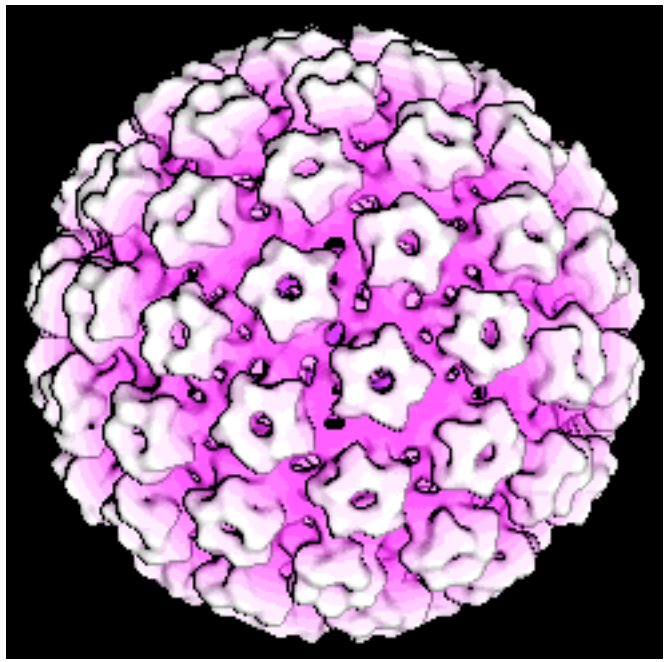
Provincial Canadian HPV vaccination: doses vs age of vaccination

Robert Smith?

Departments of Mathematics and Faculty of Medicine
The University of Ottawa

Outline

- Epidemiology of HPV



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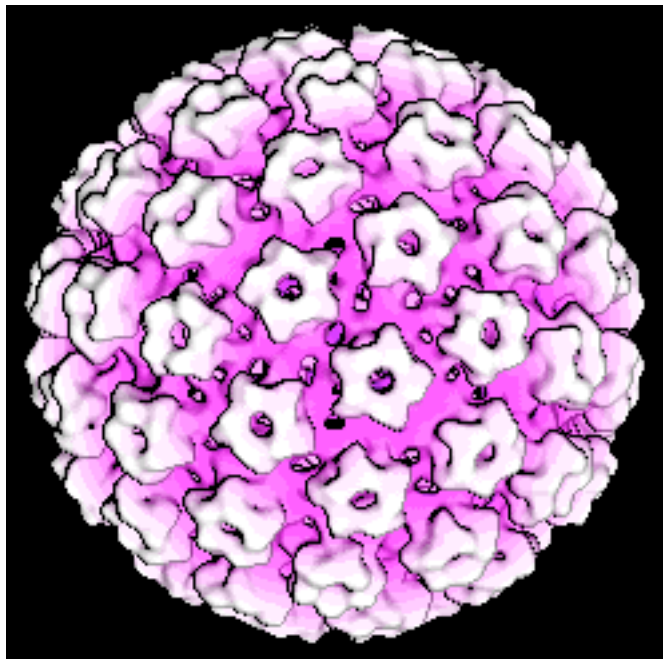

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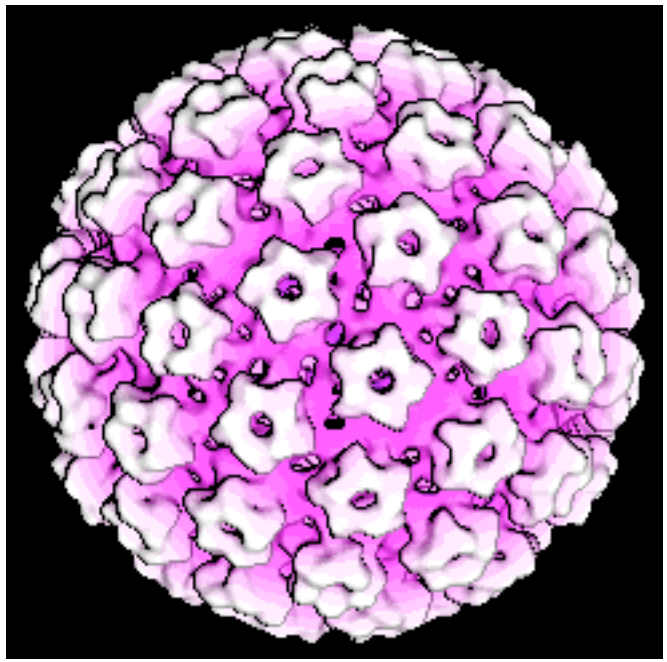

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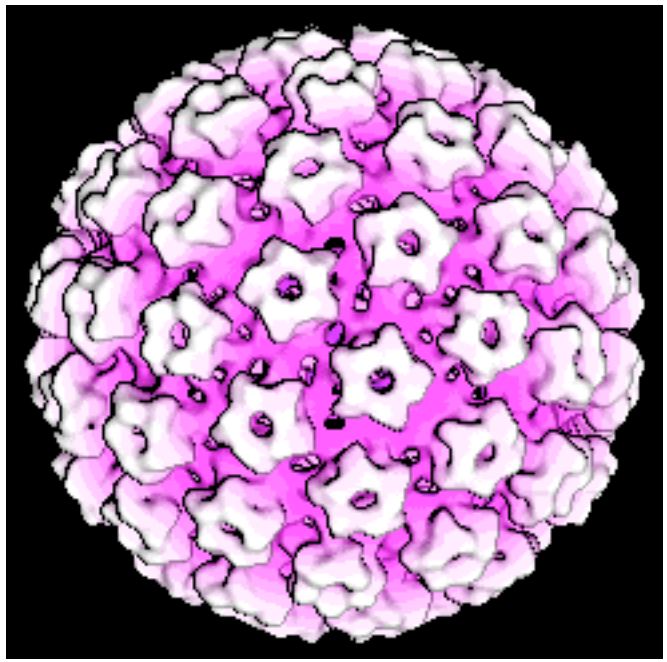

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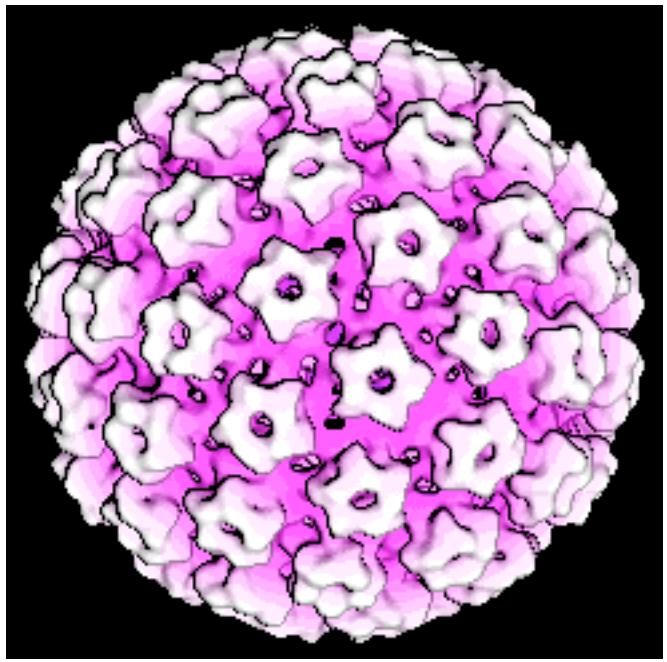

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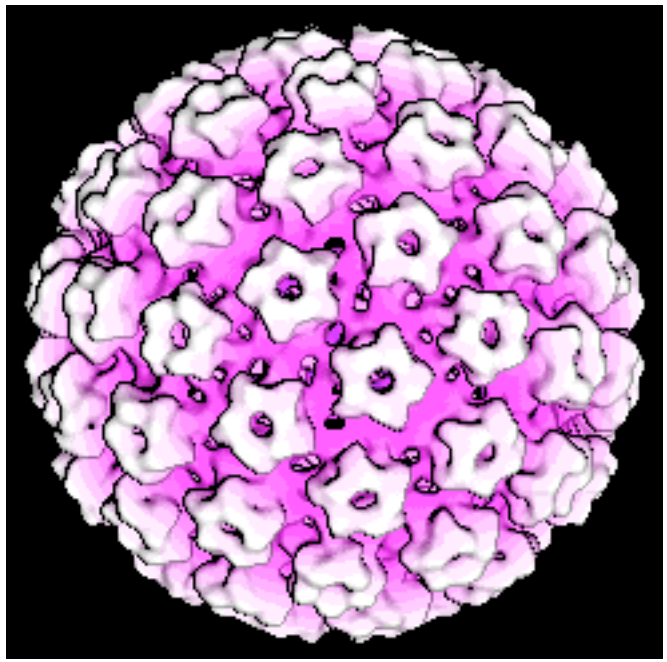

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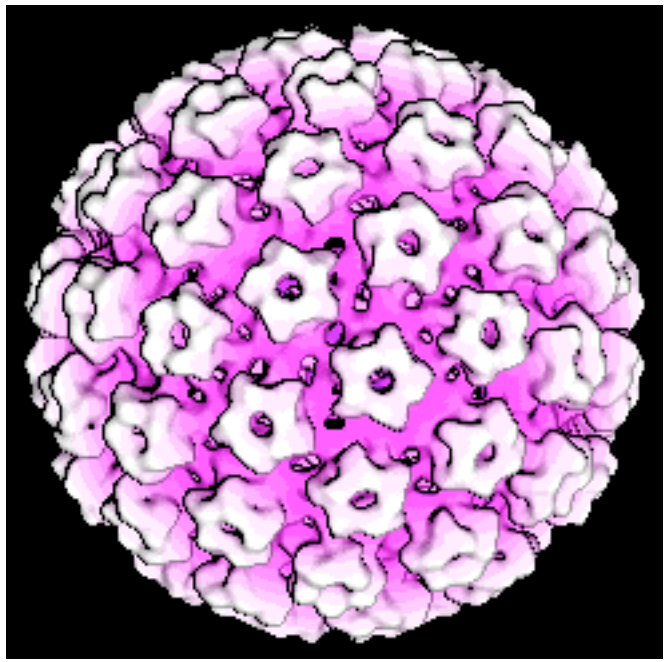

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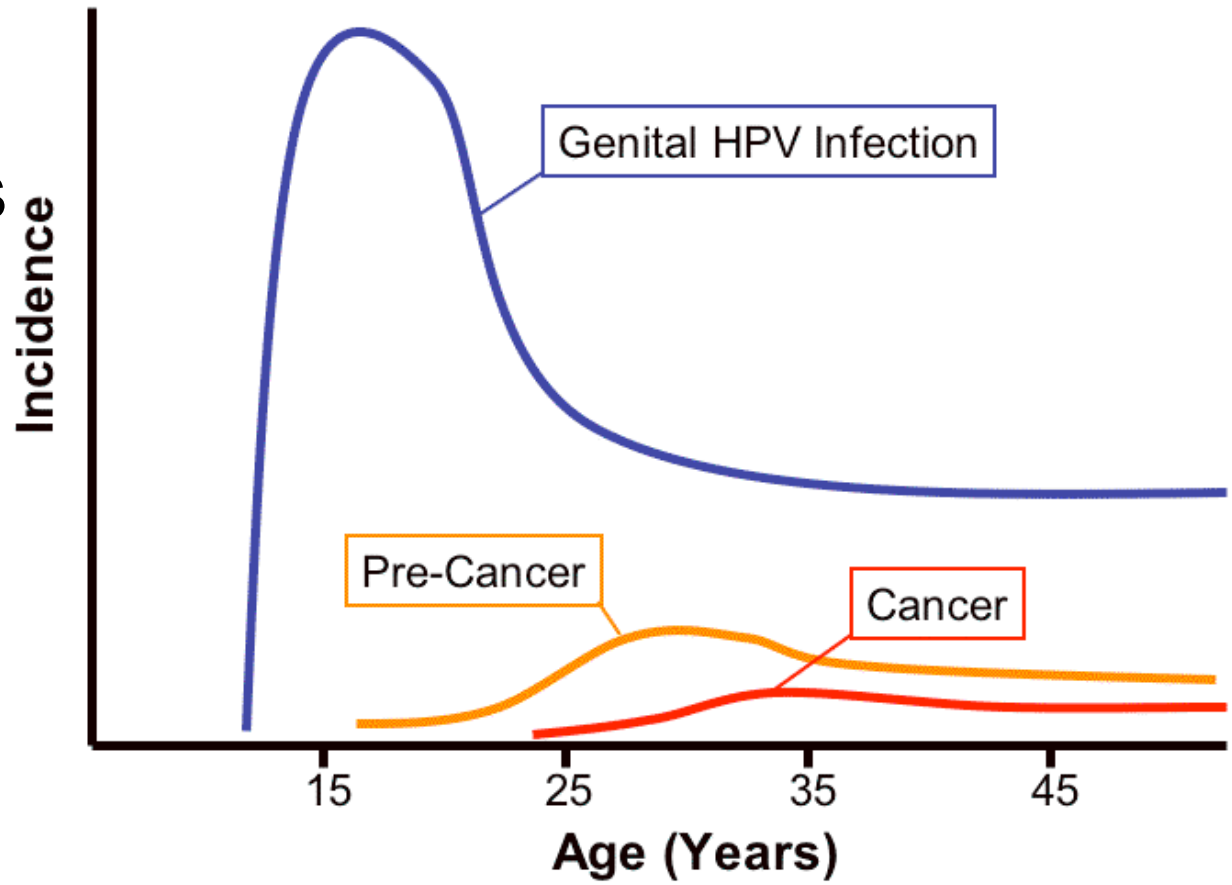

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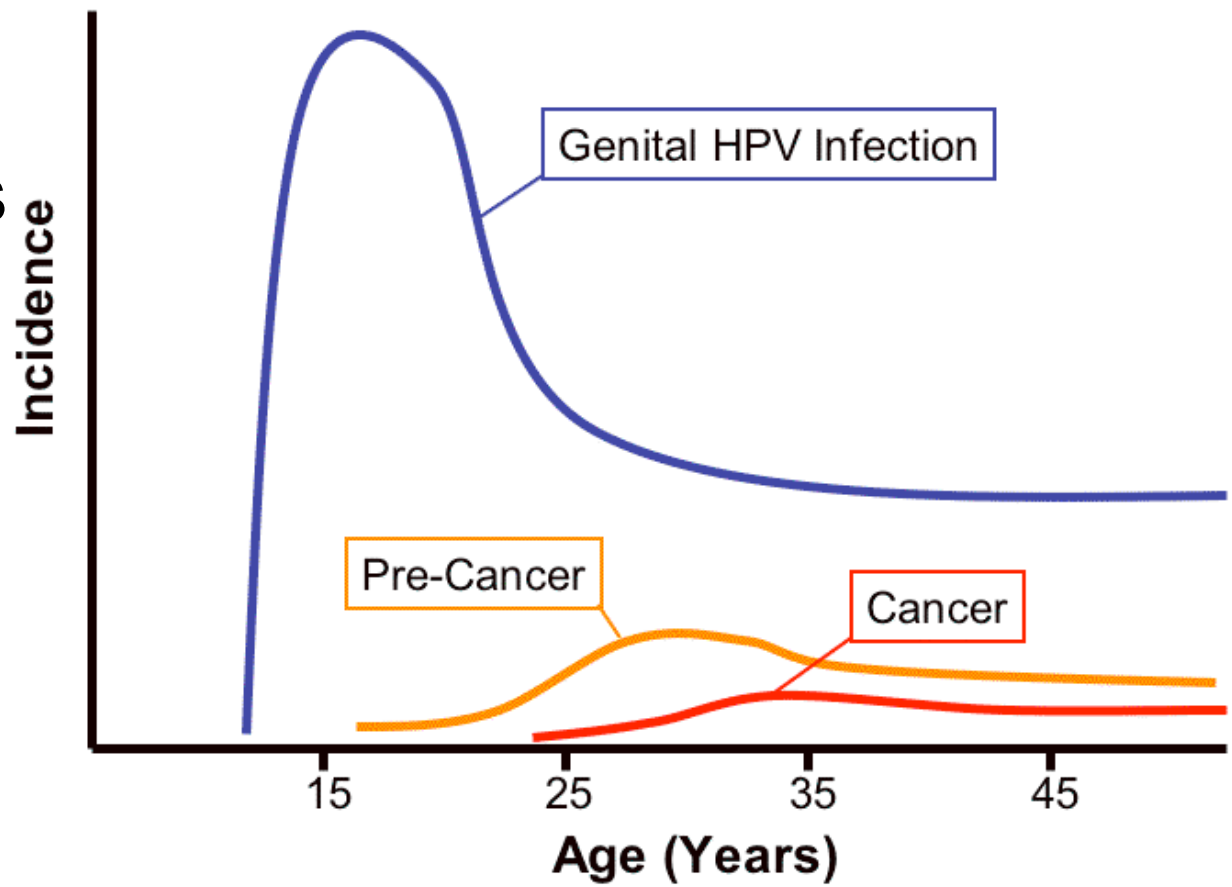

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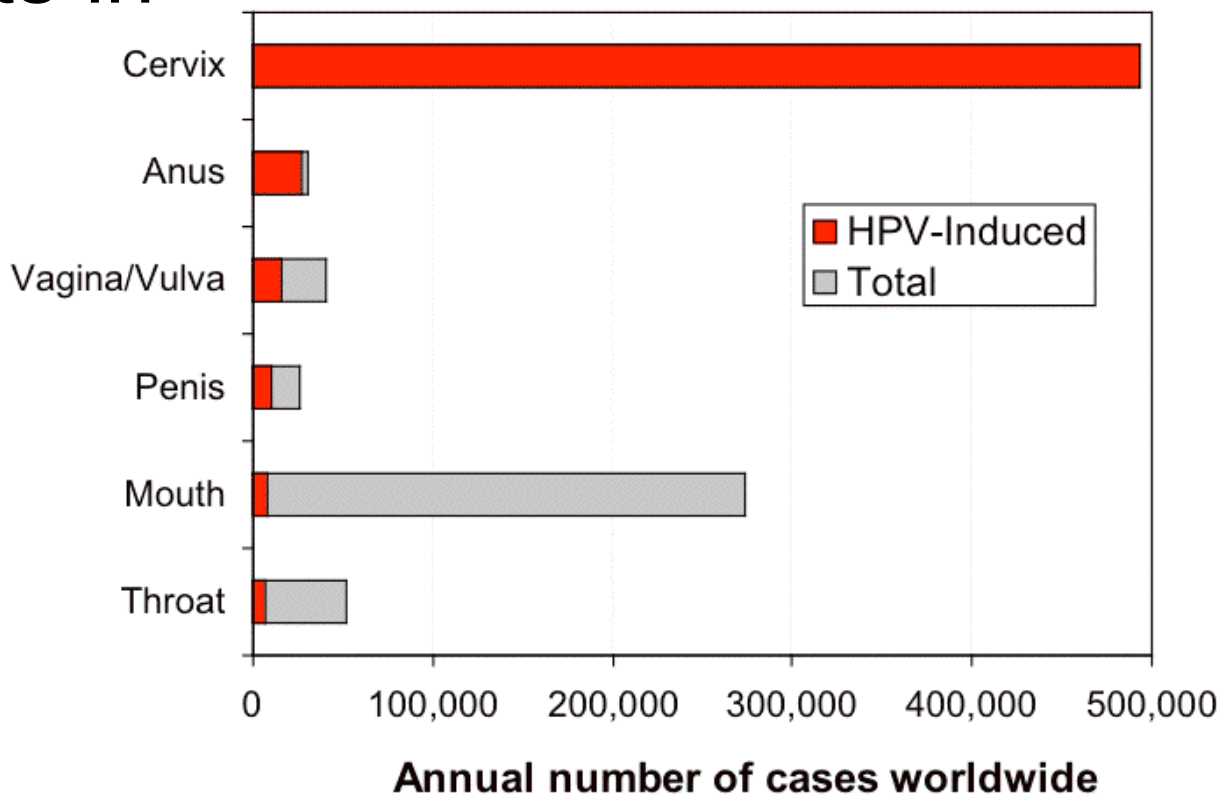

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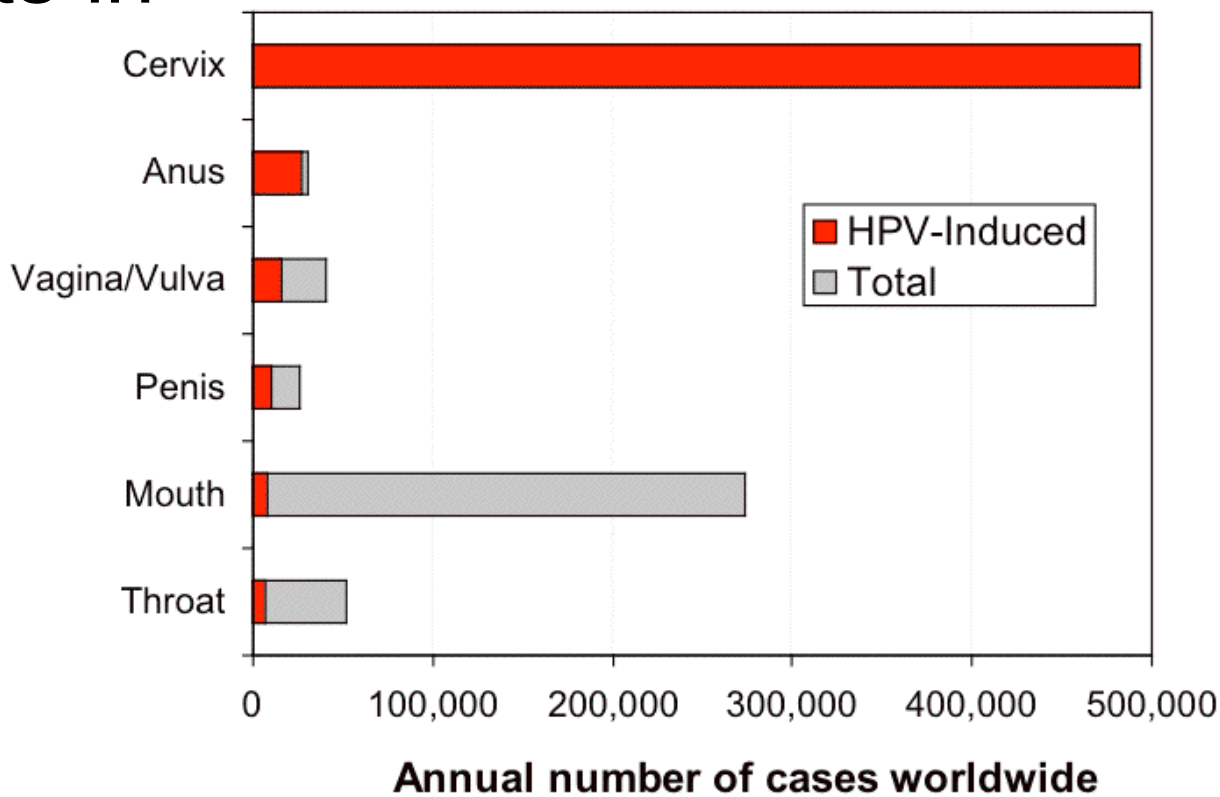

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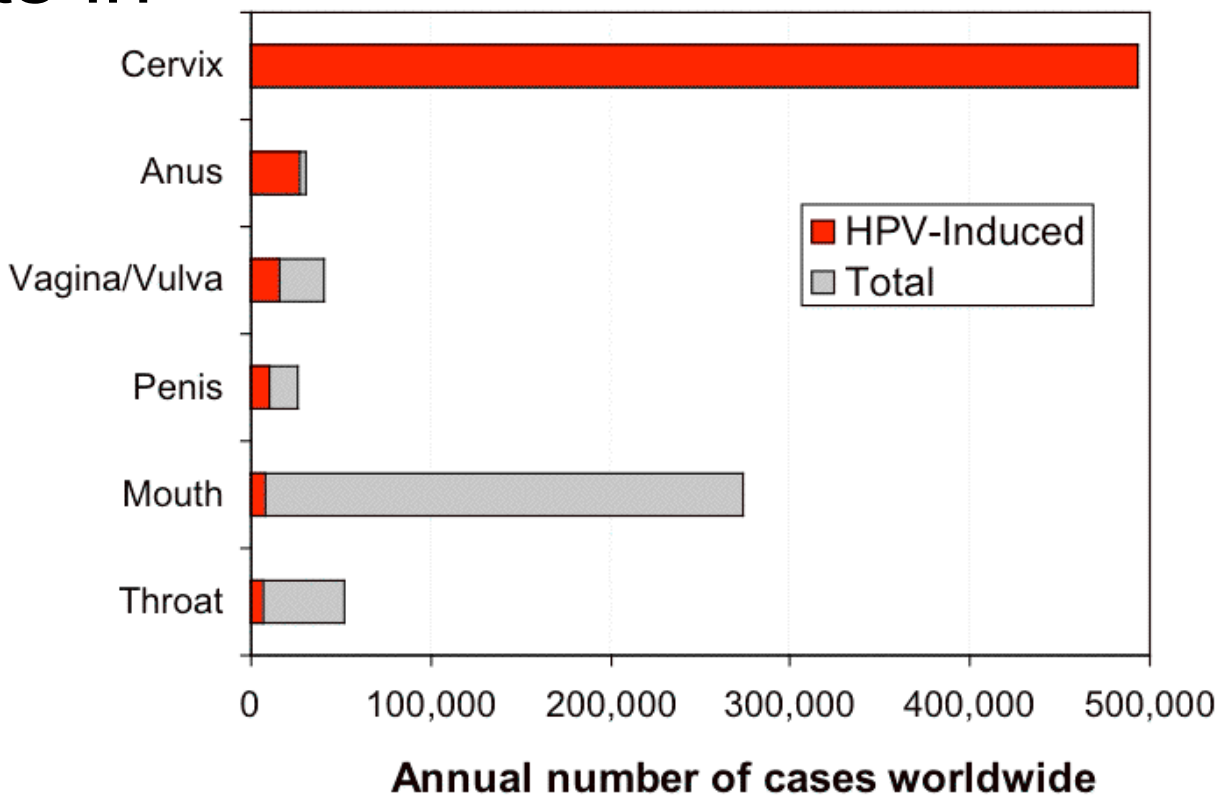

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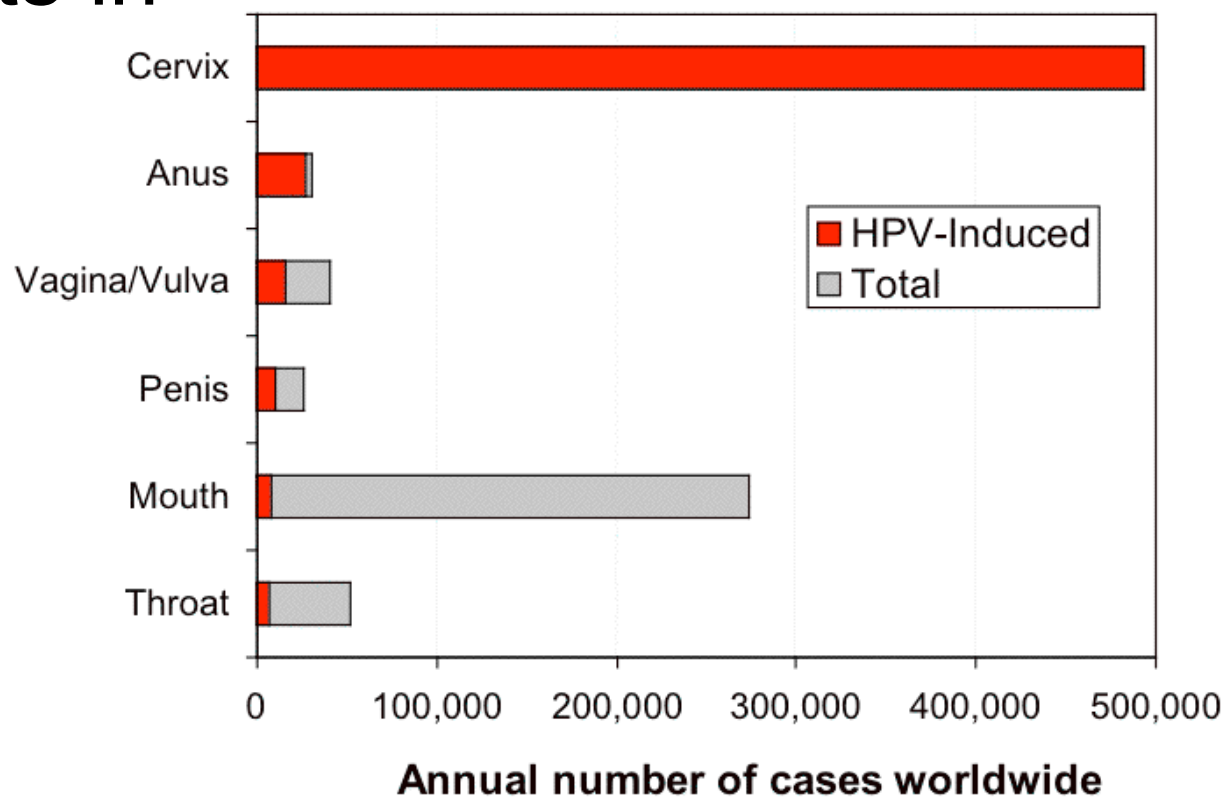

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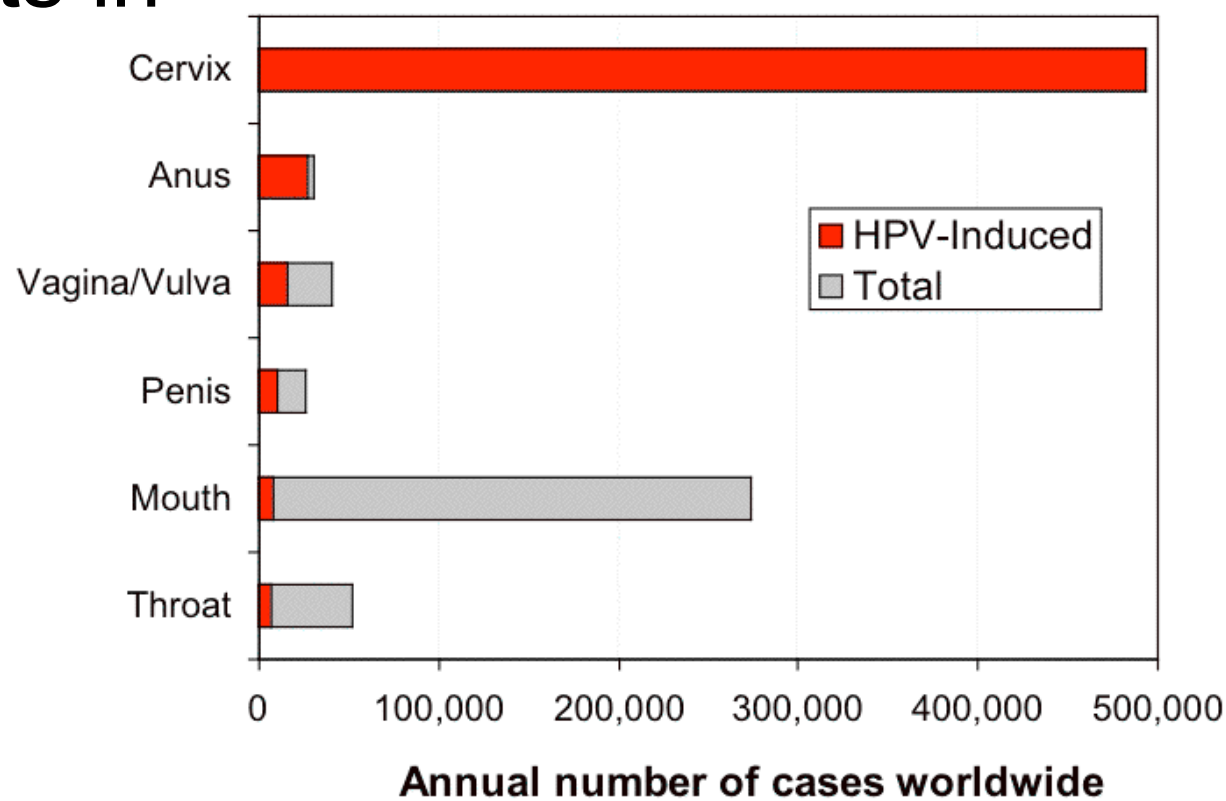

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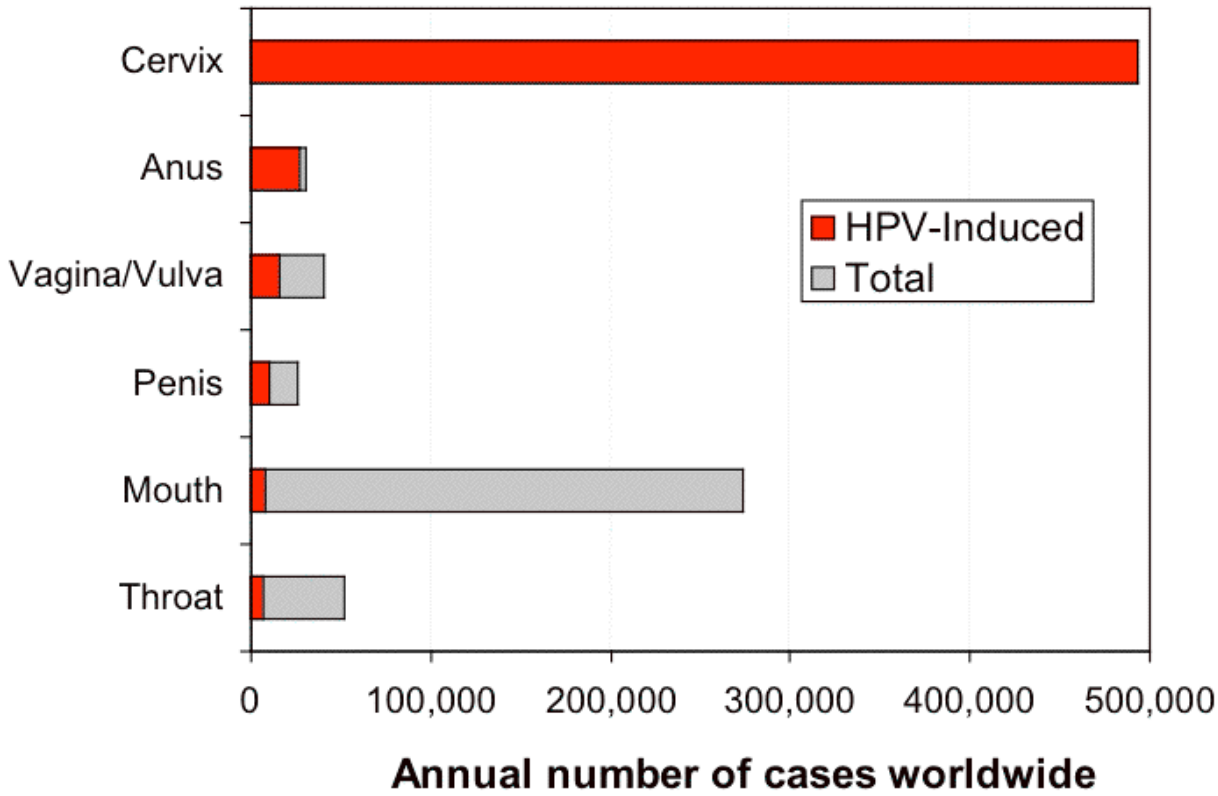

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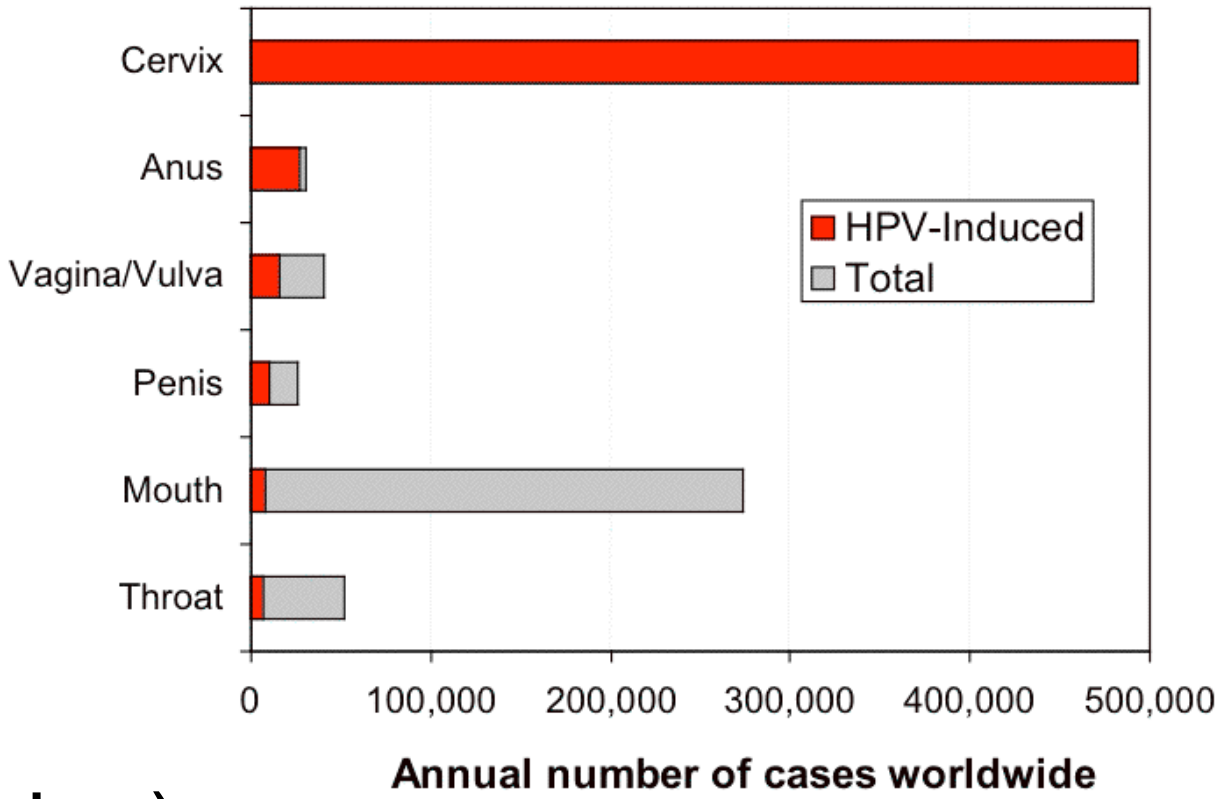

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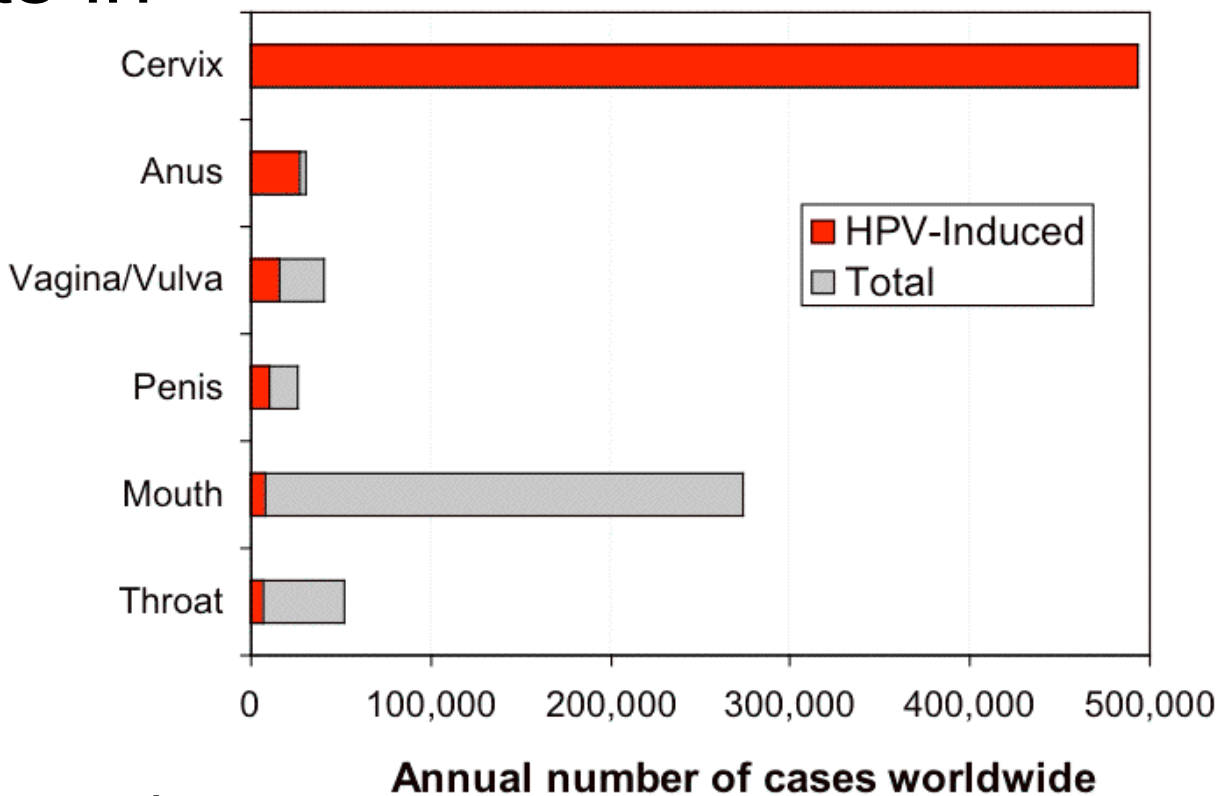
...requiring frequent surgery.



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

Infections in the US

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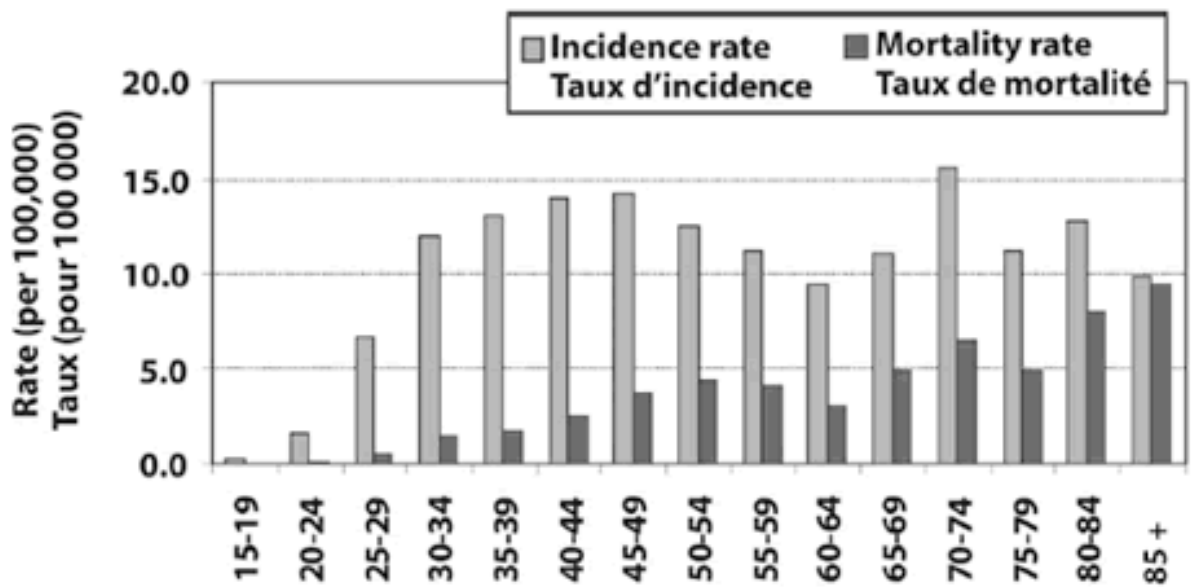

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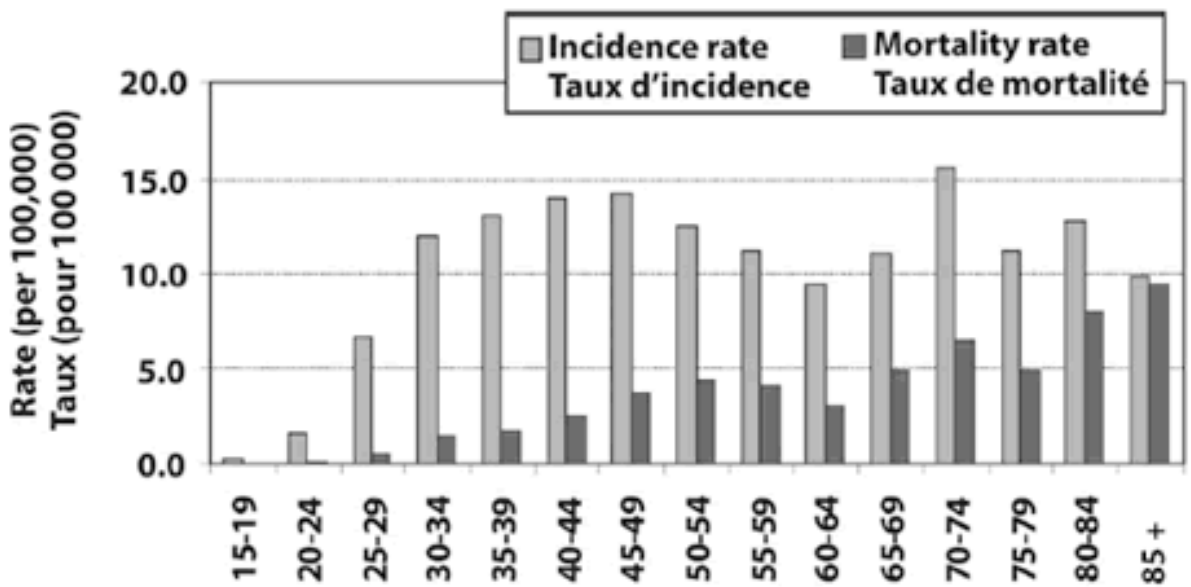

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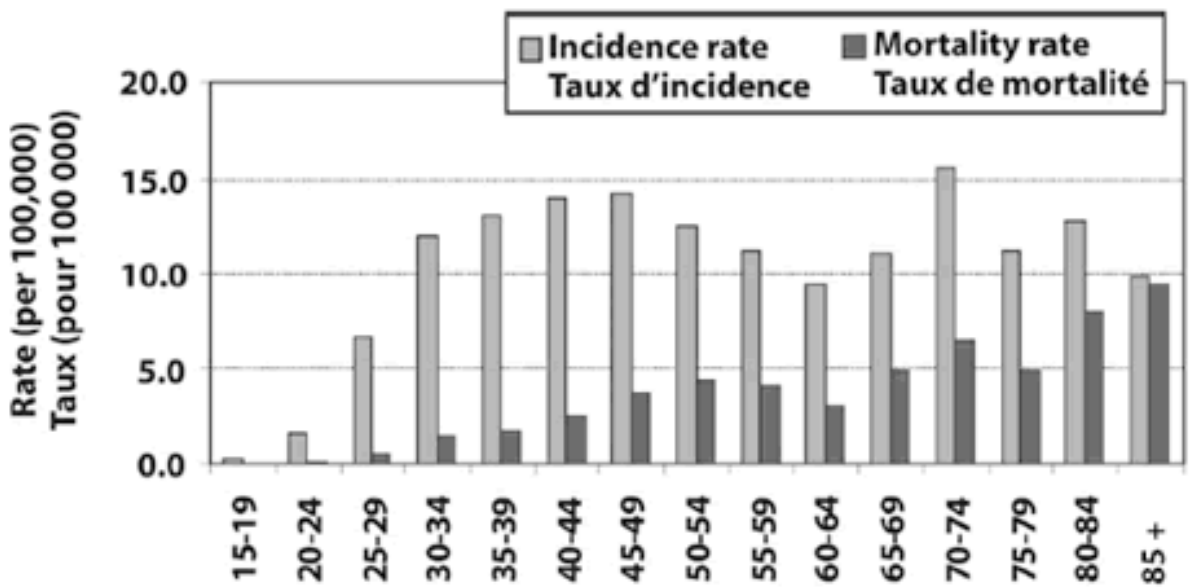

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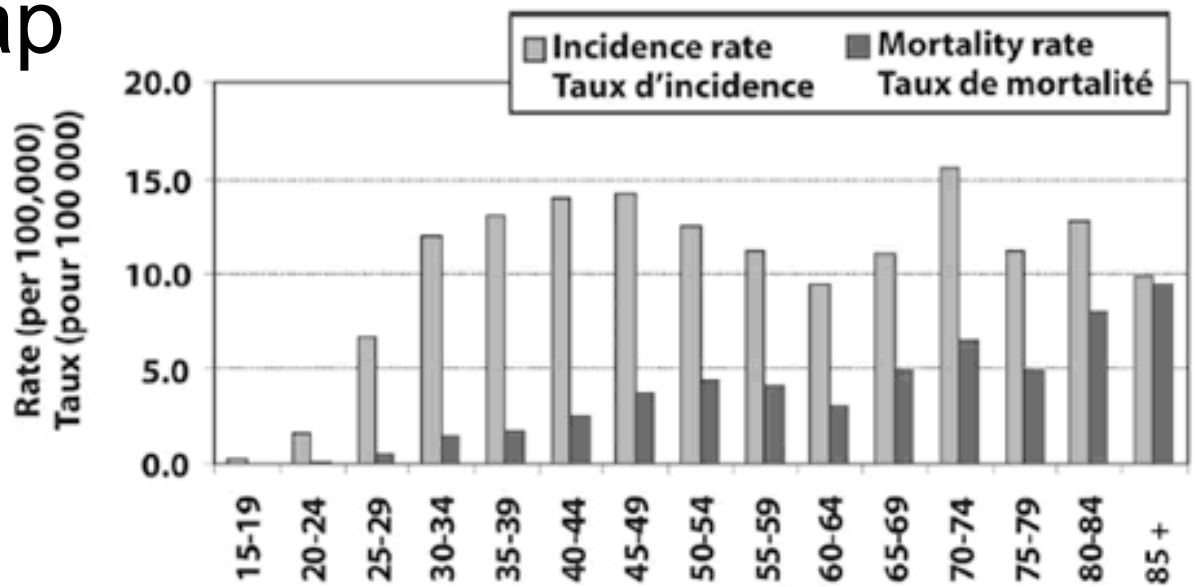
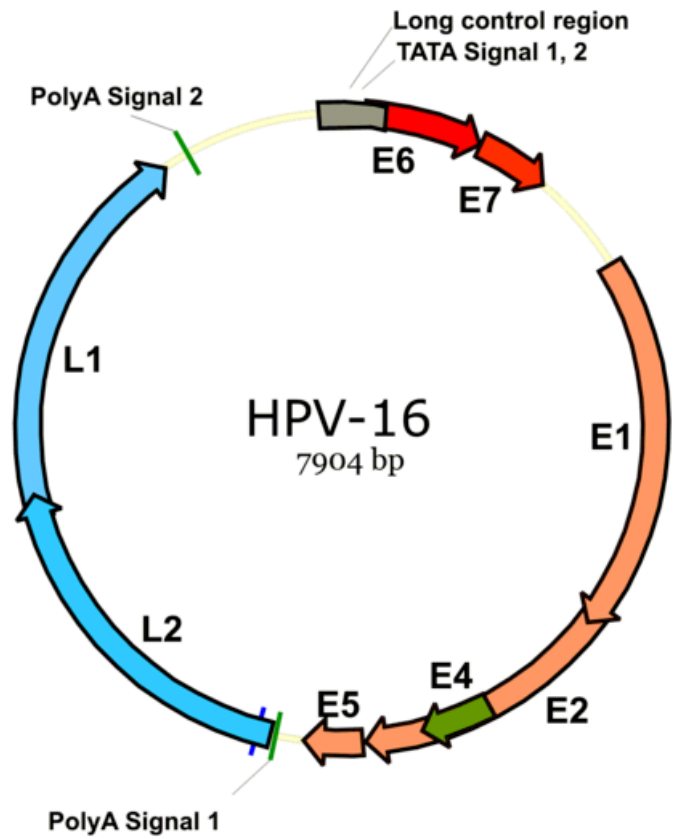
(many fewer than would be caused by HPV, due to effective pap smear screening and precancer treatments).



HPV strains of interest

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



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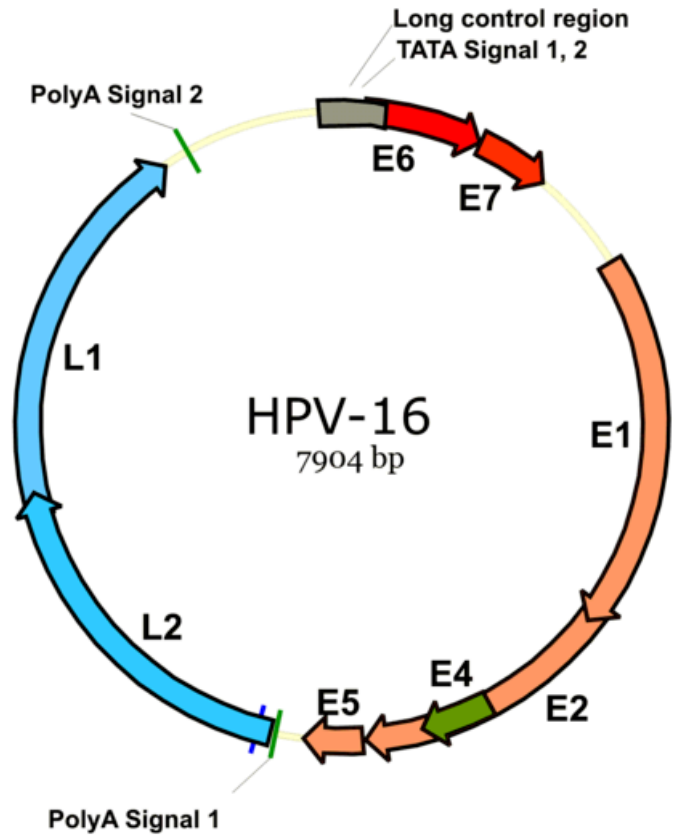

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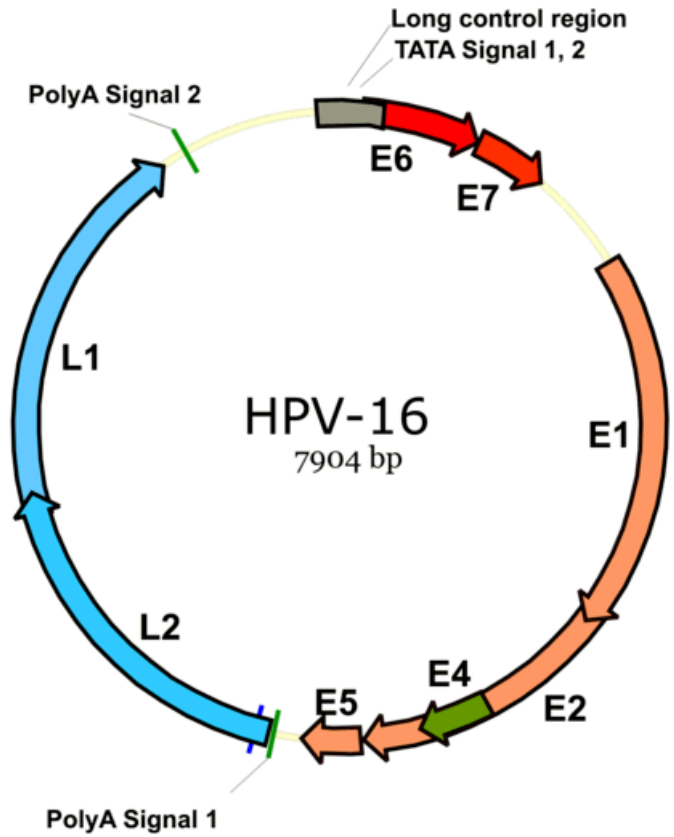

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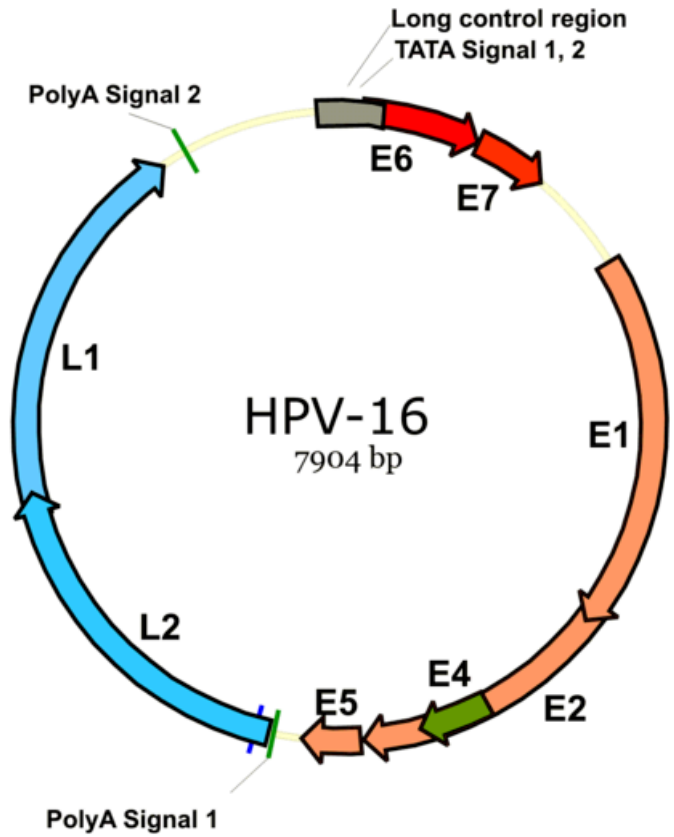
- Types 16 and 18 are responsible for 65% of cervical cancer cases.



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- Vaccines are estimated at 90–100% efficacy.

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

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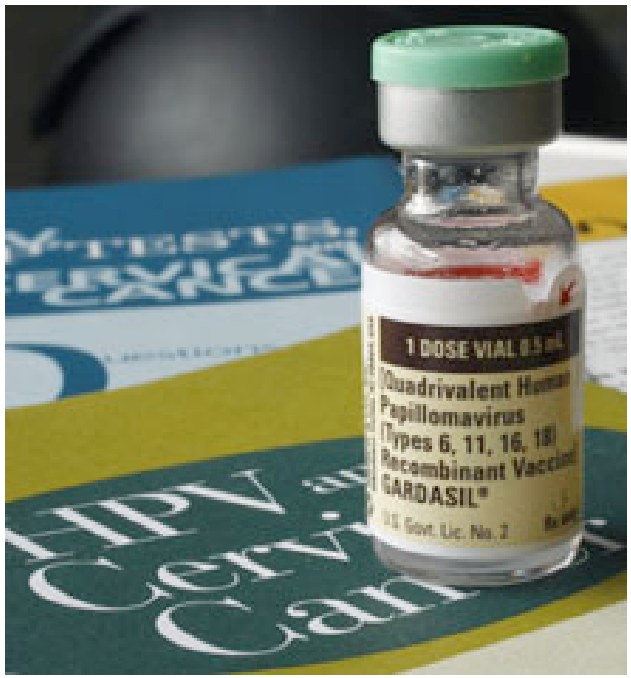

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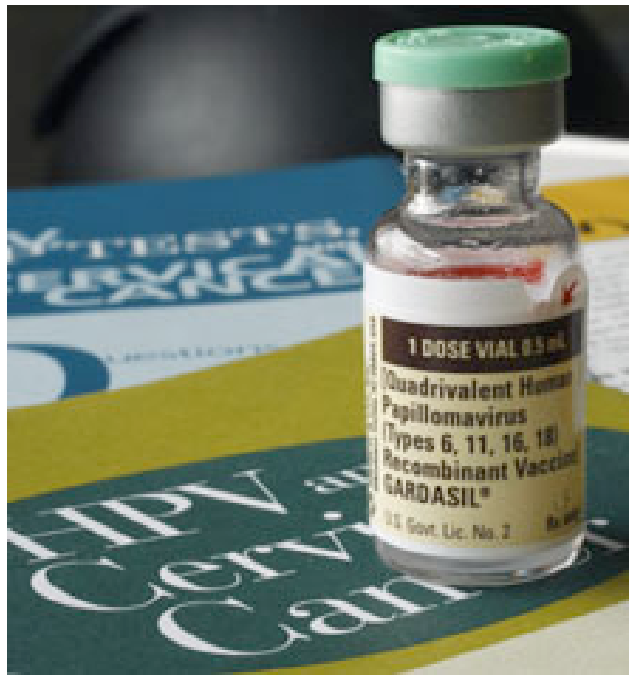

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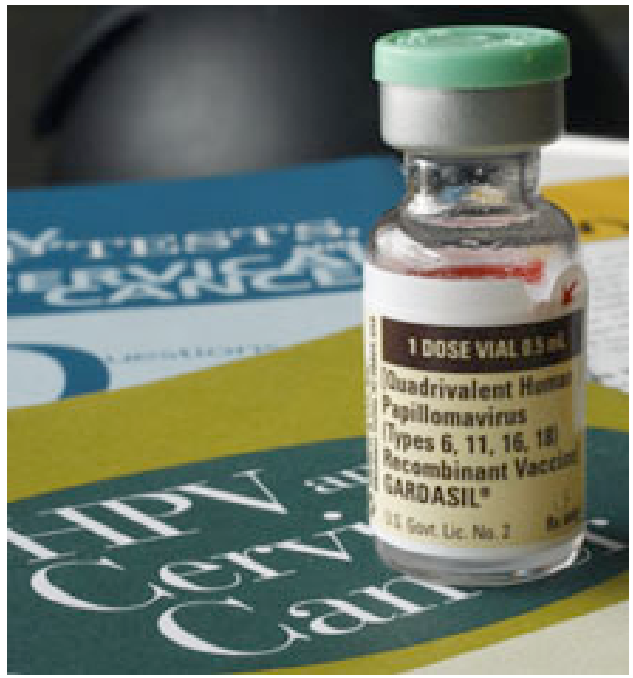

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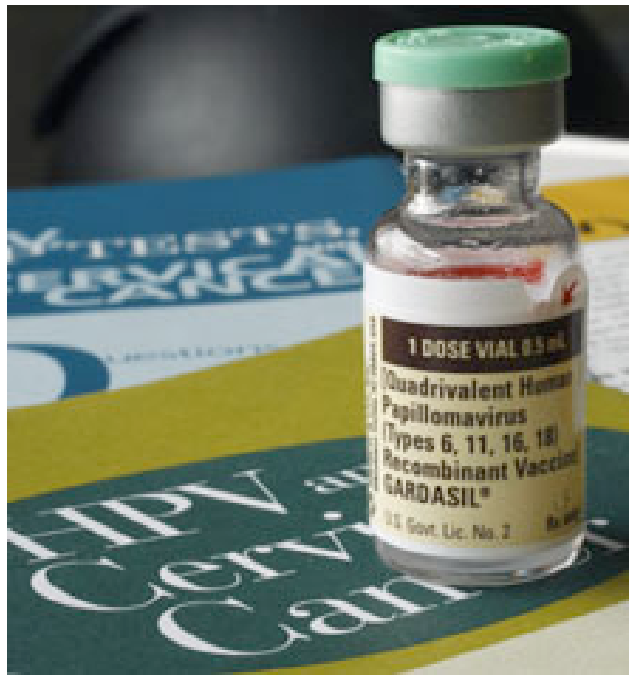

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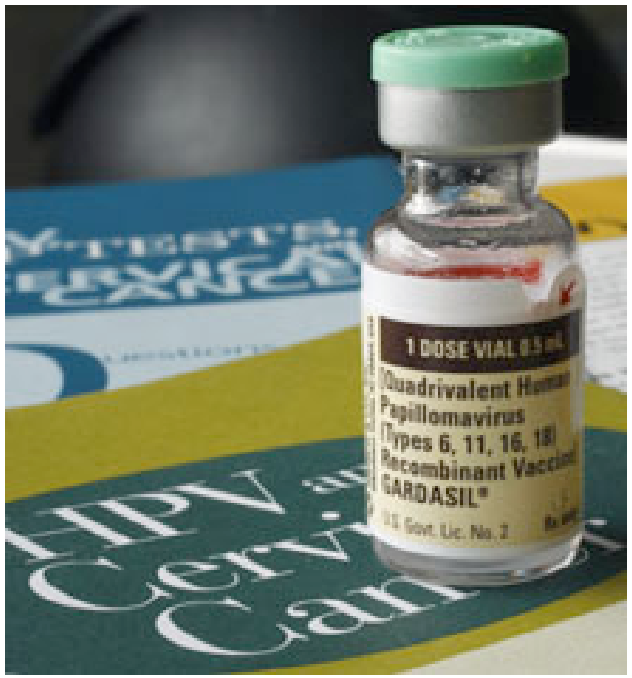

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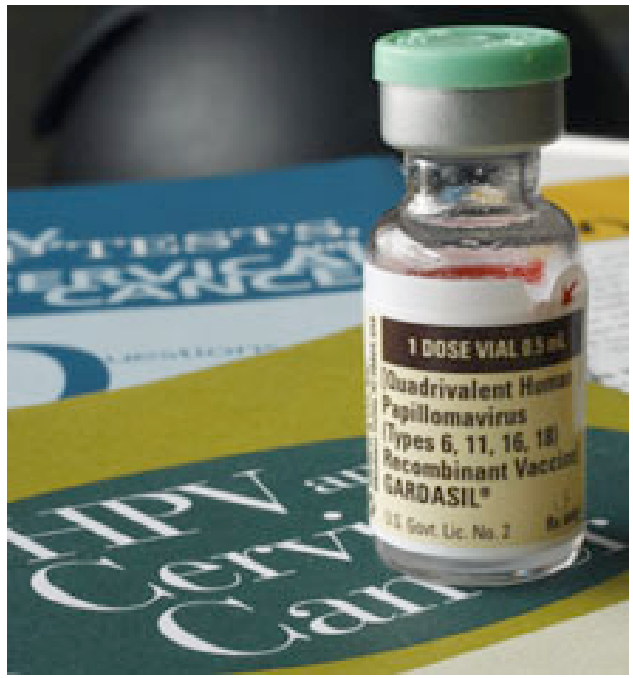

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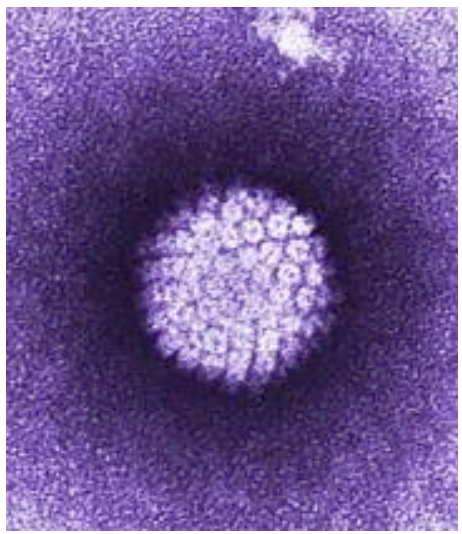

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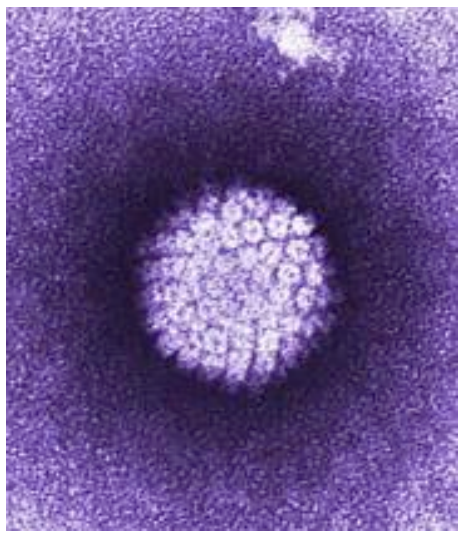

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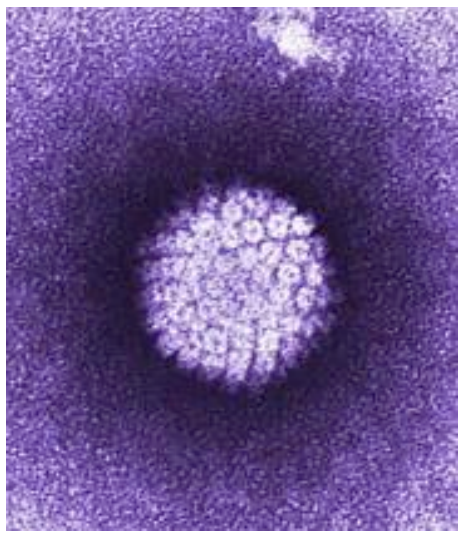
- Thus, we'll assume vaccinated men have a negligible effect on the outcome.



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- 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%

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- In the first year, Ontario reported only 53% vaccination coverage
- This has not increased substantially over subsequent years.

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  - health is provincial, but the Public Health Agency of Canada, based in Ottawa, can make recommendations.

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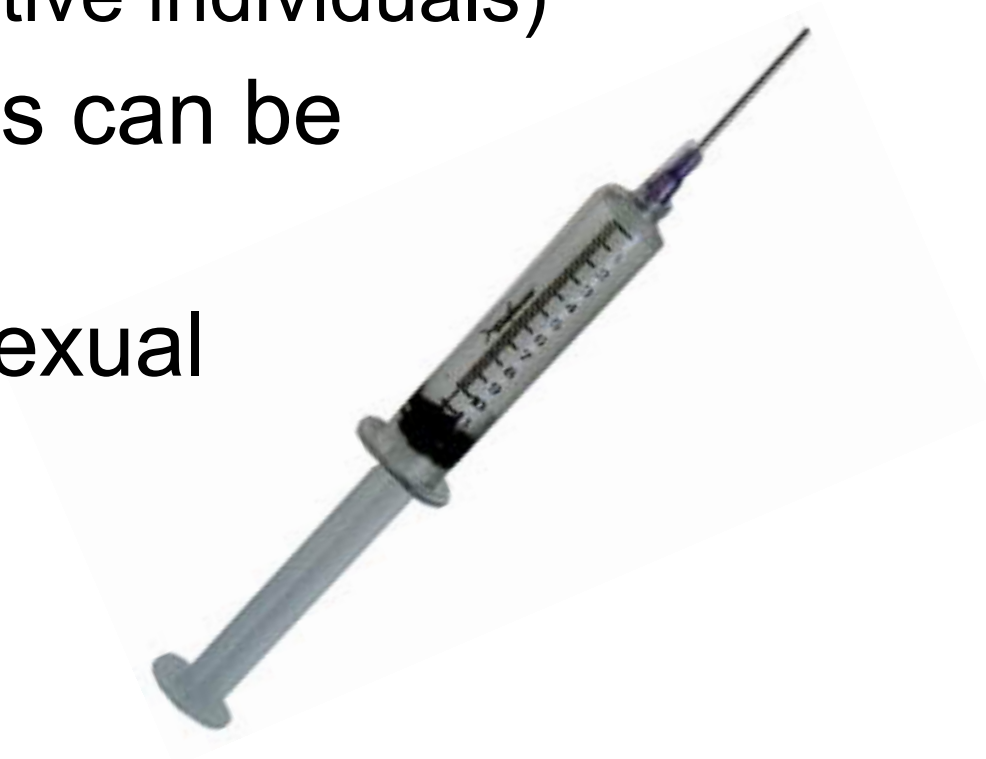

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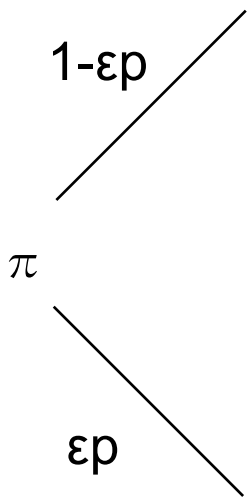

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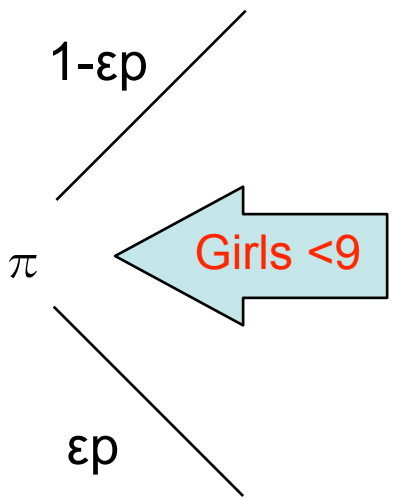

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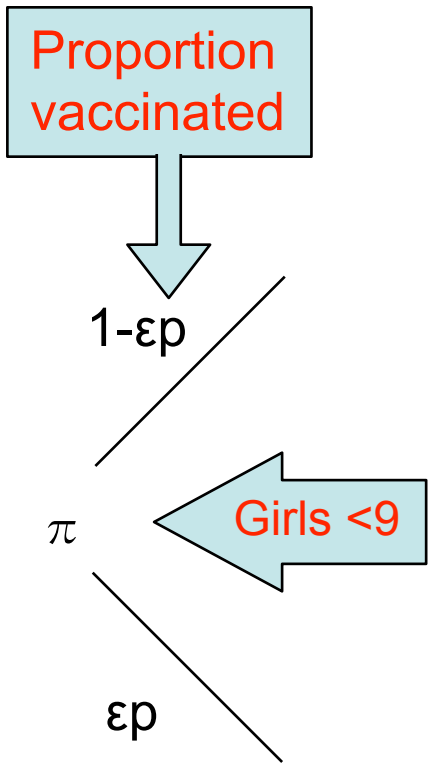

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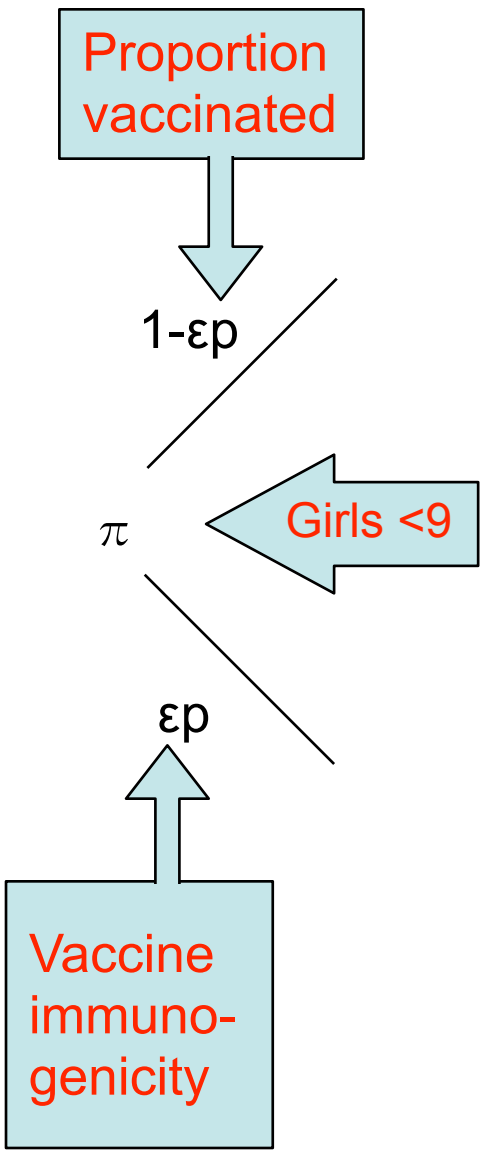
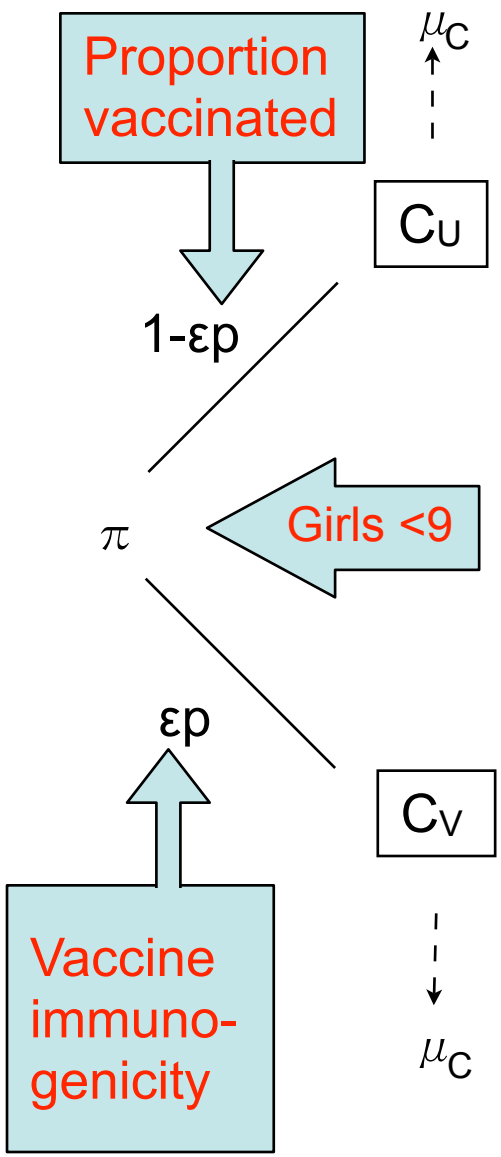
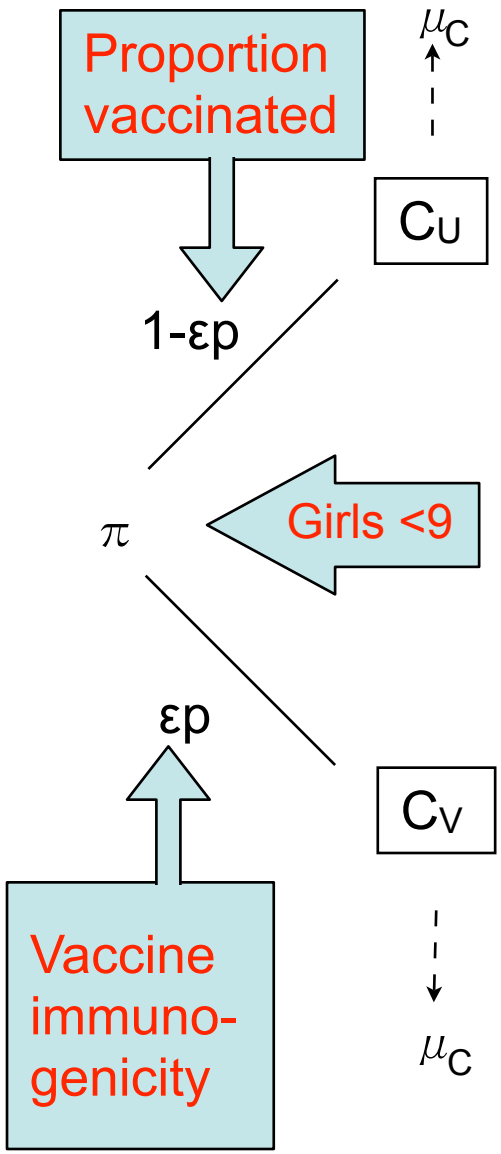

Proportion vaccinated
1-εp
π
Girls <9
εp
Vaccine immuno-genicity

The model

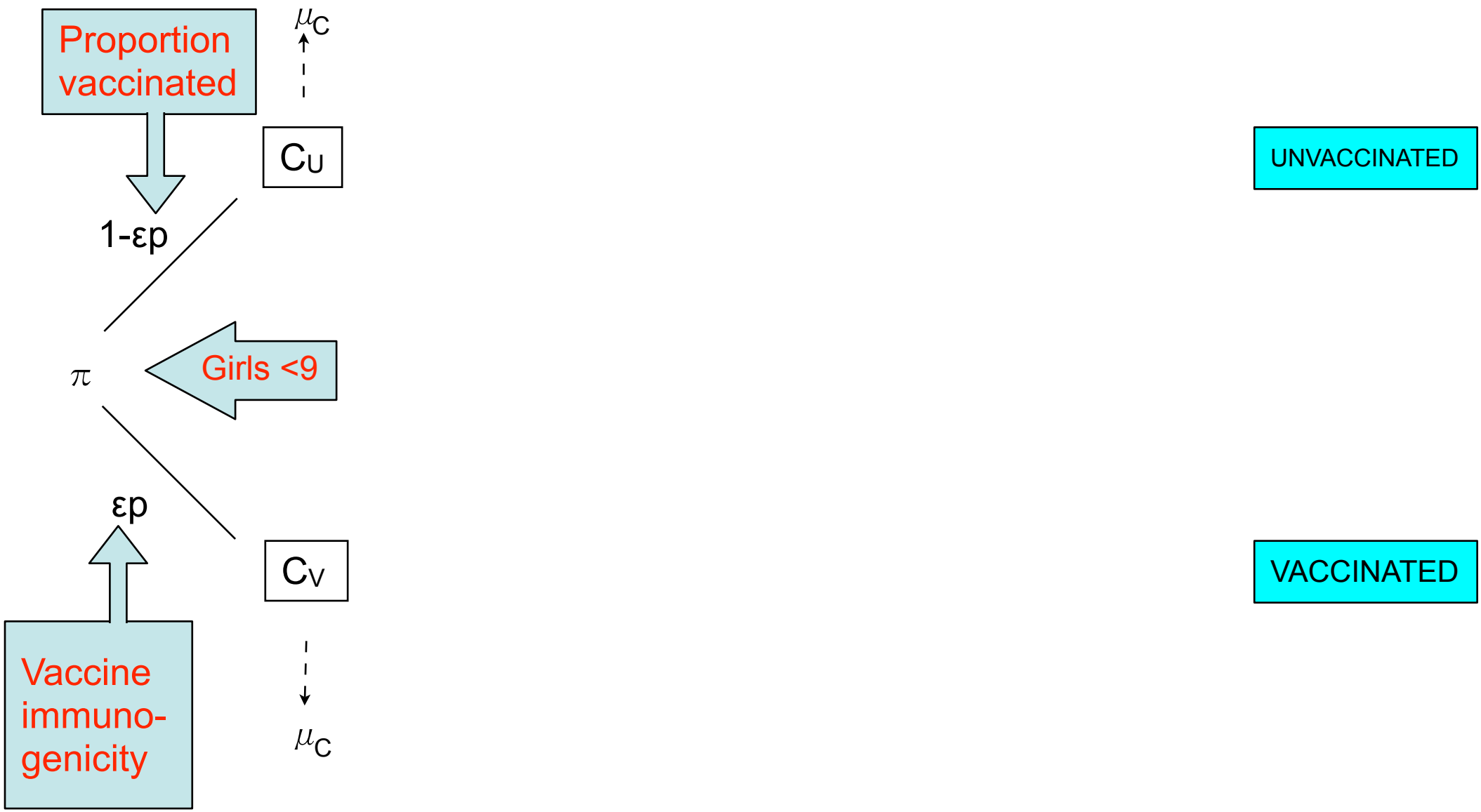

Proportion vaccinated
μ_C
C_U
1-εp
π
Girls <9
εp
C_V
Vaccine immuno-genicity
μ_C

The model



UNVACCINATED

The model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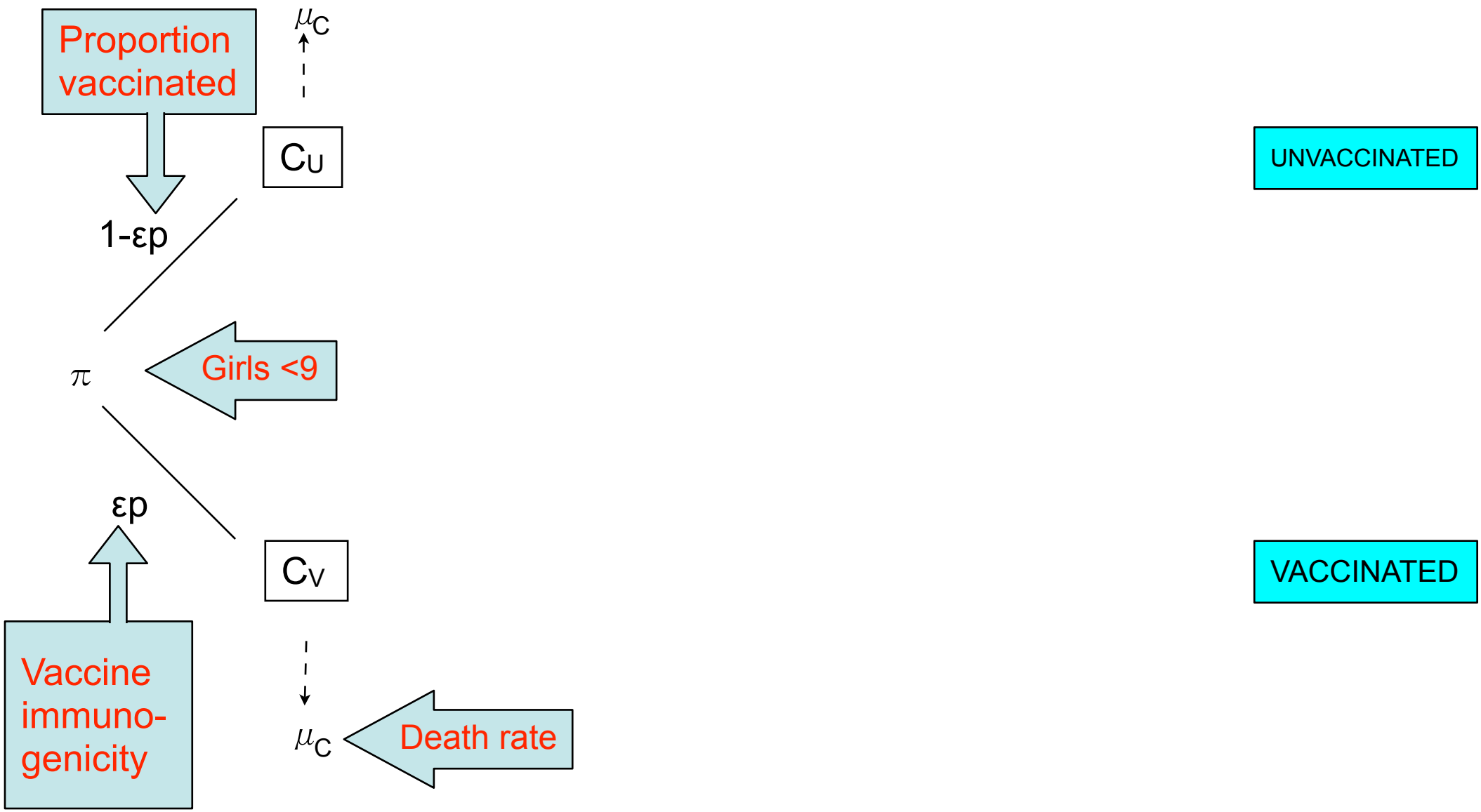
VACCINATED
Vaccine immuno-genicity
μ_C

The model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π
Girls <9
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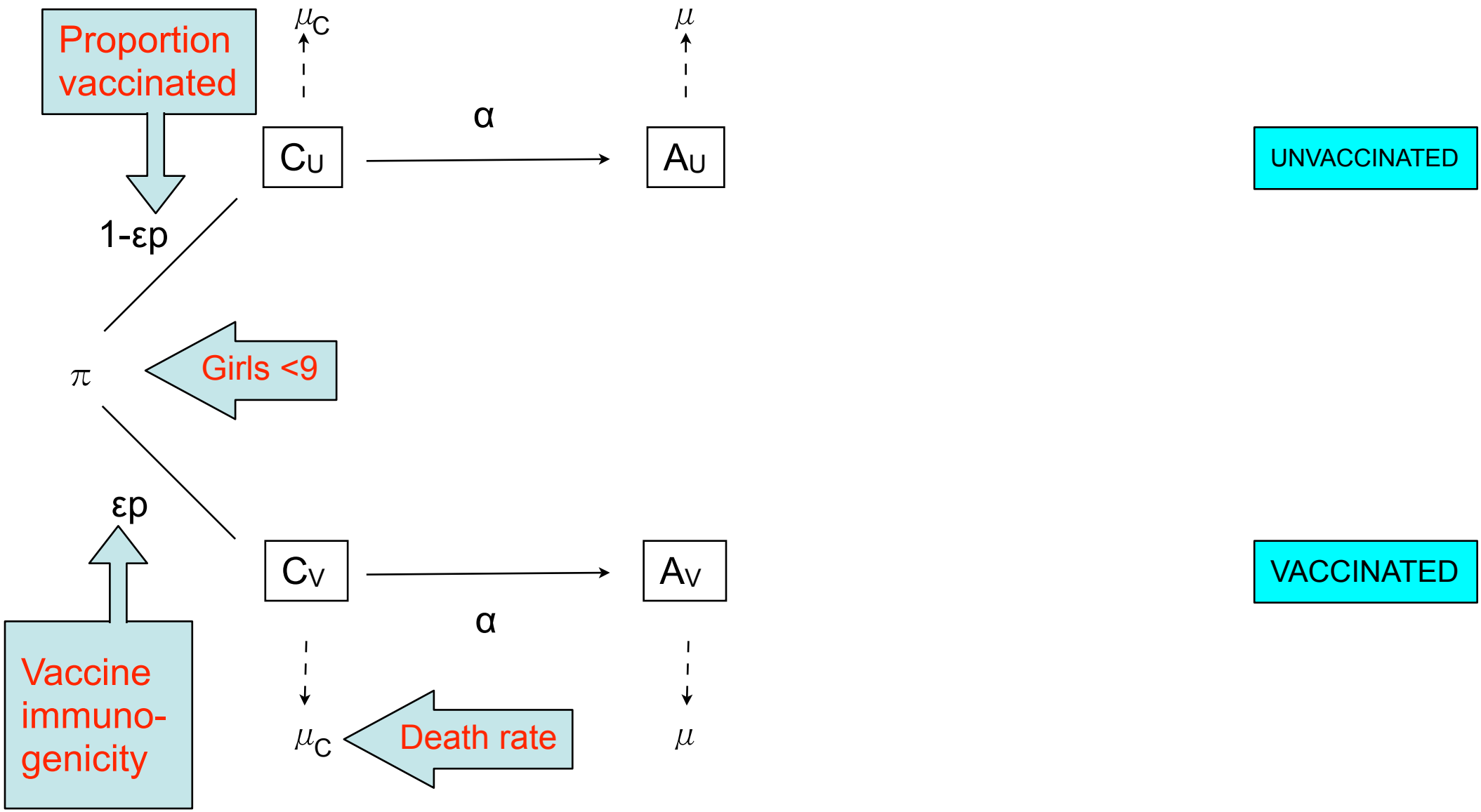
Vaccine immuno-genicity
μ_C
Death rate

The model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Vaccine immuno-genicity
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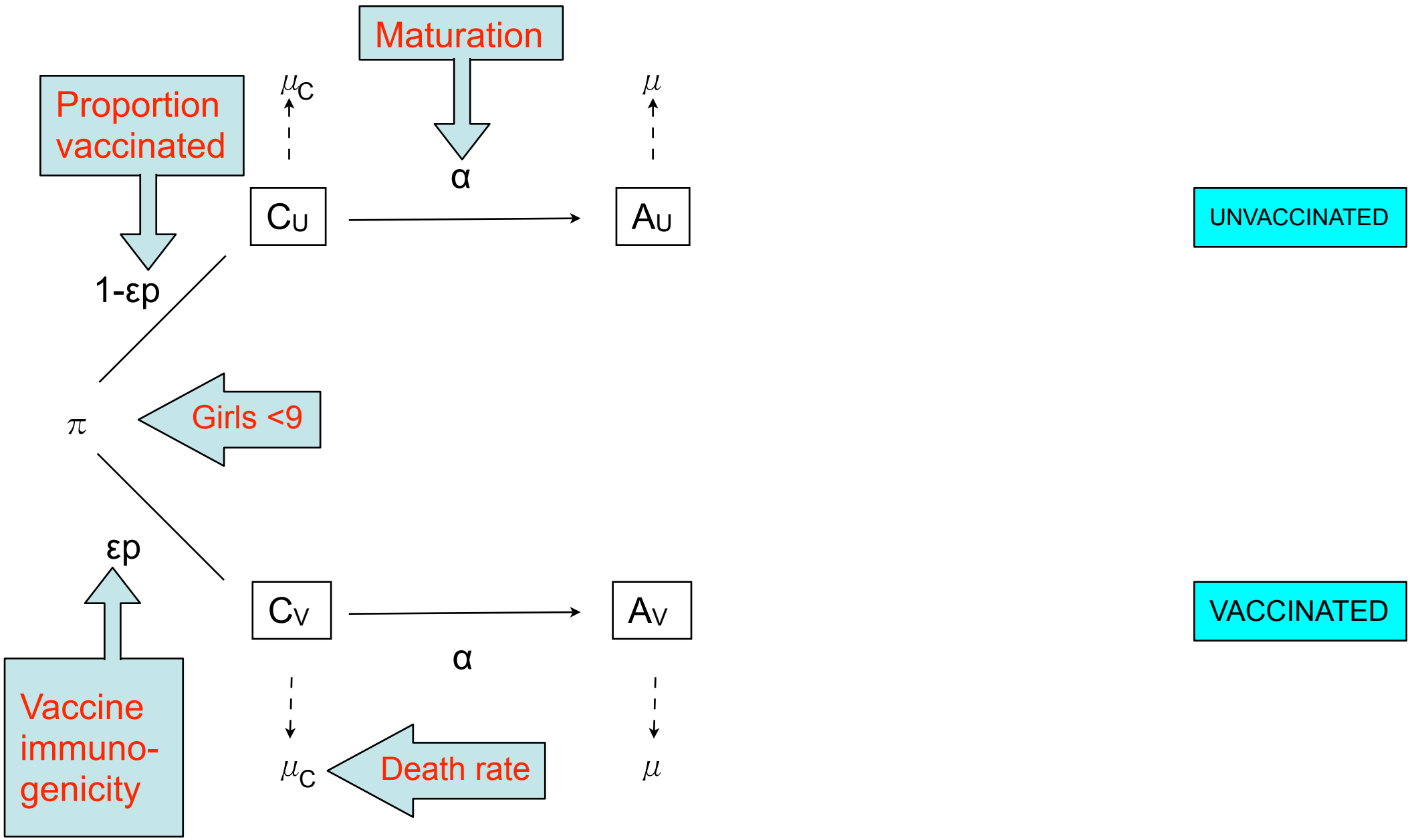
Death rate
μ

The model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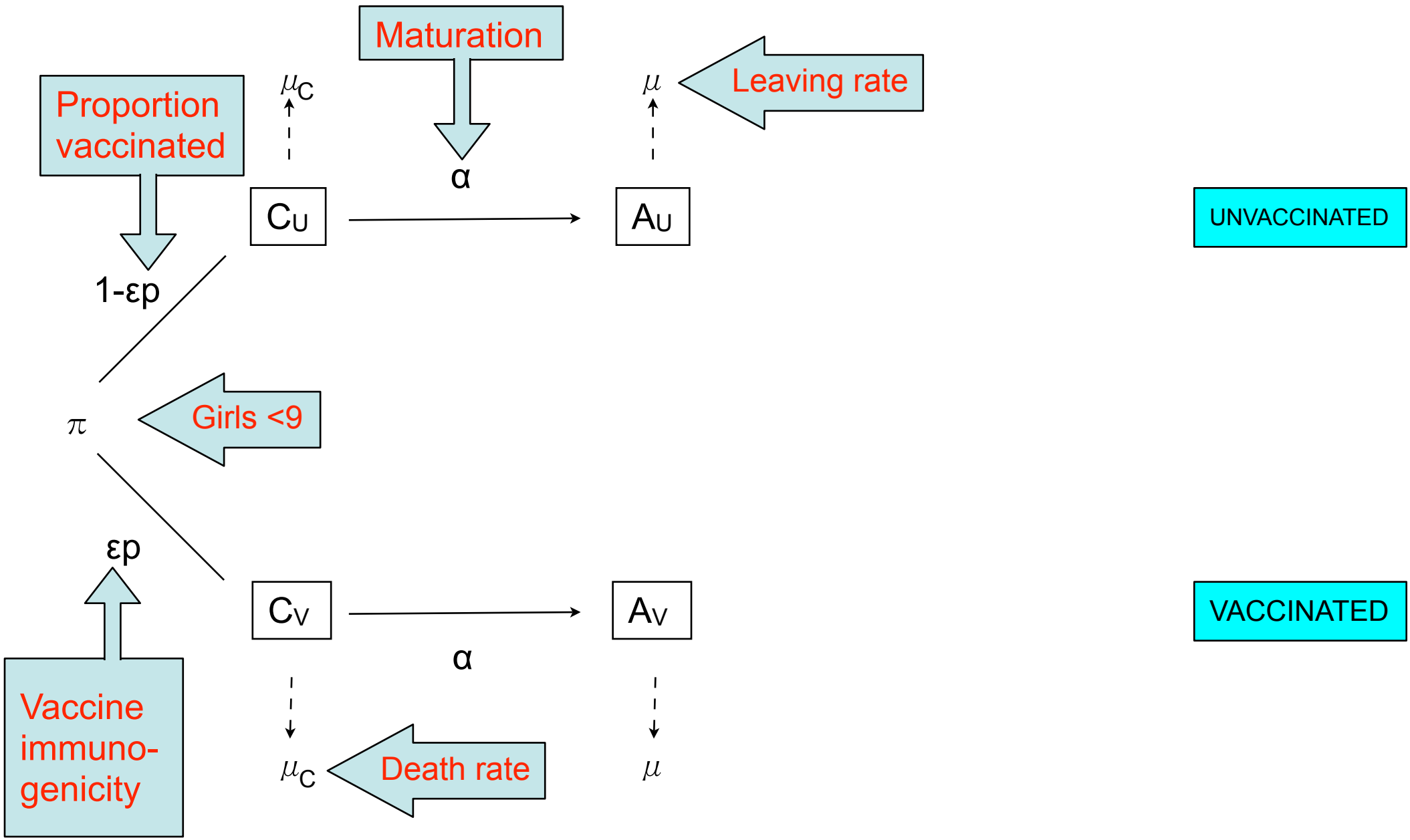
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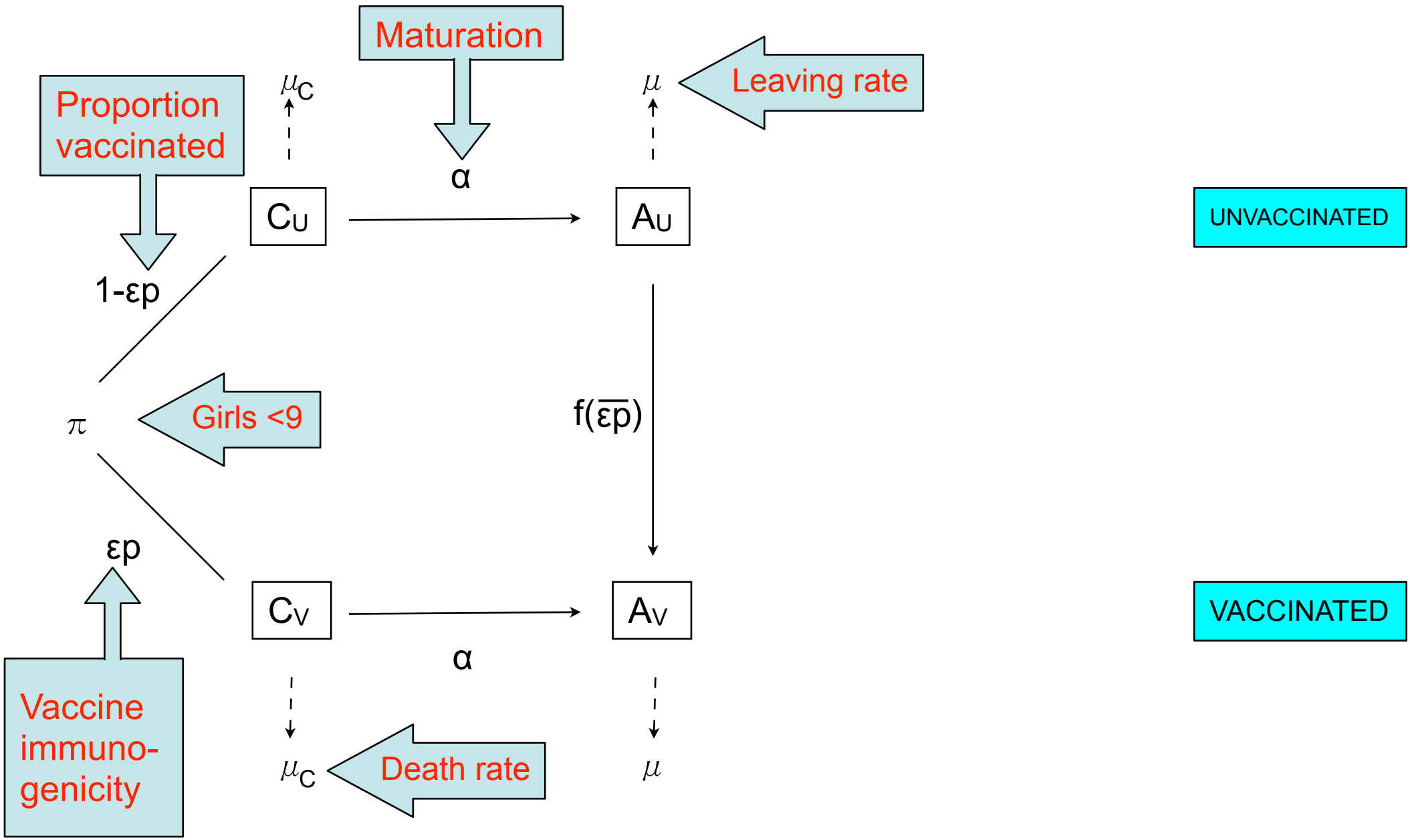
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Girls <9
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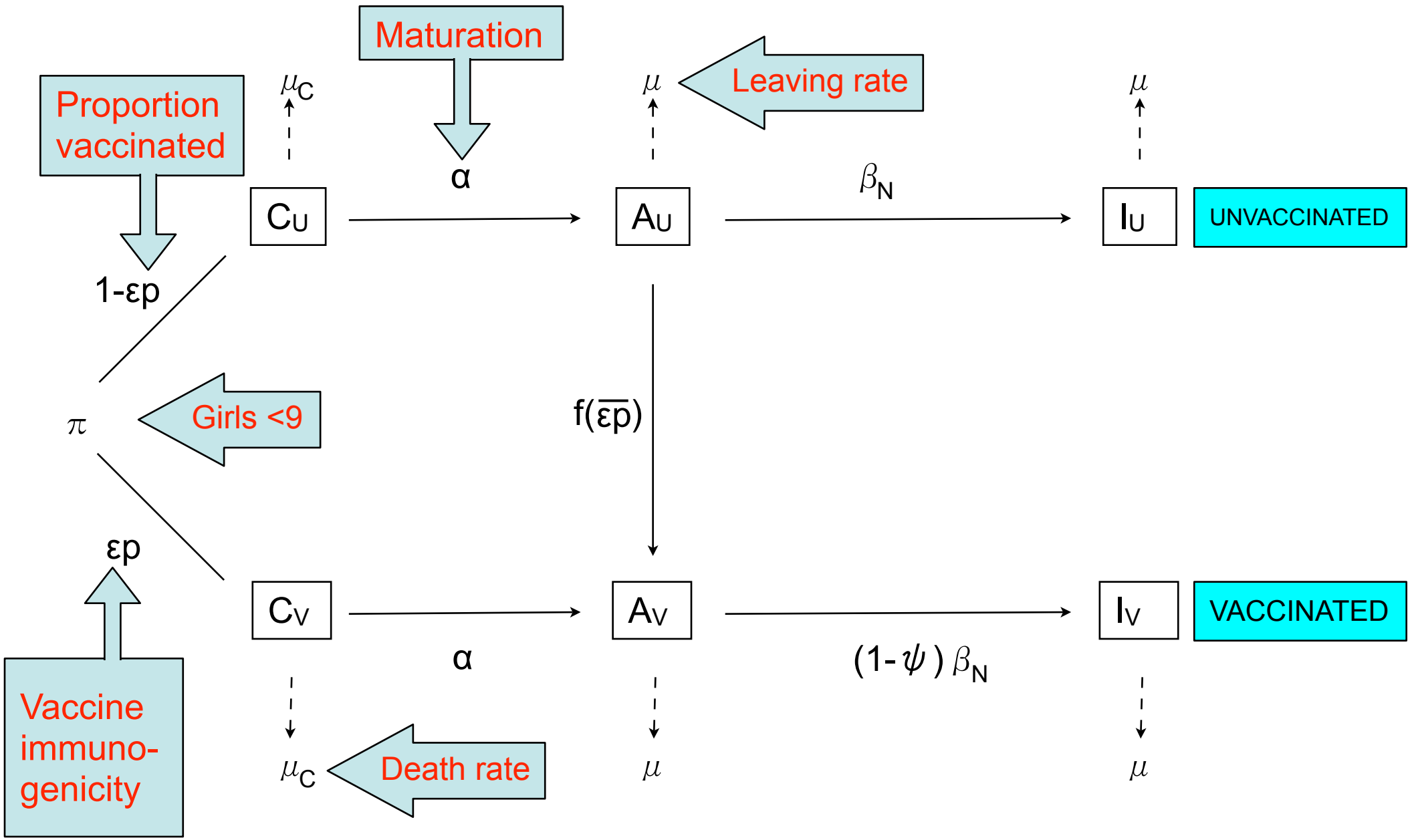
The model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Cu
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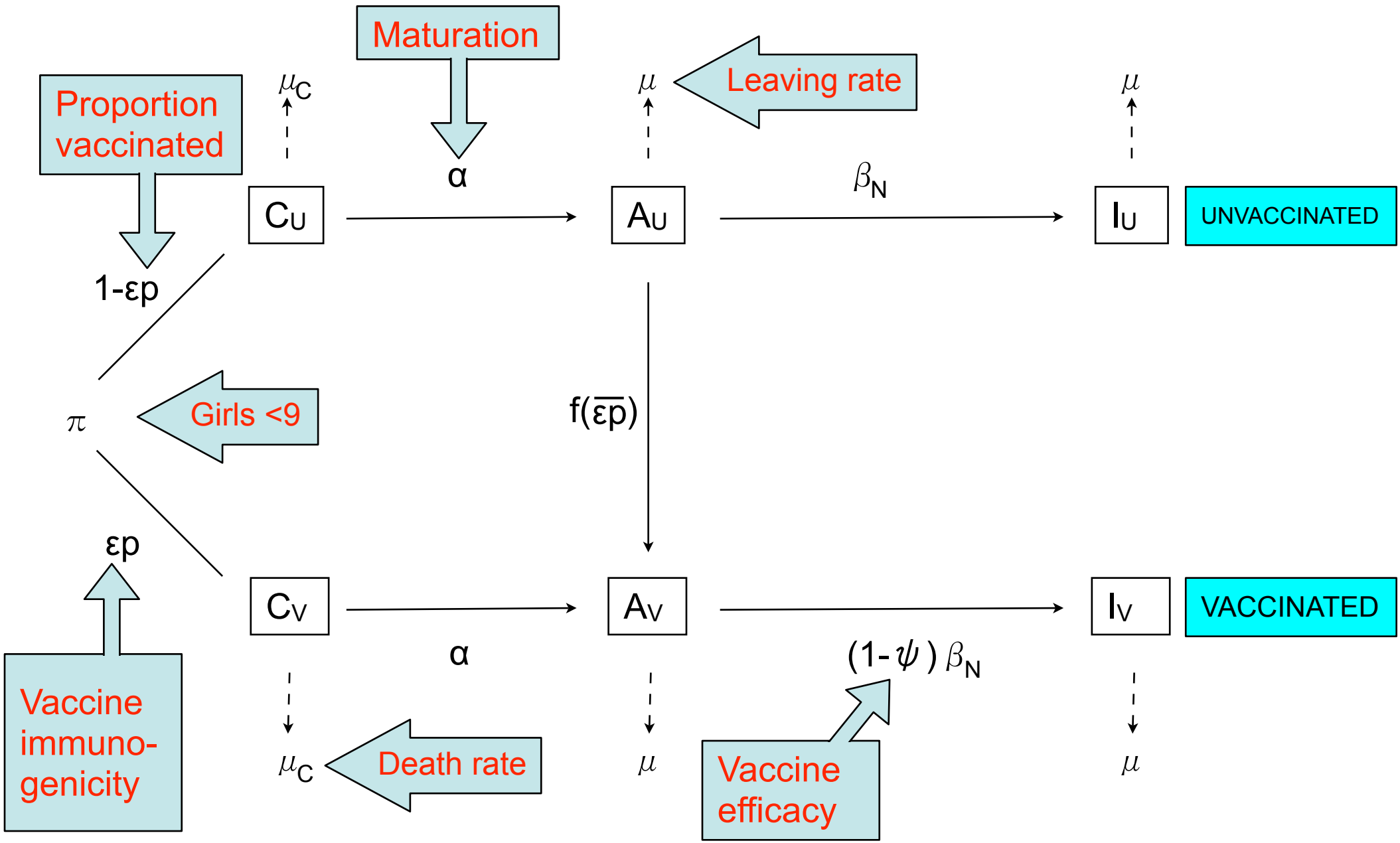
μ

The model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μ
Leaving rate
μ
α
β_N
C_U
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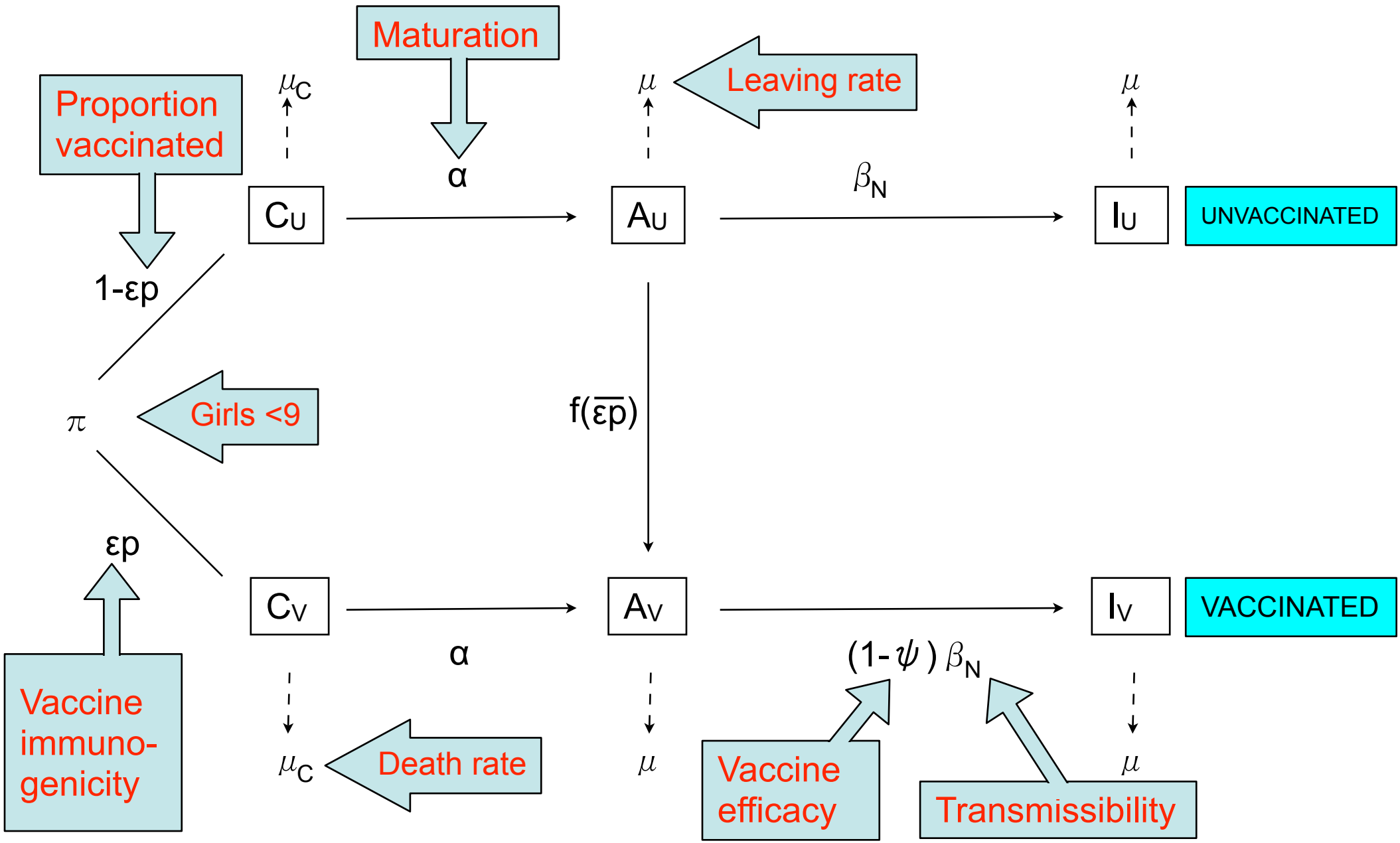
1-εp
π
Girls <9
f($\overline{\varepsilon p}$)
εp
C_V
A_V
I_V
VACCINATED
α
(1-ψ) β_N
Vaccine immuno-genicity
μ_C
Death rate
μ
Vaccine efficacy
μ

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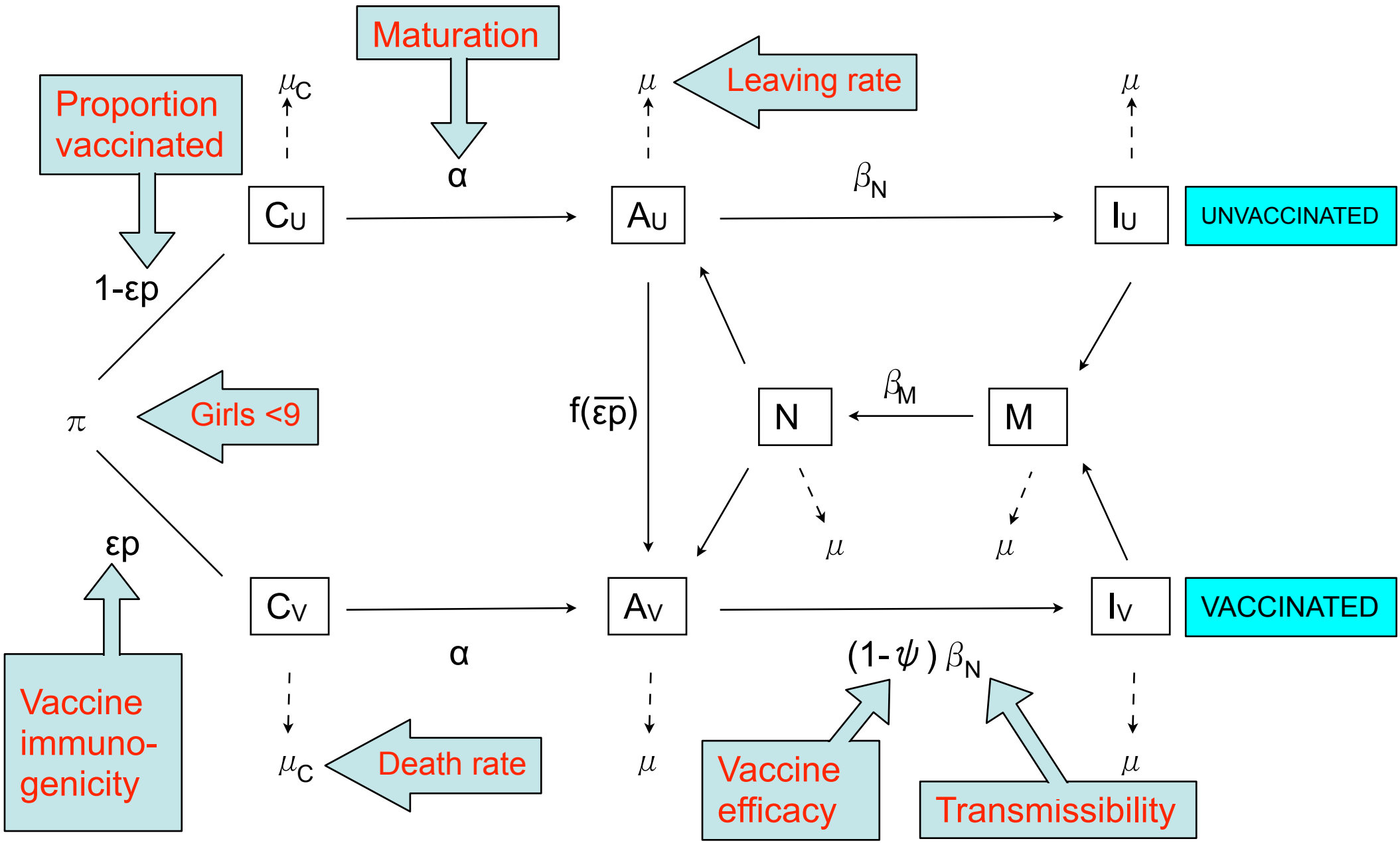
$(1-\psi)\,\beta_N$
Vaccine immuno-genicity
μ_C
Death rate
μ
Vaccine efficacy
Transmissibility
μ

The model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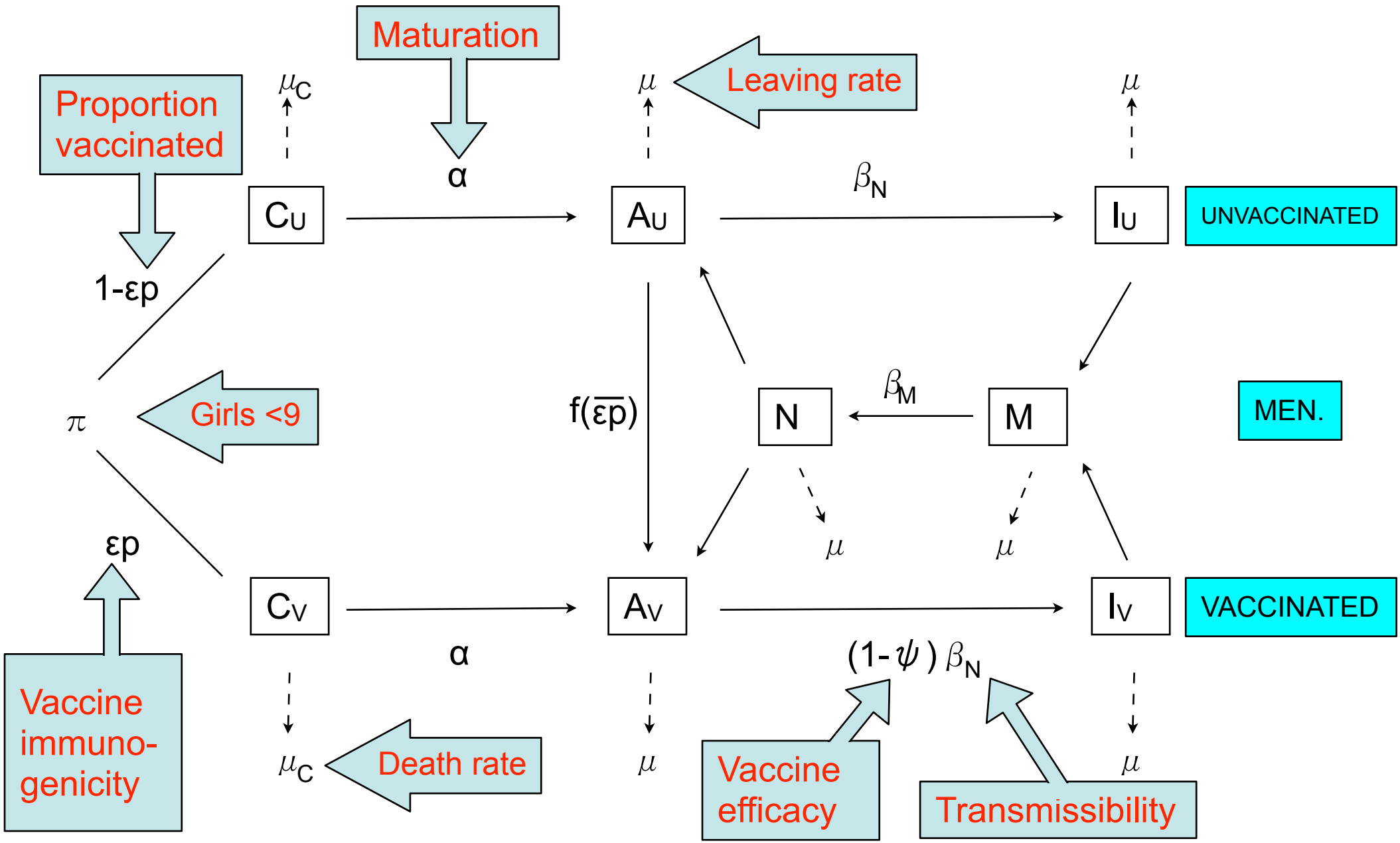
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μ
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μ
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Transmissibility

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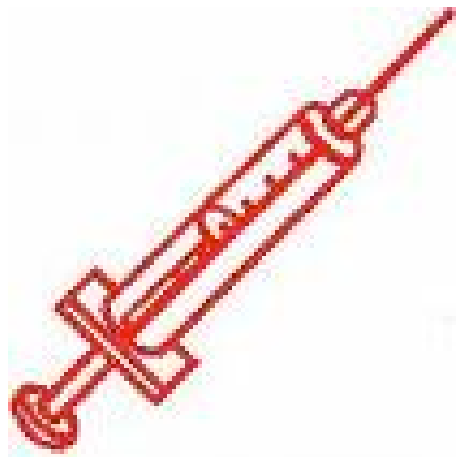

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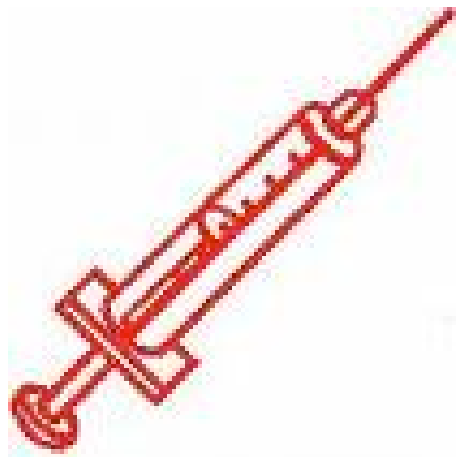
  - vaccination occurs at a particular grade
  - otherwise the vaccination rate is zero



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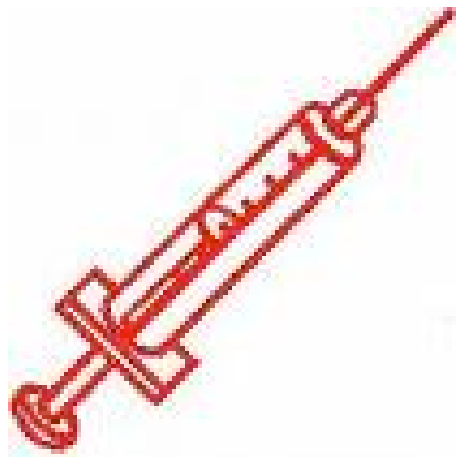

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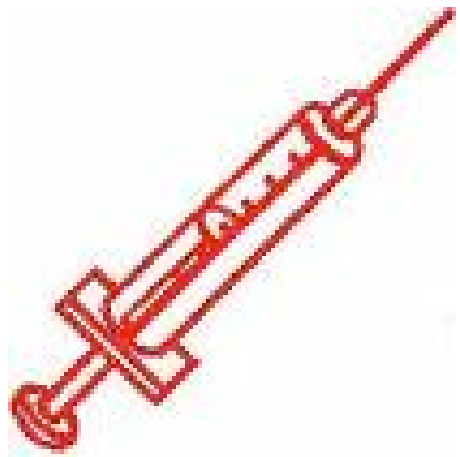
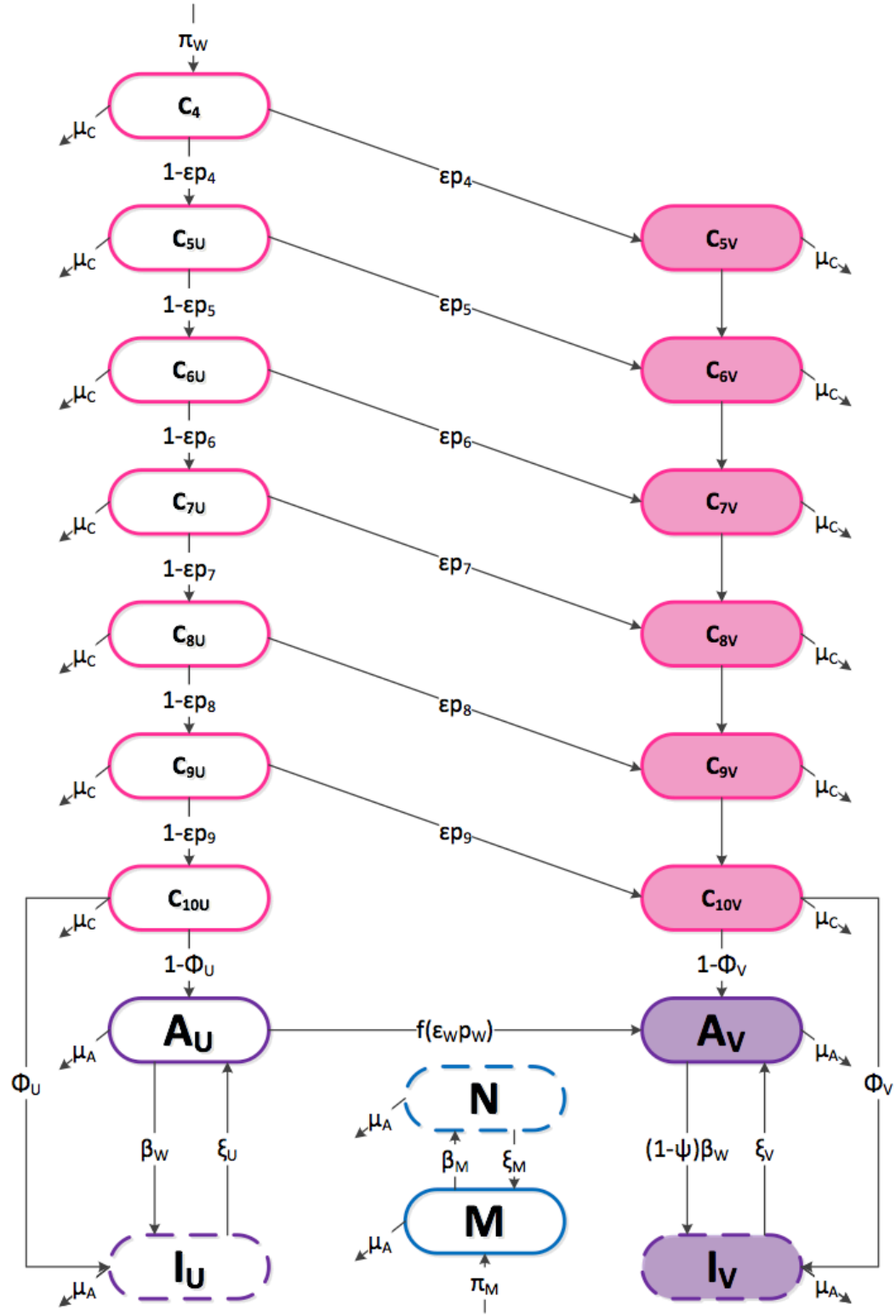
  - eg childhood sexual abuse
- These individuals will proceed directly to the infected class
- We also include recovery of infected individuals.




π_W
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εp_4
C_{5U}
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C_{6V}
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$1-\varepsilon p_7$
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C_{8V}
$1-\varepsilon p_8$
εp_8
C_{9U}
C_{9V}
$1-\varepsilon p_9$
εp_9
C_{10U}
C_{10V}
$1-\Phi_U$
$1-\Phi_V$
A_U
$f(\varepsilon_W p_W)$
A_V
μ_A
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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)

The model

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

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

Girls in grade 5 (approx. 10 years old) are described as

$$\frac{dC_{5U}}{dt} = (1-\epsilon p_4)C_4 - (1+\mu_C)C_{5U}$$

$$\frac{dC_{5V}}{dt} = \epsilon p_4 C_4 - (1+\mu_C)C_{5V}.$$

Girls in grade 6 (approx. 11 years old) are described as

$$\frac{dC_{6U}}{dt} = (1-\epsilon p_5)C_{5U} - (1+\mu_C)C_{6U}$$

$$\frac{dC_{6V}}{dt} = \epsilon p_5 C_{5U} + C_{5V} - (1+\mu_C)C_{6V}.$$

Girls in grade 7 (approx. 12 years old) are described as

$$\frac{dC_{7U}}{dt} = (1-\epsilon p_6)C_{6U} - (1+\mu_C)C_{7U}$$

$$\frac{dC_{7V}}{dt} = \epsilon p_6 C_{6U} + C_{6V} - (1+\mu_C)C_{7V}.$$

Girls in grade 8 (approx. 13 years old) are described as

$$\frac{dC_{8U}}{dt} = (1-\epsilon p_7)C_{7U} - (1+\mu_C)C_{8U}$$

$$\frac{dC_{8V}}{dt} = \epsilon p_7 C_{7U} + C_{7V} - (1+\mu_C)C_{8V}.$$

Girls in grade 9 (approx. 14 years old) are described as

$$\frac{dC_{9U}}{dt} = (1-\epsilon p_8)C_{8U} - (1+\mu_C)C_{9U}$$

$$\frac{dC_{9V}}{dt} = \epsilon p_8 C_{8U} + C_{8V} - (1+\mu_C)C_{9V}.$$

Girls in grade 10 (approx. 15 years old) are described as

$$\frac{dC_{10U}}{dt} = (1-\epsilon p_9)C_{9U} - (1+\mu_C)C_{10U}$$

$$\frac{dC_{10V}}{dt} = \epsilon p_9 C_{9U} + C_{9V} - (1+\mu_C)C_{10V}.$$

Uninfected adult women are described as

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

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

Infected adult women are described as

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

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

Uninfected men are described as

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

Infected men are described as

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

♀ and ♂

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

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$$♂ = M + N.$$

C_j=children
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Disease-free equilibrium

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

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

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

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

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

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- This is valid. so long as we have the condition $\frac{1}{\xi_V} < \frac{1}{\xi_U}$.
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- We expect this to occur.

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

A_j=uninfected adults μ_j=death rates
β_j=transmissibilities ♀=total women
Ψ=protection ξ_j=duration of infection

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

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

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

A_j=uninfected adults μ_j=death rates
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$$\overline{C_{kU}} = \frac{\pi_W}{(1+\mu_C)^{k-3}} \qquad \text{for } k \leq k^*$$

$$\overline{C_{kU}} = \frac{\pi_W(1-\epsilon p_{k-1})}{(1+\mu_C)^{k-3}} \qquad \text{for } k > k^*$$

$$\overline{C_{kV}} = 0 \qquad \text{for } k \leq k^*$$

$$\overline{C_{kV}} = \frac{\pi_W \epsilon}{(1+\mu_C)^{k-3}} \qquad \text{for } k > k^*$$

$$\overline{A_U} = \frac{\pi_W}{(f(p_W\epsilon_W)+\mu_A)(1-\mu_C)^7}$$

$$\overline{A_V} = \frac{\pi_W f}{(f(p_W\epsilon_W)+\mu_A)(1-\mu_C)^7}.$$

C_j=children A_j=uninfected adults
f=adult uptake μ_j=death rates
π_W=female birth rate ϵ_j=efficacy
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$$\epsilon^* = \frac{♀\mu_A^2(1-\mu_C)^7(\mu_A^2+\mu_A(\xi_U+\xi_V+\xi_M)+\xi_U\xi_V+\xi_U\xi_M+\xi_V\xi_M)}{\beta_W\beta_M\pi_W((1-\psi)(\mu_A+\xi_U)-(\mu_A+\xi_V))}.$$

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$$\epsilon_W^* = \frac{\mu_A(1+\gamma)(\beta_W\beta_M\pi_W\xi_V + \mu_A(1+\mu_C)^7 D)}{\beta_W\beta_M\pi_W(c+\mu_A(\mu_A+\xi_U)) - \mu_A^2(1+\mu_C)^7 D},$$

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$$\psi^* = 1 + \frac{\beta_W\beta_M(\mu_A+\xi_U)\overline{A_U} - D}{\beta_W\beta_M(\mu_A+\xi_V)\overline{A_V}}$$

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- If the vaccine protection is lower than this value, then we can never have eradication.

μ_j=death rates π_W=female birth rate
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Example

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	✓	

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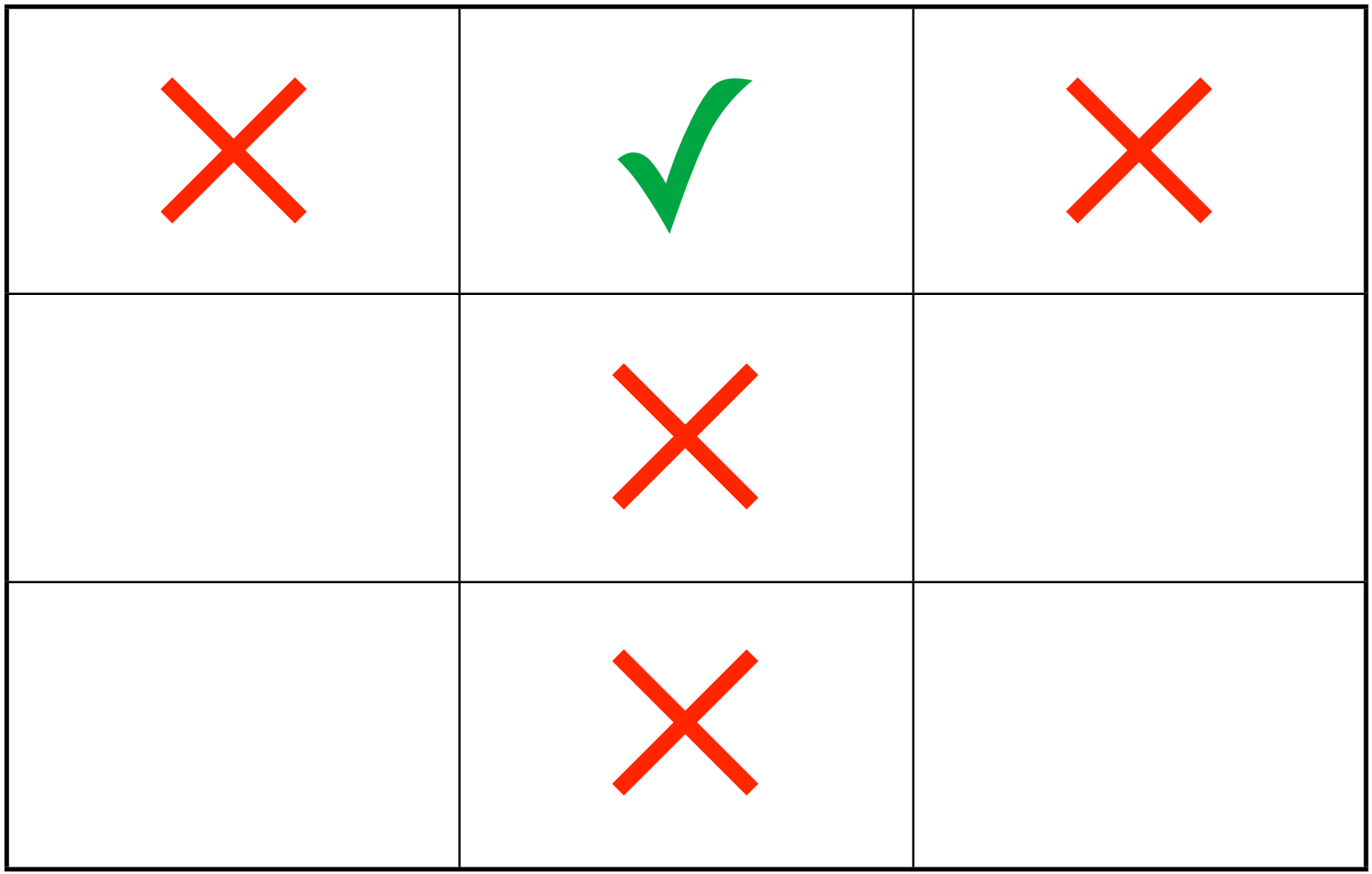

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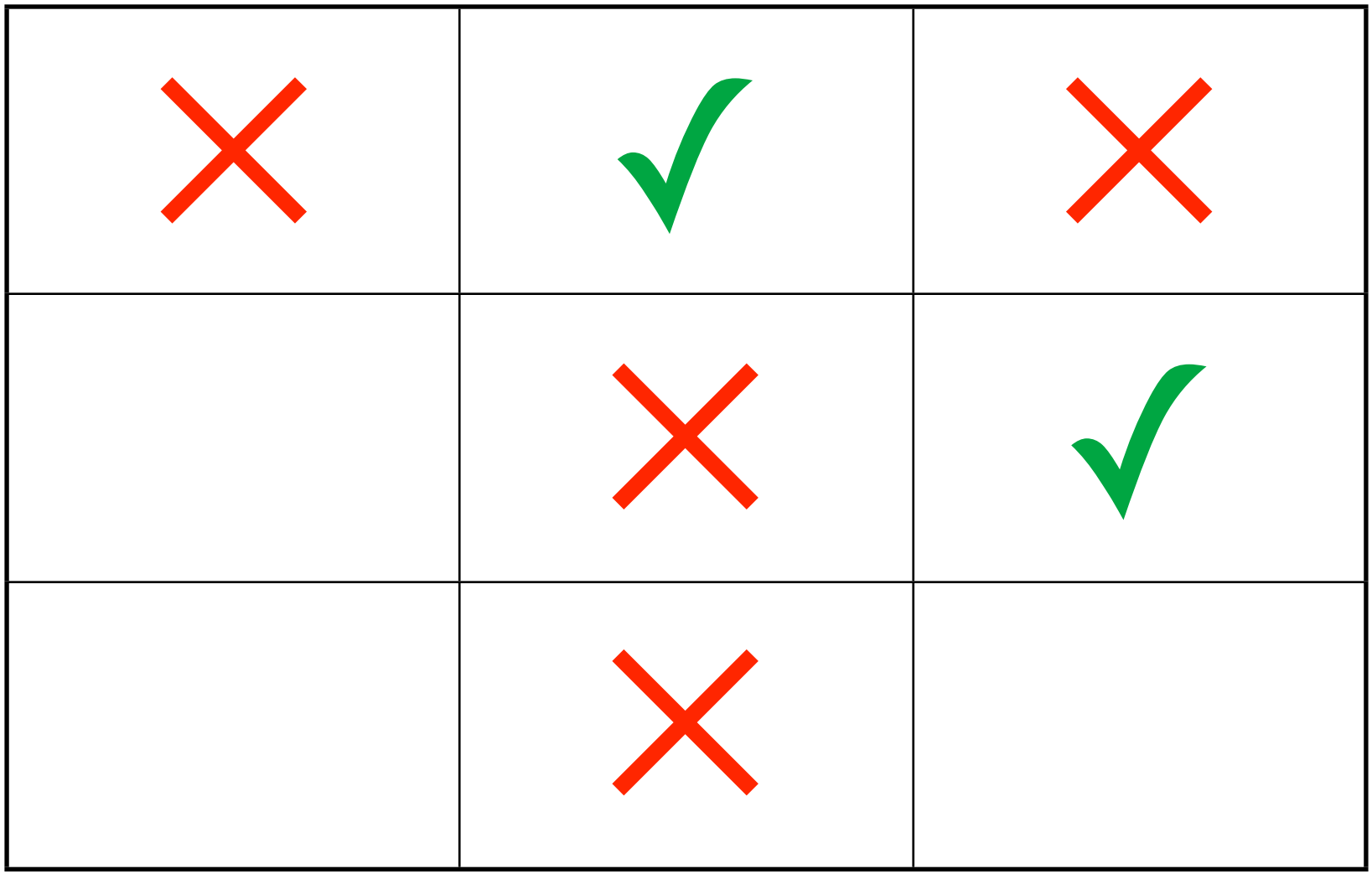

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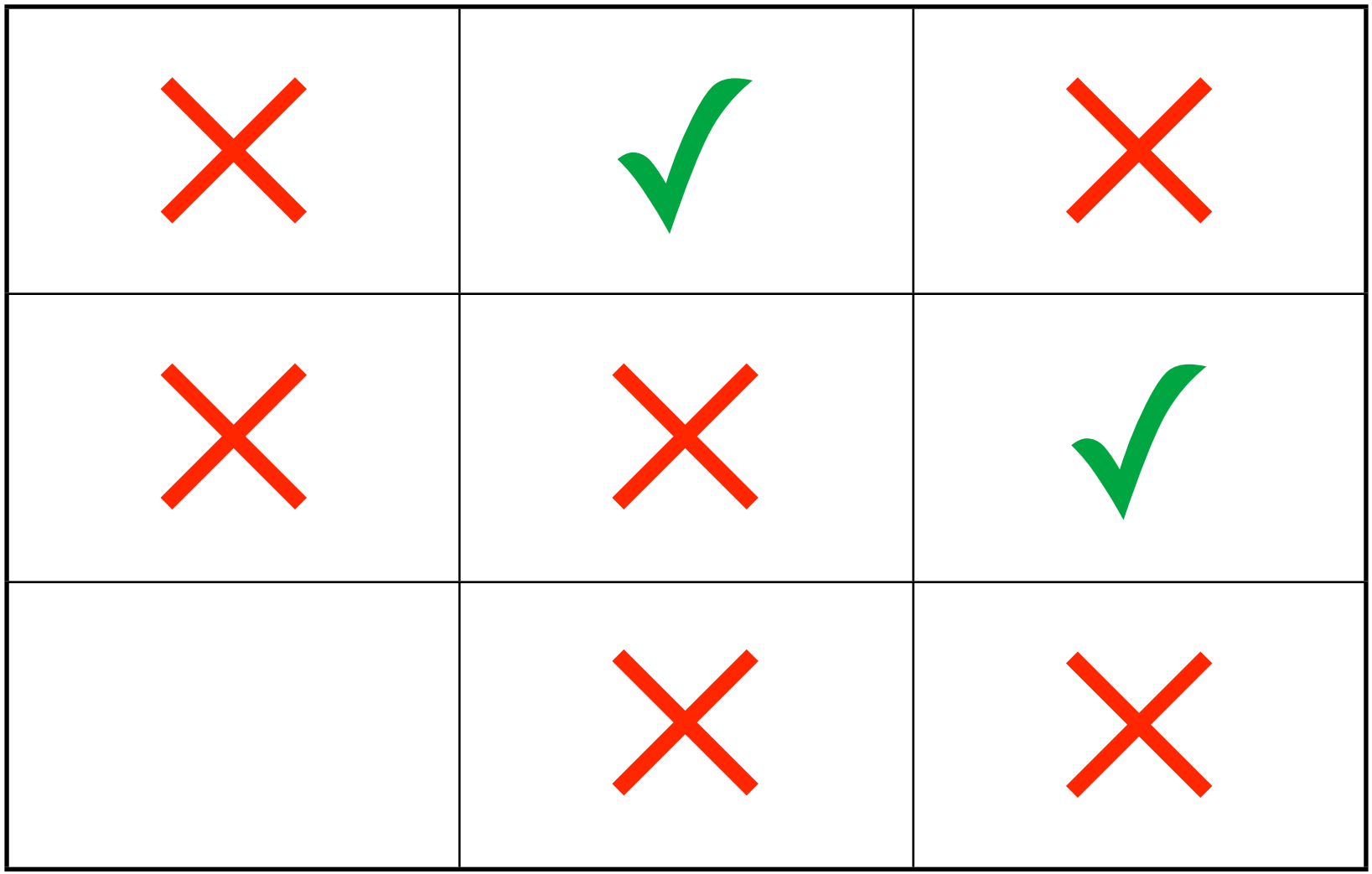

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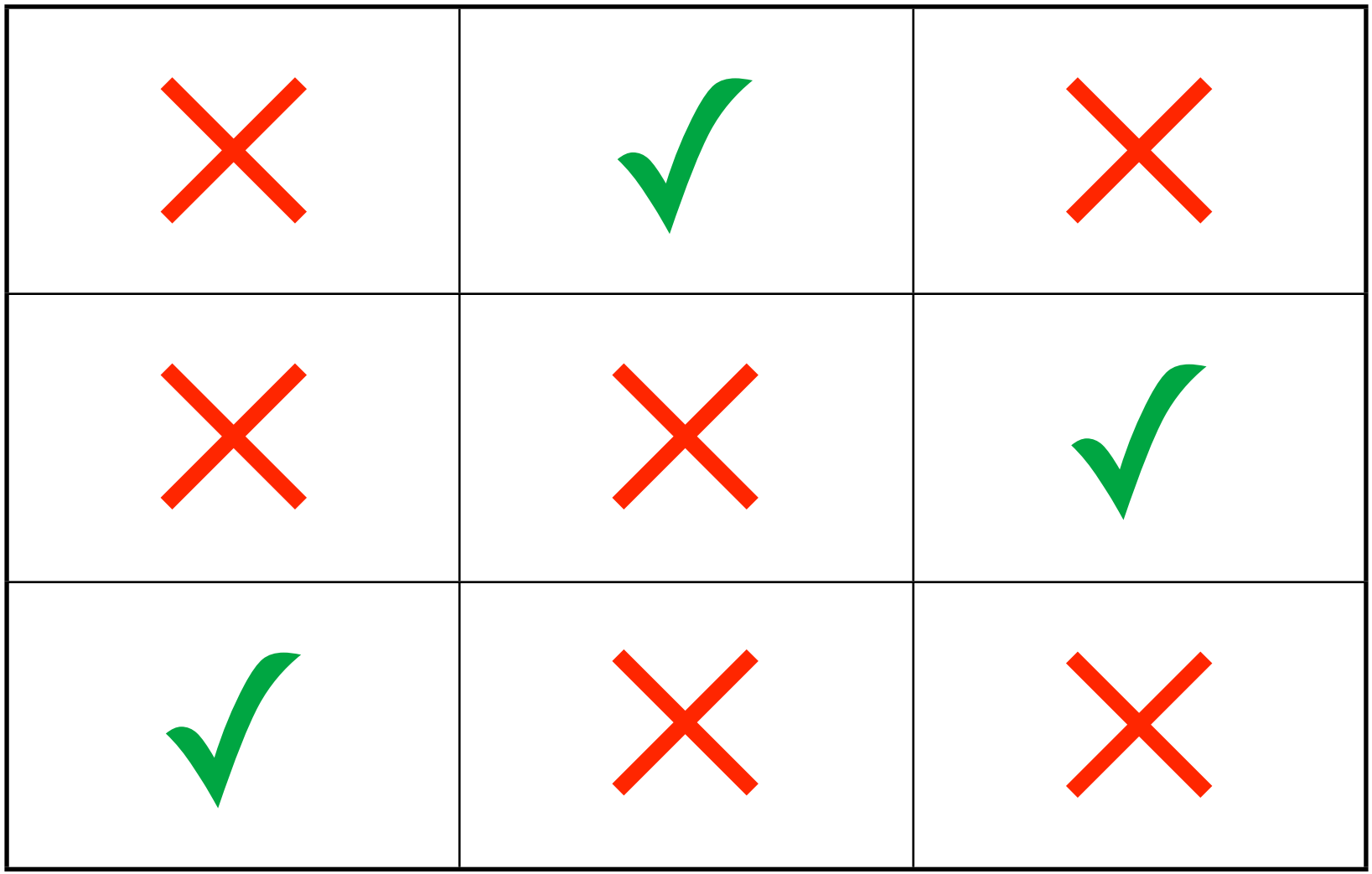

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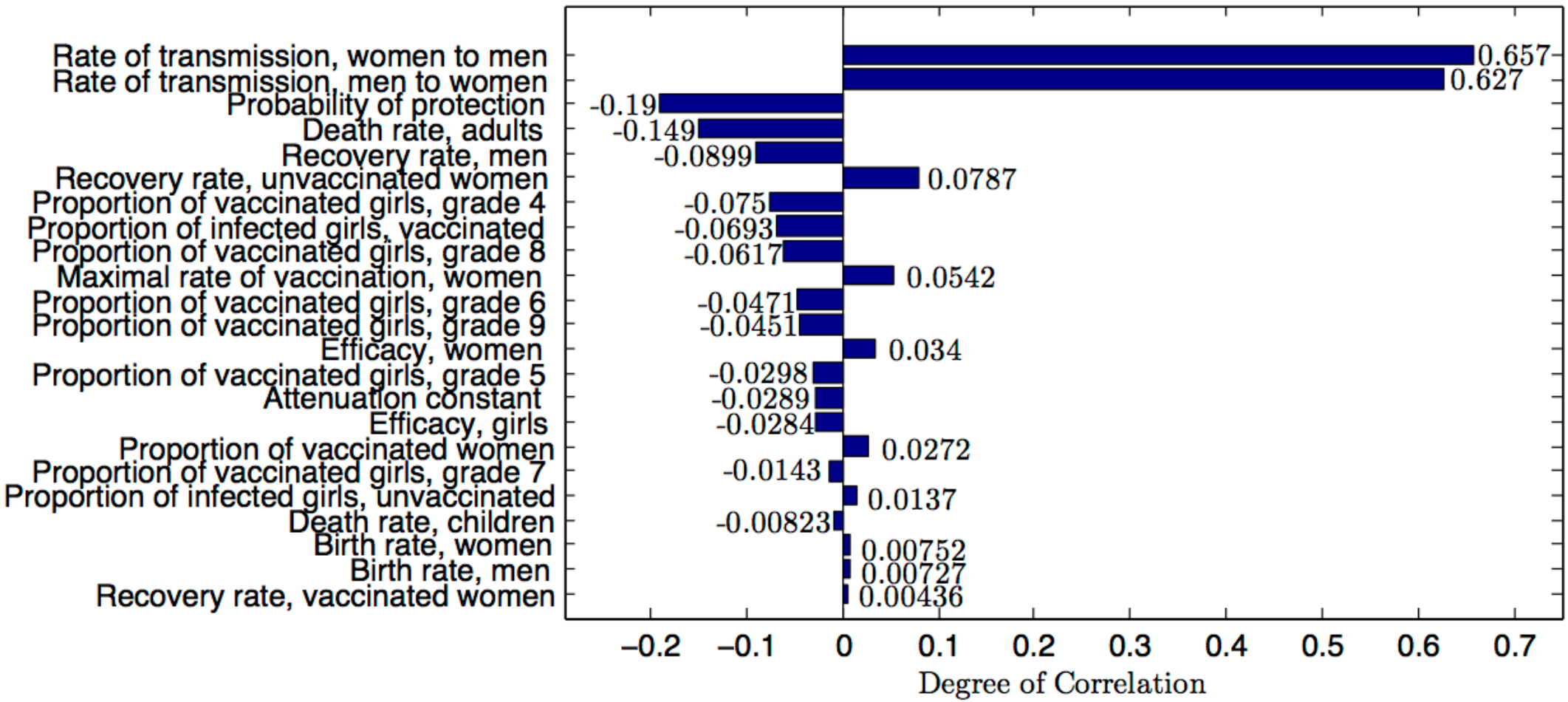
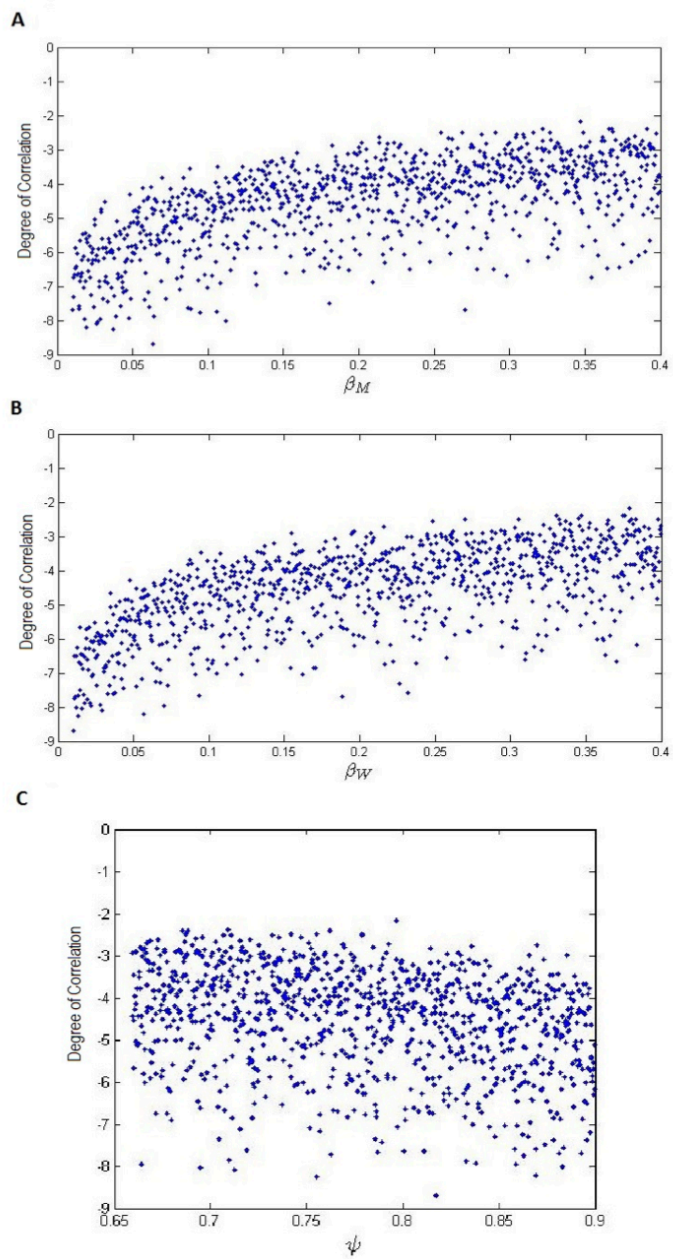
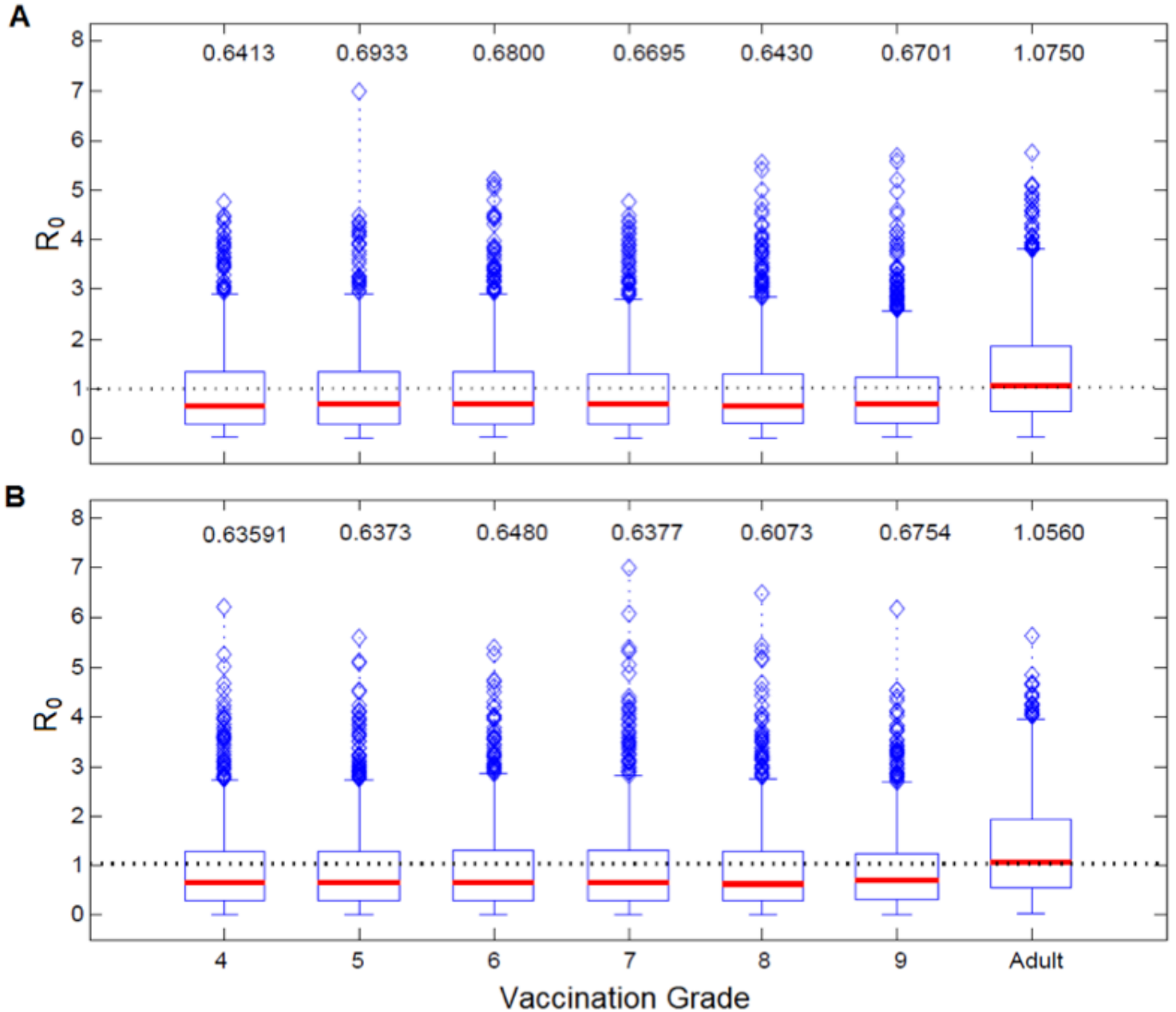
PRCCs


Rate of transmission, women to men
Rate of transmission, men to women
Probability of protection
Death rate, adults
Recovery rate, men
Recovery rate, unvaccinated women
Proportion of vaccinated girls, grade 4
Proportion of infected girls, vaccinated
Proportion of vaccinated girls, grade 8
Maximal rate of vaccination, women
Proportion of vaccinated girls, grade 6
Proportion of vaccinated girls, grade 9
Efficacy, women
Proportion of vaccinated girls, grade 5
Attenuation constant
Efficacy, girls
Proportion of vaccinated women
Proportion of vaccinated girls, grade 7
Proportion of infected girls, unvaccinated
Death rate, children
Birth rate, women
Birth rate, men
Recovery rate, vaccinated women
0.657
0.627
-0.19
-0.149
-0.0899
0.0787
-0.075
-0.0693
-0.0617
0.0542
-0.0471
-0.0451
0.034
-0.0298
-0.0289
-0.0284
0.0272
-0.0143
0.0137
-0.00823
0.00752
0.00727
0.00436
–0.2
–0.1
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
Degree of Correlation

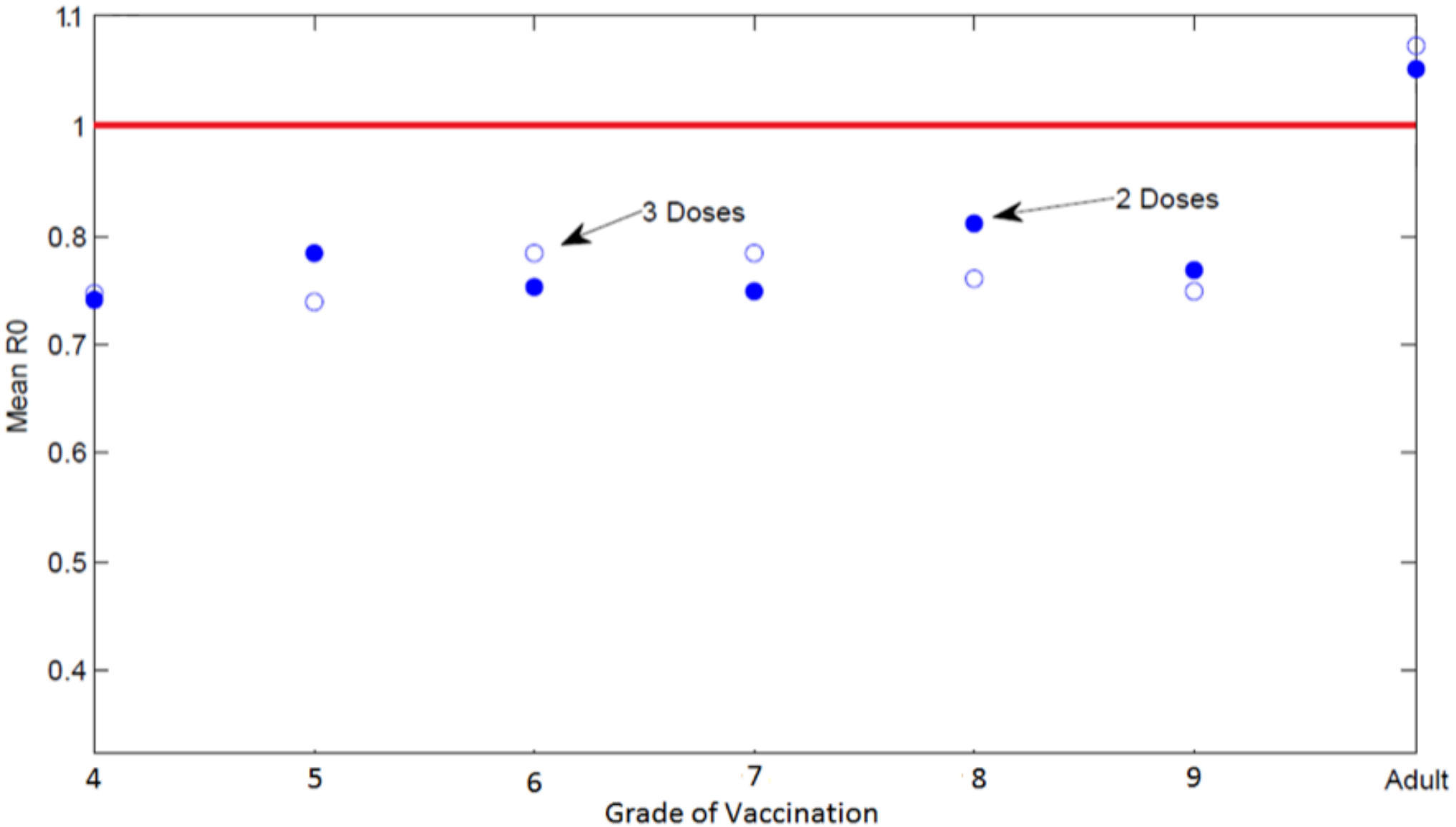
Monte Carlo simulations



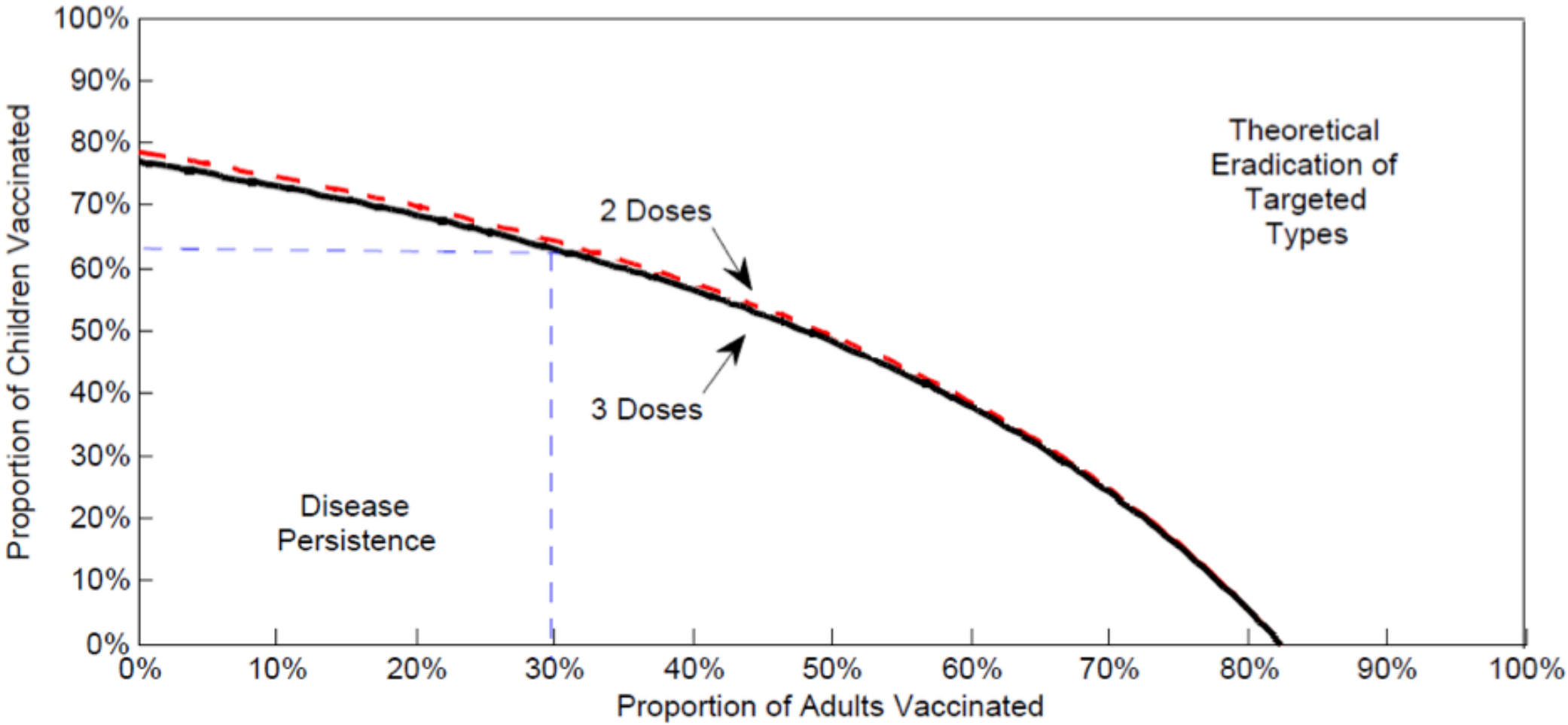
Two doses vs three doses



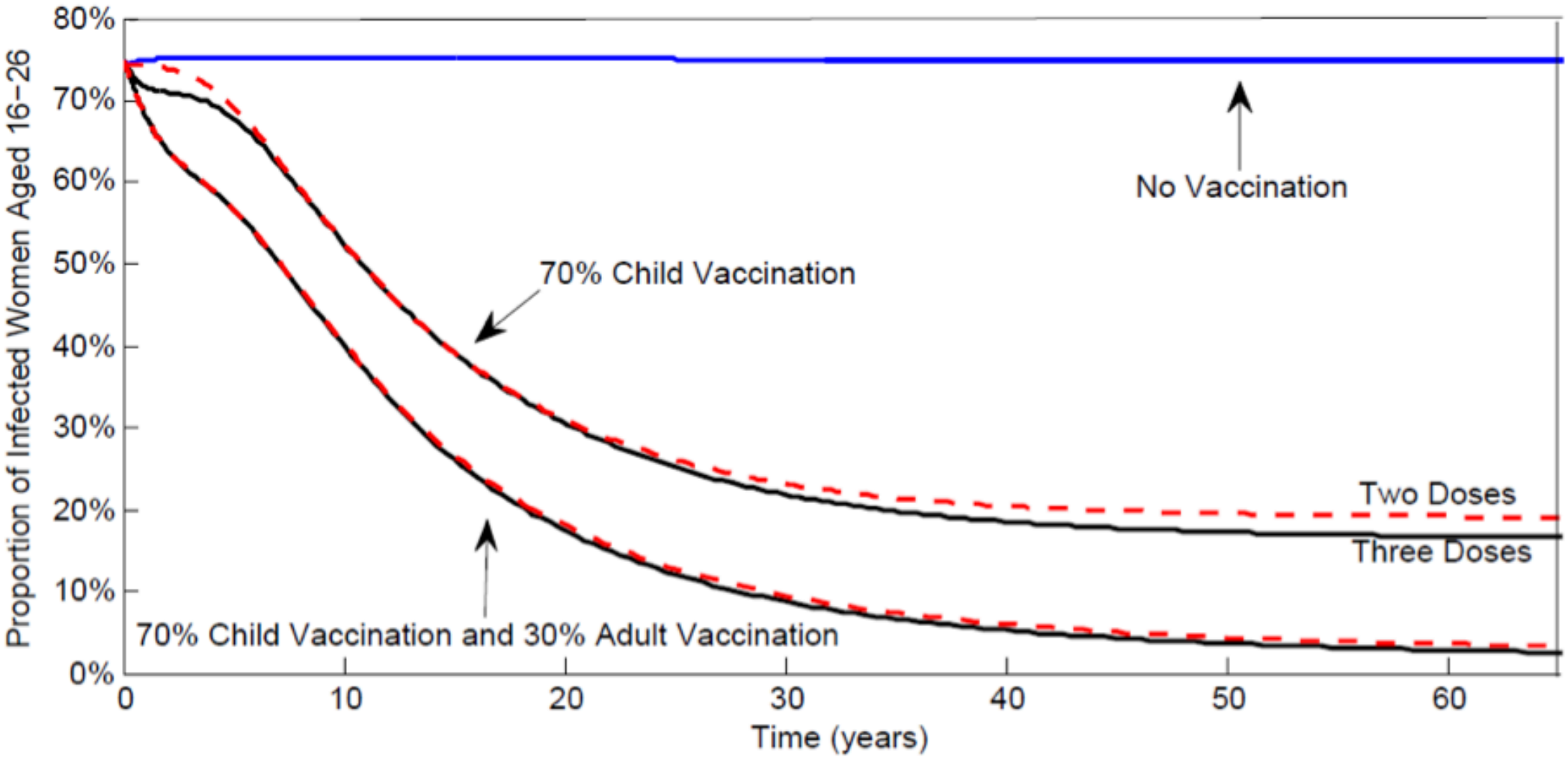
Mean R_0 values



Vaccination coverage rates



Timecourse of infection



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- This suggests that eradication is feasible.

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- As a result of this research, Quebec changed its HPV vaccination policy in August 2013 from three to two doses.

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- This illustrates the cycle of modelling.

Using math to solve real problems

Biological problem

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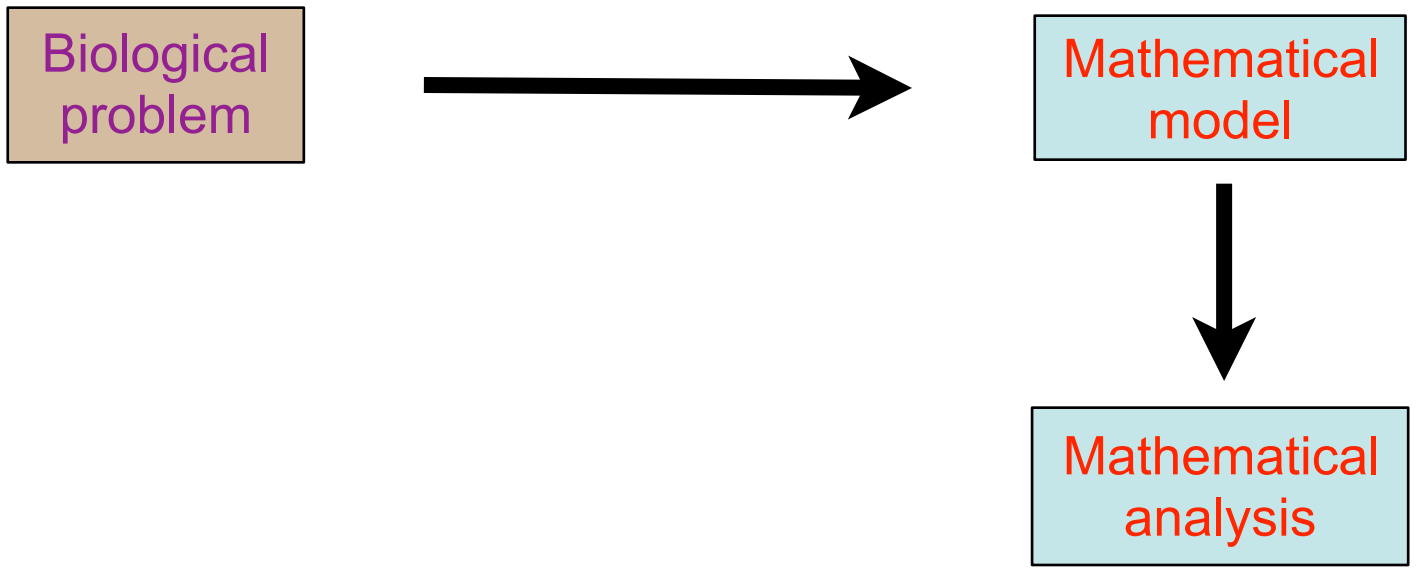

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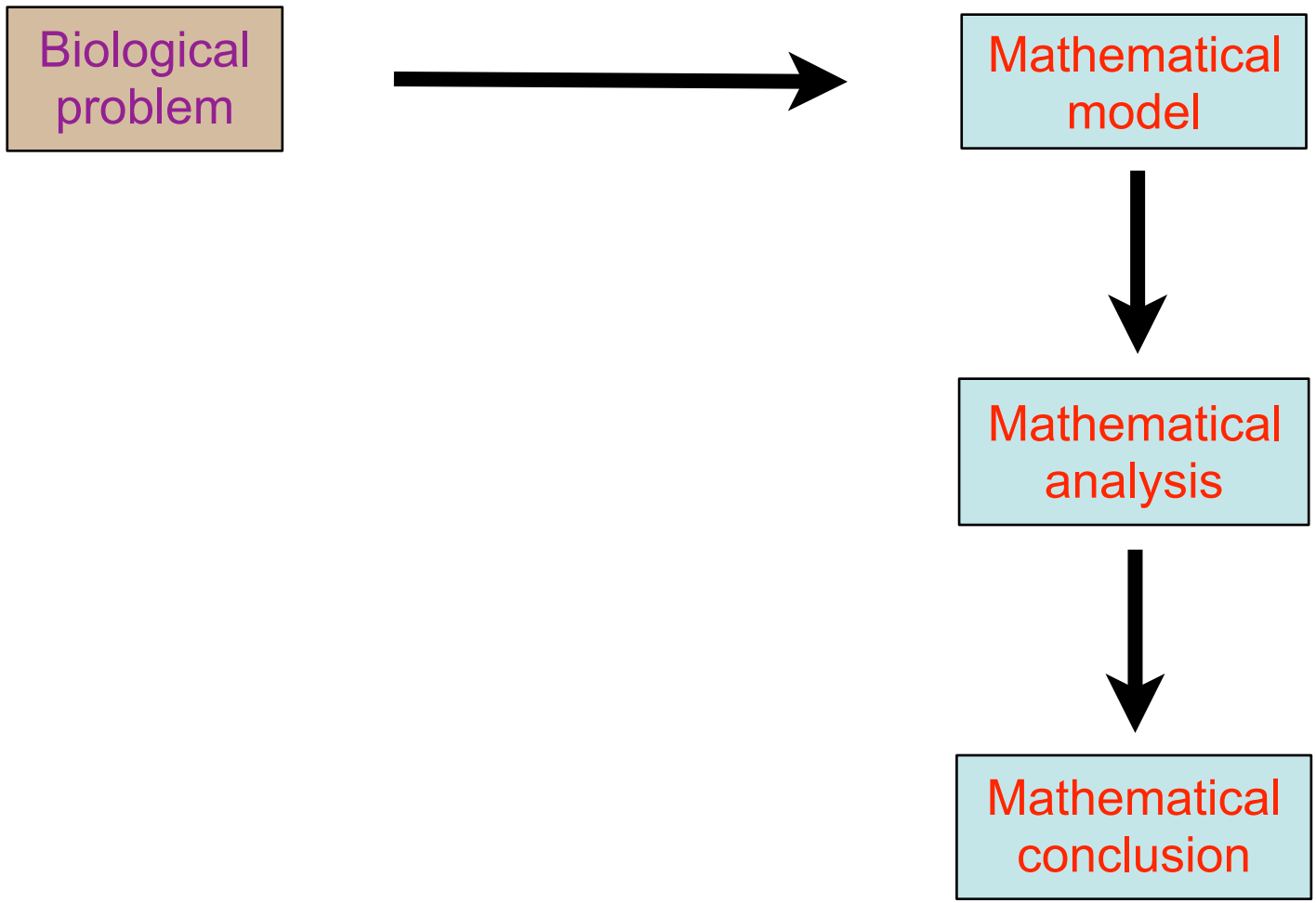

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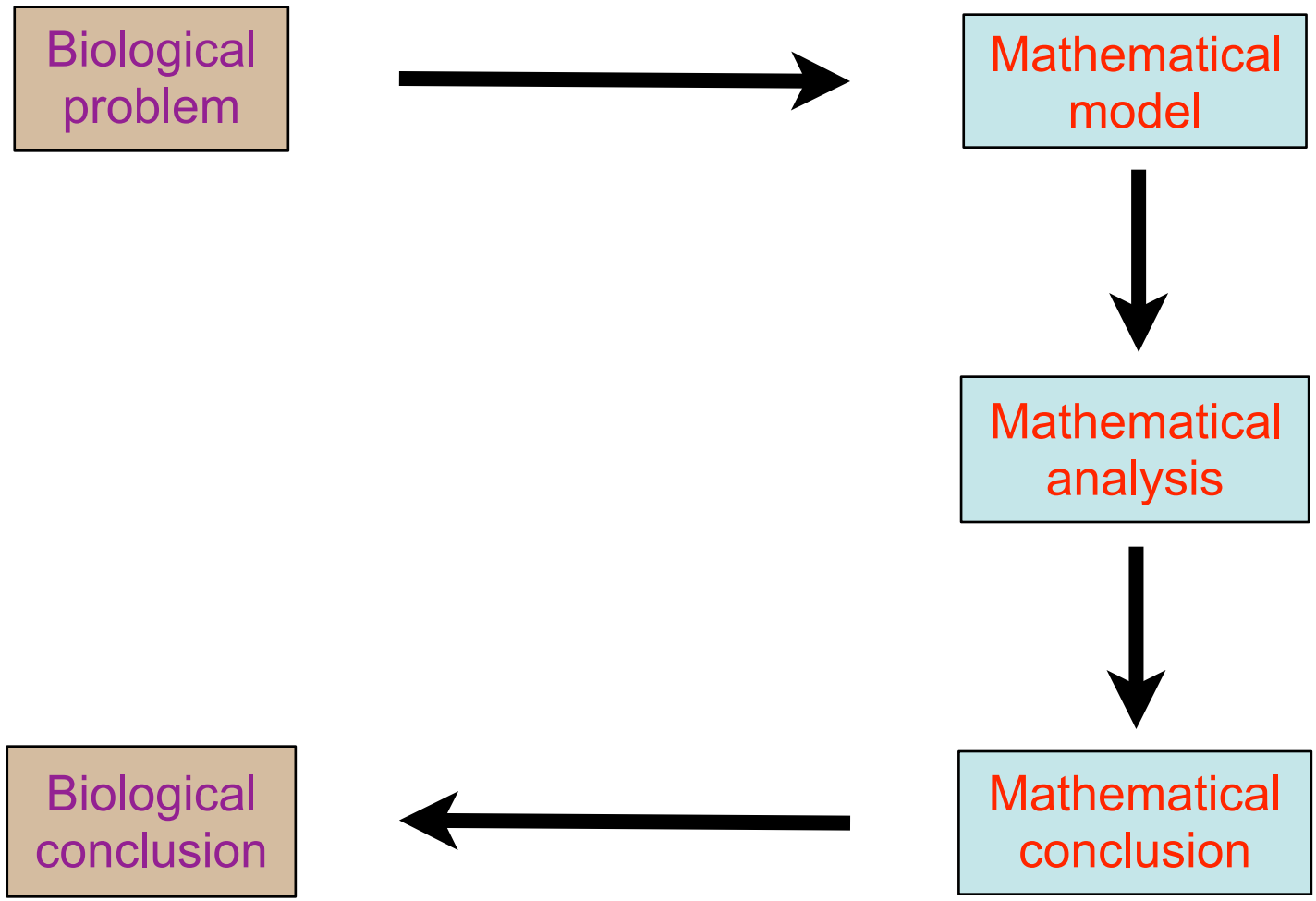

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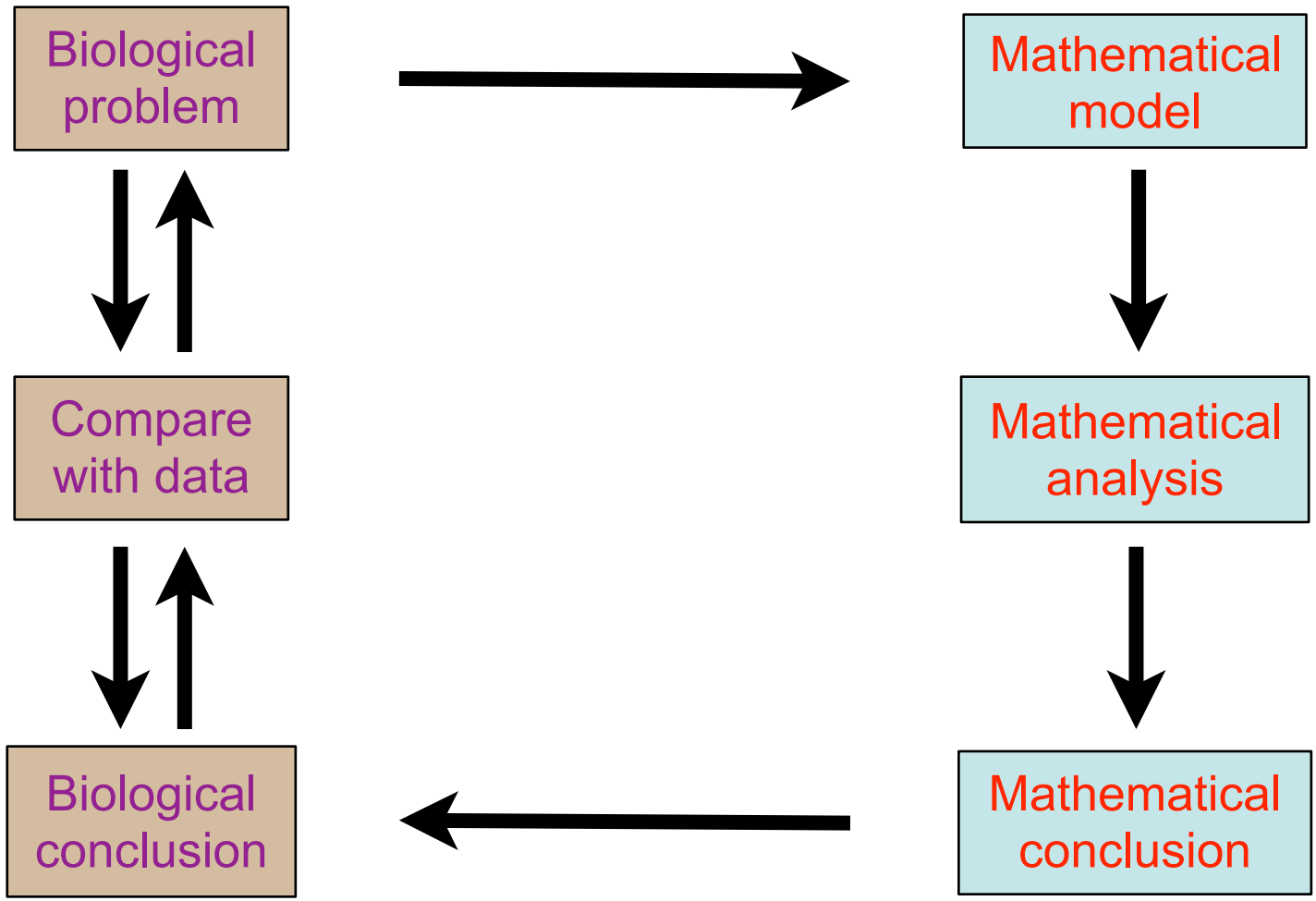

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- This could be achieved by enhanced HPV awareness programs in colleges/universities.

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