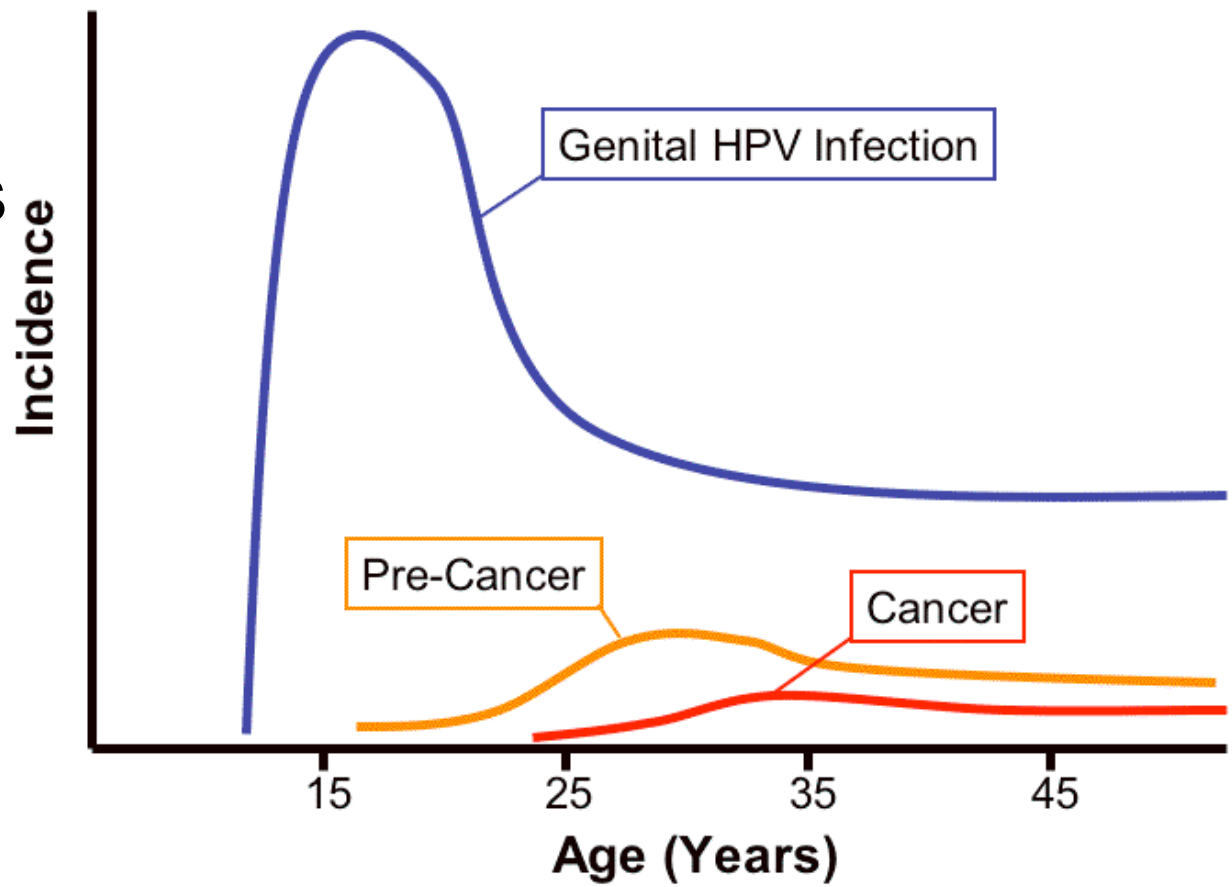
# Human papillomavirus

- Over 100 different strains
- 30-40 strains are transmitted through sexual contact
- HPV causes:
  - 5% of all cancers
  - 10% of all cancers in women.

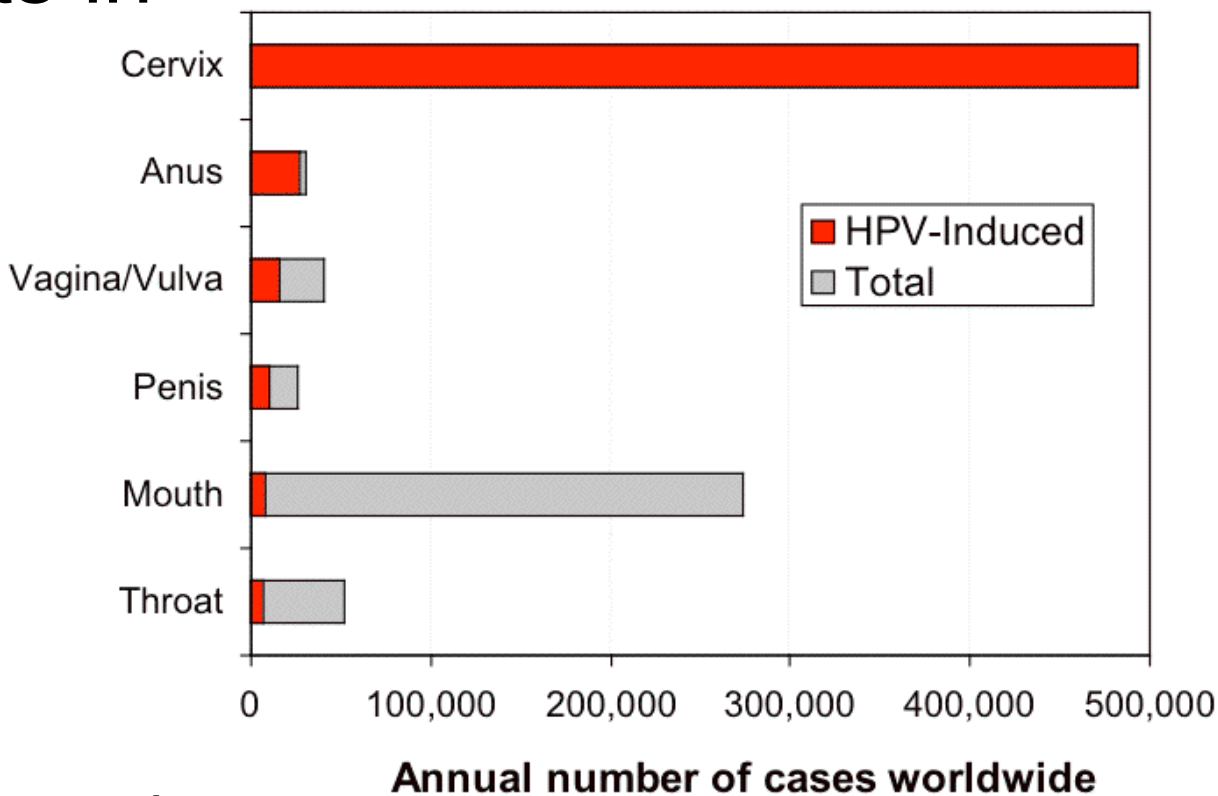


# HPV infections

HPV infection results in

- genital warts
- cervical cancer
- penile cancer
- anal cancer
- respiratory papillomatosis (vertical transmission)

...requiring frequent surgery.



# Prevalence in women

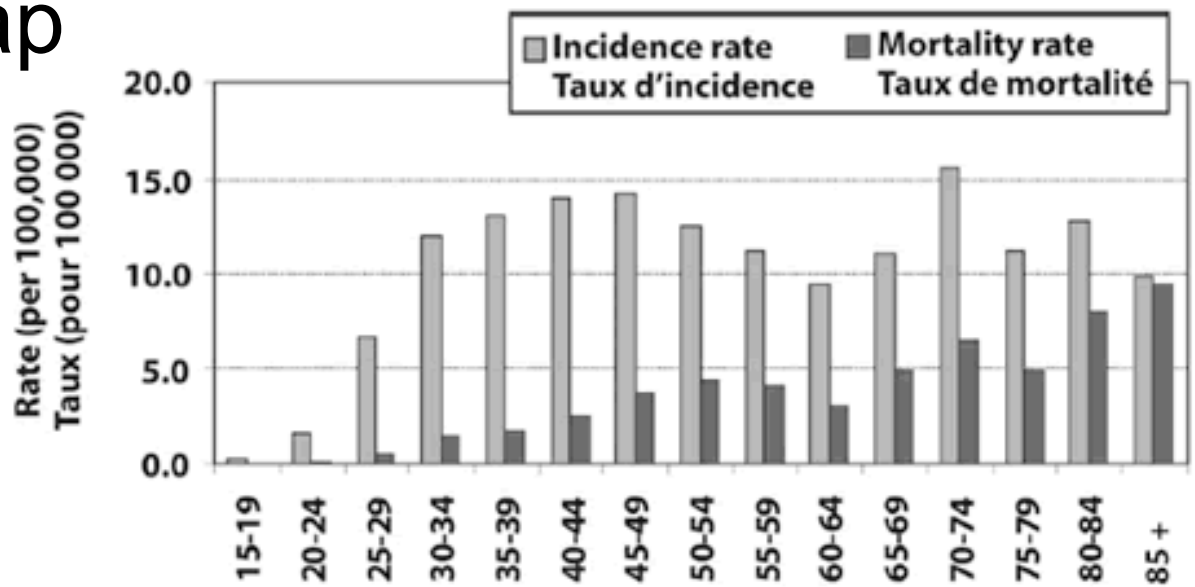
- Including harmless strains, estimates are:
- 20 year old women: 20-40%
- College women: >40%
- Lifetime risk: 75%

  (detection relies upon the pap smear, which detects cellular abnormalities caused by HPV)
- Acquisition to malignancy takes >10 years
- Cervical cancer is the second most common cause of death from cancer in women.

# Infections in the US

- 6,200,000 infections per year
- 14,000 women diagnosed with cervical cancer each year, leading to...
- 3,900 deaths

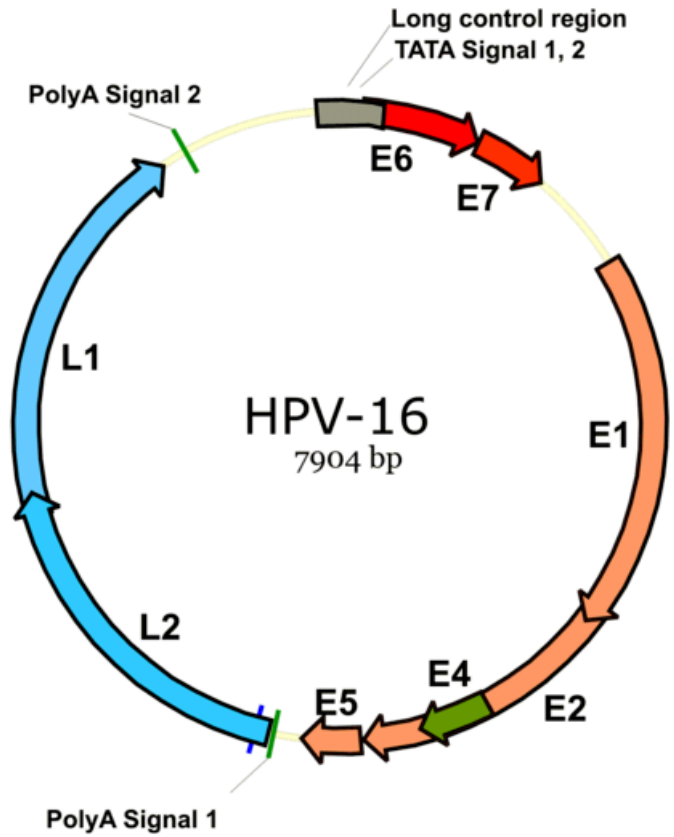
(many fewer than would be caused by HPV, due to effective pap smear screening and precancer treatments).



# HPV strains of interest

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

  (as well as respiratory papillomatosis)
- Types 16, 18, 31 and 45 lead to cancer
- Types 16 and 18 are responsible for 65% of cervical cancer cases.

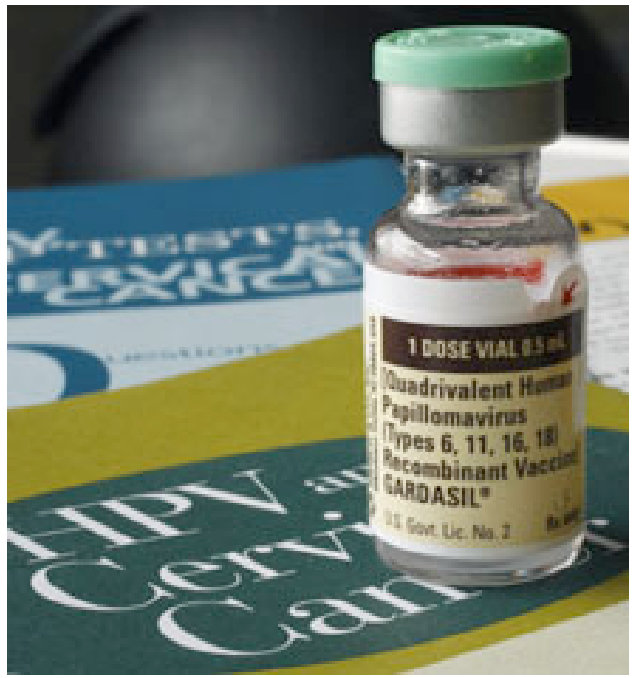


# Prevention

- Without condom use, risk of transmission is close to 90%
- With condom use, risk is close to 40%
- No antivirals have been developed for HPV
- Vaccines are estimated at 90–100% efficacy.

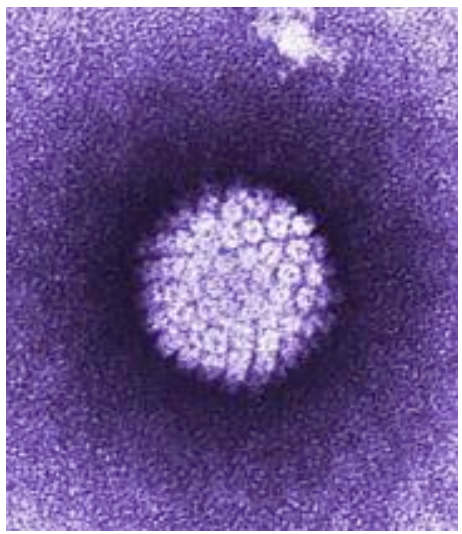
# Gardasil

- Protects against both persistent and incident infections
- No side effects
- Three shots over six months, costing $US360
- Recommended for women aged 9–26
- Highly efficacious
- Greater than 90% when all three doses are taken.



# Men?

- The vaccine has recently been approved for men
- However, uptake rates are low
- Thus, we'll assume vaccinated men have a negligible effect on the outcome.



# The rollout program

- Canadian provinces are now vaccinating girls aged 9–13

  (ie before they become sexually active)
- The vaccine is available to women aged 14–26, but is not covered by Canadian health plans
- However, different provinces vaccinate at different ages
- Some also give two doses instead of three
  - piggybacking on other vaccination programs tends to result in greater uptake rates.

# Provincial vaccination strategies

| *Strategy* | *Province(s)* | *Grade* | *Doses* | *Coverage Rate* |
|---|---|---|---|---|
| 1 | NWT | 4 | 3 | unknown |
| 2 | QU | 4, 9 | 2, 1(last) | 81-86% |
| 3 | AB | 5 | 3 | 50-60% |
| 4 | BC | 6,9 | 2 | 62% |
| 5 | NL | 6,9 | 3 | 85% |
| 6 | MB | 6 | 3 | 52-61% |
| 6 | NU | 6 | 3 | unknown |
| 6 | PE | 6 | 3 | 85% |
| 6 | SK | 6 | 3 | 58-66% |
| 6 | YK | 6 | 3 | unknown |
| 7 | NS | 7 | 3 | 85% |
| 7 | NB | 7 | 3 | unknown |
| 8 | ON | 8 | 3 | 49- 59% |

# Coverage levels

- Initial surveys suggested that the majority of parents (77%) would be receptive to their children being vaccinated, if suitably informed about HPV
- In the first year, Ontario reported only 53% vaccination coverage
- This has not increased substantially over subsequent years.

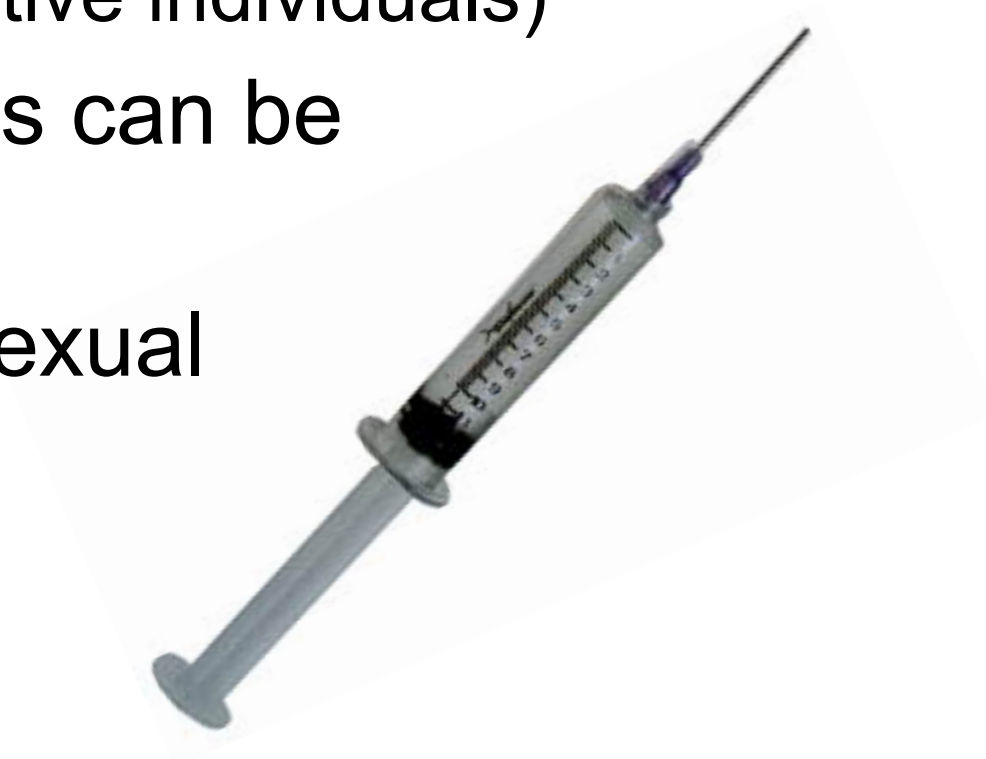
# Research questions

- Does the age at which girls are vaccinated significantly affect the outcome?
  - we'll use grade instead of age, in line with how the program is organised
- What are the implications of two vs three doses?
- Should we attempt to standardise across Canada?
  - health is provincial, but the Public Health Agency of Canada, based in Ottawa, can make recommendations.

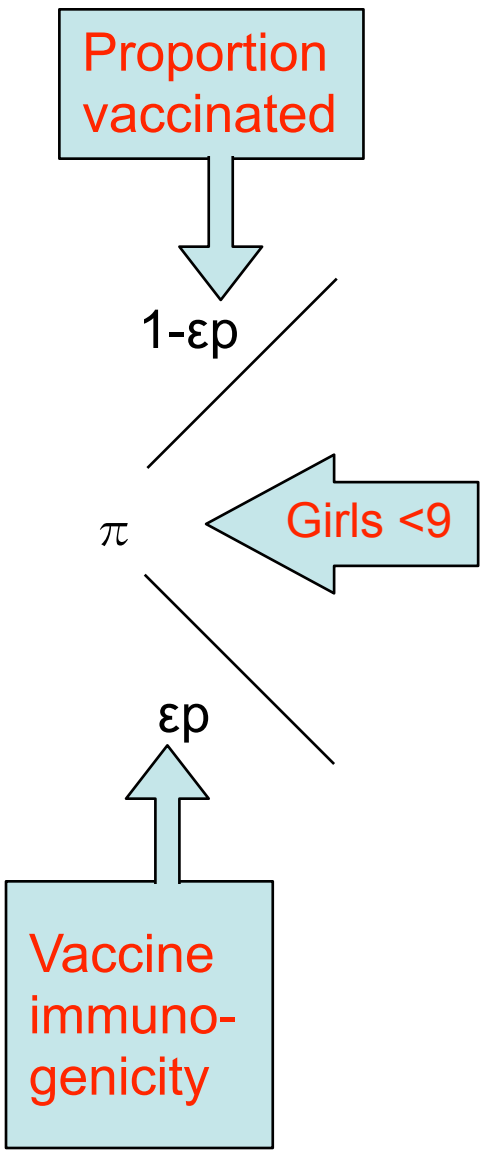
# Baseline model

- Our first approximation considered a single childhood class
- Children progress to adults

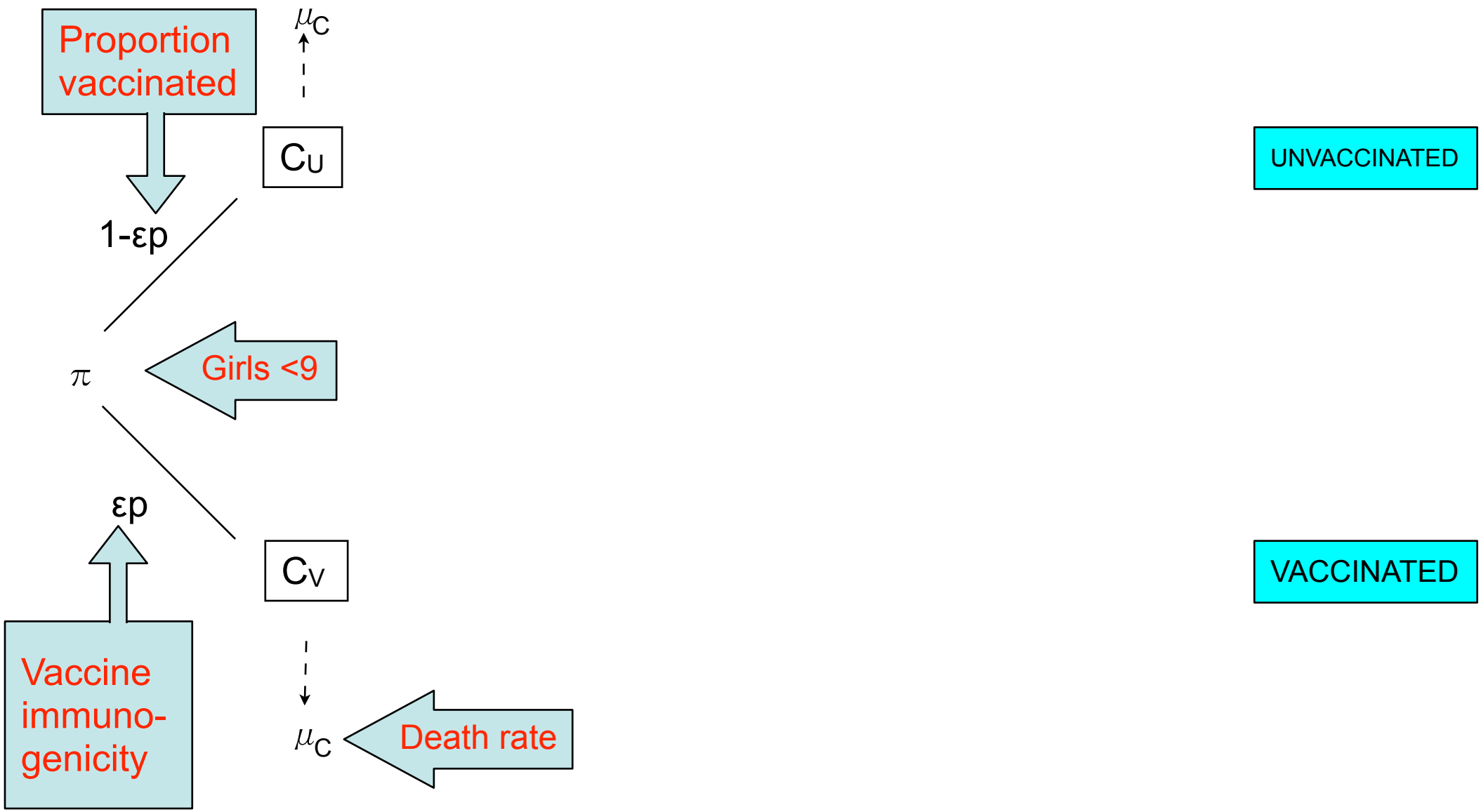
  (defined as sexually active individuals)
- Either children or adults can be vaccinated
- We only study heterosexual transmission.



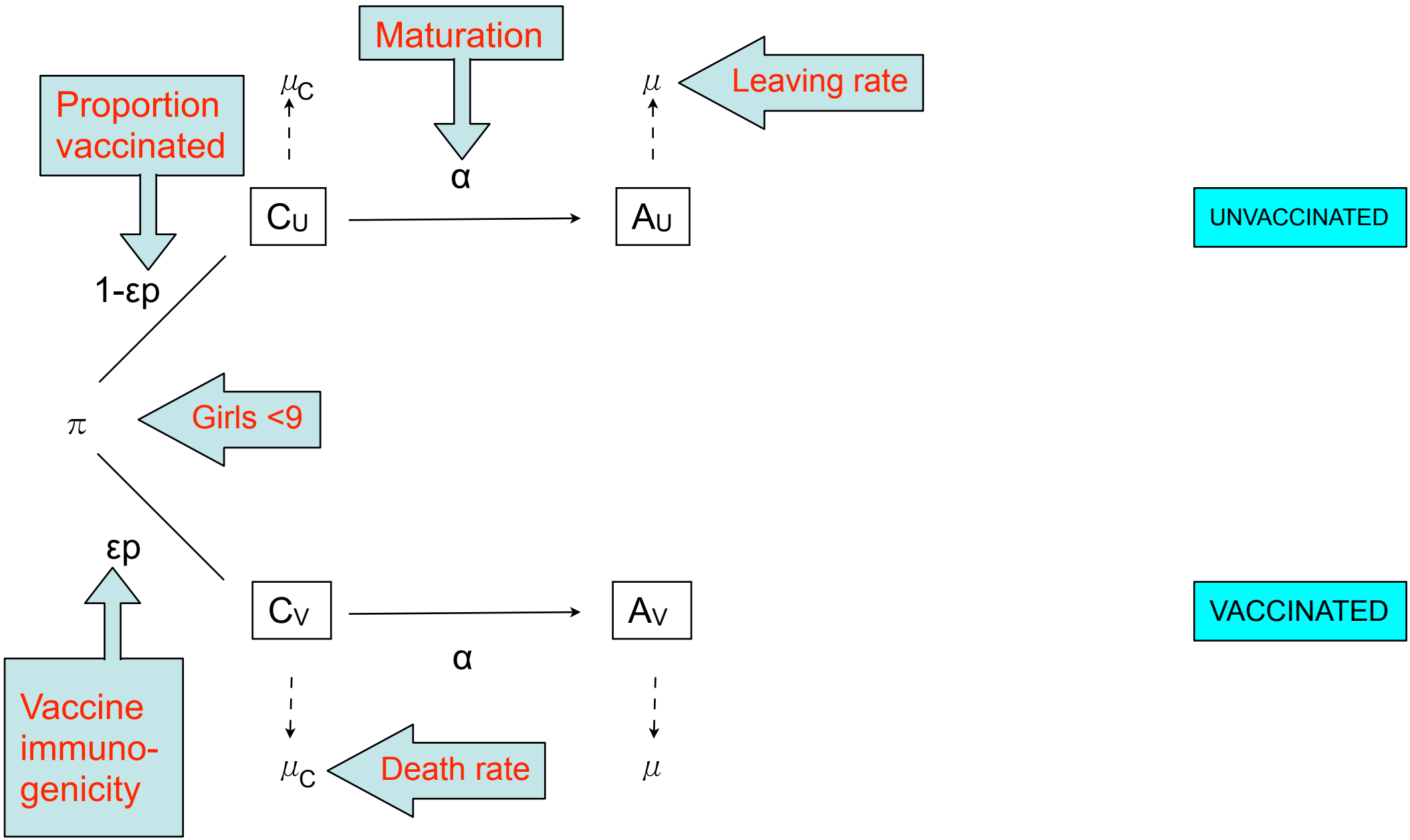
# The model


Proportion vaccinated
1-εp
π
Girls <9
εp
Vaccine immuno-genicity

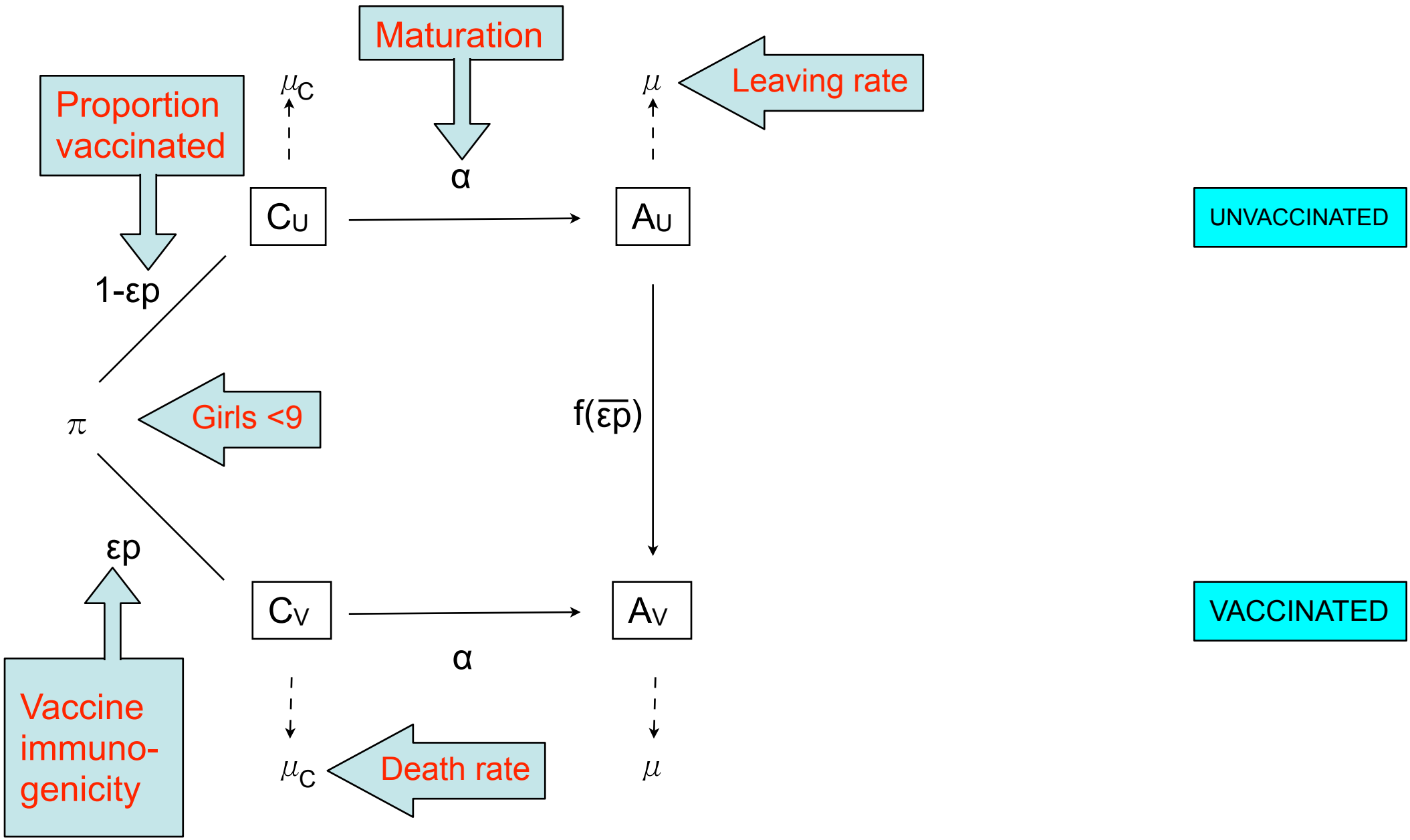
# The model


Proportion vaccinated
$\mu_C$
$C_U$
UNVACCINATED
1-εp
π
Girls <9
εp
$C_V$
VACCINATED
Vaccine immuno-genicity
$\mu_C$
Death rate

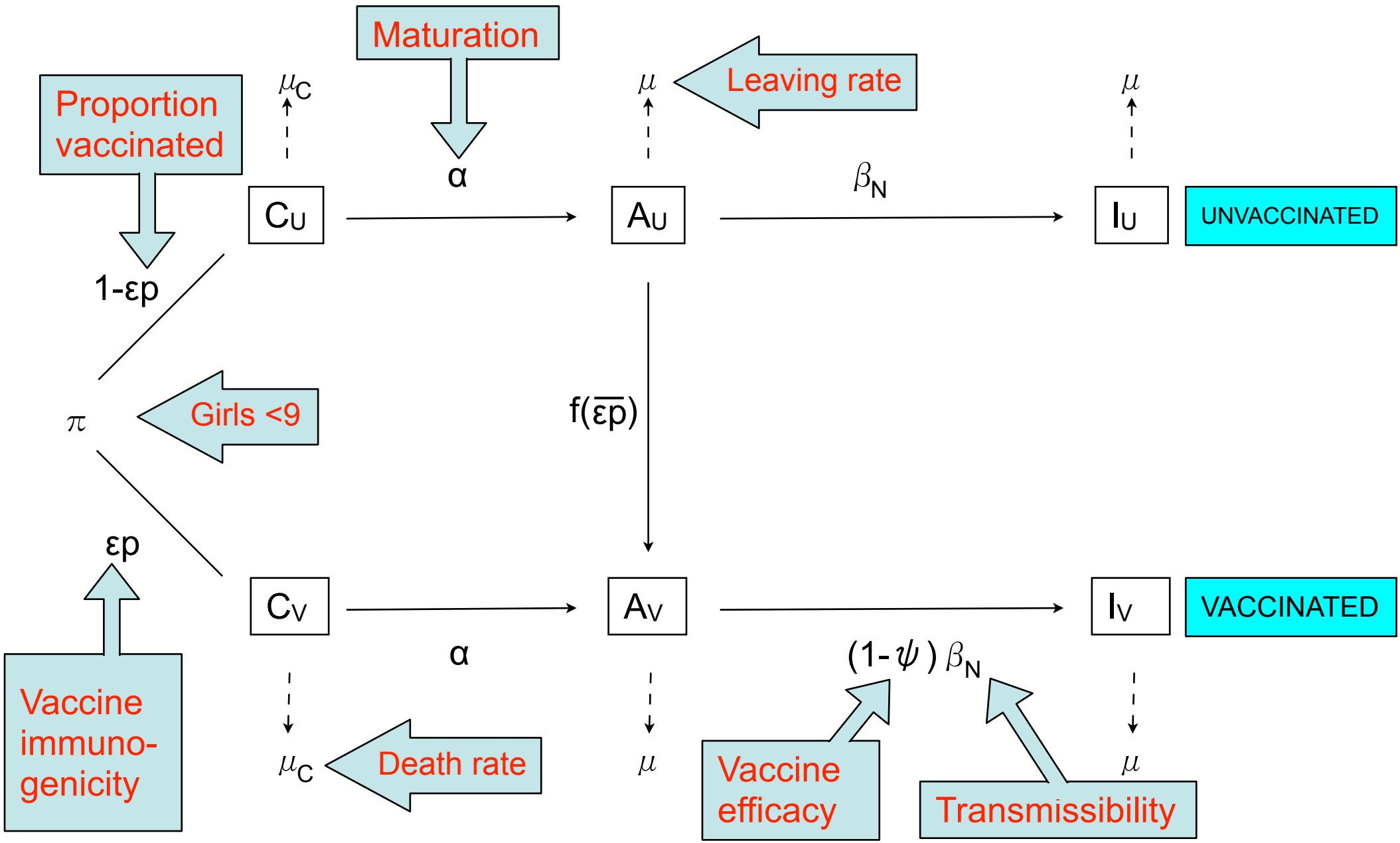
# The model


Maturation
Proportion vaccinated
$\mu_C$
$\mu$
Leaving rate
α
$C_U$
$A_U$
UNVACCINATED
1-εp
$\pi$
Girls <9
εp
$C_V$
$A_V$
VACCINATED
α
Vaccine immuno-genicity
$\mu_C$
Death rate
$\mu$

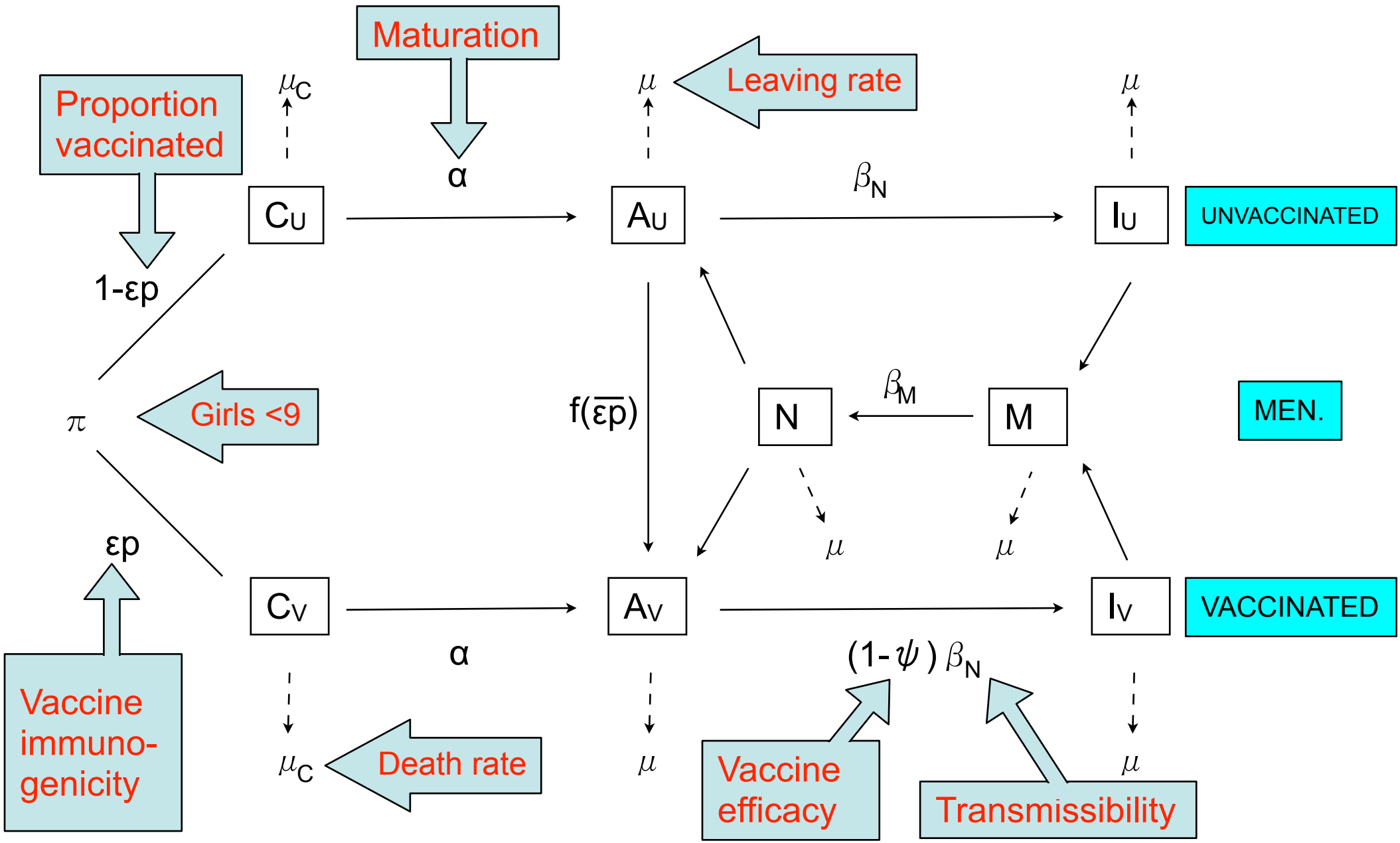
# The model


Maturation
Proportion vaccinated
$\mu_C$
$\mu$
Leaving rate
α
$C_U$
$A_U$
UNVACCINATED
1-εp
$\pi$
Girls <9
f(εp)
εp
$C_V$
$A_V$
VACCINATED
α
Vaccine immuno-genicity
$\mu_C$
Death rate
$\mu$

# The model


Maturation
Proportion vaccinated
$\mu_C$
$\mu$
Leaving rate
$\mu$
α
$\beta_N$
$C_U$
$A_U$
$I_U$
UNVACCINATED
1-εp
$\pi$
Girls <9
f($\overline{\varepsilon p}$)
εp
$C_V$
$A_V$
$I_V$
VACCINATED
α
$(1-\psi)\,\beta_N$
Vaccine immuno-genicity
$\mu_C$
Death rate
$\mu$
Vaccine efficacy
Transmissibility
$\mu$

# The model


Maturation
Proportion vaccinated
Leaving rate
$\mu_C$
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$\mu$
α
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$I_U$
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1-εp
$\pi$
Girls <9
f(εp)
N
$\beta_M$
M
MEN.
$\mu$
$\mu$
εp
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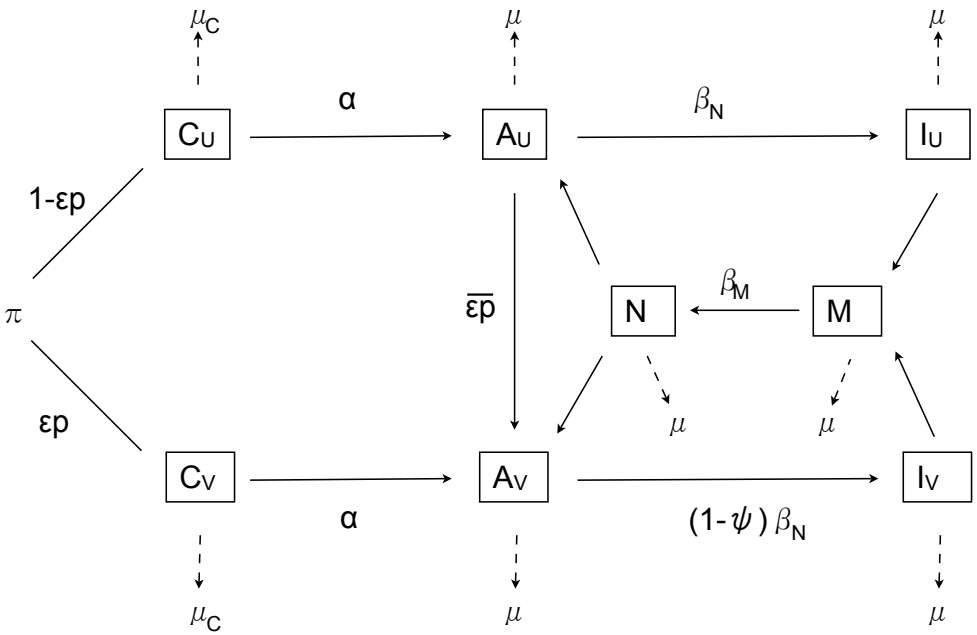
VACCINATED
α
$(1-\psi)\,\beta_N$
Vaccine immuno-genicity
$\mu_C$
Death rate
$\mu$
Vaccine efficacy
$\mu$
Transmissibility

# The ODEs




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

# Adult vaccination rate

- The rate of vaccination of adults is

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

  where $c/\gamma$ 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.

$\varepsilon$=*immunogenicity (adults)*
*p=coverage (adults)*

# Model assumptions

- Men do not get vaccinated
- Children progress to the sexually active pool after 3 years
- Women and men are in the sexually active pool for 10 years

  (after this time, women cannot be vaccinated)
- The vaccine may not confer 100% protection
- Overall prevalence matched the Canadian average (24%).

# Disease-free equilibrium

- The disease-free equilibrium is

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

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

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

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

*$C_j$=children $A_j$=uninfected women*
*$I_j$=infected adults M=uninfected men*
*N=infected men $\pi_M$=boys $\pi_W$=girls*
*$\varepsilon$=immunogenicity p=coverage*
*$\alpha$=maturation rate f=adult vaccination*
*$\mu$=leaving rate $\mu_C$= childhood mortality*

# Jacobian

- The Jacobian at the disease-free equilibrium is

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

*$A_j$=uninfected women  M=uninfected men*
*$\alpha$=maturation rate  f=adult vaccination*
*$\mu$=leaving rate  $\mu_C$= childhood mortality*
*$\beta_j$=transmission rate  $\psi$=vaccine efficacy*

# Critical coverage threshold

- The critical vaccine coverage threshold is

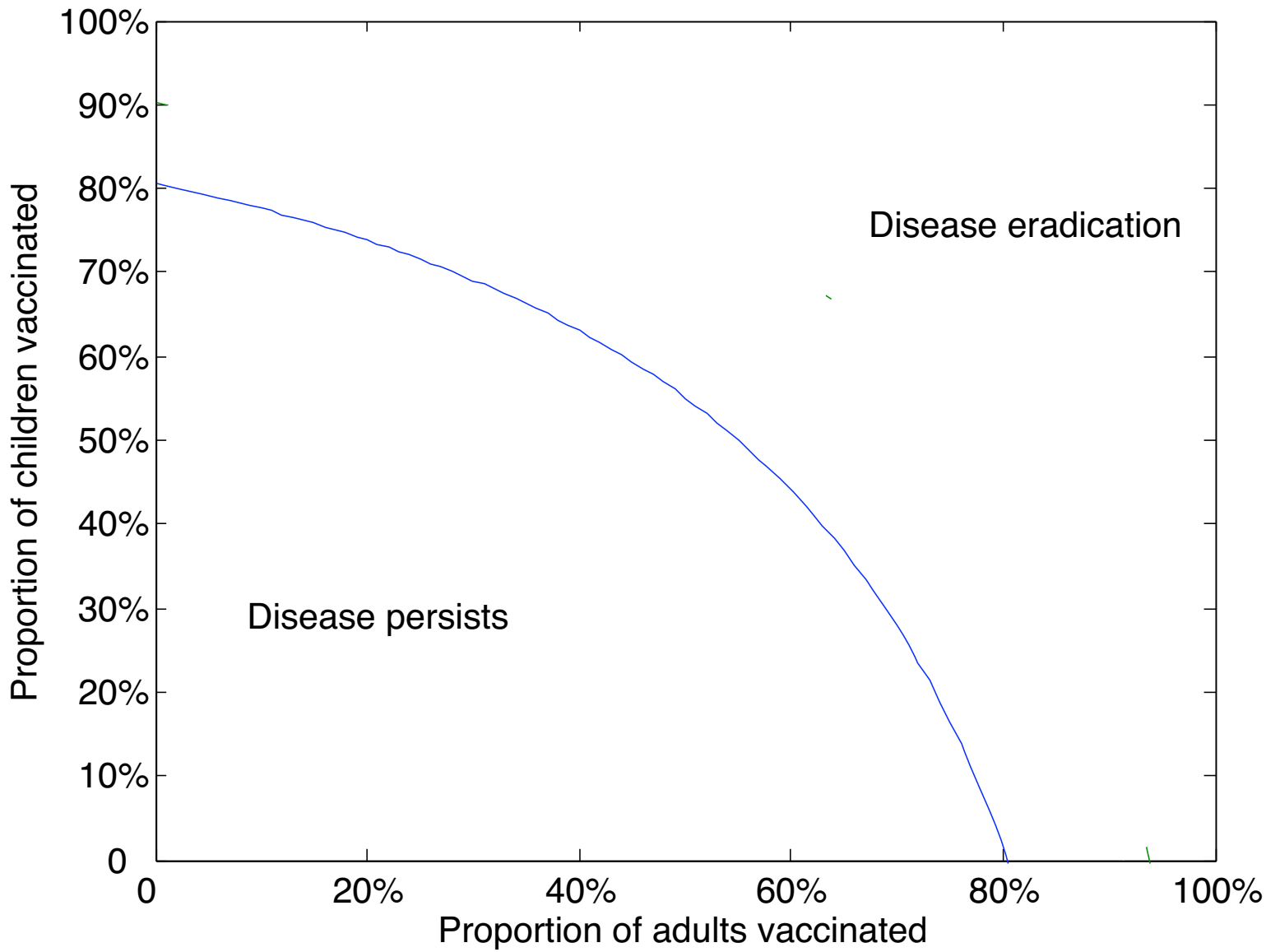
$$\epsilon p \quad = \quad \frac{1}{\psi\mu}\left[\mu + f(\bar{\epsilon}\bar{p})(1-\psi) - \frac{\mu^4(\mu + f(\bar{\epsilon}\bar{p}))(\alpha+\mu_C)}{\beta_M\beta_N\pi_M\pi_W\alpha}\right]$$

(See HPV Vaccination Notes)

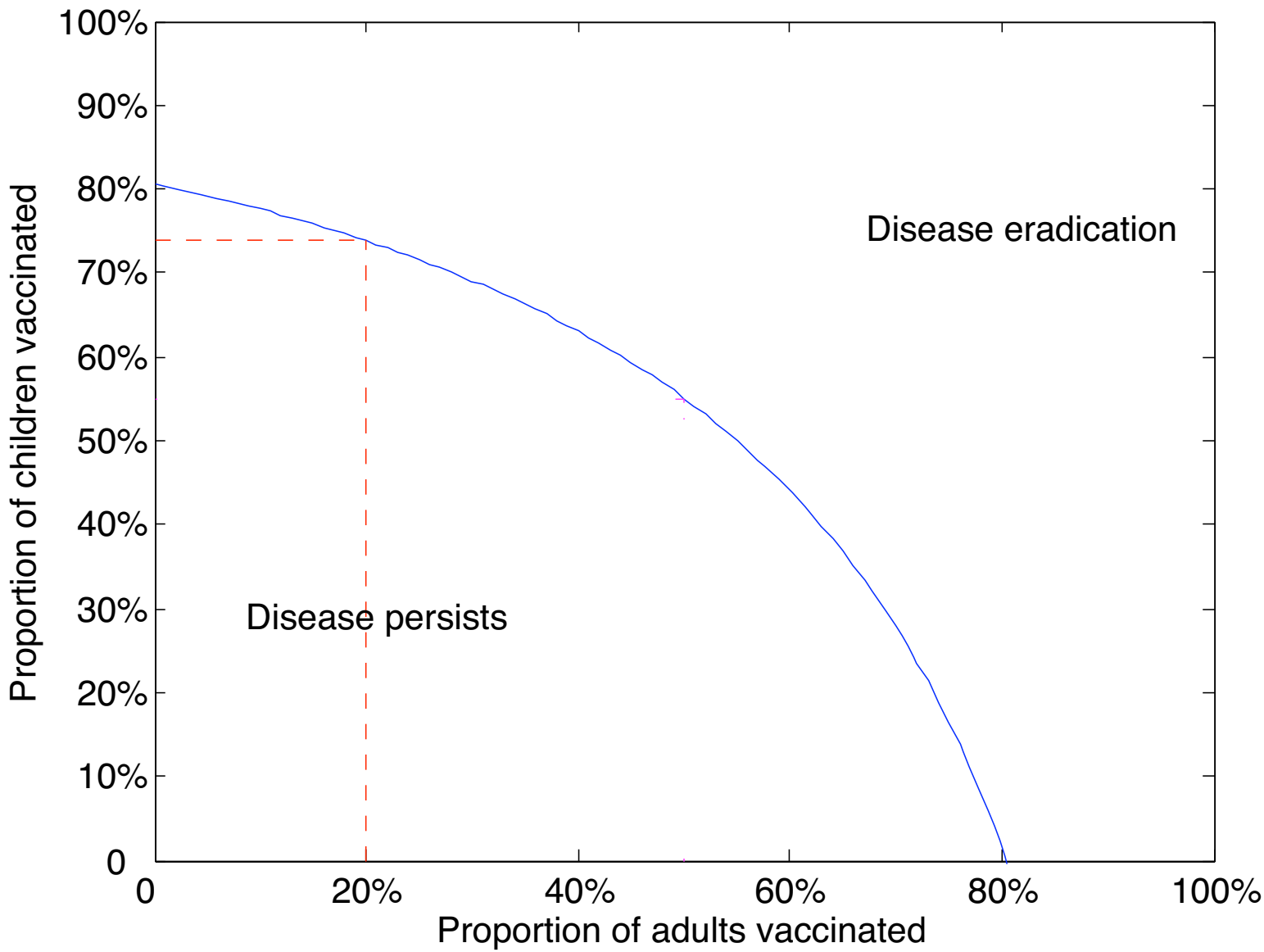
- If coverage exceeds this level, then we have eradication.

$\pi_M$=boys $\pi_W$=girls $\varepsilon$=immunogenicity
$p$=coverage $\beta_j$=transmission rate
$\psi$=vaccine efficacy $\alpha$=maturation rate
$f$=adult vaccination $\mu$=leaving rate
$\mu_C$= childhood mortality

# 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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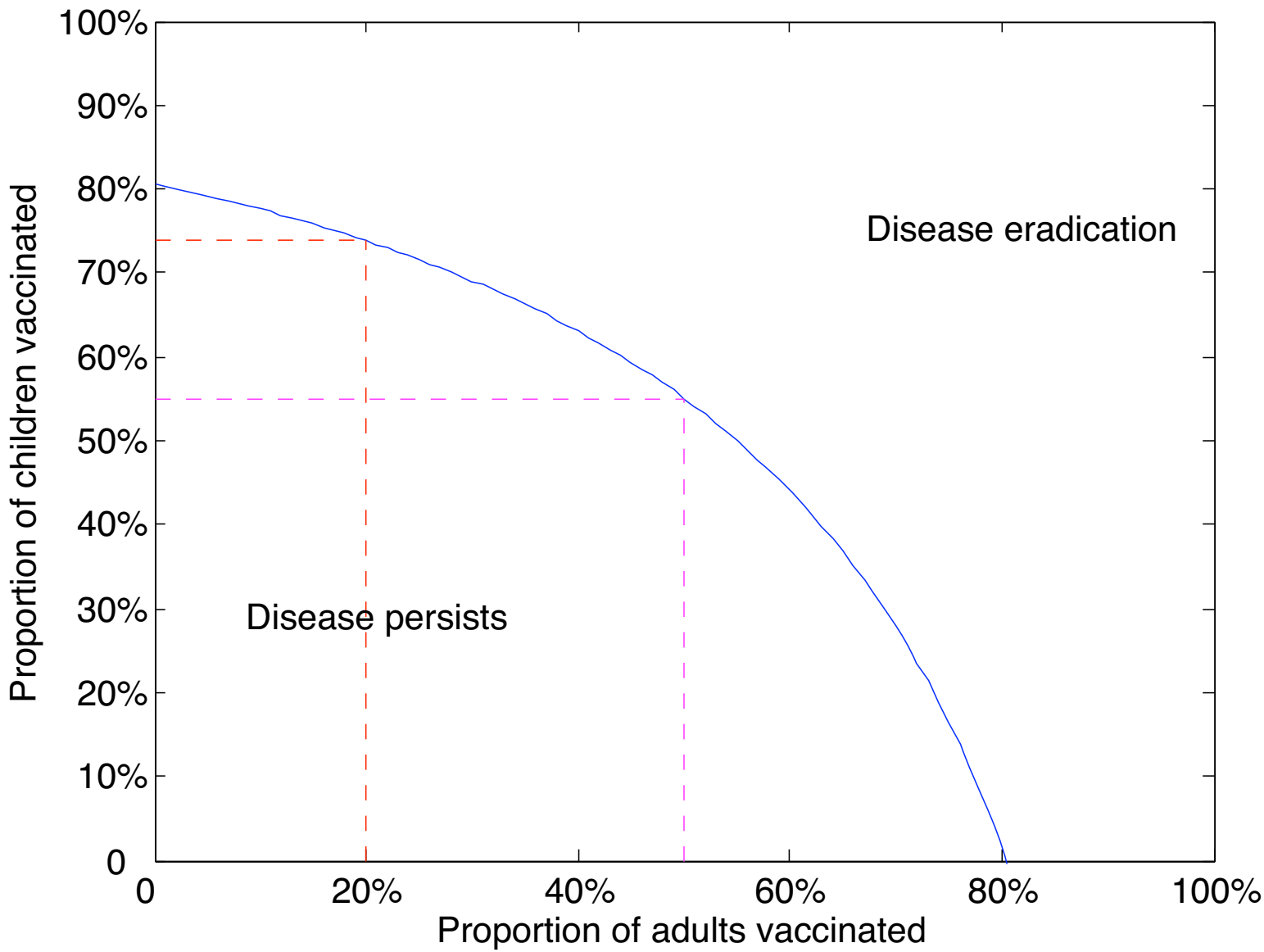
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100%
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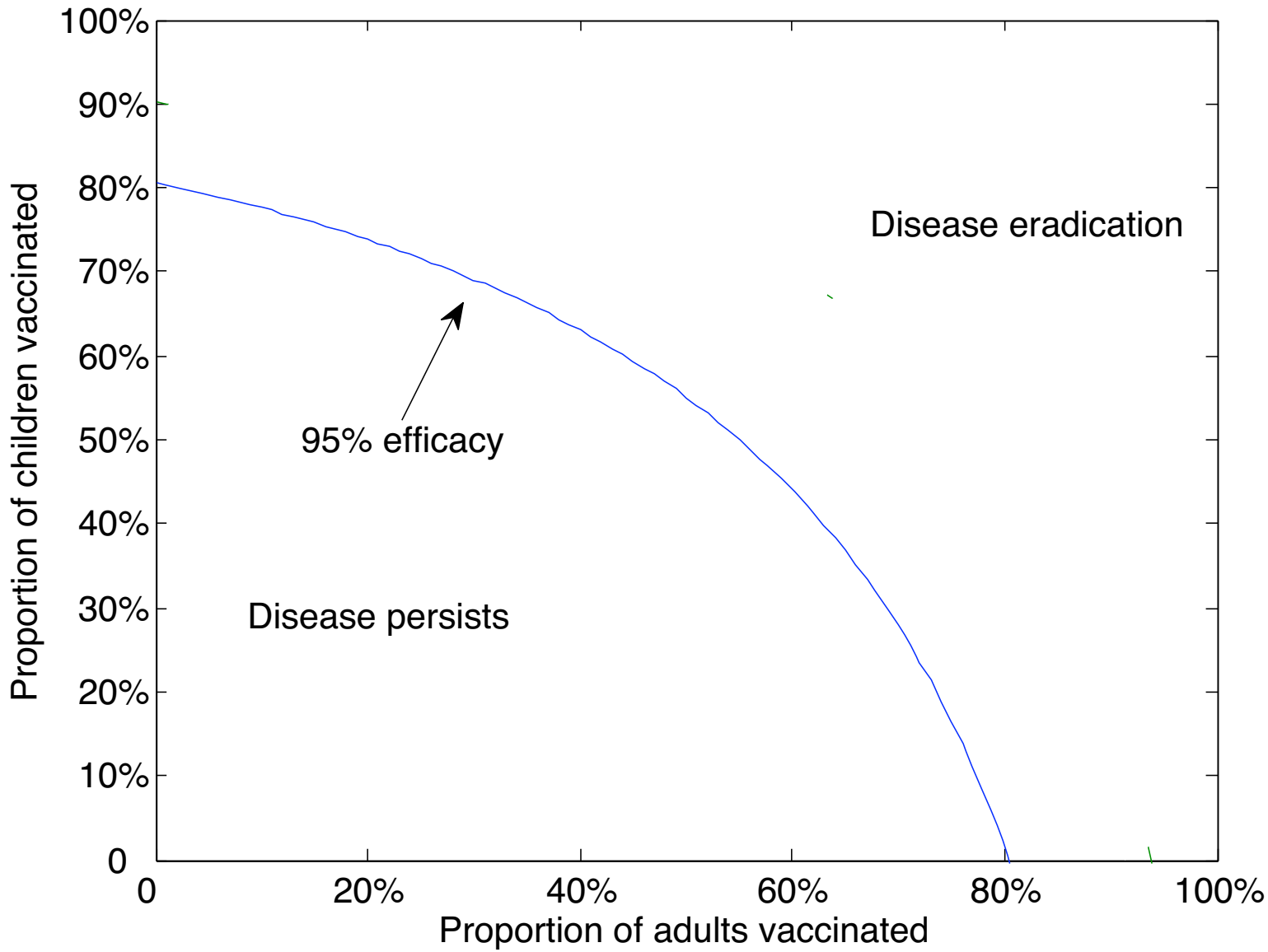
# What happens as the efficacy decreases?



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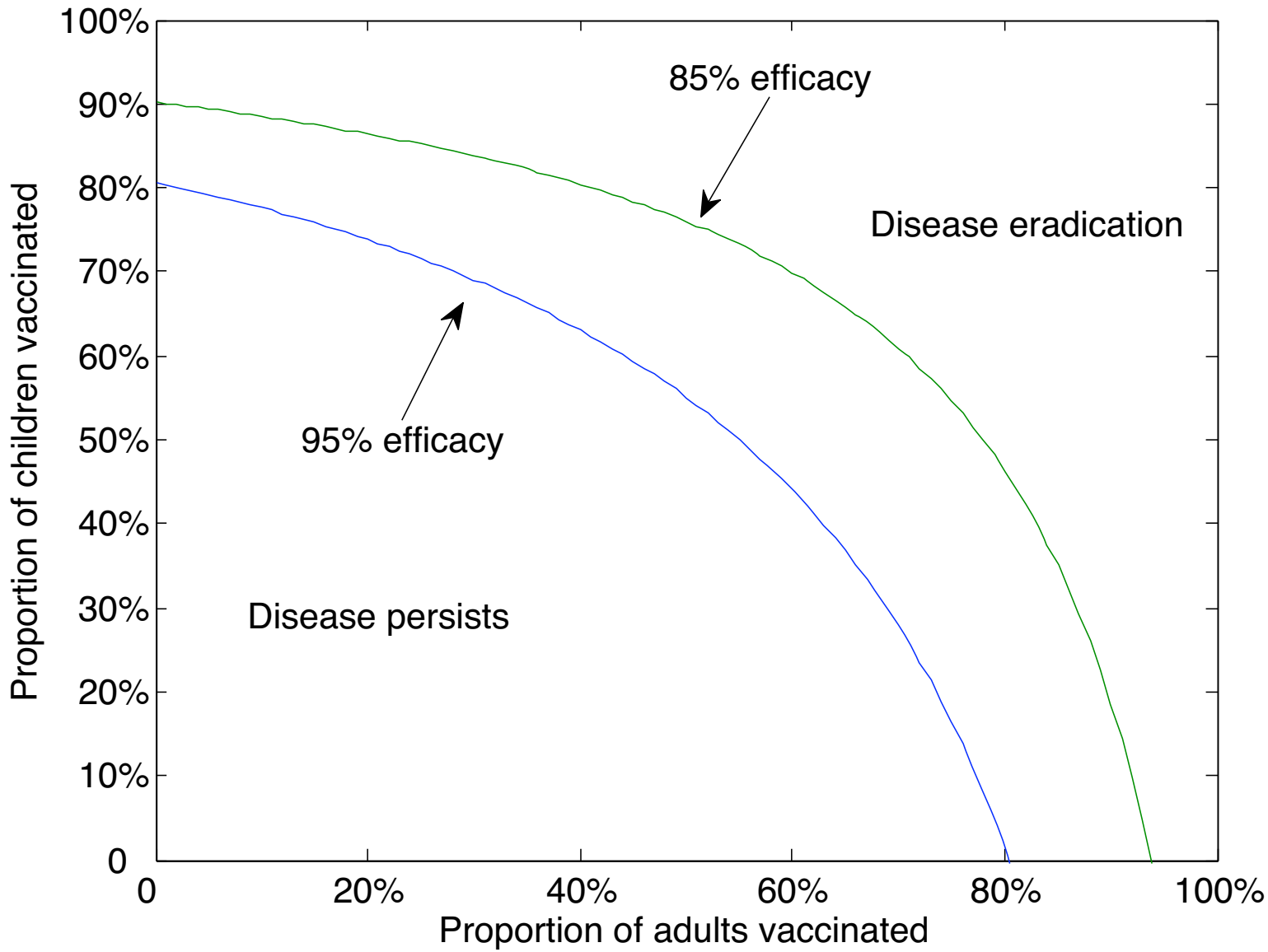
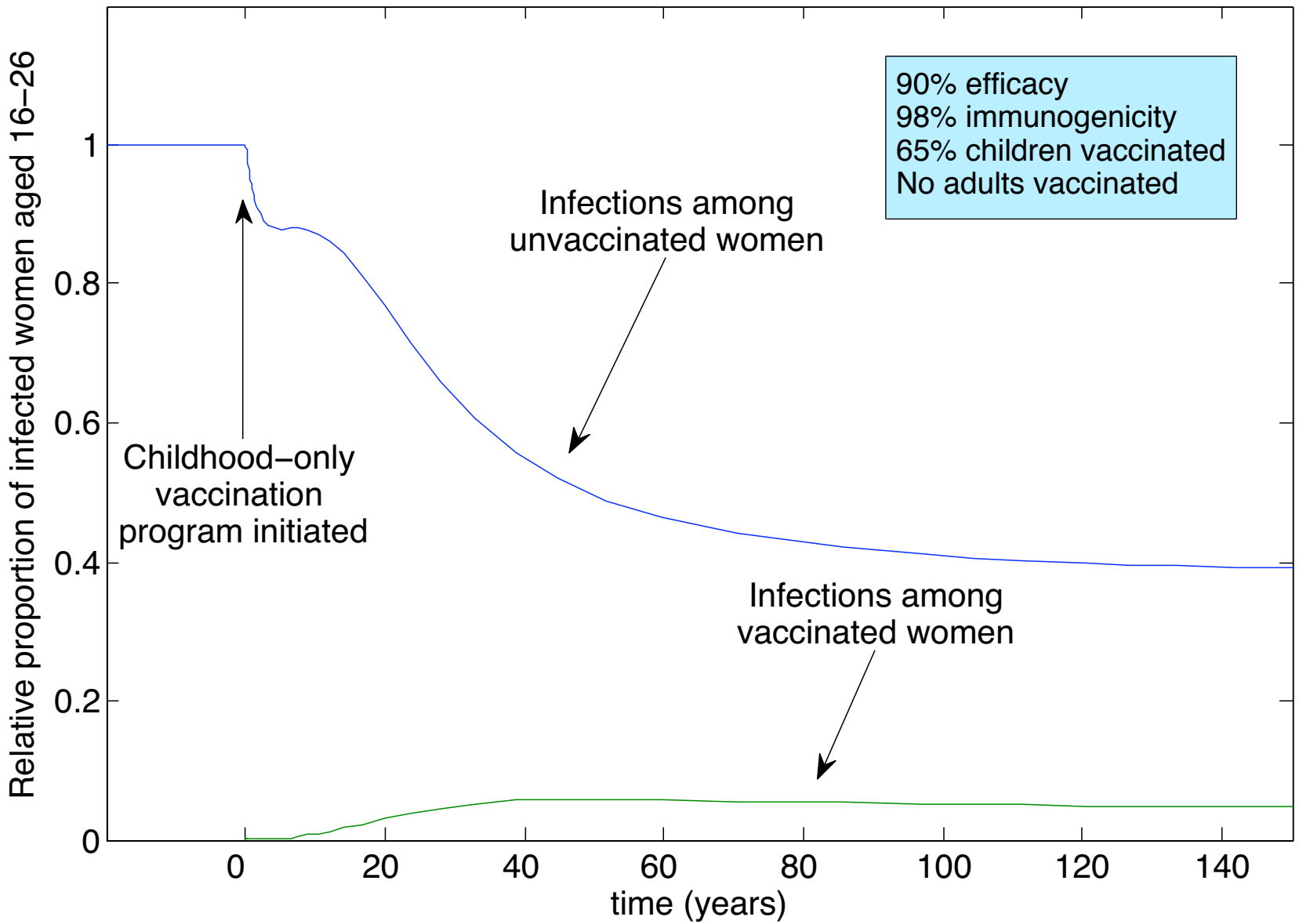


# Vaccinating children vs both



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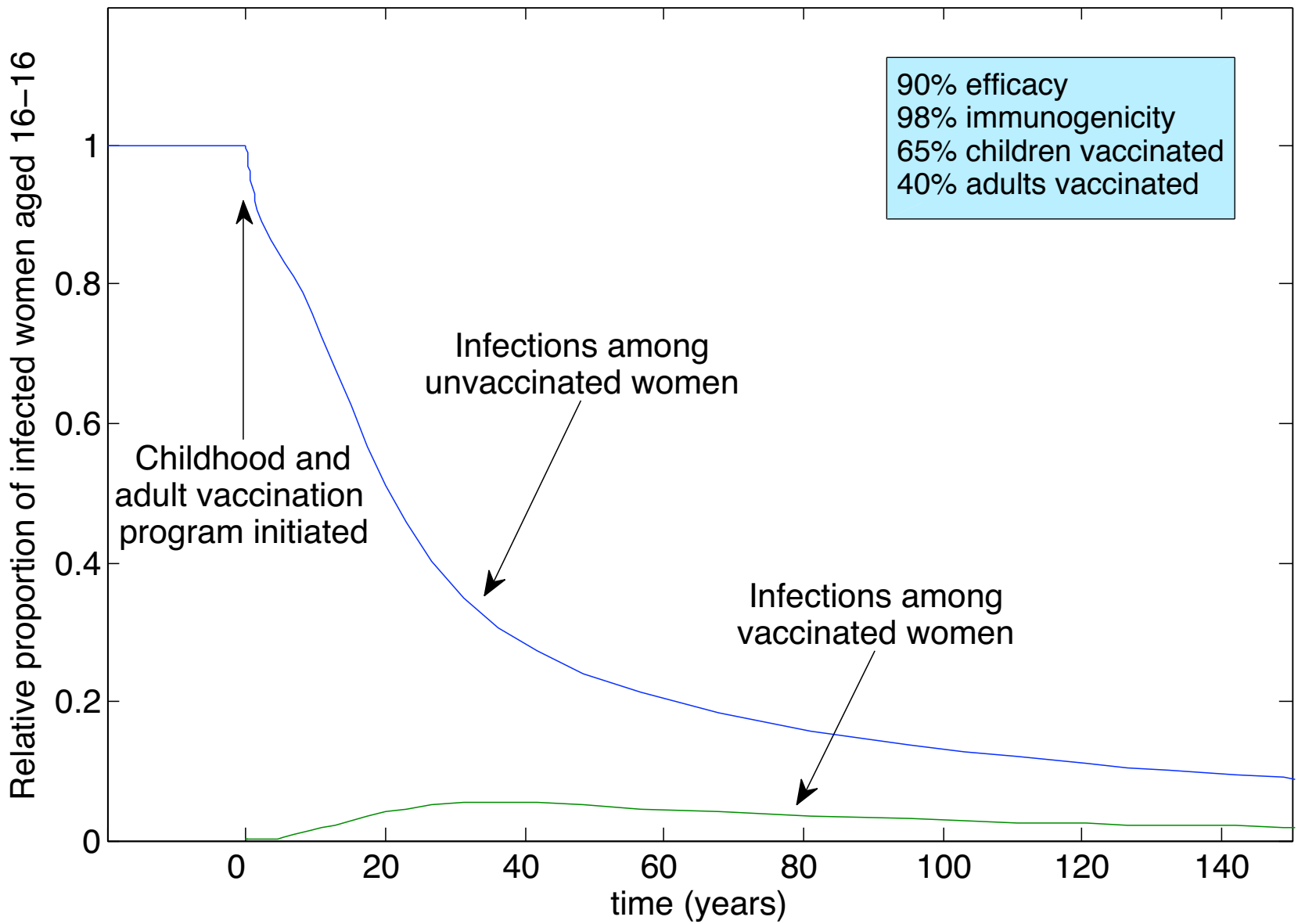


# What could go wrong?

- The vaccine efficacy might be suboptimal

  (ie the vaccine might only protect a fraction of the time)
- The vaccine immunogenicity might be suboptimal

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

# Critical efficacy

- The critical vaccine efficacy is

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

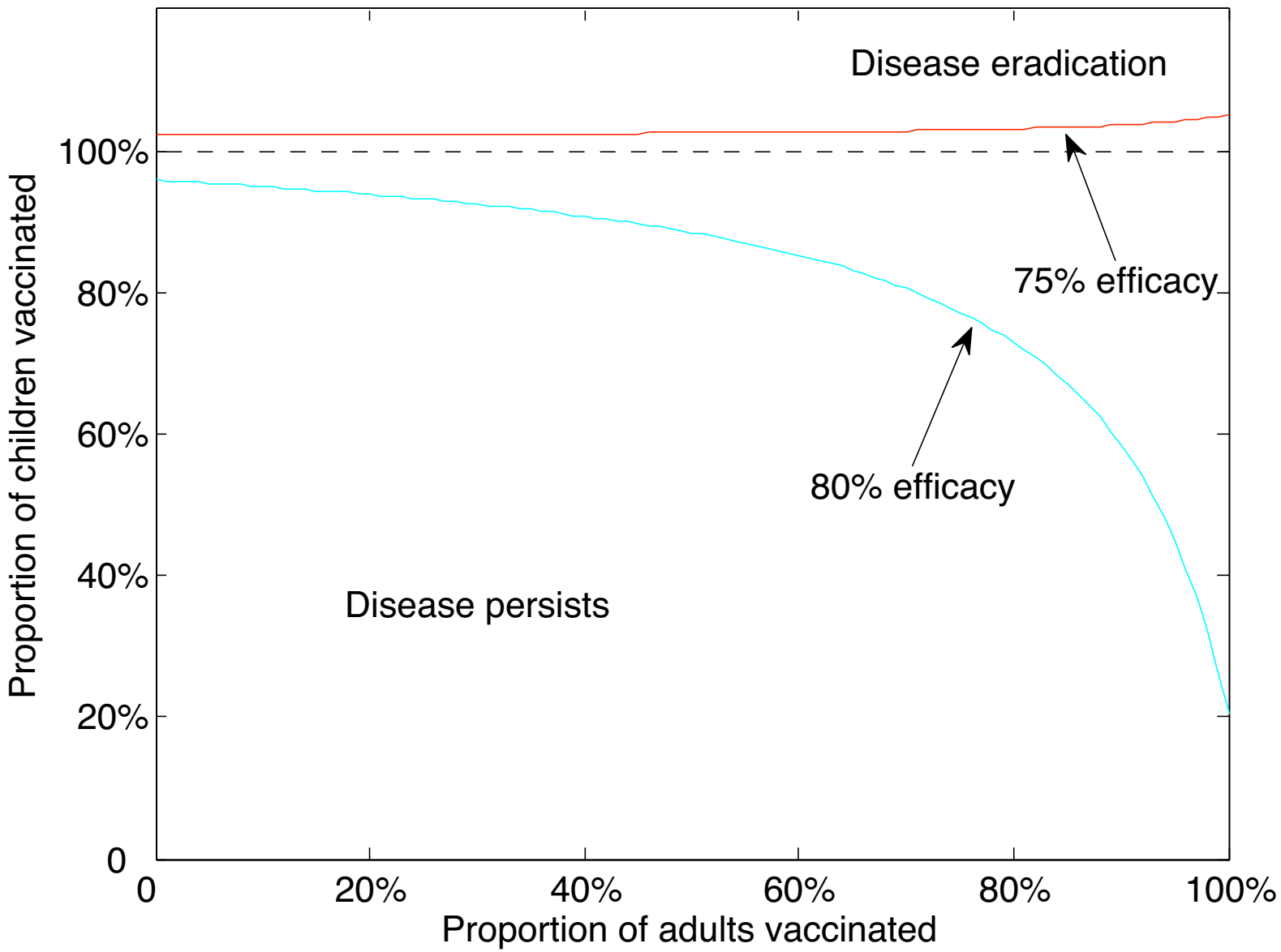
(See HPV Vaccination Notes)

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

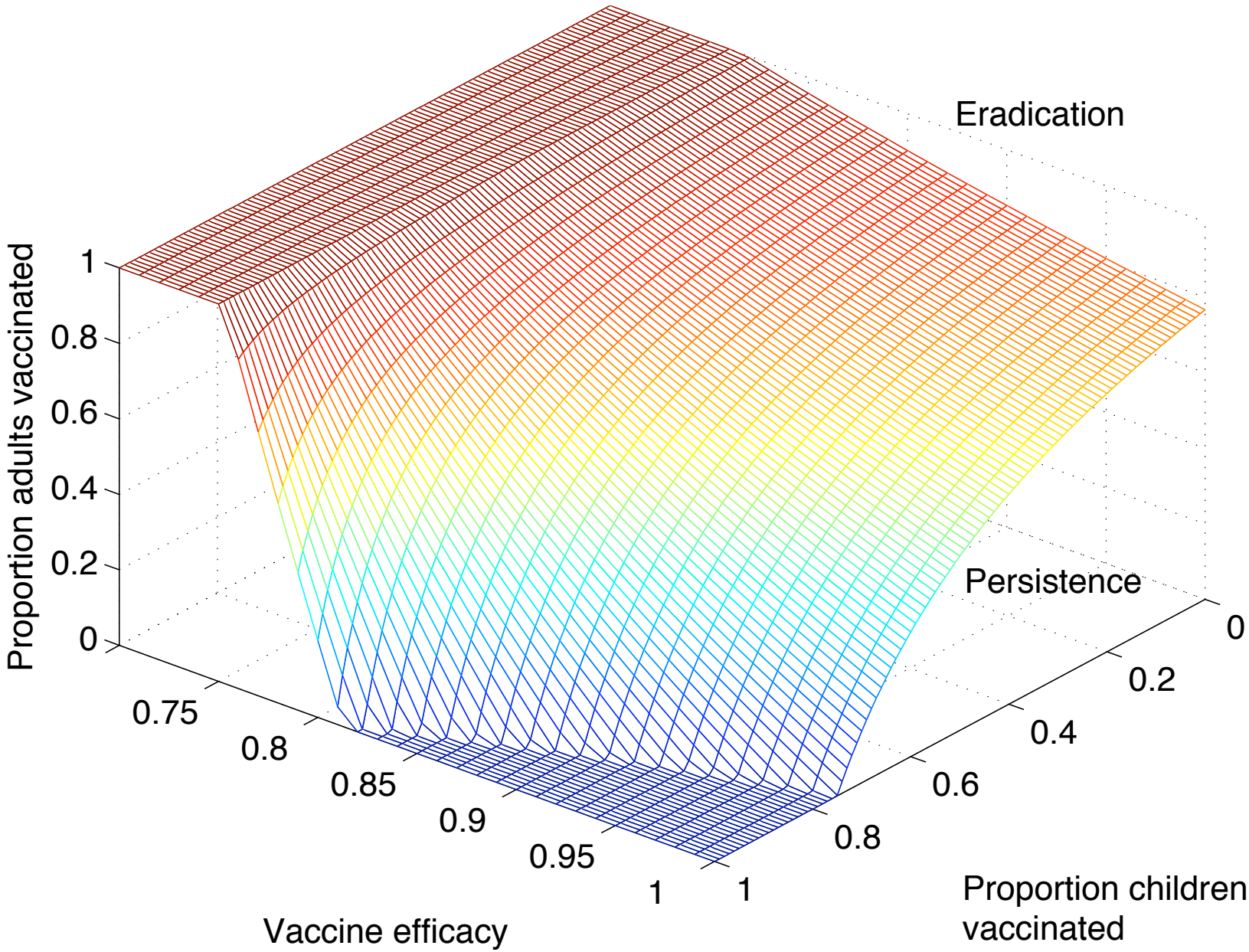
  (even if we had perfect coverage and the vaccine mounted a perfect immune response).

$\pi_M$=*boys* $\pi_W$=*girls* $\varepsilon$=*immunogenicity*
$\beta_j$=*transmission rate* $\psi$=*vaccine efficacy*
$\alpha$=*maturation rate* $\mu$=*leaving rate*
$\mu_C$= *childhood mortality*

# What if the vaccine has suboptimal efficacy?



# Dependence on efficacy



# Critical immunogenicity

- The critical immunogenicity is

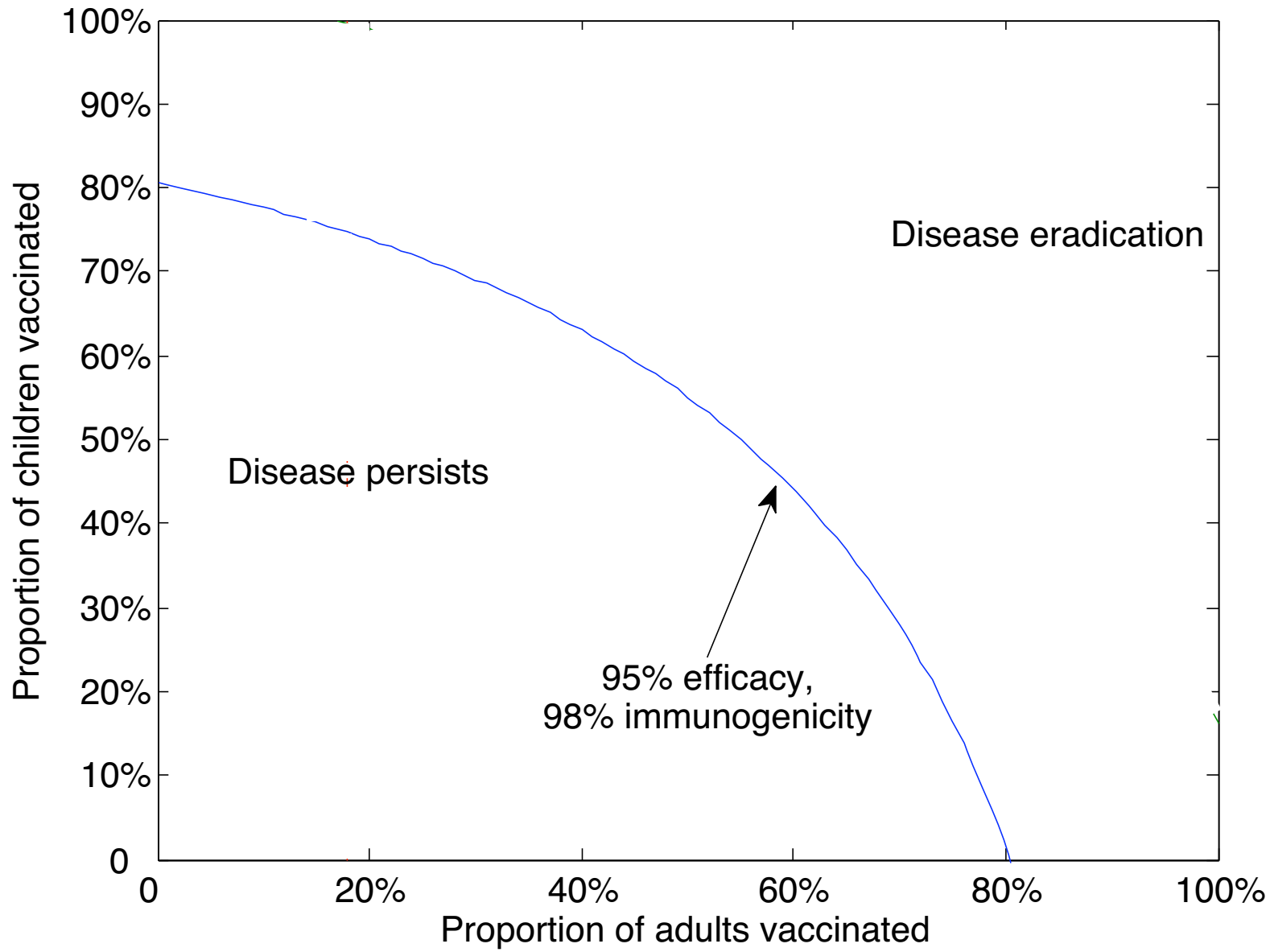
$$\epsilon^* = \frac{1}{\psi}\left[1 - \frac{\mu^4(\alpha + \mu_C)}{\beta_N \beta_M \pi_M \pi_W \alpha}\right]$$

(See HPV Vaccination Notes)

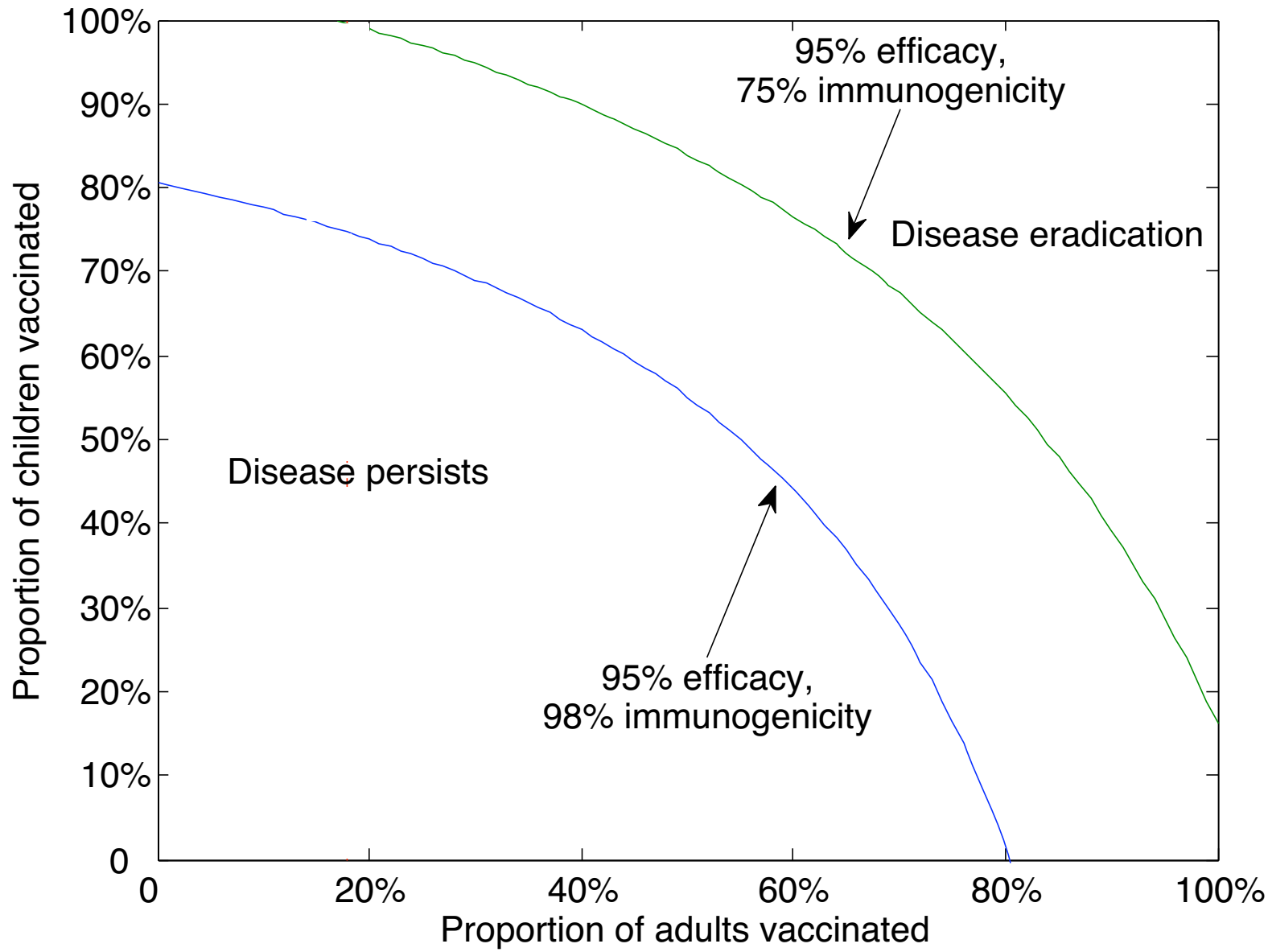
- If the imunogenicity is less than this, then even 100% childhood vaccination will not lead to eradication.

$\pi_M$=boys $\pi_W$=girls $\varepsilon$=immunogenicity
$\beta_j$=transmission rate $\psi$=vaccine efficacy
$\alpha$=maturation rate $\mu$=leaving rate
$\mu_C$= childhood mortality

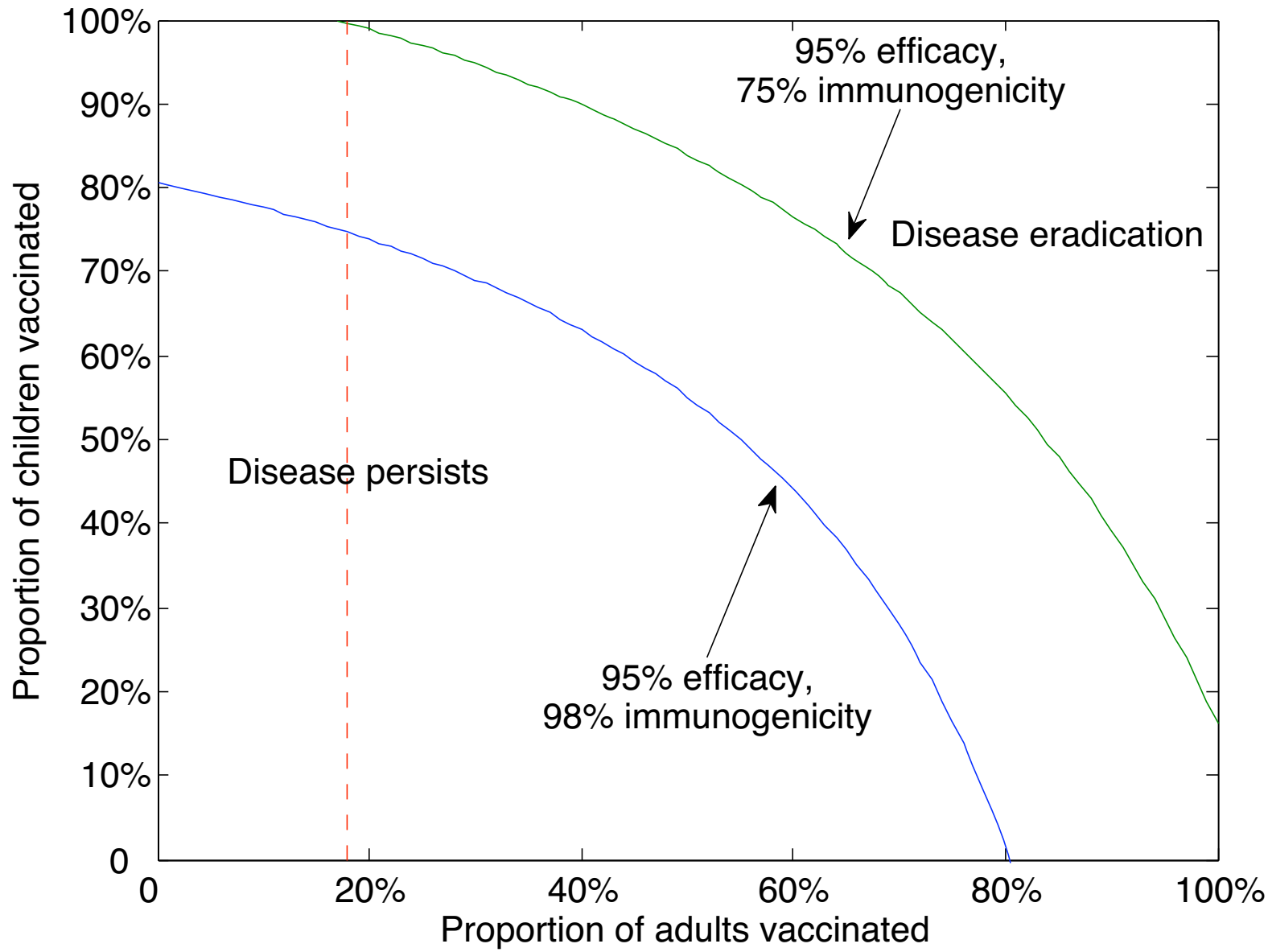
# What if the vaccine has suboptimal immunogenicity?



# What if the vaccine has suboptimal immunogenicity?



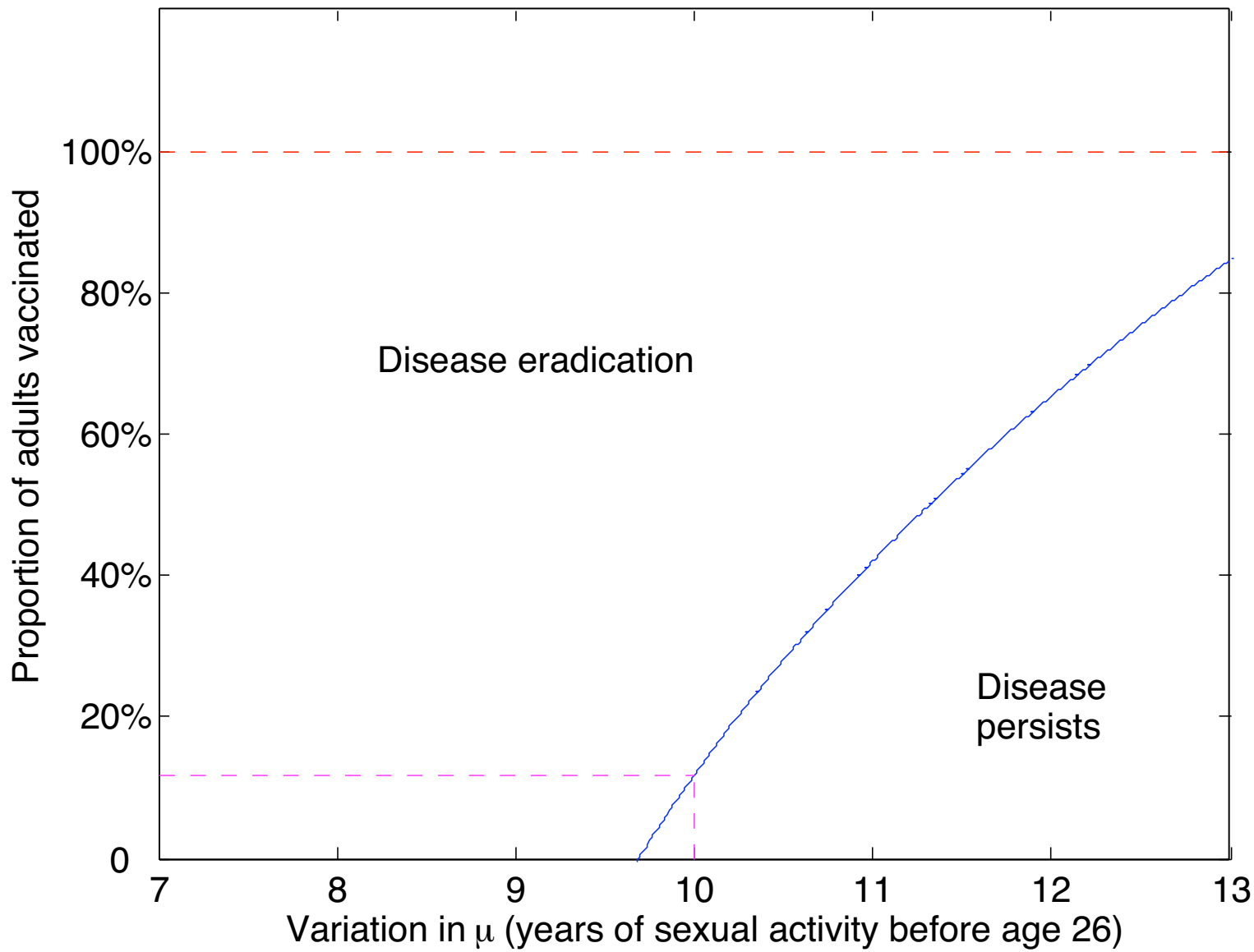
# What if the vaccine has suboptimal immunogenicity?



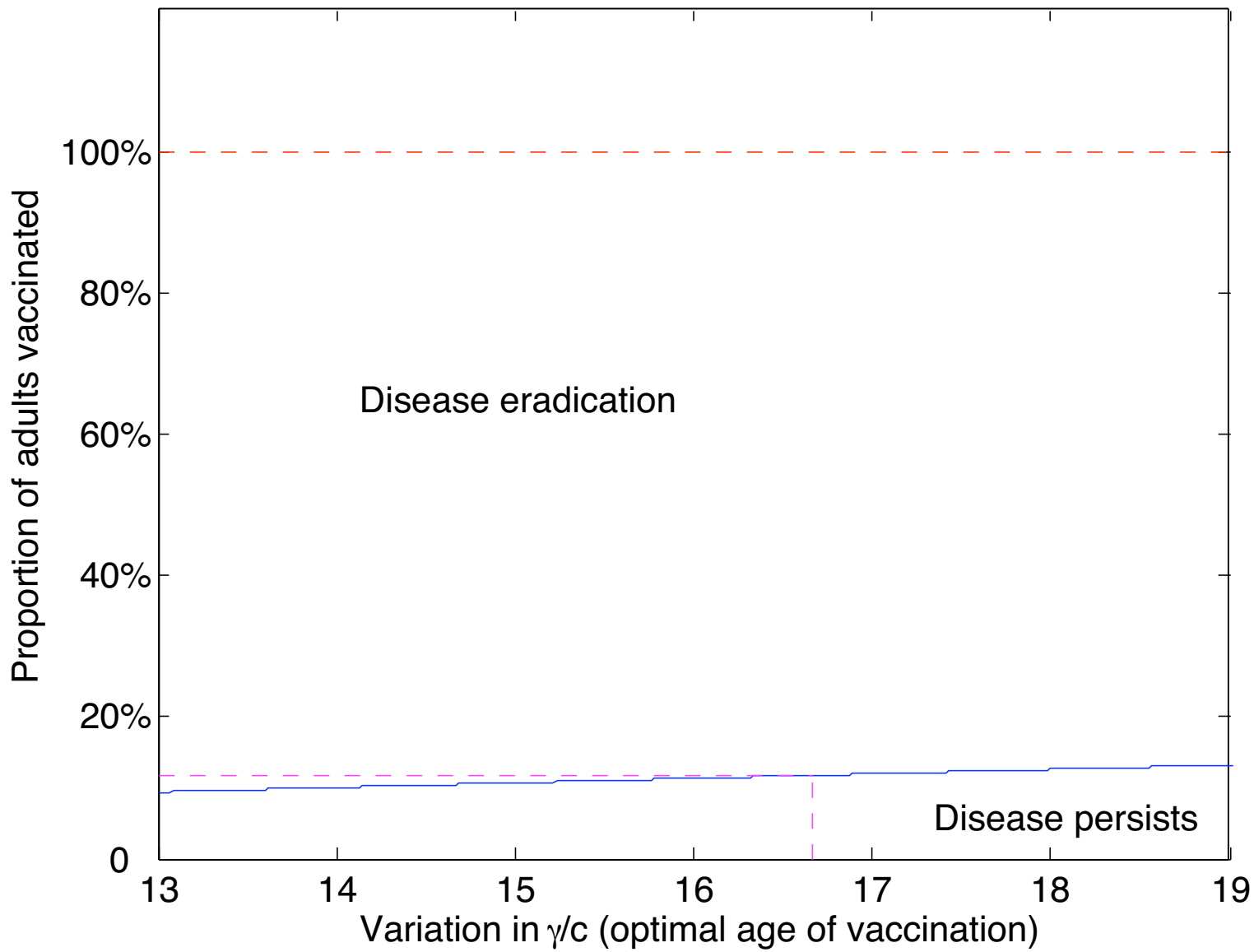
# Parameter sensitivity

- 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.

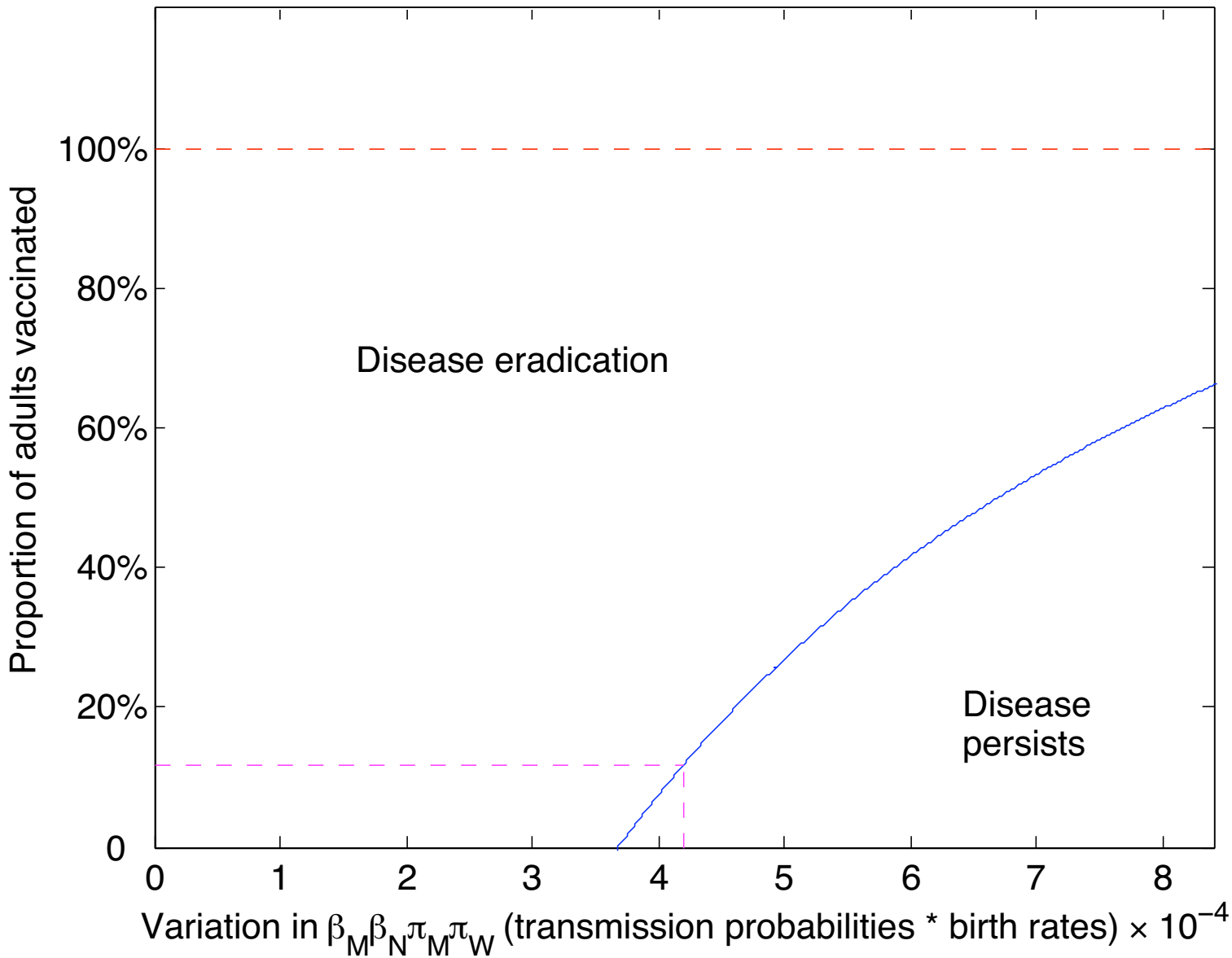
# Dependence on years of sexual activity



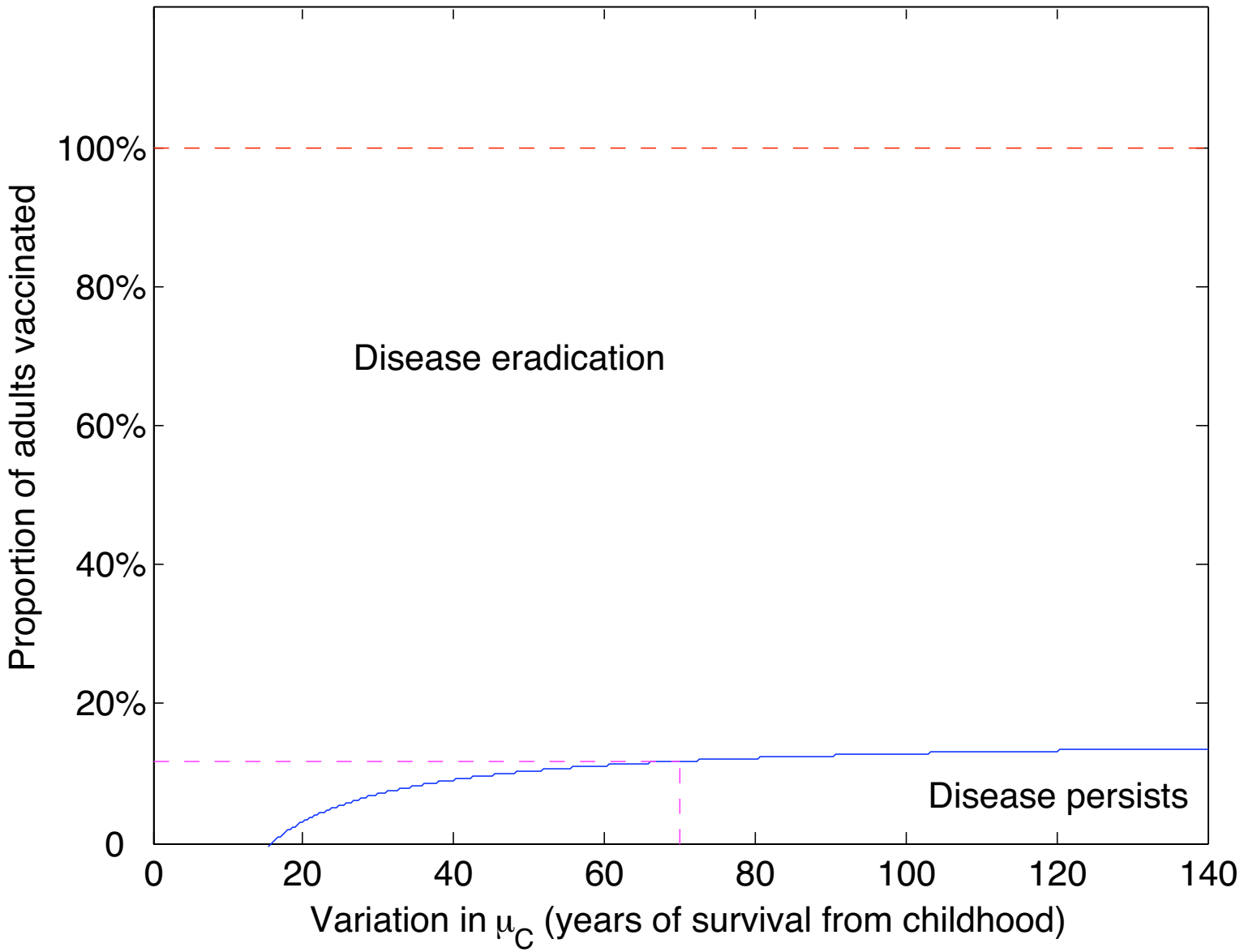
# Dependence on the optimal age of vaccination



# Dependence on the transmission and birth rates



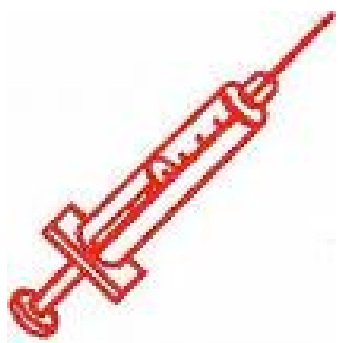
# Dependence on years of survival since childhood



# 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
- Dependence upon the
  - vaccine efficacy
  - vaccine immunogenicity
  - all other parameters.



# Conclusions (Part 1)

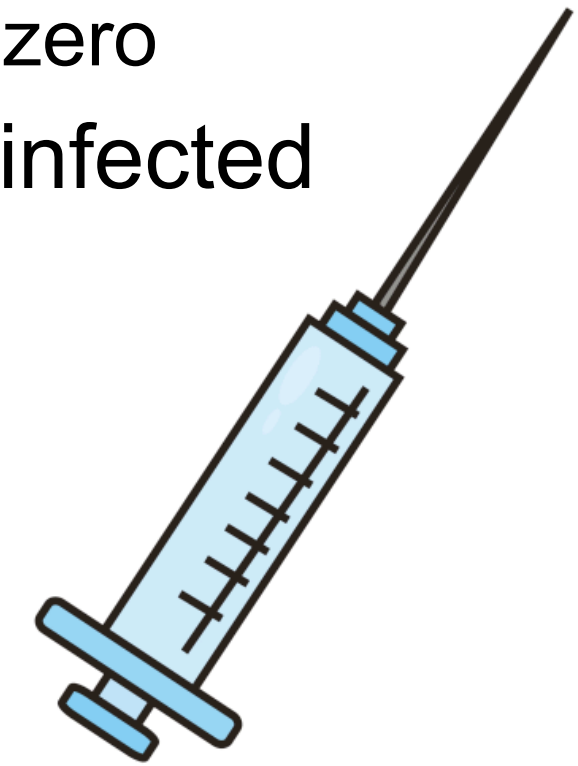
- Eradication of HPV is feasible
- Childhood vaccination programs should be supplemented by adult vaccination
- There is a critical vaccine efficacy (77%) below which eradication is not possible
- There is a critical vaccine immunogenicity (80%) below which even 100% childhood vaccination cannot eradicate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

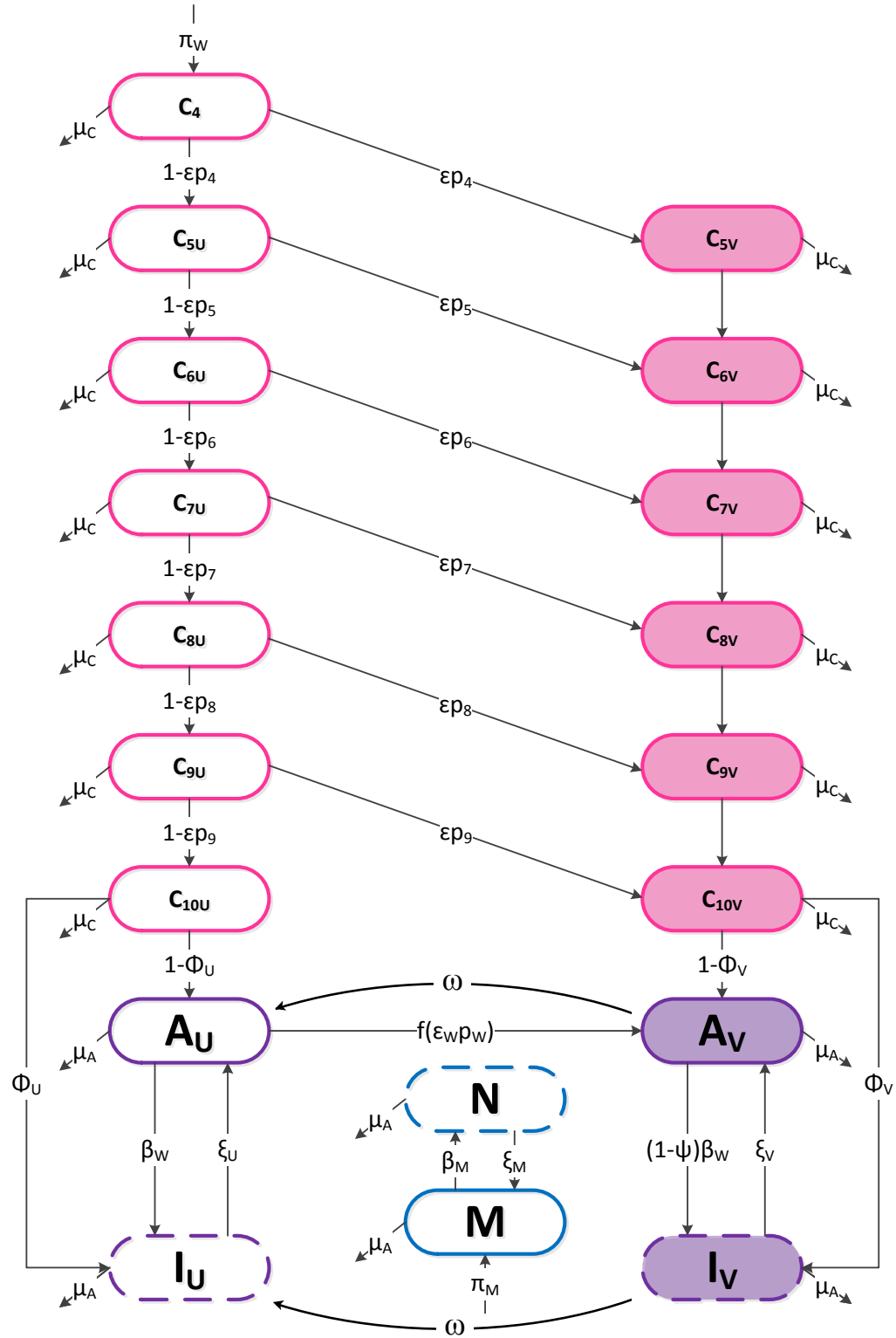
# Recommendation

- Recall that vaccination rates in Ontario are at 53%
- 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.

# Full model

- We now extend the baseline model to multiple classes of children
  - these represent different school grades
  - vaccination occurs at a particular grade
  - otherwise the vaccination rate is zero
- Some children may already be infected
  - eg childhood sexual abuse
- These individuals will proceed directly to the infected class
- We also include recovery of infected individuals.




πW
C4
μC
1-εp4
εp4
C5U
C5V
1-εp5
εp5
C6U
C6V
1-εp6
εp6
C7U
C7V
1-εp7
εp7
C8U
C8V
1-εp8
εp8
C9U
C9V
1-εp9
εp9
C10U
C10V
1-ΦU
1-ΦV
ω
AU
AV
f(εWpW)
μA
ΦU
ΦV
N
βW
ξU
βM
ξM
(1-ψ)βW
ξV
M
IU
IV
πM

# The model

Girls in grade 4 (approx. 9 years old) are described as

$$\frac{dC_4}{dt} = \pi_W - (1+\mu_C)C_4.$$

For girls in grade $i$, where $5 \leq i \leq 10$, we have

$$\frac{dC_{(i+1)U}}{dt} = (1-\epsilon p_i)C_{iU} - (1+\mu_C)C_{(i+1)U}$$

$$\frac{dC_{(i+1)V}}{dt} = \epsilon p_i C_{iU} + C_{iV} - (1+\mu_C)C_{(i+1)V}$$

Uninfected adult women are described as

$$\frac{dA_U}{dt} = (1-\phi_U)C_{10U} + \xi_U I_U - f(\epsilon_W p_W)A_U - \frac{\beta_W A_U N}{♂} - \mu_A A_U + \omega A_V$$

$$\frac{dA_V}{dt} = (1-\phi_V)C_{10V} + \xi_V I_V + f(\epsilon_W p_W)A_U - \frac{(1-\psi)\beta_W A_V N}{♂} - \mu_A A_V - \omega A_V.$$

Infected adult women are described as

$$\frac{dI_U}{dt} = \phi_U C_{10U} + \frac{\beta_W A_U N}{♂} - \xi_U I_U - \mu_A I_U + \omega I_V$$

$$\frac{dI_V}{dt} = \phi_V C_{10V} + \frac{(1-\psi)\beta_W A_V N}{♂} - \xi_V I_V - \mu_A I_V - \omega I_V$$

Uninfected men are described as

$$\frac{dM}{dt} = \pi_M - \frac{\beta_M I_U M}{♀} - \frac{\beta_M I_V M}{♀} + \xi_M N - \mu_A M$$

Infected men are described as

$$\frac{dN}{dt} = \frac{\beta_M I_U M}{♀} + \frac{\beta_M I_V M}{♀} - \xi_M N - \mu_A N.$$

*$C_j$=children $A_j$=uninfected adults $I_j$=infected adults M,N=men f=adult uptake $\mu_j$=death rates $\pi_W$=female birth rate $\pi_M$=male birth rate $\epsilon_j$=efficacy $p_j$=coverage $\Phi_j$=childhood infection $\omega$=waning $\beta_j$=transmissibilities $\Psi$=protection $\xi_j$=duration of infection ♀=total women ♂=total men*

# ♀ and ♂

- The denominators are the total numbers of women (including girls) and men:

$$\begin{aligned}♀ =& C_4 + C_{5U} + C_{5V} + C_{6U} + C_{6V} + C_{7U} + C_{7V} + C_{8U} + C_{8V} + C_{9U} + C_{9V} \\ &+ C_{10U} + C_{10V} + A_U + A_V + I_U + I_V,\end{aligned}$$

$$♂ = M + N$$

- We also include waning of the vaccine.


*$C_j$=children*
*$A_j$=uninfected adults*
*$I_j$=infected adults*
*M,N=men*

# Disease-free equilibrium

- The DFE is

$$(\overline{C_4}, \overline{C_{5U}}, \overline{C_{5V}}, \overline{C_{6U}}, \overline{C_{6V}}, \overline{C_{7U}}, \overline{C_{7V}}, \overline{C_{8U}}, \overline{C_{8V}}, \overline{C_{9U}}, \overline{C_{9V}}, \overline{C_{10U}}, \overline{C_{10V}}, \overline{A_U}, \overline{A_V}, \overline{I_U}, \overline{I_V}, \overline{M}, \overline{N}),$$

where

$$\overline{C_4} = \frac{\pi_W}{1+\mu_C}$$

- For 4≤i≤10, we have

$$\overline{C_{iU}} = \frac{(1-\epsilon p_{(i-1)})\overline{C_{(i-1)U}}}{1+\mu_C} \qquad \overline{C_{iV}} = \frac{\epsilon p_{(i-1)}\overline{C_{(i-1)U}} + \overline{C_{(i-1)V}}}{1+\mu_C}$$

$$\overline{A_U} = \frac{(1-\phi_U)\overline{C_{10U}}}{f(\overline{\epsilon_W}\,\overline{p_W})+\mu_A} \qquad \overline{A_V} = \frac{f(\overline{\epsilon_W}\,\overline{p_W})\overline{A_U} + (1-\phi_V)\overline{C_{10V}}}{\mu_A}$$

$$\overline{I_U} = 0 \qquad \overline{I_V} = 0$$

$$\overline{M} = \frac{\pi_M}{\mu_A} \qquad \overline{N} = 0.$$

*$C_j$=children $A_j$=uninfected adults*
*$I_j$=infected adults M,N=men*
*f=adult uptake $\mu_j$=death rates*
*$\pi_M$=male birth rate $\epsilon_j$=efficacy*
*$p_j$=coverage $\Phi_j$=childhood infection*

# Stability

- We found the Jacobian matrix and used the Routh–Hurwitz criterion to determine stability of the DFE
- This is valid, so long as we have the condition $\frac{1}{\xi_V} < \frac{1}{\xi_U}$.
  - i.e. the duration of infection for vaccinated individuals is shorter than the duration of infection for unvaccinated individuals
- We expect this to occur.

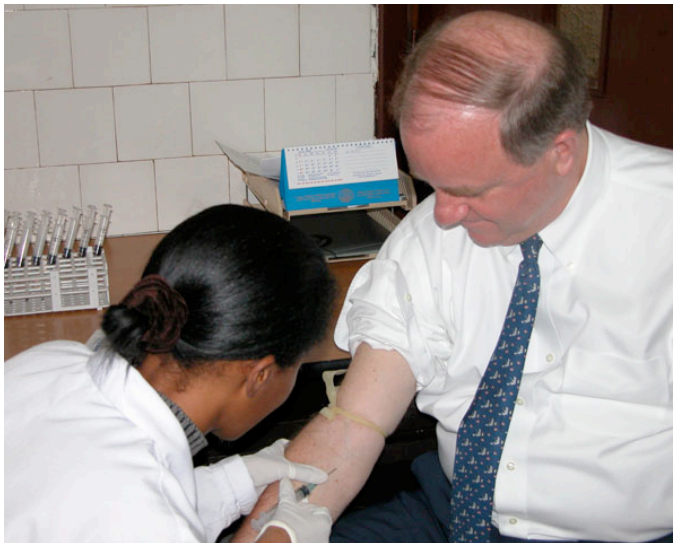
# Basic reproduction number

- The stability comes down to the sign of the constant term in the characteristic polynomial
- From this, we find

$$R_0 = \frac{\beta_W \beta_M ((1-\psi)(\mu_A + \xi_U + \omega)\overline{A_V} + (\mu_A + \xi_V + \omega)\overline{A_U})}{♀[{\mu_A}^3 + \mu_A^2(\xi_U + \xi_V + \xi_M + \omega) + \mu_A(\xi_U(\xi_V + \omega) + \xi_U\xi_M + (\xi_V + \omega)\xi_M) + \xi_U(\xi_V + \omega)]}$$

where the $A_U$ and $A_V$ values are evaluated at the disease-free equilibrium.

*$A_j$=uninfected adults $\mu_j$=death rates*
*$\beta_j$=transmissibilities ♀=total women*
*$\Psi$=protection $\omega$=waning*
*$\xi_j$=duration of infection*



# Critical childhood vaccine immunogenicity

- We can evaluate the critical vaccine immunogenicity for children $\epsilon^*$
- We set $R_0=1$ and use our reformulated equilibrium values
- We solve for $\epsilon^*$ by looking at childhood-only vaccination
  - we thus set $p_W=0$
- Then we have

$$\epsilon^* = \frac{\beta_W \beta_M (\mu_A + \xi_U + \omega)(1-\phi_U)\pi_W \mu_A - \mu_A^3 (1+\mu_C)^{7}\text{♀}(\mu_A^2 + \mu_A(\xi_U + \xi_V + \xi_M + \omega) + \xi_U(\xi_V + \omega) + \xi_U \xi_M + (\xi_V + \omega)\xi_M)}{\beta_M \beta_M [\mu_A(\mu_A + \xi_V + \omega)(1-\phi_U)\pi_W - \mu_A(1-\phi_U)\pi_W]}$$

*$\mu_j$=death rates $\epsilon_j$=efficacy $p_j$=coverage $\Phi_j$=childhood infection $\omega$=waning $\beta_j$=transmissibilities ♀=total women $\xi_j$=duration of infection $\pi_W$=female birth rate*

# Other critical values

- Similarly, we can find the critical vaccine efficacy for adults:

$$\epsilon_W^* = \frac{(1+\gamma)[\beta_W \beta_M \pi_W (\mu_A + \xi_U + \omega)(1-\phi_U)\mu_A - \mu_A D}{D(c-\mu_A) - \beta_W \beta_M \pi_W (\mu_A + \xi_U + \omega)(1-\phi_U)[(1-\psi)c - \mu_A]}$$

  where D is given by

$$D = (1+\mu_C)^7 \varphi \mu_A(\mu_A^3 + \mu_A^2(\xi_U+\xi_V+\xi_M+\omega) + \mu_A(\xi_U(\xi_V+\omega)+\xi_U\xi_M+(\xi_V+\omega)\xi_M) + \xi_U(\xi_V+\omega))$$

- If the efficacy is below this value, then an adult-only vaccine cannot lead to eradication.

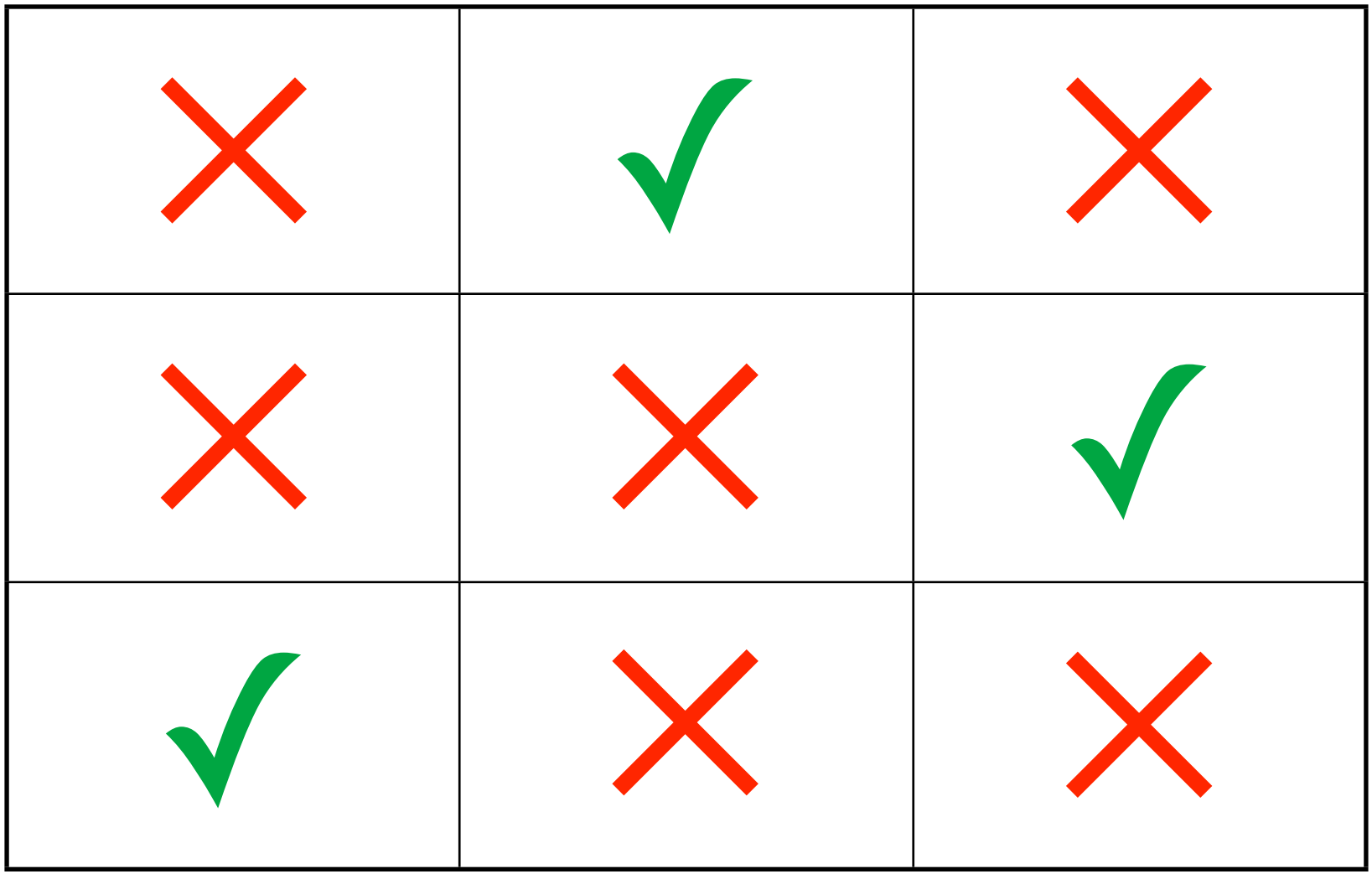
*$\mu_j$=death rates $\pi_W$=female birth rate*
*$\beta_j$=transmissibilities ♀=total women*
*$\Psi$=protection $\xi_j$=duration of infection*
*$c/\gamma$=max possible vaccination*

# Latin Hypercube Sampling

- We explored the sensitivity of $R_0$ to parameter variations using
  - Latin Hypercube Sampling
  - Partial Rank Correlation Coefficients
- Latin Hypercube Sampling
  - samples parameters from a random grid
  - resamples, but not from the same row or column

    (a bit like tic tac toe)
  - runs 1,000 simulations.

# Example

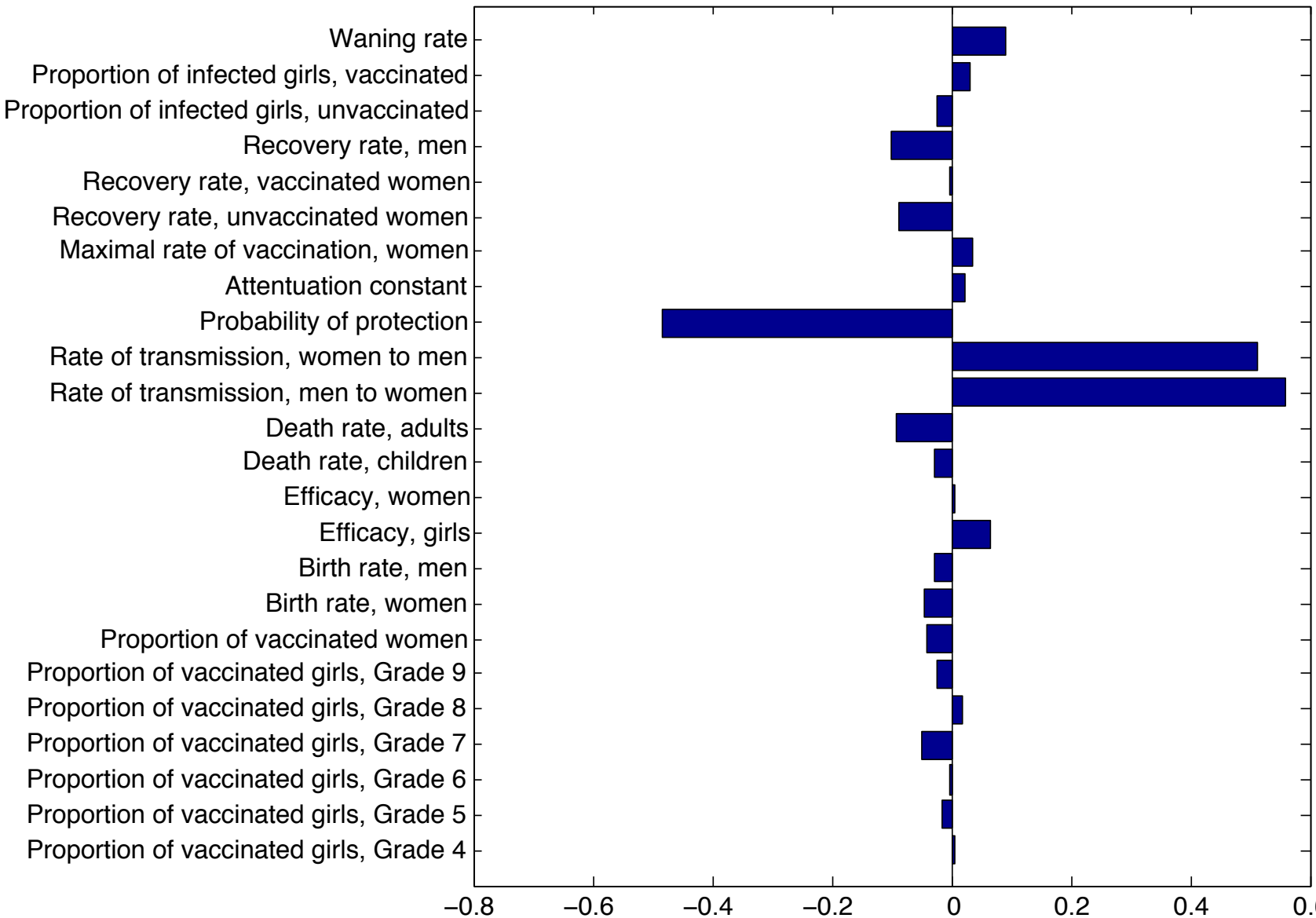


# Partial Rank Correlation Coefficients

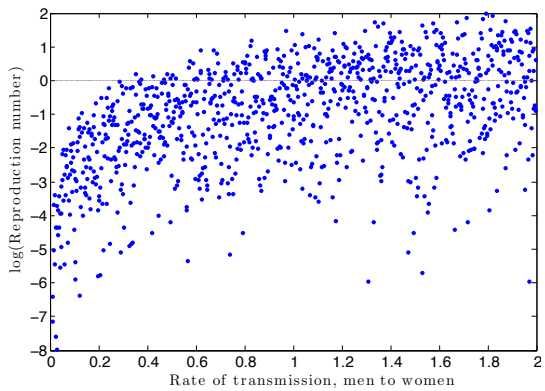
- Partial Rank Correlation Coefficients (PRCCs)
  - test individual parameters while holding all other parameters at median values
  - rank parameters by the amount of effect on the outcome
- PRCCs > 0 will increase $R_0$ when they are increased
- PRCCs < 0 will decrease $R_0$ when they are increased.

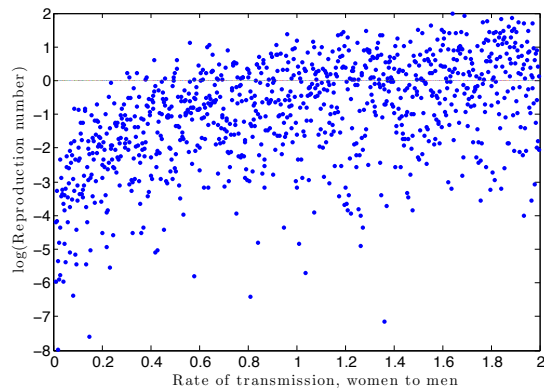
*$R_0$=basic reproductive ratio*

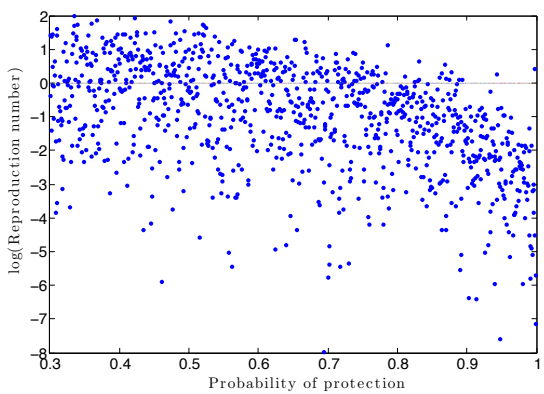
# PRCCs

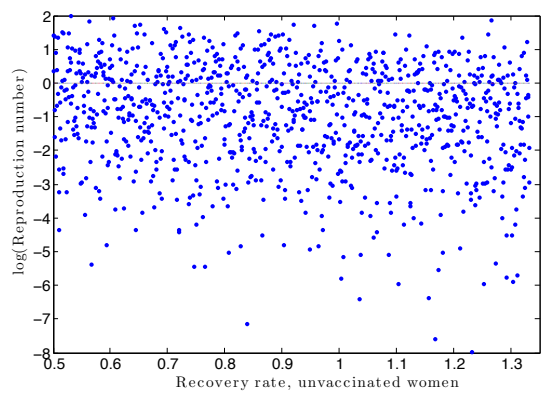

Waning rate
Proportion of infected girls, vaccinated
Proportion of infected girls, unvaccinated
Recovery rate, men
Recovery rate, vaccinated women
Recovery rate, unvaccinated women
Maximal rate of vaccination, women
Attentuation constant
Probability of protection
Rate of transmission, women to men
Rate of transmission, men to women
Death rate, adults
Death rate, children
Efficacy, women
Efficacy, girls
Birth rate, men
Birth rate, women
Proportion of vaccinated women
Proportion of vaccinated girls, Grade 9
Proportion of vaccinated girls, Grade 8
Proportion of vaccinated girls, Grade 7
Proportion of vaccinated girls, Grade 6
Proportion of vaccinated girls, Grade 5
Proportion of vaccinated girls, Grade 4
−0.8
−0.6
−0.4
−0.2
0
0.2
0.4
0.6

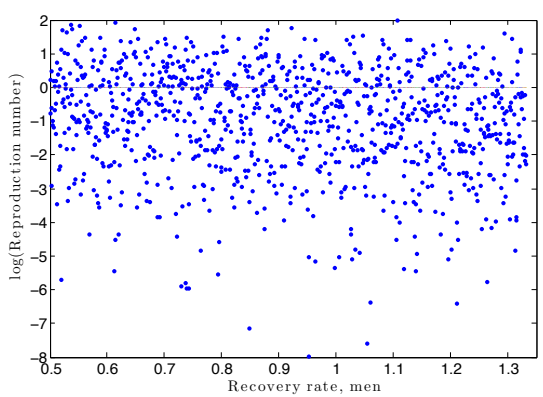
# Monte Carlo simulations

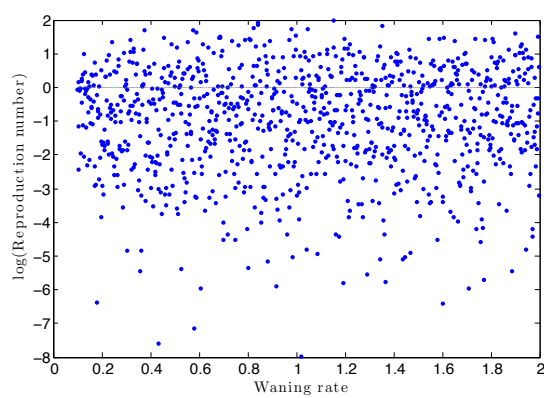


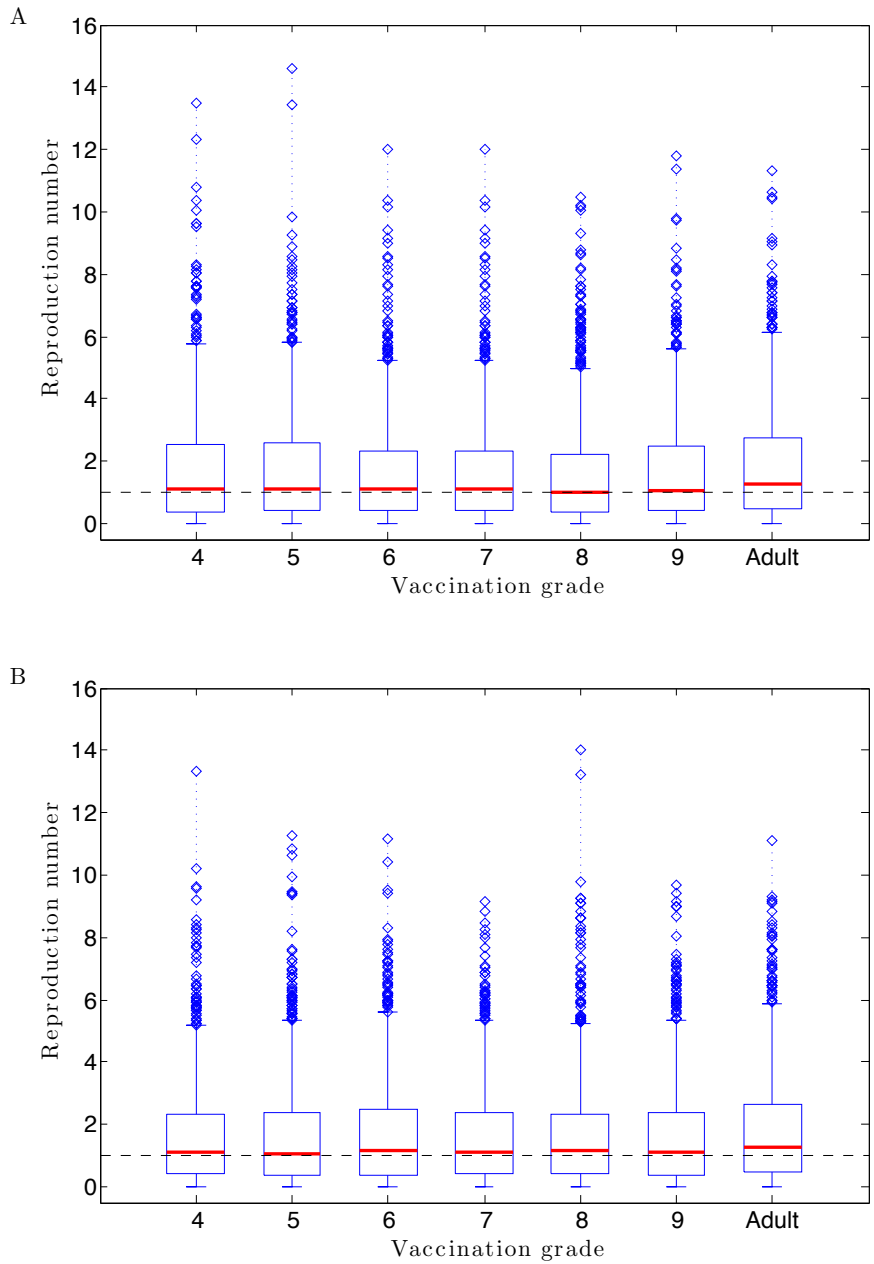



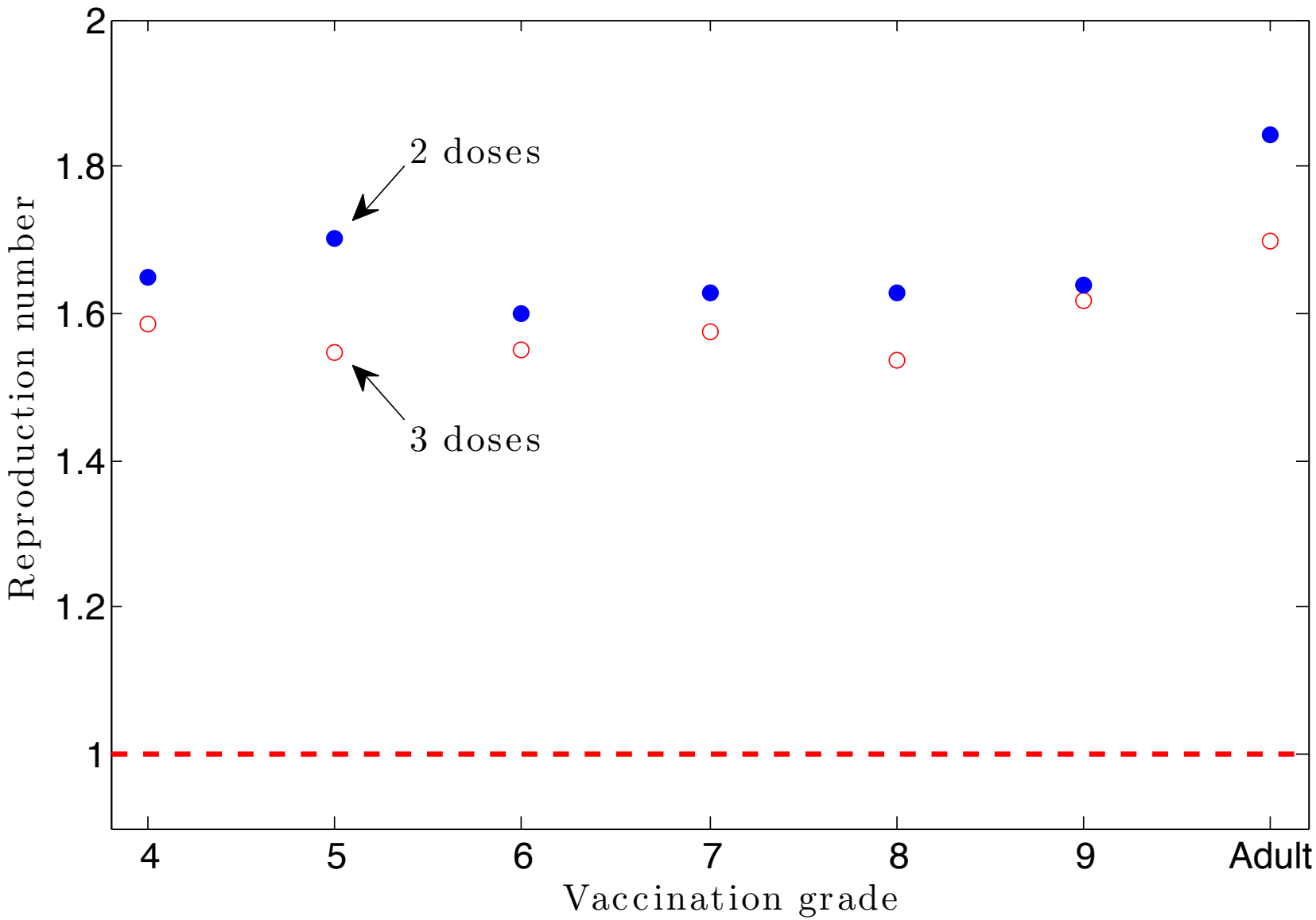



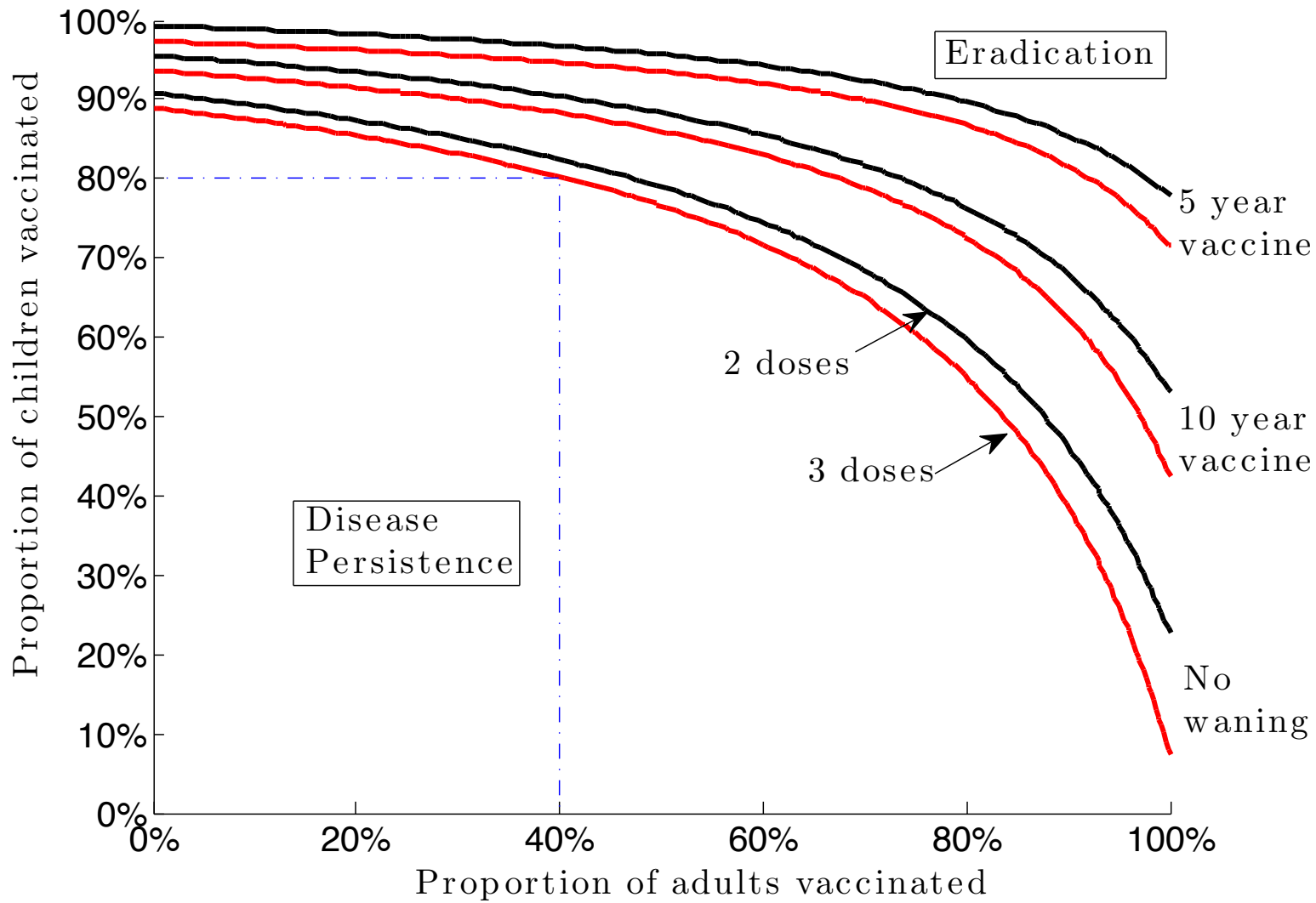
# Two doses vs three doses



# Mean $R_0$ values



# Vaccination coverage rates



# Summary

- Three doses is more effective than two, but not greatly
  - this is in line with clinical evaluations of provinces that use two vs three doses
- The age of vaccination does not matter terribly much for childhood vaccination
  - thus the grade of vaccination should be chosen based on vaccination-program limitations
- What matters most is coverage levels
- Childhood vaccination needs to be supplemented by moderate adult vaccination.

# Conclusions (Part 2)

- The most effective way to decrease $R_0$ is to decrease transmission probabilities
  - either through condom distribution or through changes in sexual behaviour
- The vaccination age is not a crucial parameter
- The number of doses barely affects the outcome, except to facilitate greater uptake
- Childhood vaccination should be supplemented by moderate adult vaccination
  - this could be achieved by enhanced HPV awareness programs in colleges/universities.

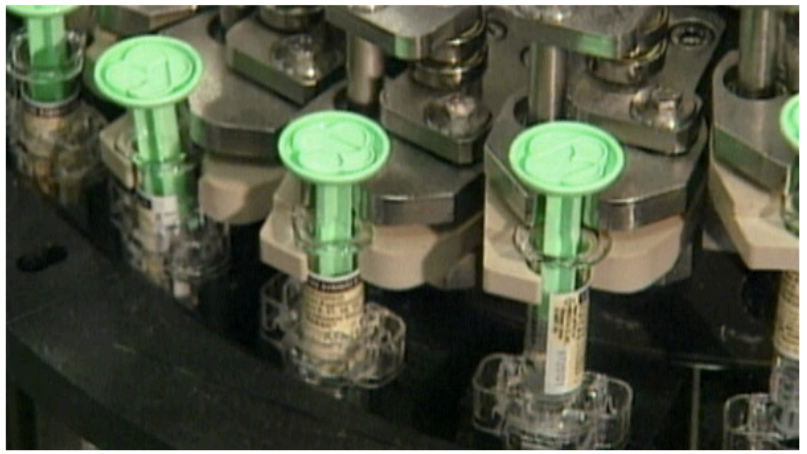
# Interaction with PHAC

- This research was undertaken as part of a MITACS internship by Carley Rogers, as part of her M.Sc. at the University of Ottawa
- Carley worked at the Public Health Agency of Canada for four months
  – from May–August 2013
- The model was developed in collaboration with PHAC members
  – they also had access to provincial vaccination data.

# A policy outcome

- Specific additions by PHAC were:
  - including recovery for both women and men
  - adding in children who were pre-infected
- As a result of this research, Quebec changed its HPV vaccination policy in August 2013 from three to two doses.

**Quebec reduces HPV vaccine doses, only two shots now needed**



Share: Share 6 Tweet +1 Recommend 2 Text: (0)

The Canadian Press
Published Friday, August 23, 2013 3:26PM EDT

Quebec girls will become the first in the country to benefit from new research that suggests the HPV vaccine is so effective that two doses -- rather than the recommended three -- may be all that's needed.

The province's health ministry has decided to forgo the third dose of HPV vaccine for girls entering Secondary 3 -- the equivalent of Grade 9 -- this fall, Karine White, a spokesperson for the ministry, confirmed in an interview. The decision was made based on a recommendation from an expert panel.

# Timeline

| | |
|---|---|
| Fall 2010 | Carly began her M.Sc. |
| Winter 2011 | Carly had idea in class |
| Summer 2012 | Internship proposed, funding secured from MITACS |
| Oct 2012 | Model revised by PHAC |
| *(six months pass)* | *PHAC bureaucracy* |
| Apr–Aug 2013 | Carly's internship |
| Aug 2013 | Policy changed in Quebec |
| Aug 2013 | Carly defends thesis. (She passes.) |

# Mathematics and policy

- This shows that we can have a direct influence on policy
- However, it has to be done collaboratively
- Our aim is to have a conversation between mathematicians and non-mathematicians
- Only be designing the model together, so that all parties have input, will we be able to construct models that the intended audience have faith in
  - thus we have to build models from the ground up.

# Another modelling success story

- The West African River Blindness Control Program was hailed as a success due to integrated modelling and control efforts
- Modelling predicted that 14 years of vector control would reduce the risk to less than 1%
- Helped convince donors that control was feasible
- Models were refined using subsequent data to include treatment
- Modelling retained a prominent role in subsequent policy discussions.

# Can math change the world?

- It's estimated that malaria has killed one in two humans who ever lived
- In 1911, Sir Ronald Ross discovered mosquitoes were responsible
  - this made many people very upset
- Kermack and McKendrick used an SIR model and $R_0$ to outline eradication methods
  - these were largely successful
- Thus, many of us are alive because malaria is no longer endemic in developed countries.