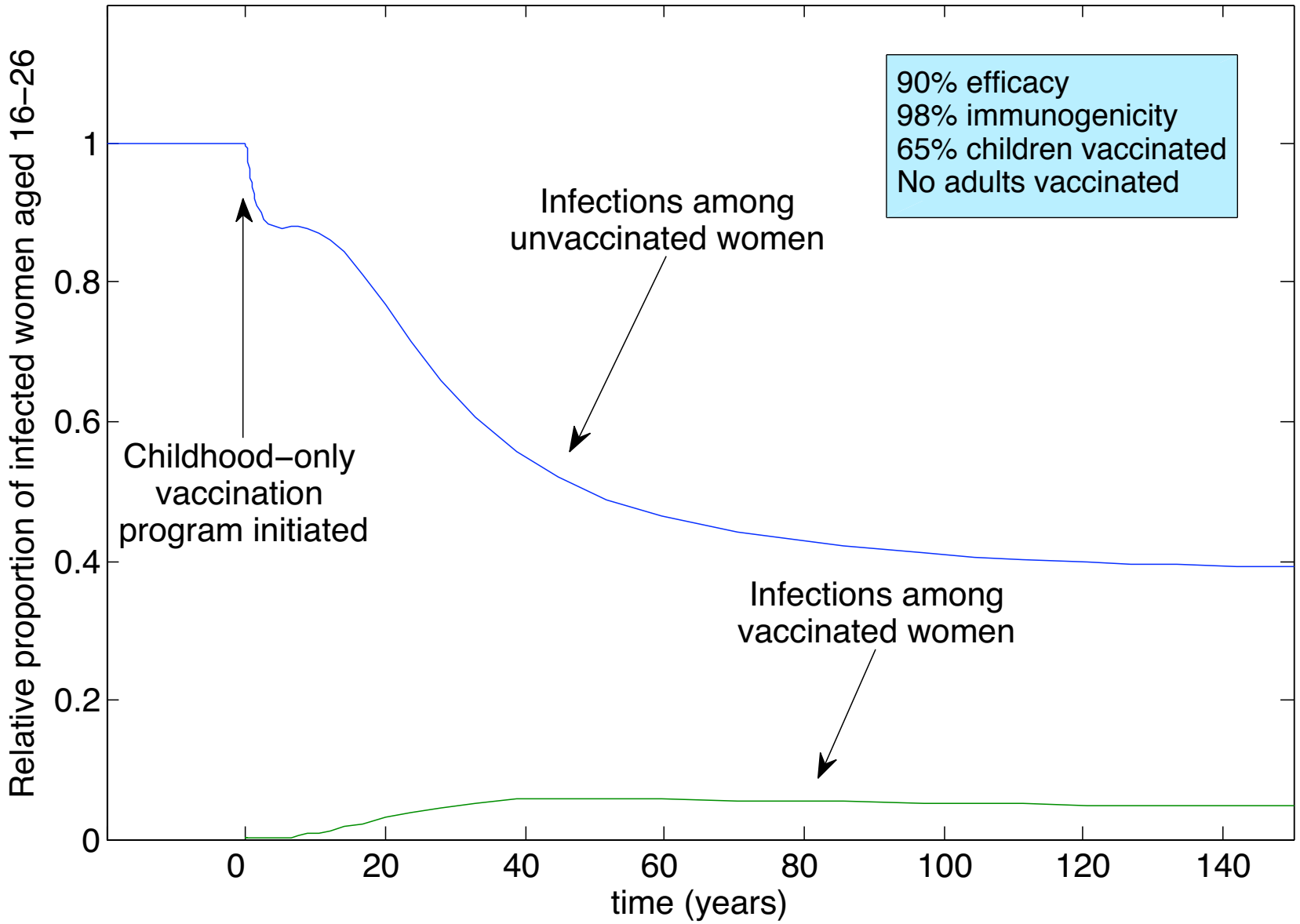


Vaccinating children vs both



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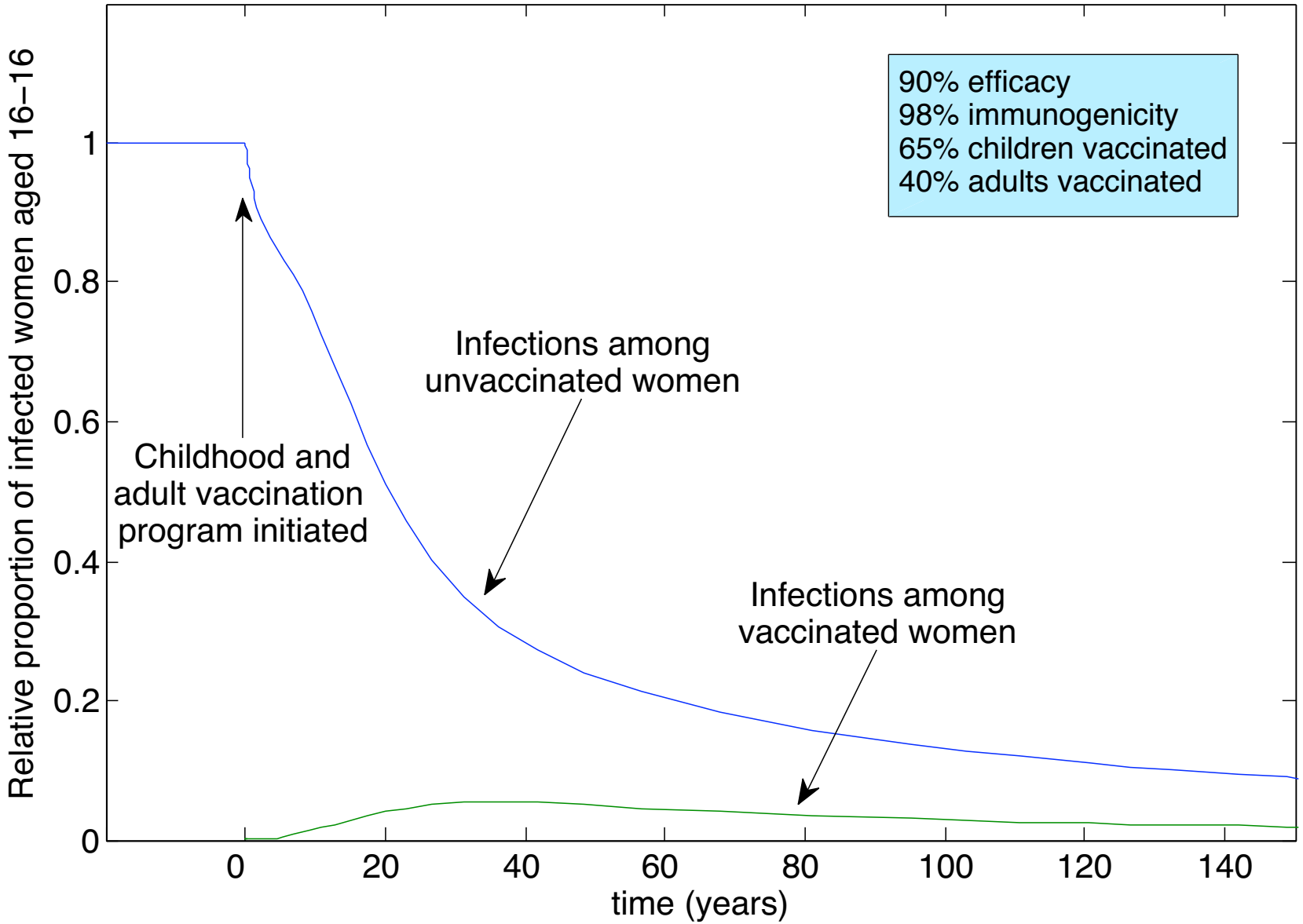

What could go wrong?

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  (ie the vaccine might only create an antibody response a fraction of the time).

Critical efficacy

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Critical efficacy

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$$\psi^* \quad = \quad 1 - \frac{\mu^4(\alpha + \mu_C)}{\beta_M \beta_N \pi_M \pi_W \alpha}$$

π_M=boys π_W=girls ε=immunogenicity
β_j=transmission rate ψ=vaccine efficacy
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$$\psi^* \quad = \quad 1 - \frac{\mu^4(\alpha + \mu_C)}{\beta_M \beta_N \pi_M \pi_W \alpha}$$

- If the efficacy is lower than this critical value, then we can never have eradiation

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- If the efficacy is lower than this critical value, then we can never have eradiation

  (even if we had perfect coverage and the vaccine mounted a perfect immune response).

π_M=boys π_W=girls ε=immunogenicity
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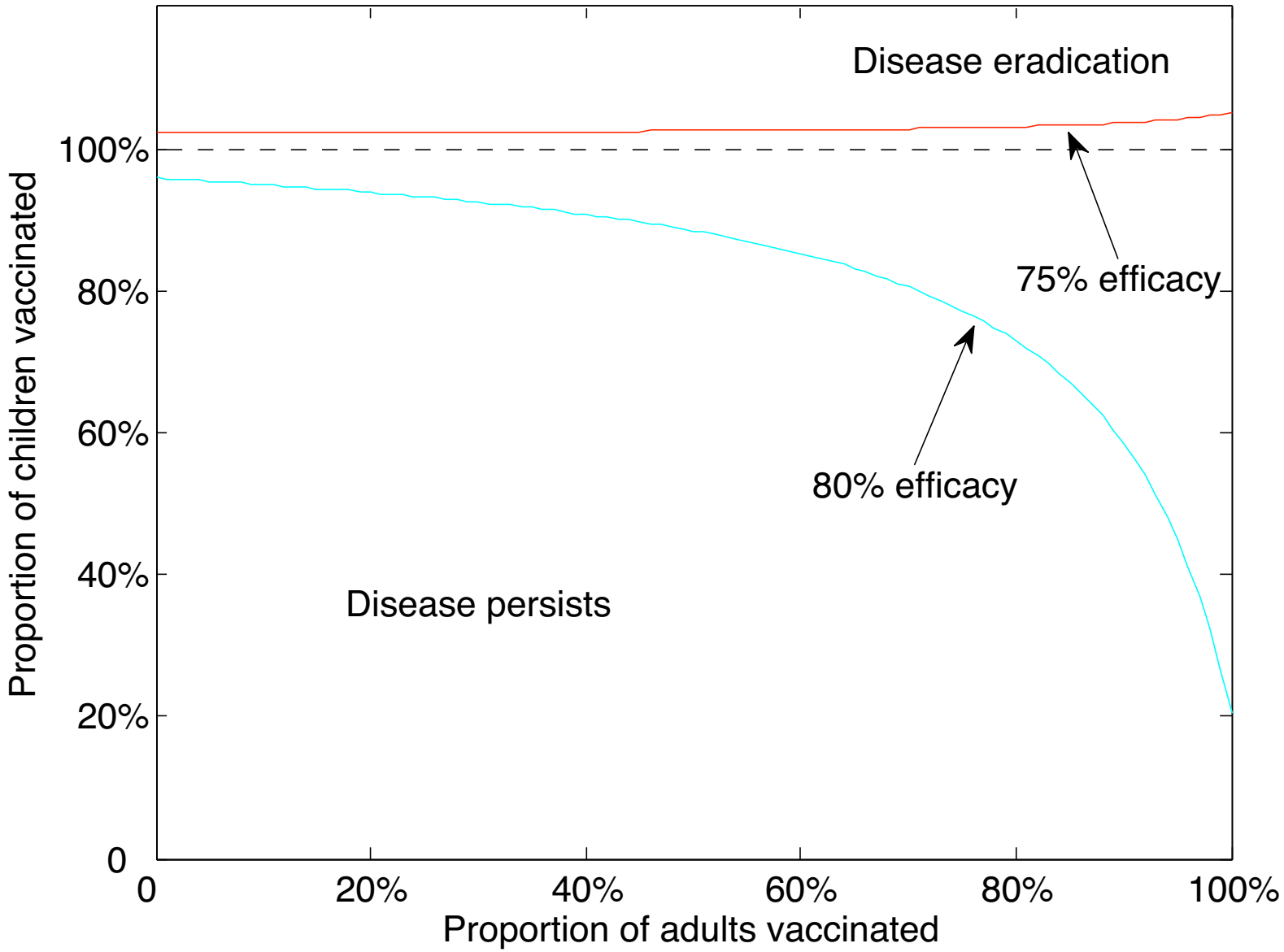
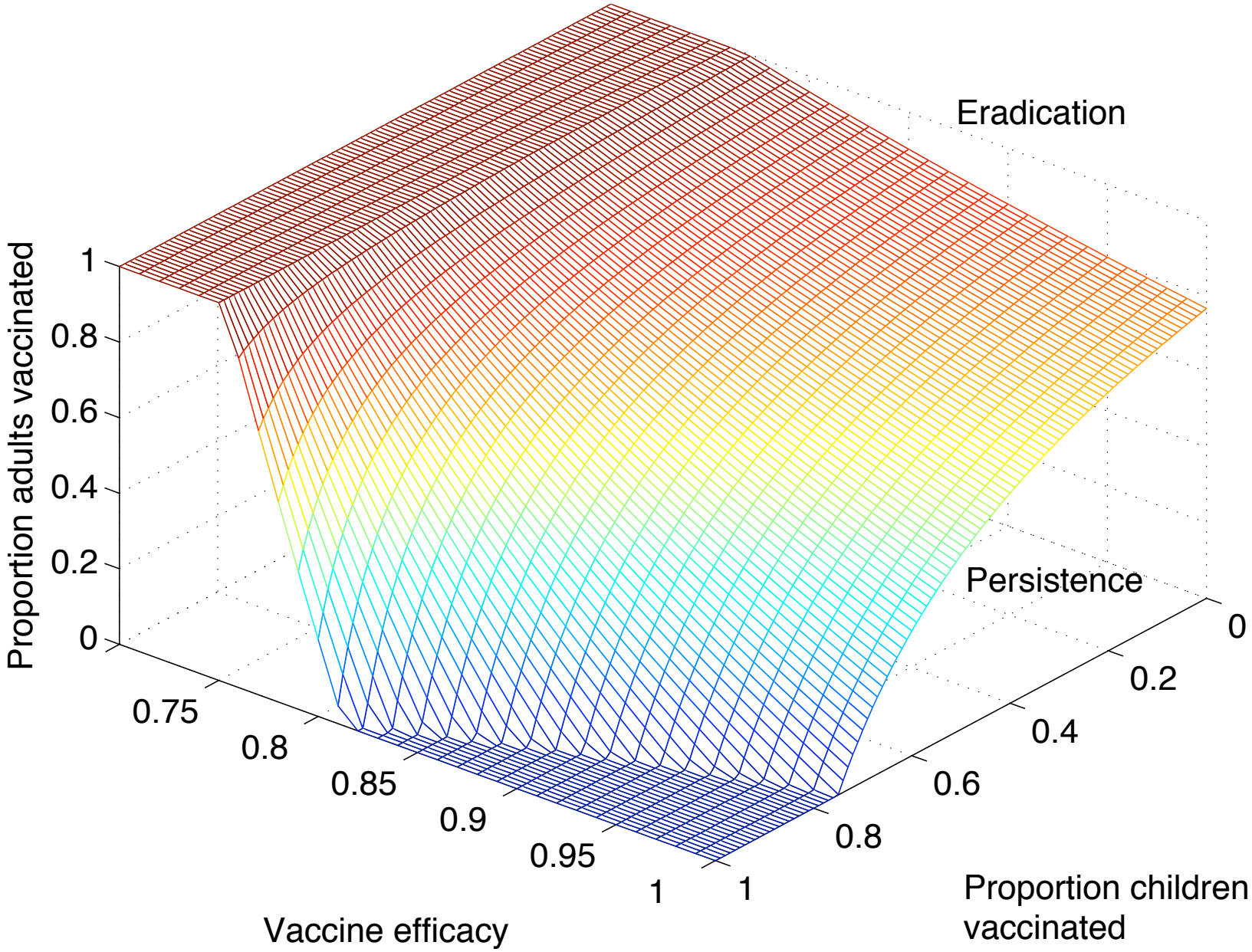
μ_C= childhood mortality

What if the vaccine has suboptimal efficacy?



Dependence on efficacy



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$$\epsilon^* = \frac{1}{\psi}\left[1 - \frac{\mu^4(\alpha + \mu_C)}{\beta_N \beta_M \pi_M \pi_W \alpha}\right]$$

- If the imunogenicity is less than this, then even 100% childhood vaccination will not lead to eradication.

π_M=*boys* π_W=*girls* ε=*immunogenicity*
β_j=*transmission rate* ψ=*vaccine efficacy*
α=*maturation rate* μ=*leaving rate*
μ_C= *childhood mortality*

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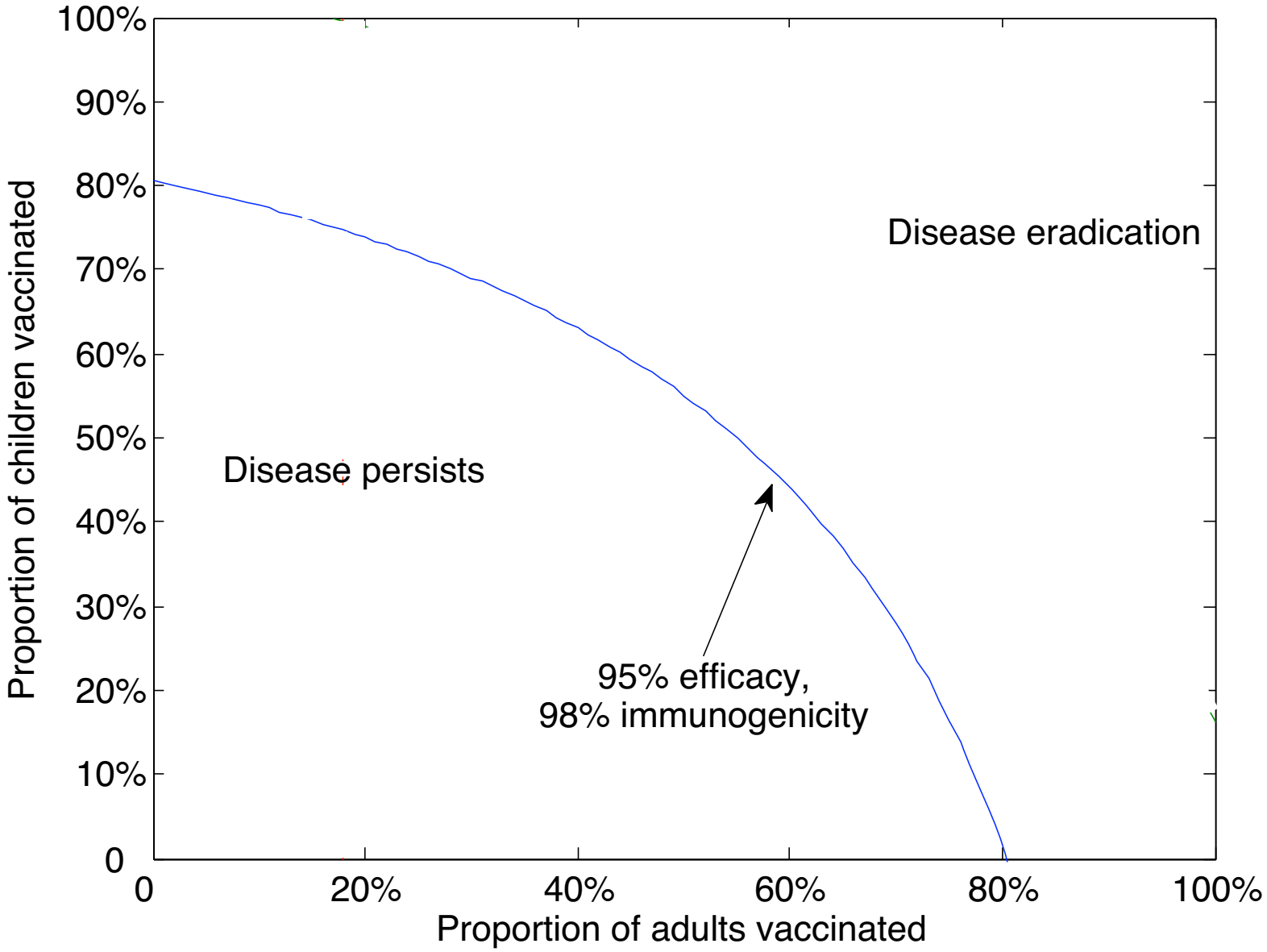

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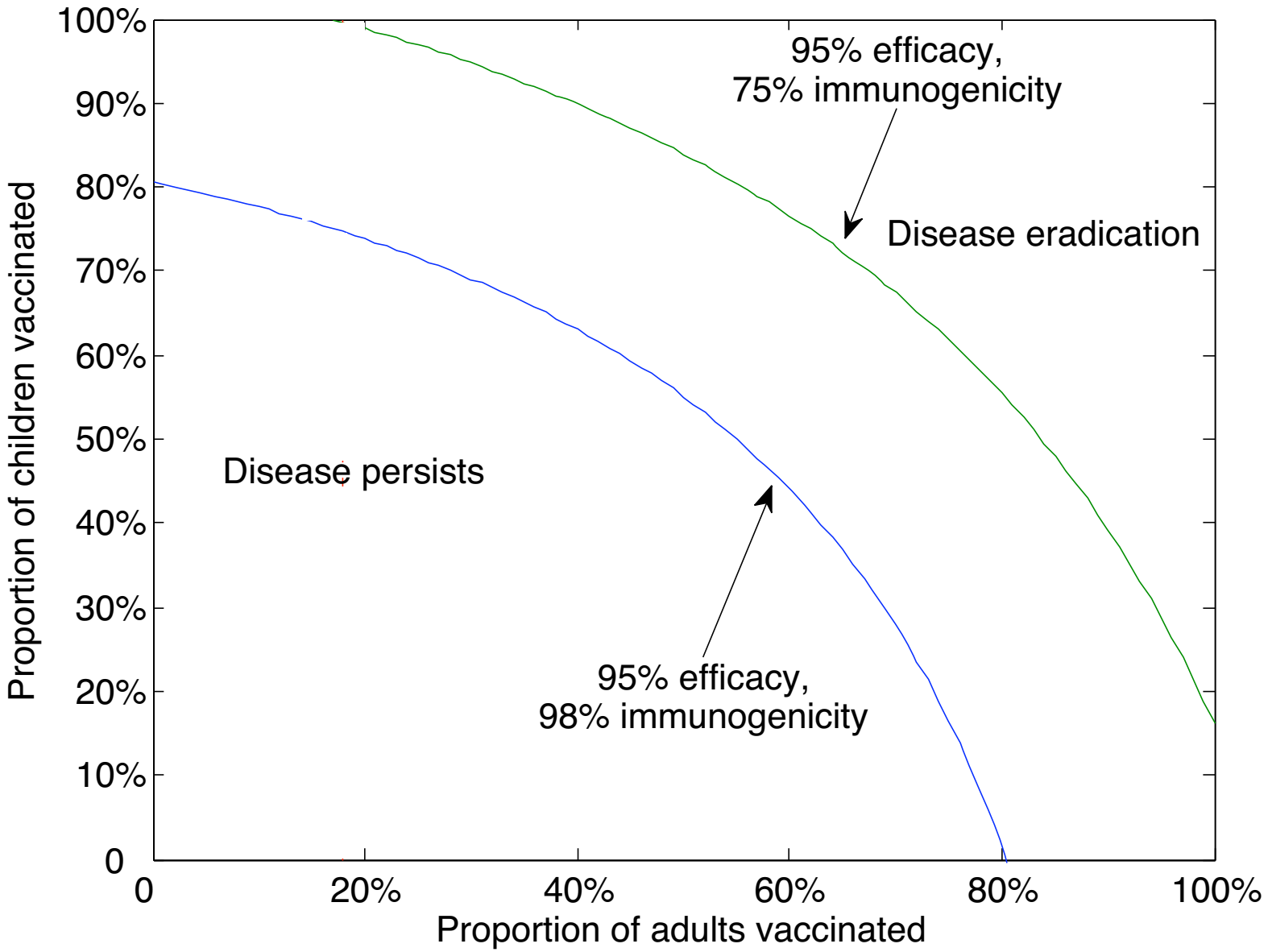

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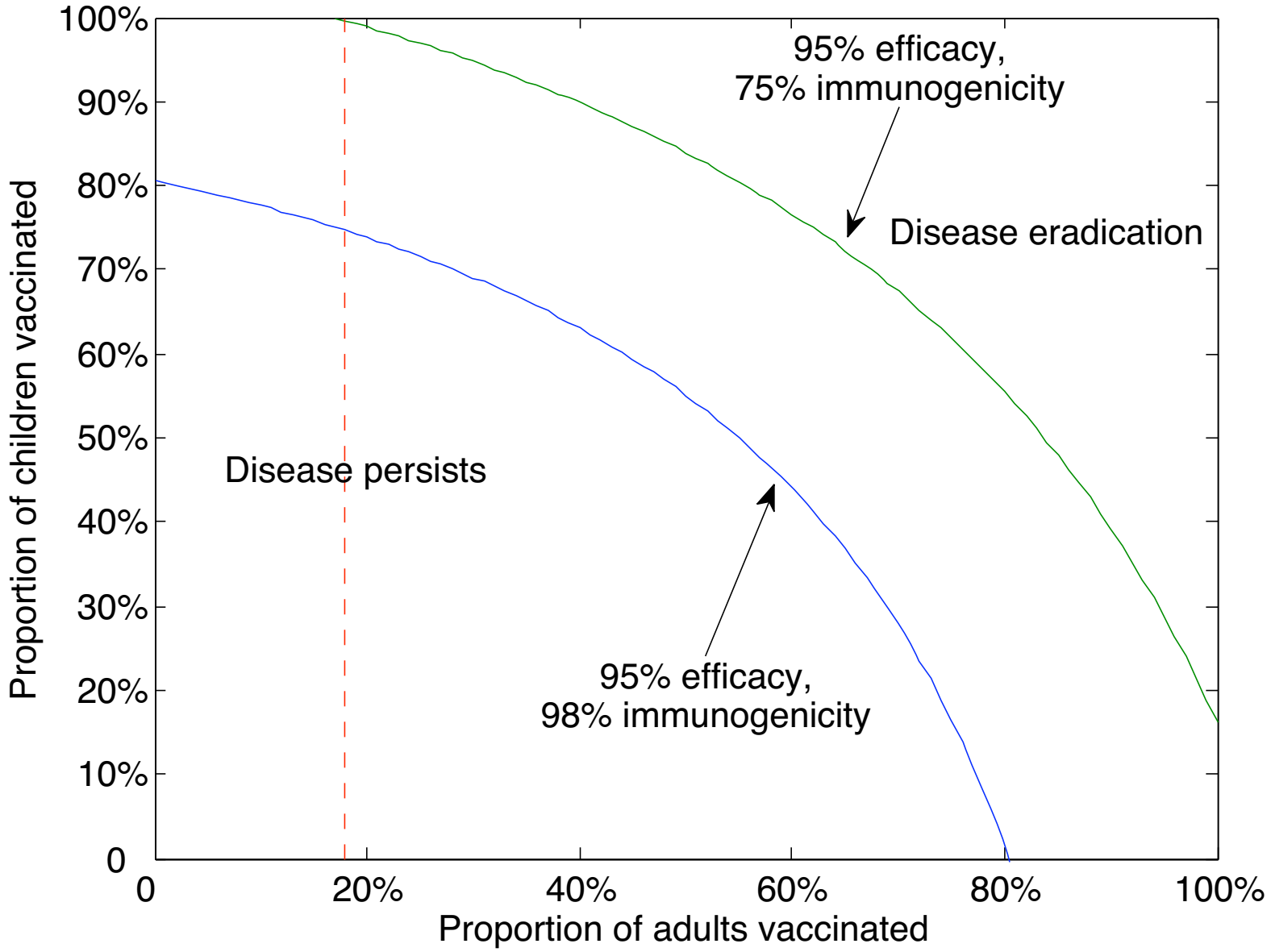

Parameter sensitivity

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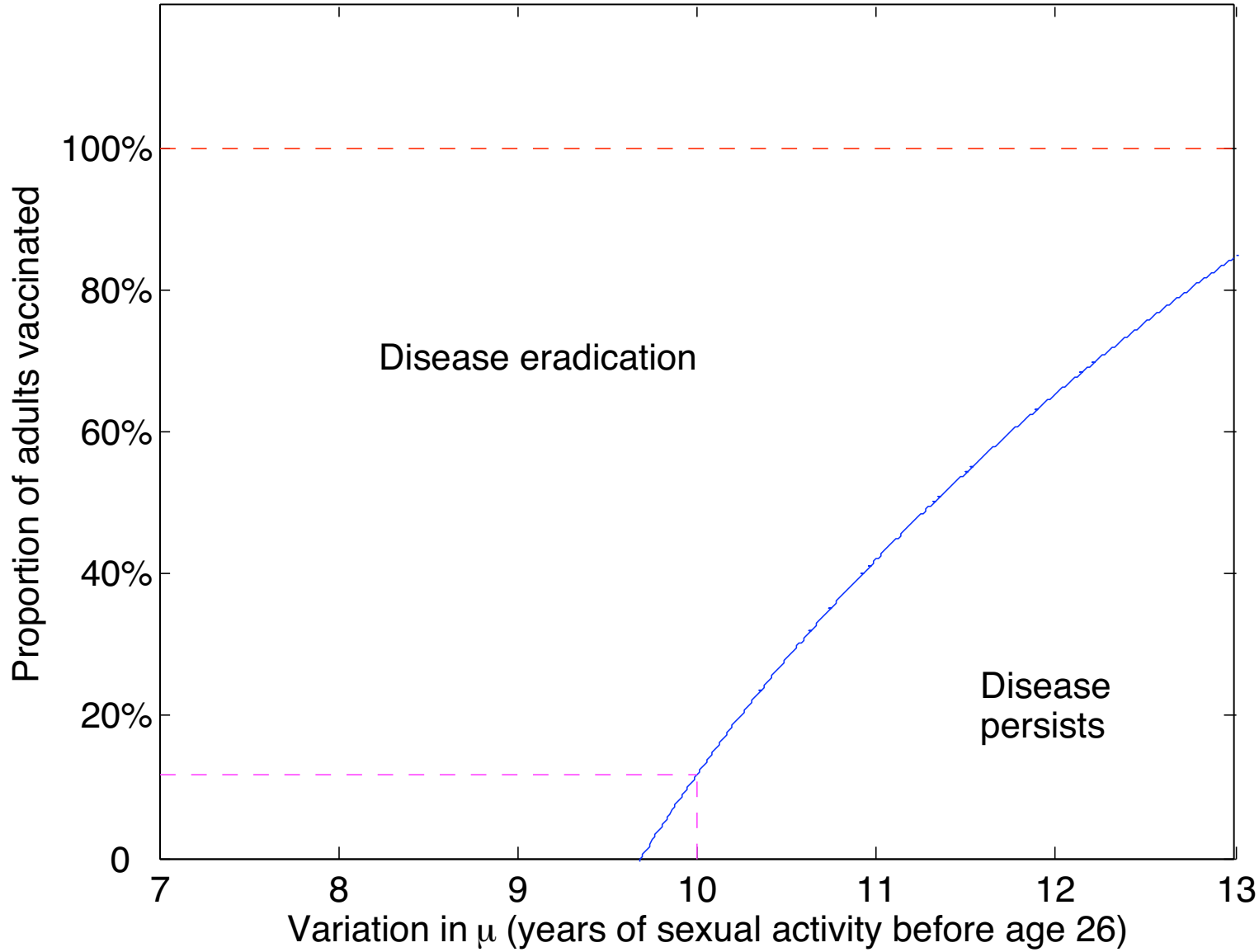
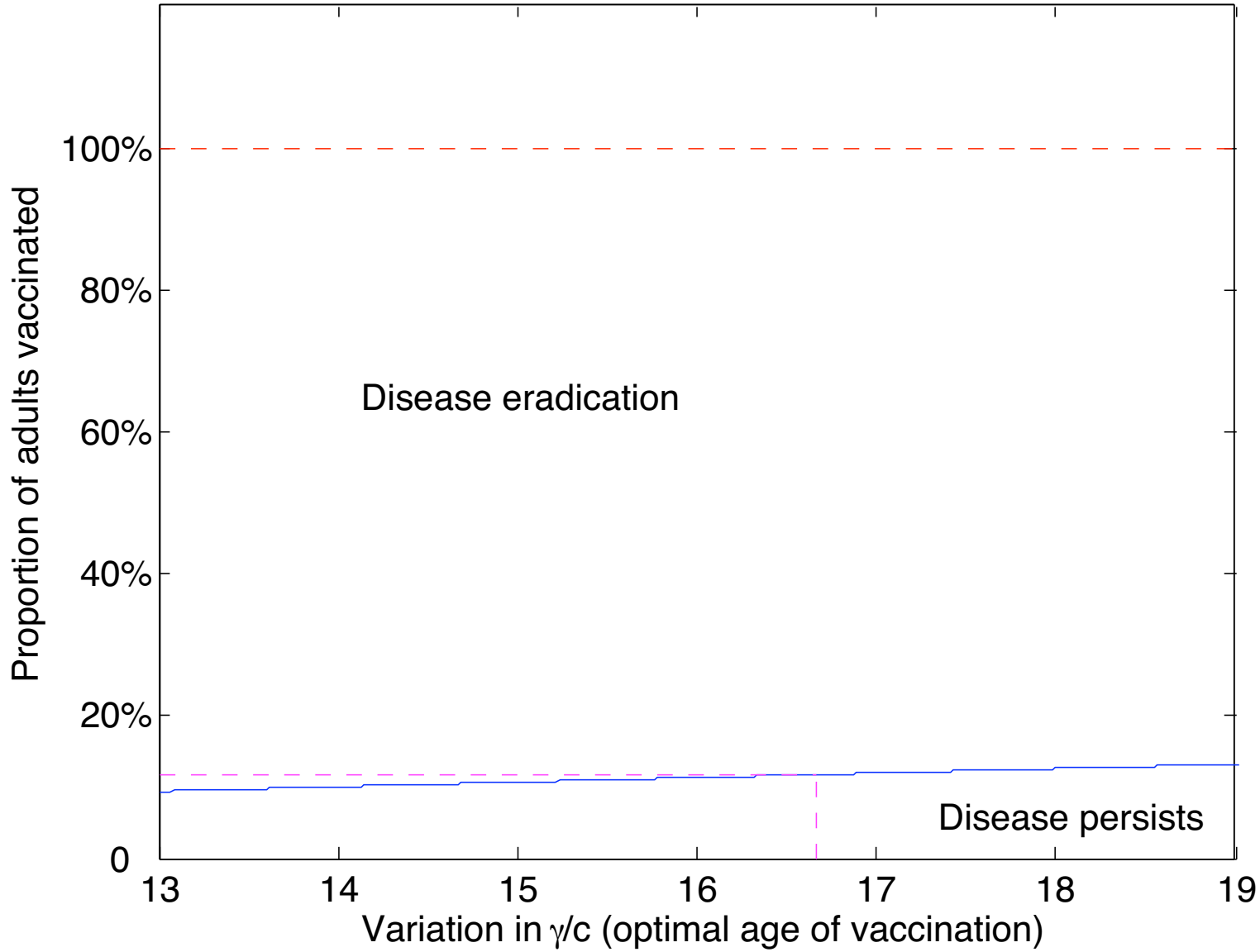
- How do the results depend on our other parameters?
- We varied the
  - years of sexual activity before age 26
  - optimal age of infection
  - transmission probabilities and birth rates
  - years of survival from childhood
- Our output variable was the proportion of adults needing to be vaccinated, assuming 77% childhood vaccination.

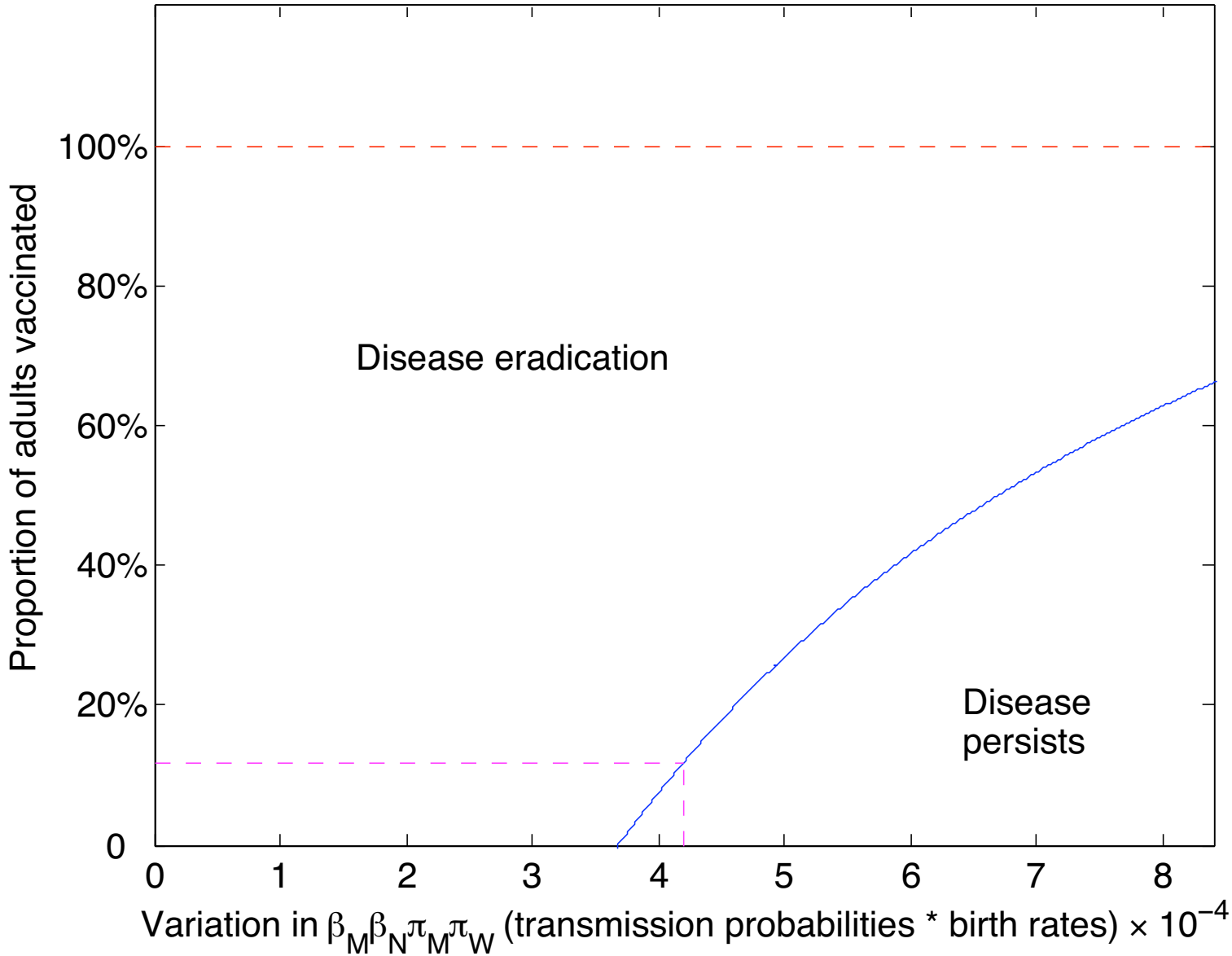
Dependence on years of sexual activity



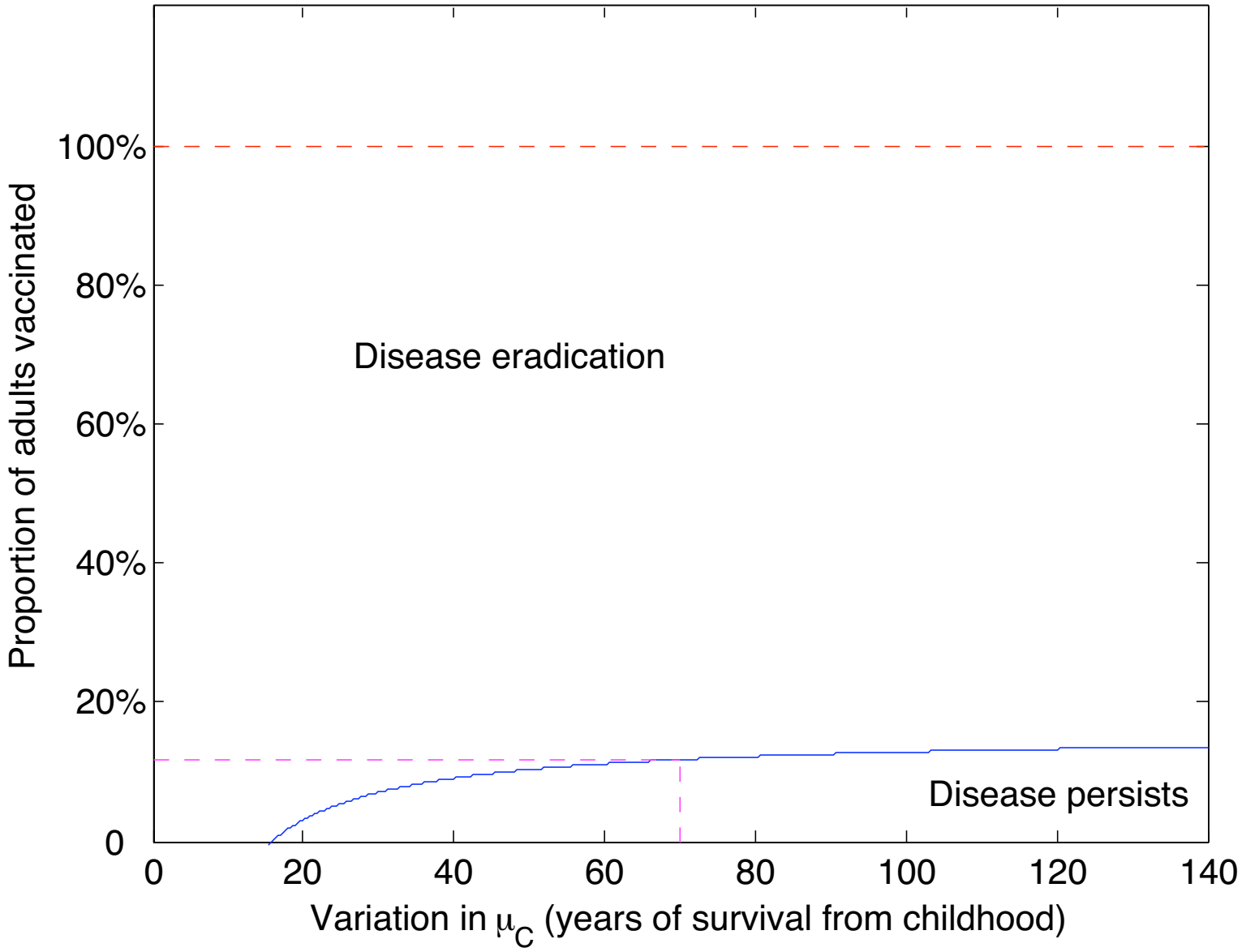
Dependence on the optimal age of vaccination



Dependence on the transmission and birth rates



Dependence on years of survival since childhood



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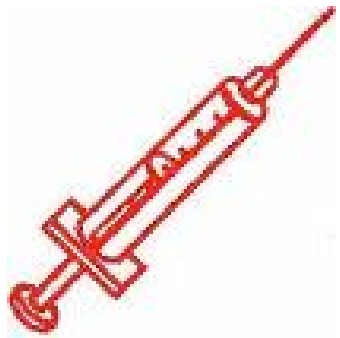

Results (summary)

Using this model, we determined

- A threshold for eradication of the disease
- The amount of vaccination for a childhood-only program
- The amount by which childhood-only vaccination will be offset by adult vaccination
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Conclusions

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- Childhood vaccination programs should be supplemented by adult vaccination
- There is a critical vaccine efficacy (77%) below which eradication is not possible
- There is a critical vaccine immunogenicity (80%) below which even 100% childhood vaccination cannot eradicate the epidemic.

Recommendation

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- This is less than required for eradication (>80%) if only children are to be vaccinated
- Thus, voluntary adult vaccination should be covered by Canadian health care.

Key references

- M. Al-arydah and R.J. Smith? (2011) An age-structured model of human papillomavirus vaccination (Mathematics and Computersin Simulation 82:629-642)
- M. Llamazares and R.J. Smith? (2008) Evaluating human papillomavirus vaccination programs in Canada: should provincial healthcare pay for voluntary adult vaccination? (BMC Public Health 8:114).

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