Can mathematics change the world?

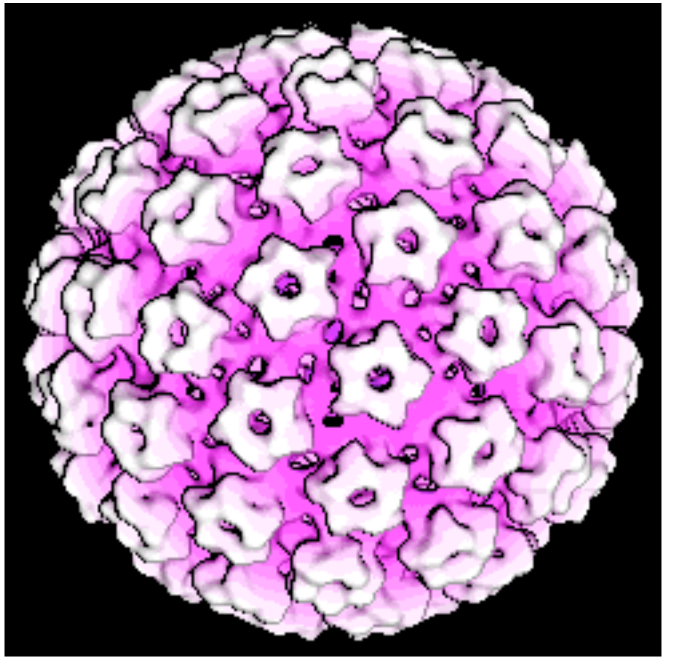
Insights into policy changes, using HPV modelling as an example

Robert Smith?

Departments of Mathematics and Faculty of Medicine
The University of Ottawa

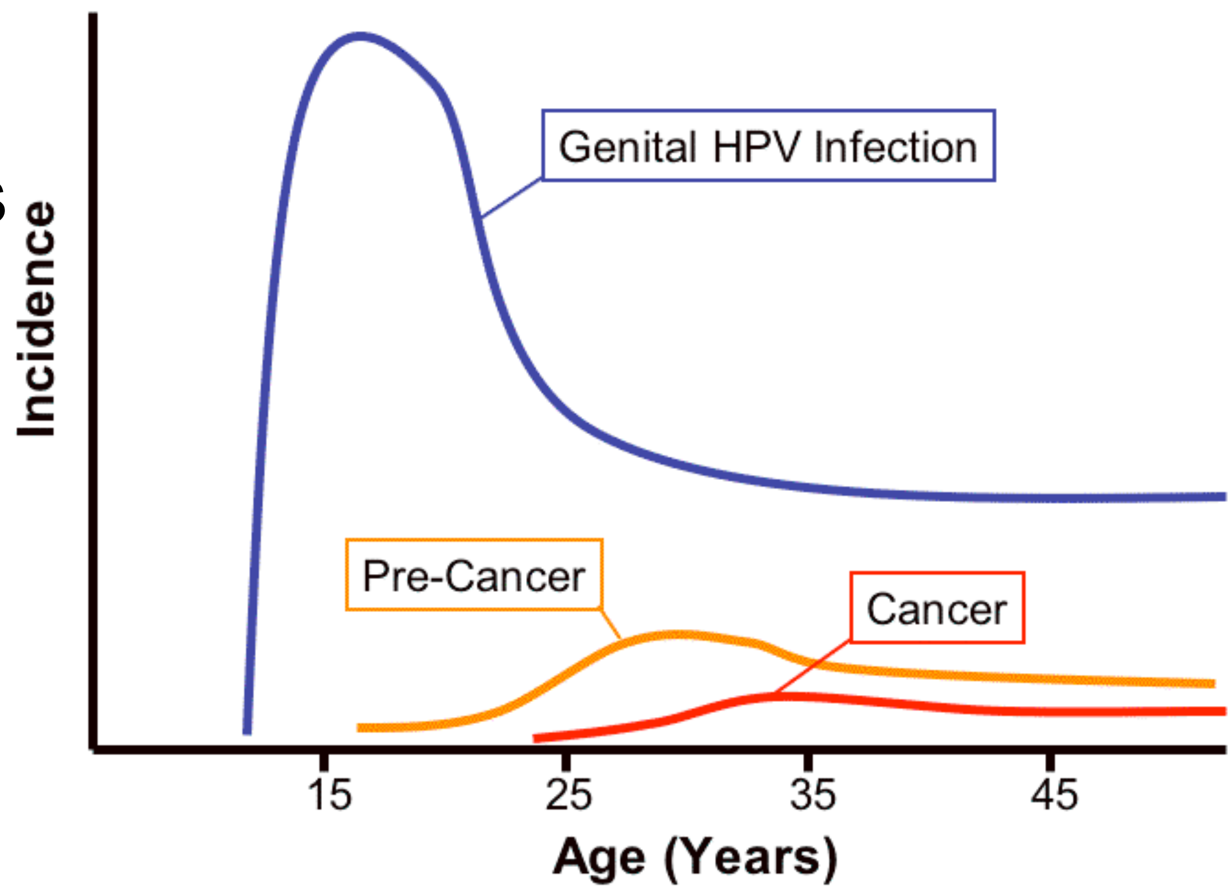
Outline

- Epidemiology of HPV
- Details of the vaccine
- Research questions
- The mathematical model
- Derive thresholds
- Number of doses vs age
- Applications to policy.



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.

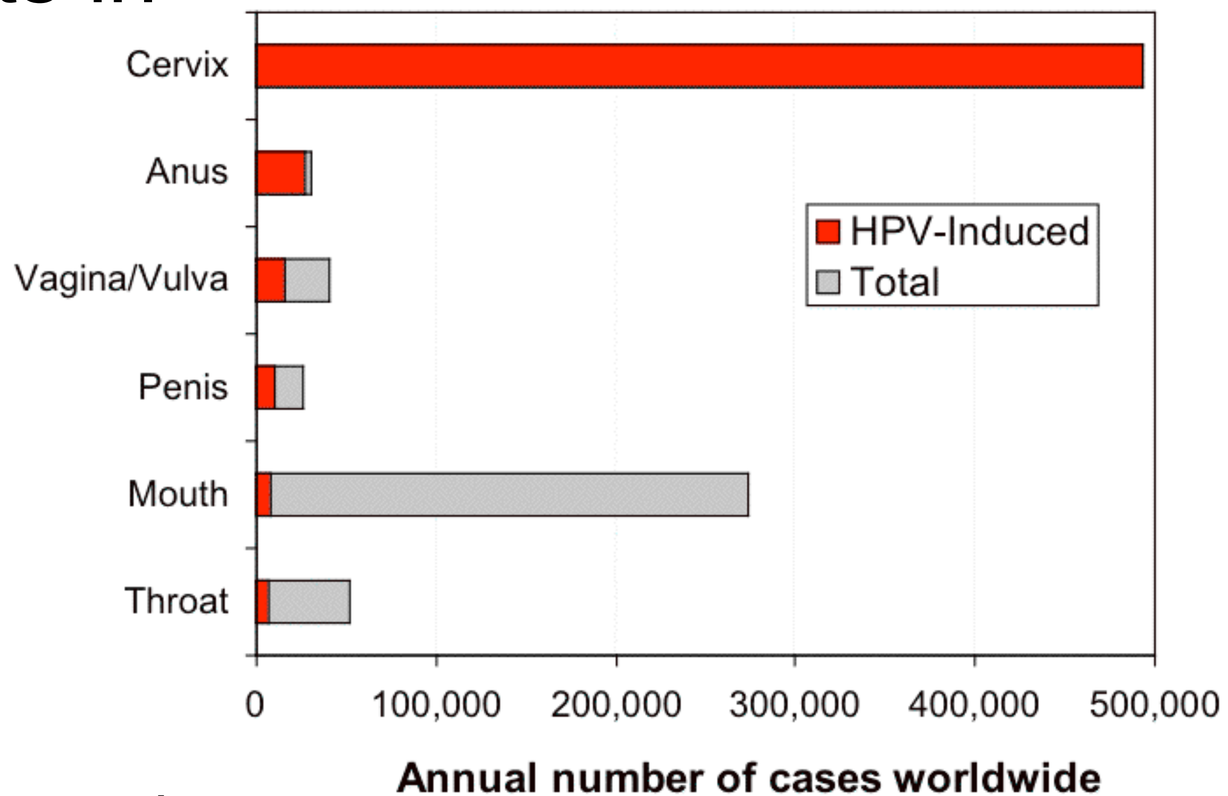


HPV infections

HPV infection results in

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

...requiring frequent surgery.



Prevalence in women

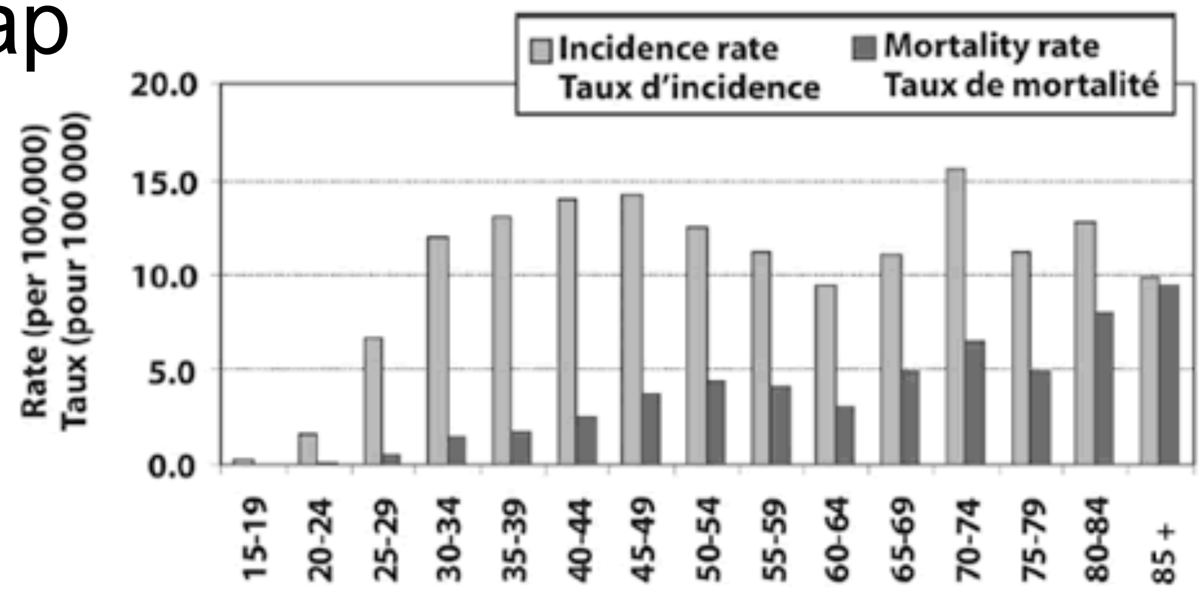
- Including harmless strains, estimates are:
- 20 year old women: 20-40%
- College women: >40%
- Lifetime risk: 75%

  (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

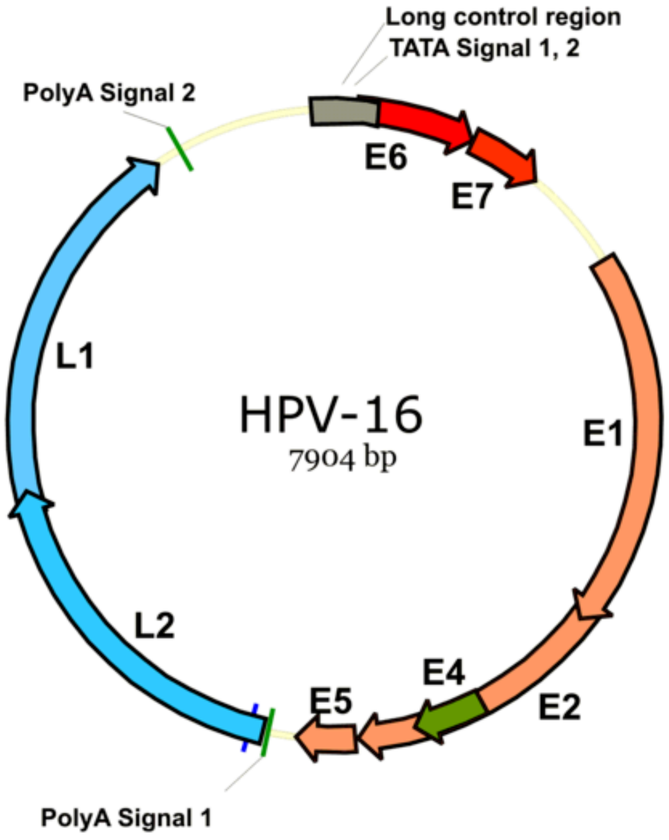
  (many fewer than would be caused by HPV, due to effective pap smear screening and precancer treatments).



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.

The vaccines

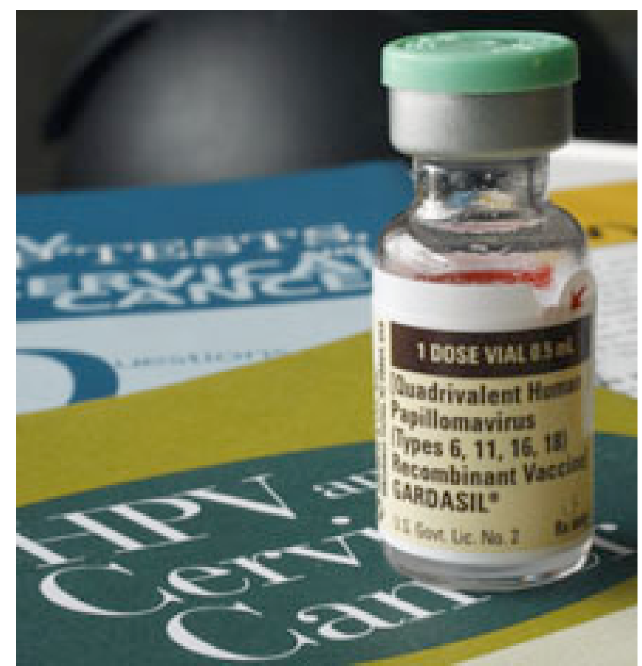
- Gardasil (Merck) protects against strains 6, 11, 16 and 18

  (the four most common strains)
- Cervarix (GSK) protects against strains 16 and 18

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

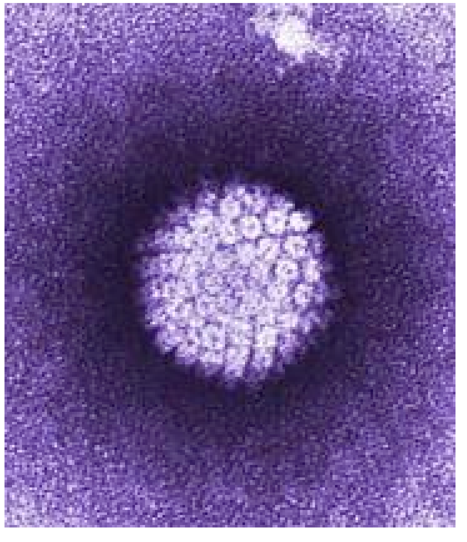
Gardasil

- 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.

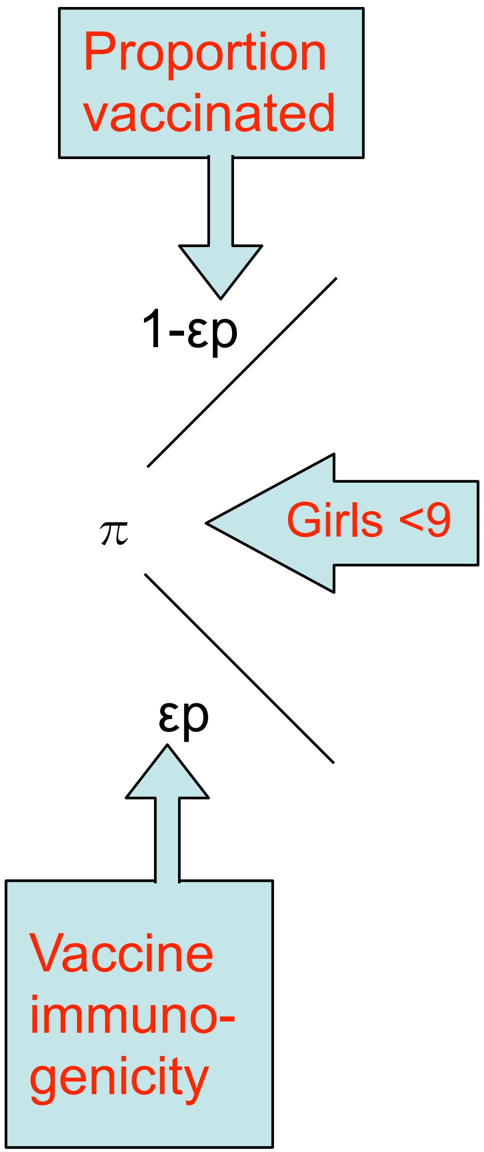
Research questions

- 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.

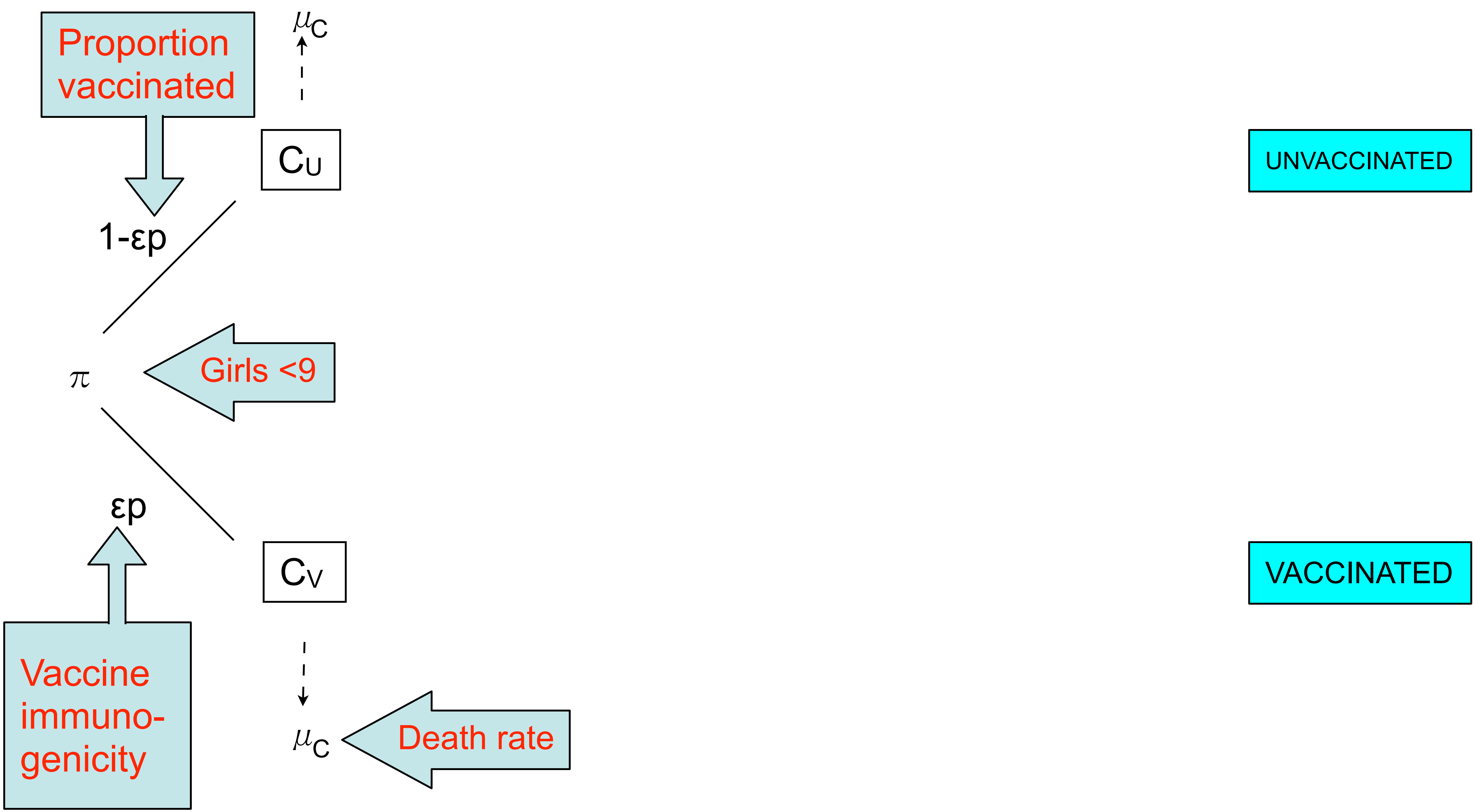
Baseline model

- 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

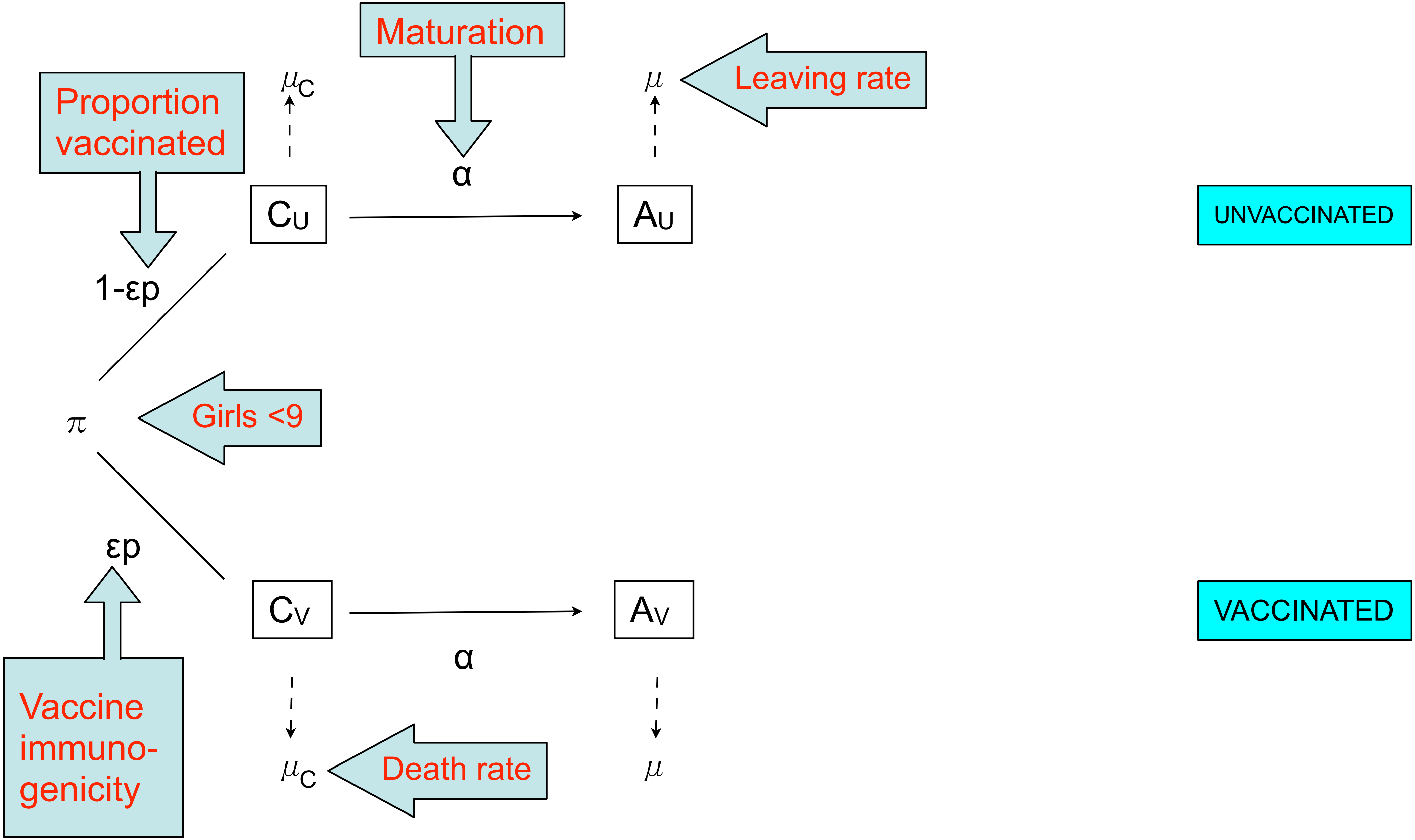

Proportion vaccinated
1-εp
π
Girls <9
εp
Vaccine immuno-genicity

The model



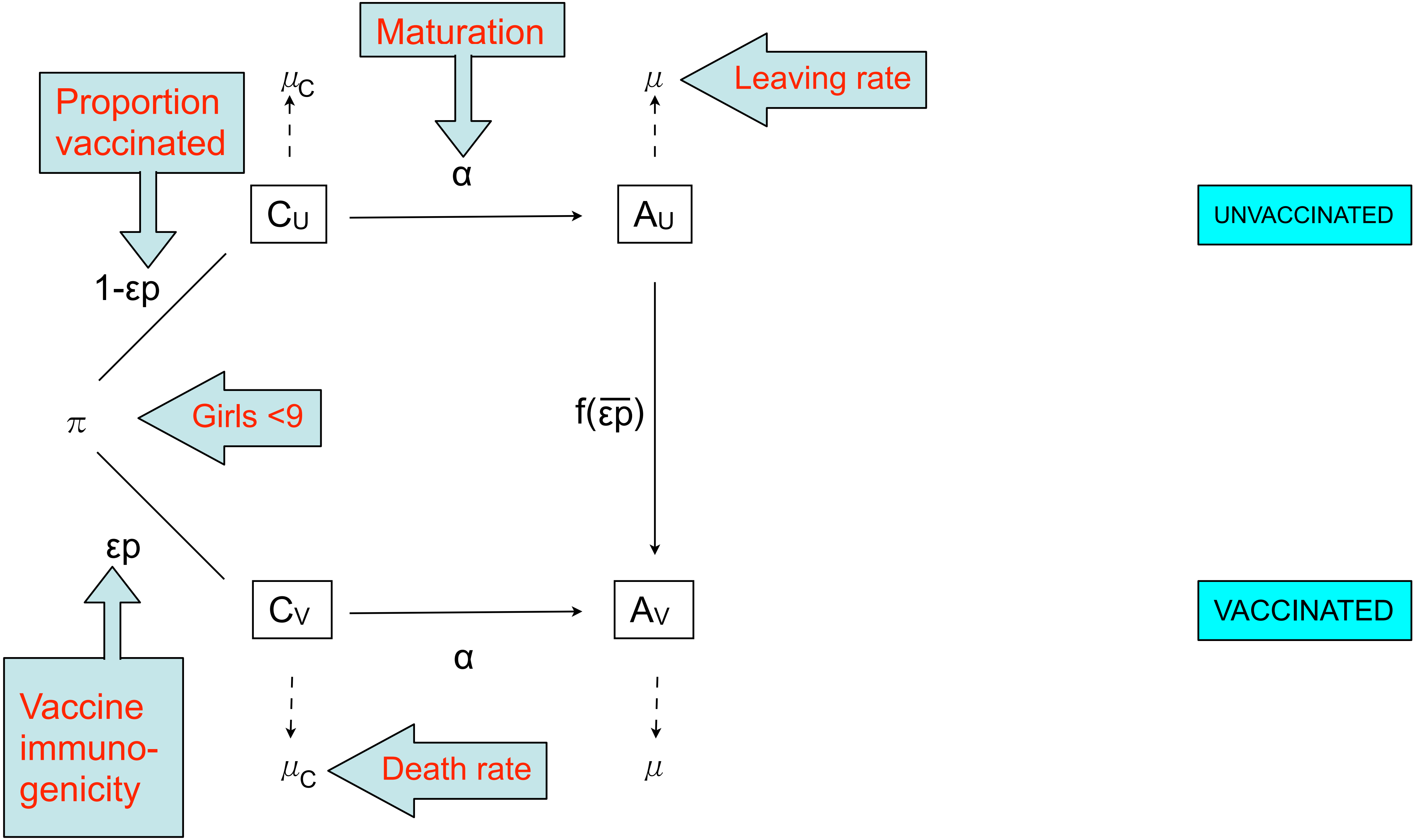
Proportion vaccinated
μ_C
C_U
UNVACCINATED
1-εp
π
Girls <9
εp
C_V
VACCINATED
Vaccine immuno-genicity
μ_C
Death rate

The model



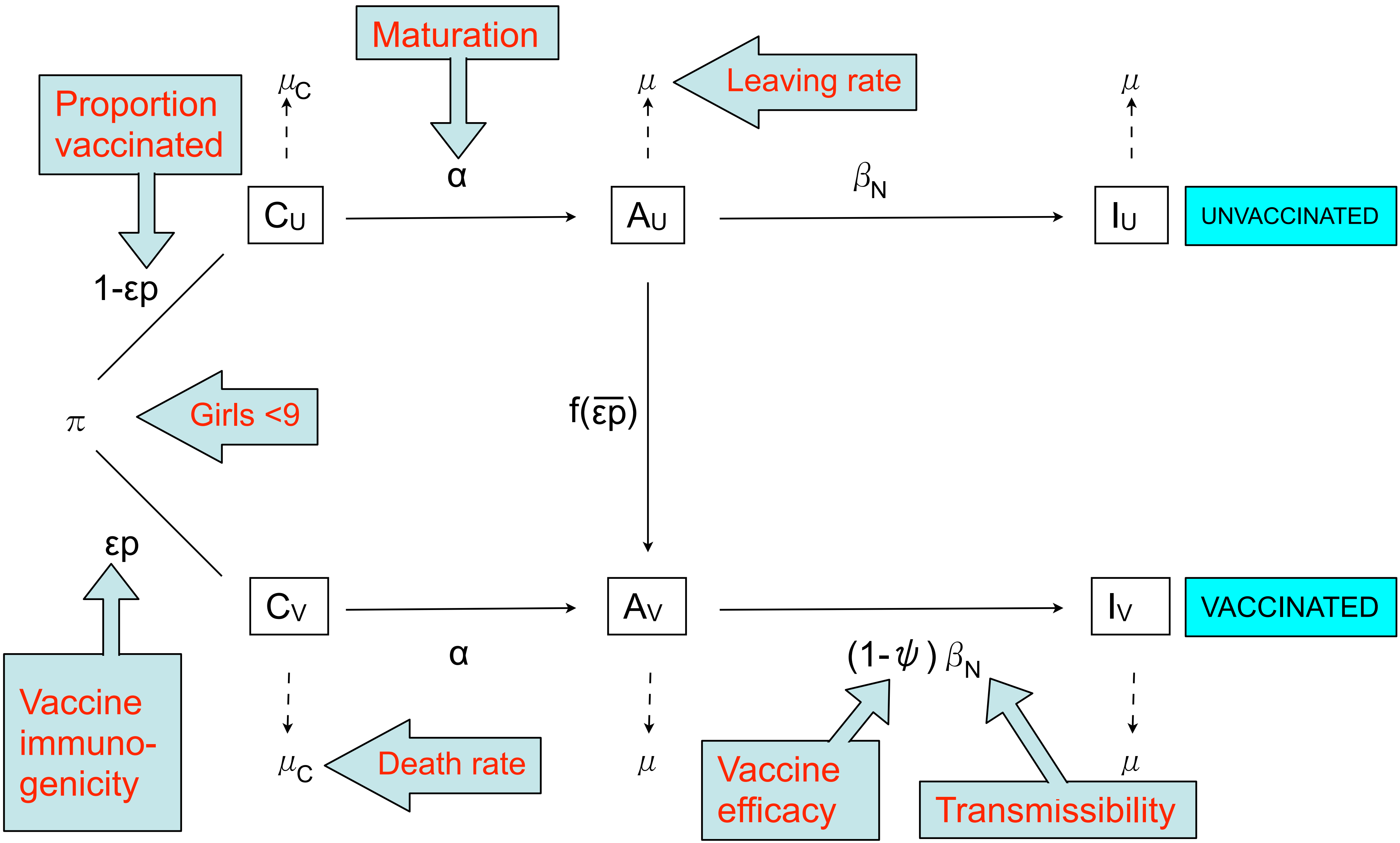
Maturation
Proportion vaccinated
Leaving rate
μ_C
μ
α
C_U
A_U
UNVACCINATED
1-εp
π
Girls <9
εp
C_V
A_V
VACCINATED
α
Vaccine immuno-genicity
μ_C
Death rate
μ

The model

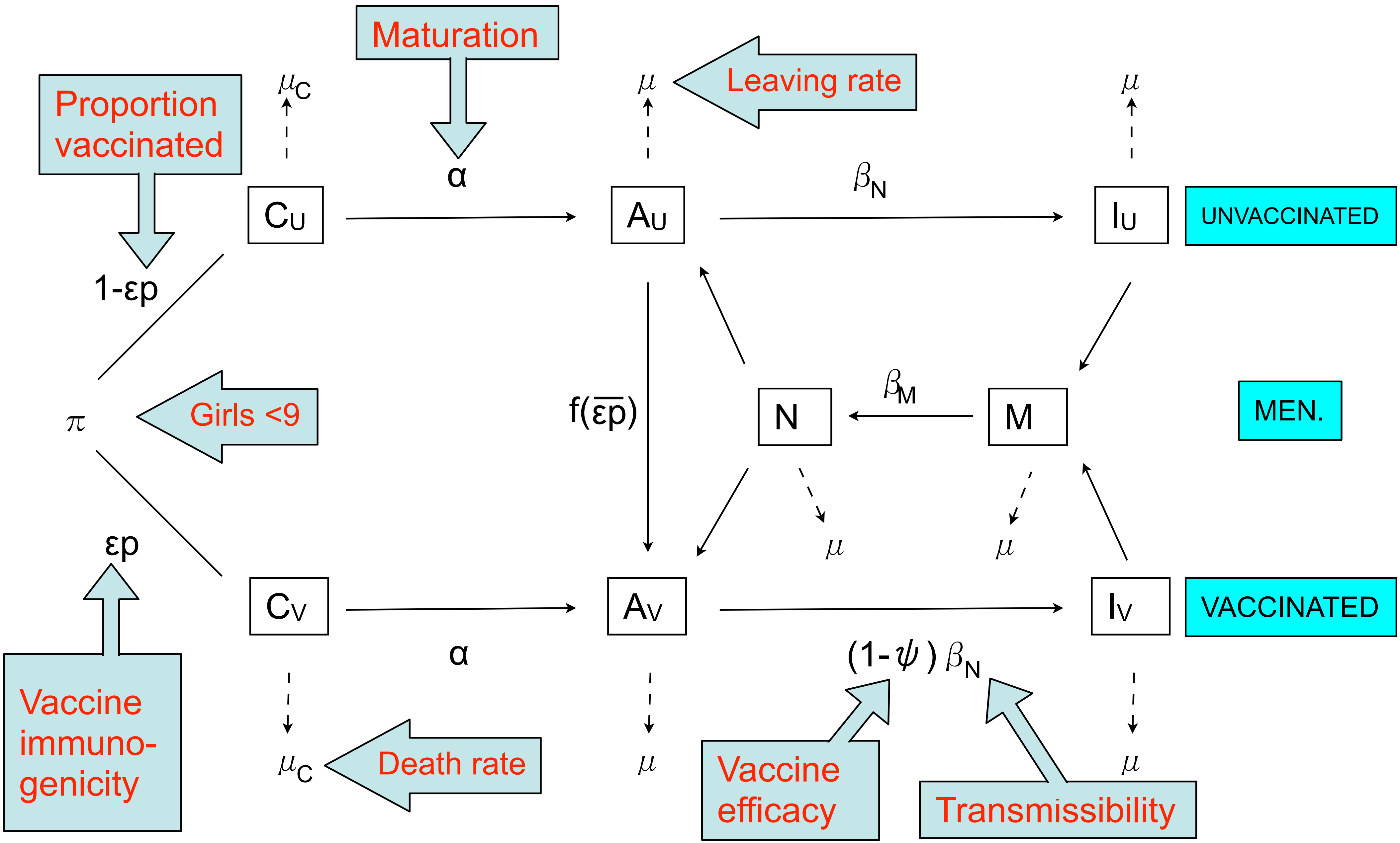


Maturation
Proportion vaccinated
Leaving rate
μ_C
μ
α
C_U
A_U
UNVACCINATED
1-εp
π
Girls <9
f($\overline{εp}$)
εp
C_V
A_V
VACCINATED
α
Vaccine immuno-genicity
μ_C
Death rate
μ

The model


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

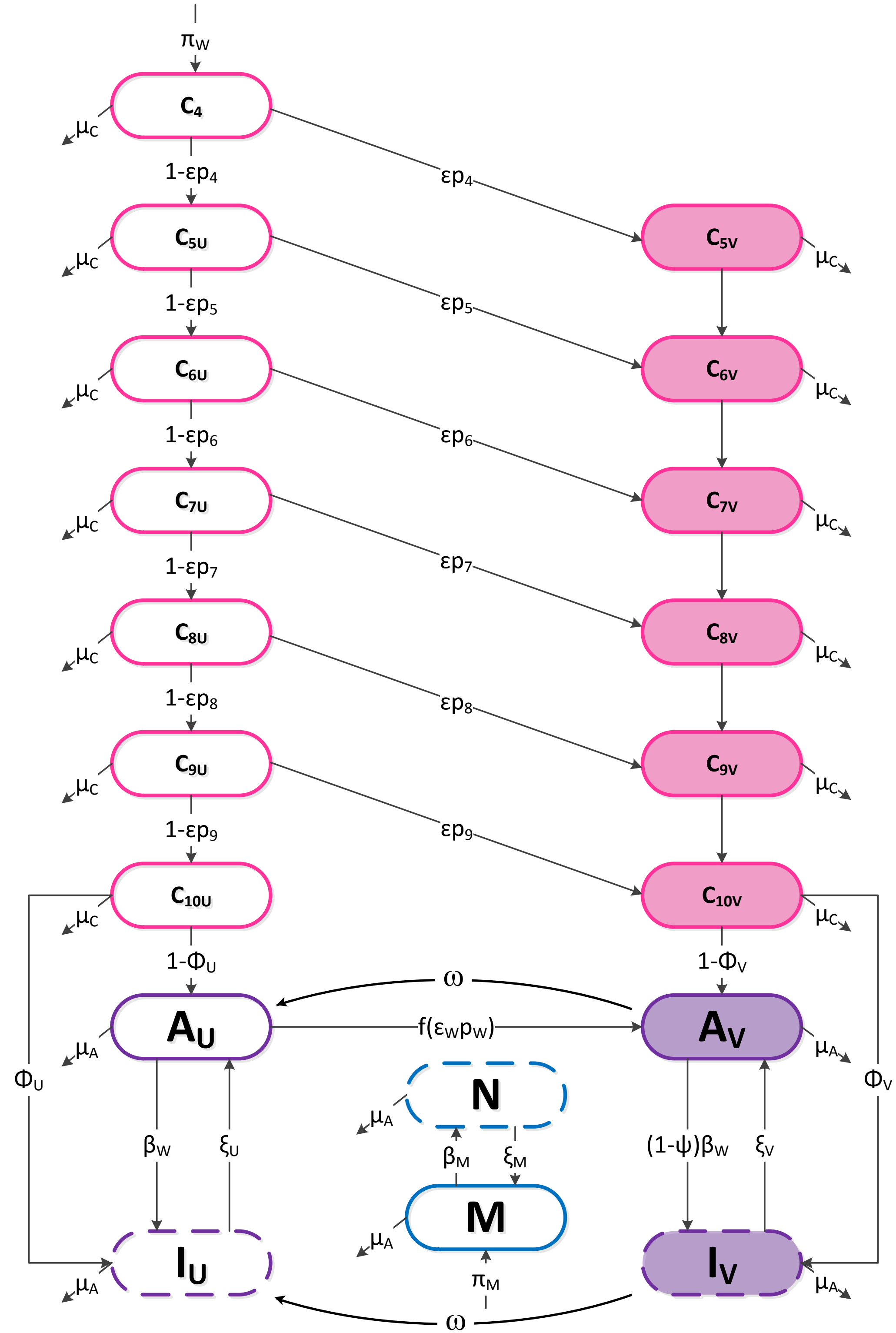
The model



Maturation
Proportion vaccinated
Leaving rate
μ_C
μ
μ
α
β_N
C_U
A_U
I_U
UNVACCINATED
1-εp
π
Girls <9
f($\overline{εp}$)
β_M
N
M
MEN.
μ
μ
εp
C_V
A_V
I_V
VACCINATED
α
(1- ψ) β_N
Vaccine immuno-genicity
μ_C
Death rate
μ
Vaccine efficacy
Transmissibility
μ

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.



π_W
C_4
μ_C
$1-\varepsilon p_4$
εp_4
C_{5U}
C_{5V}
$1-\varepsilon p_5$
εp_5
C_{6U}
C_{6V}
$1-\varepsilon p_6$
εp_6
C_{7U}
C_{7V}
$1-\varepsilon p_7$
εp_7
C_{8U}
C_{8V}
$1-\varepsilon p_8$
εp_8
C_{9U}
C_{9V}
$1-\varepsilon p_9$
εp_9
C_{10U}
C_{10V}
$1-\Phi_U$
$1-\Phi_V$
ω
A_U
$f(\varepsilon_W p_W)$
A_V
μ_A
Φ_U
Φ_V
N
β_W
ξ_U
β_M
ξ_M
$(1-\psi)\beta_W$
ξ_V
M
I_U
π_M
I_V
ω

Adult vaccination rate

- The rate of vaccination of adults is

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

  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
- We also include waning of the vaccine.

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

The model

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

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

For girls in grade i, where $5 \le i \le 10$, 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 μ_j=death rates π_W=female birth rate π_M=male birth rate ϵ_j=efficacy p_j=coverage Φ_j=childhood infection ω=waning β_j=transmissibilities Ψ=protection ξ_j=duration of infection ♀=total women ♂=total men

♀ and ♂

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

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

$$♂ = M + N.$$

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 μ_j=death rates
π_M=male birth rate ϵ_j=efficacy
p_j=coverage Φ_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 μ_j=death rates
β_j=transmissibilities ♀=total women
Ψ=protection ω=waning
ξ_j=duration of infection

Critical childhood vaccine immunogenicity

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

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

μ_j=death rates ϵ_j=efficacy p_j=coverage Φ_j=childhood infection ω=waning β_j=transmissibilities ♀=total women ξ_j=duration of infection π_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

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

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

μ_j=death rates π_W=female birth rate
β_j=transmissibilities ♀=total women
Ψ=protection ξ_j=duration of infection
c/γ=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

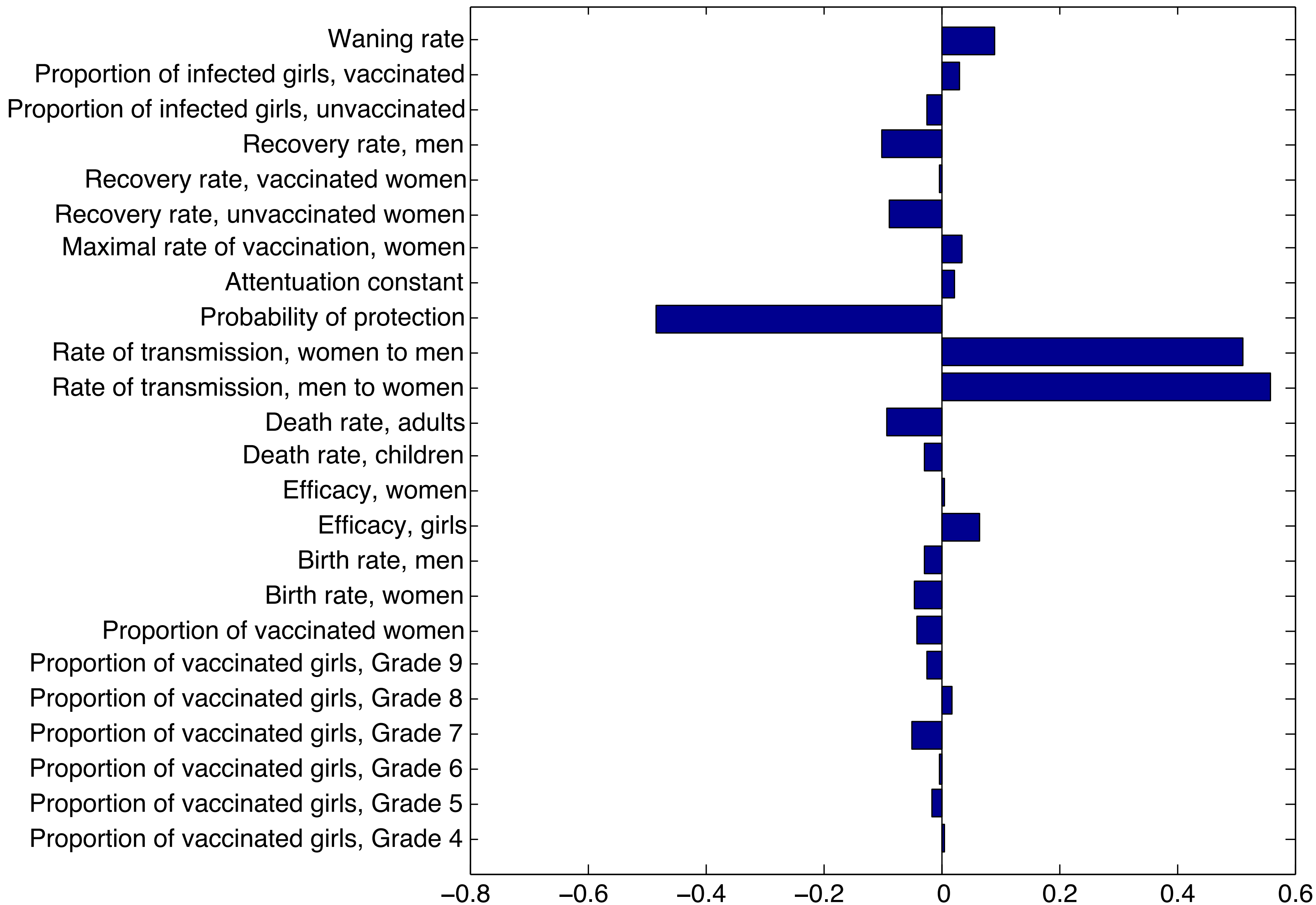
✗	✓	✗
✗	✗	✓
✓	✗	✗

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.

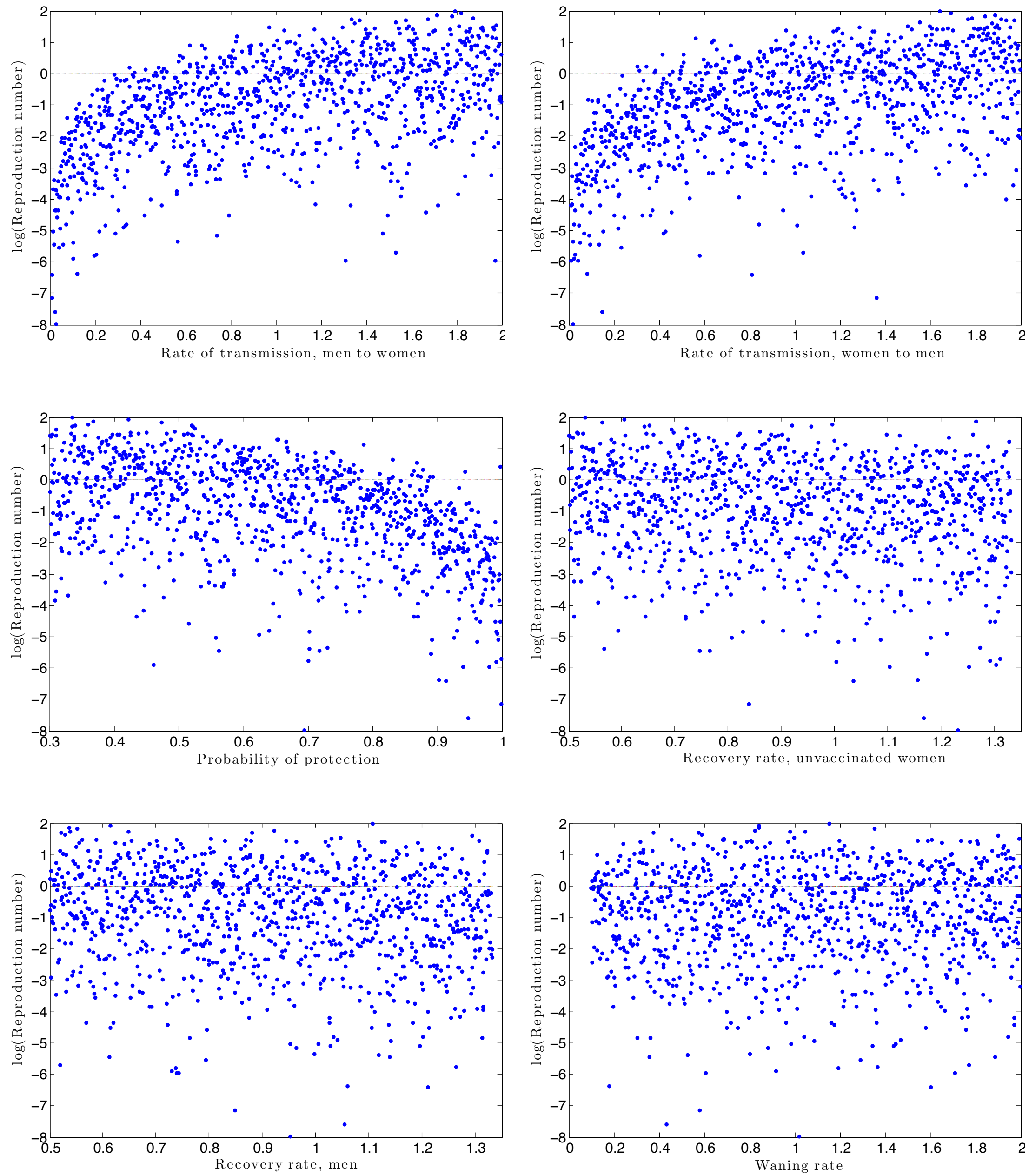
R_0=basic reproductive ratio

PRCCs

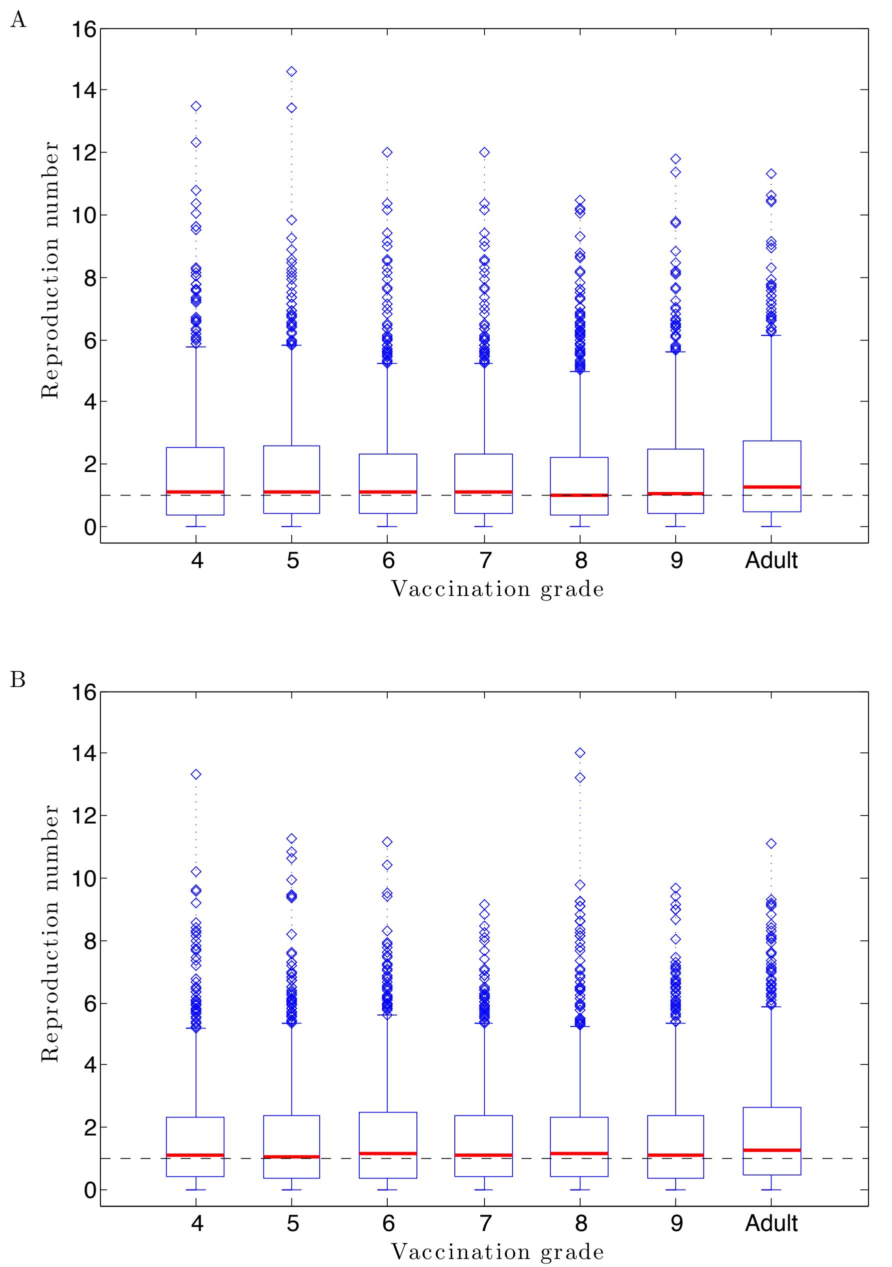


Waning rate
Proportion of infected girls, vaccinated
Proportion of infected girls, unvaccinated
Recovery rate, men
Recovery rate, vaccinated women
Recovery rate, unvaccinated women
Maximal rate of vaccination, women
Attentuation constant
Probability of protection
Rate of transmission, women to men
Rate 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

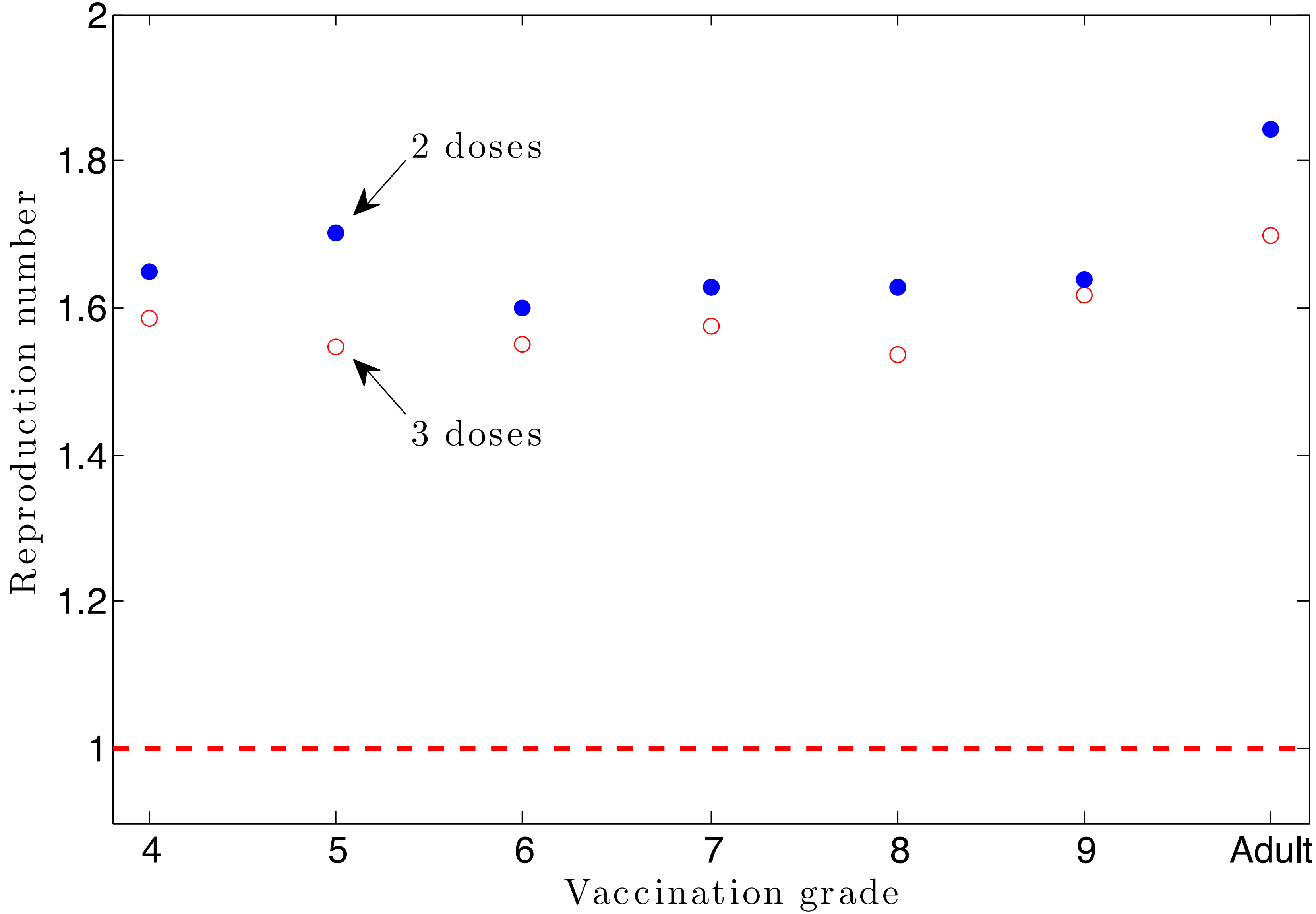
Monte Carlo simulations



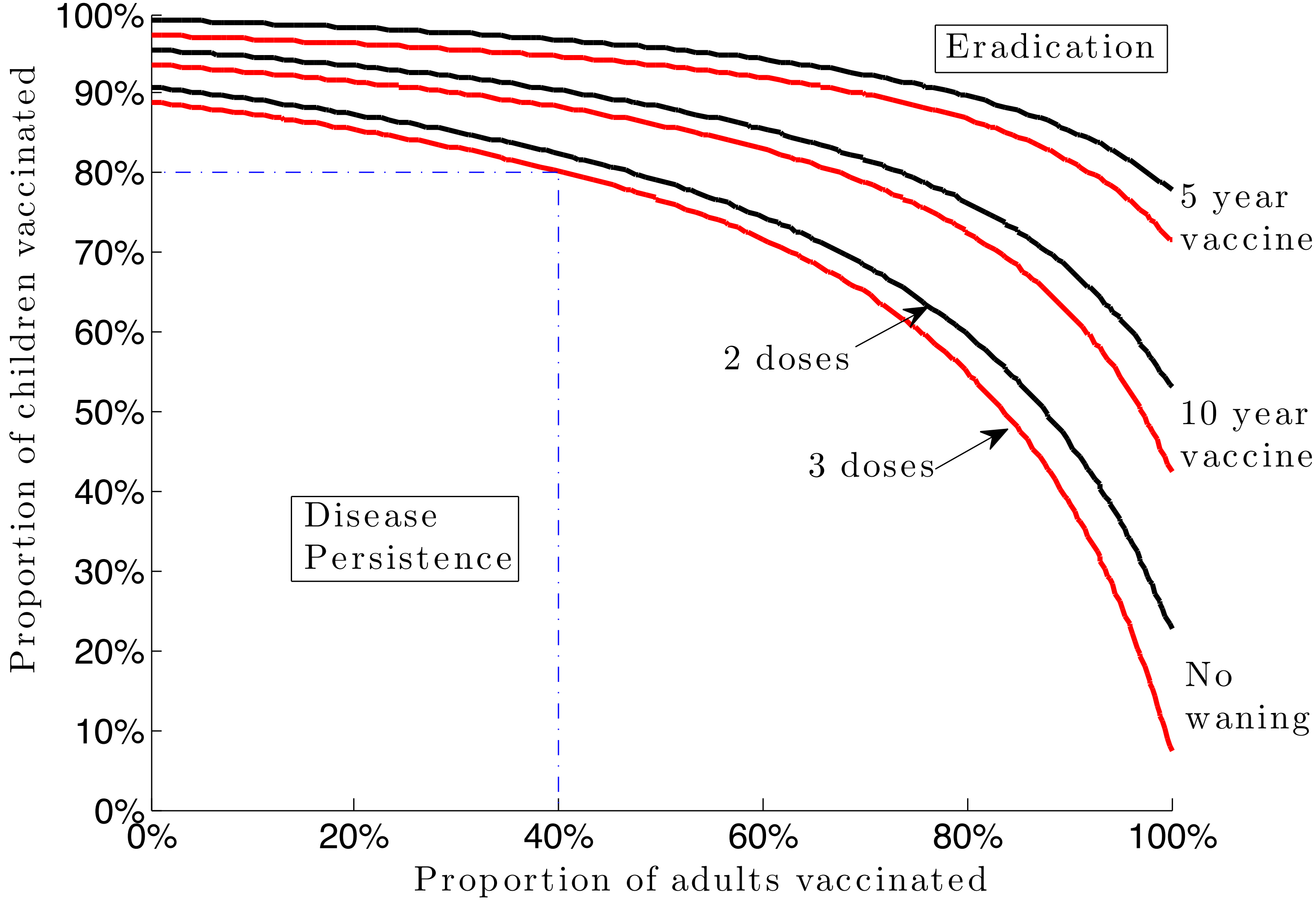
Two doses vs three doses



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

- 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 g+1 Recommend 2 Text: (0)

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

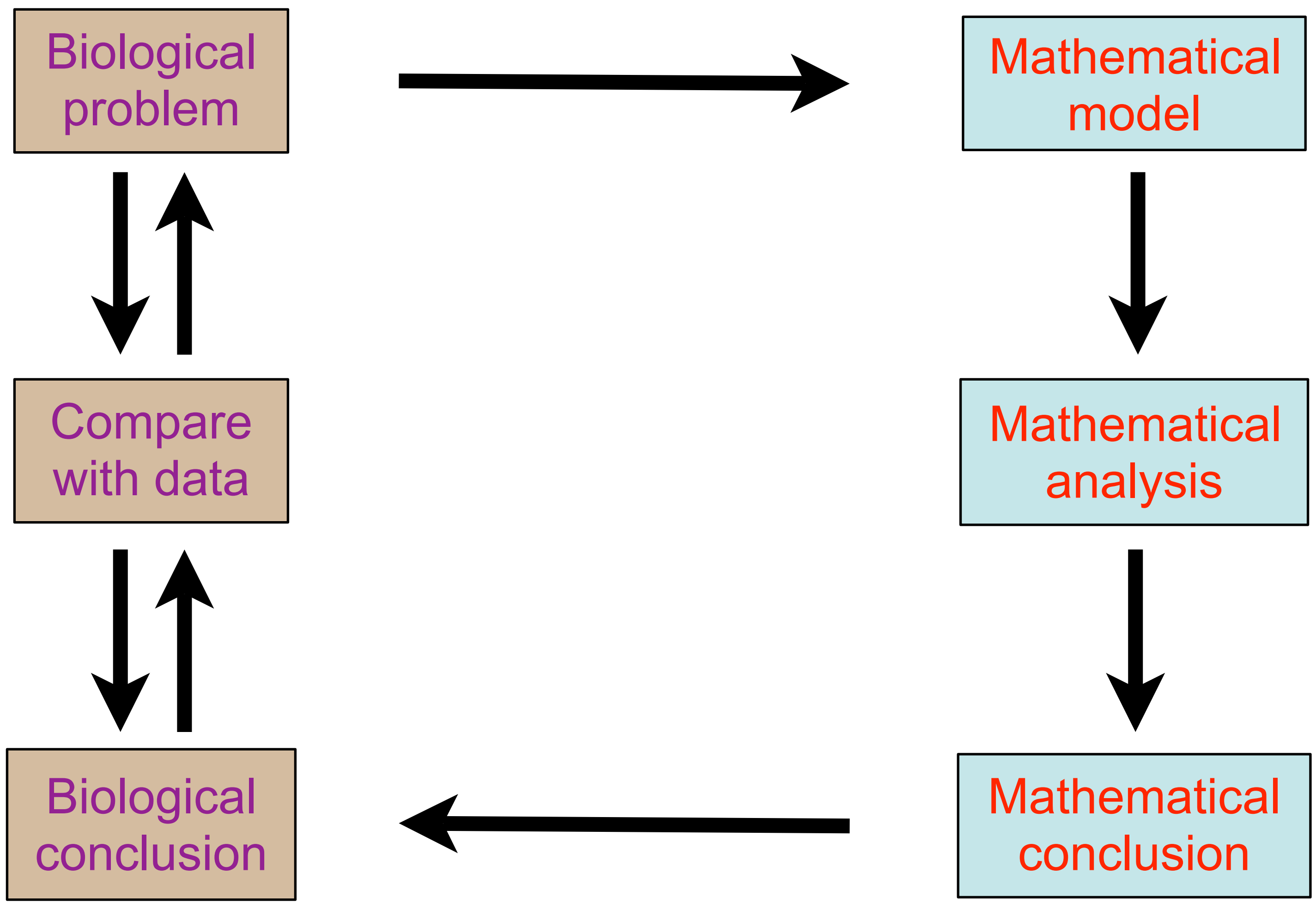
Quebec girls will become the first in the country to benefit from new research that suggests the HPV vaccine is so effective that two doses -- rather than the recommended three -- may be all that's needed.

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.

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
- This illustrates the cycle of modelling.

Using math to solve real problems



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.

Key references

- C. Rogers and R.J. Smith? (2015) Examining provincial HPV vaccination schemes in Canada: should we standardise the grade of vaccination or the number of doses? (International Scholarly Research Notices)
- M. Al-arydah and R.J. Smith? (2011) An age-structured model of human papillomavirus vaccination (Mathematics and Computers in 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