Overview

- New methods of preventing or reducing HIV transmission hold great hope for containing the spread of the disease
- However, such methods are initially likely to have poor efficacy
- They may result in a net increase in infections.

Vaccines

- For many years, the holy grail of HIV research has been the vaccine
- The World Health Organisation recently declared that a vaccine with efficacy as low as 35% would be acceptable.

Behaviour changes?

- The advent of drugs has led to an increase in unprotected sex
- If people hear a vaccine is available they may change their risky behaviour
- This may happen for those who were vaccinated, or those who weren't.

Candidate vaccines

- Several candidate vaccines are currently in phase I and II clinical trial evaluation
- The majority appear likely to permit infection but reduce viral load
- We call these “disease-modifying” vaccines.

Disease-modifying vaccines

Disease-modifying vaccines may:

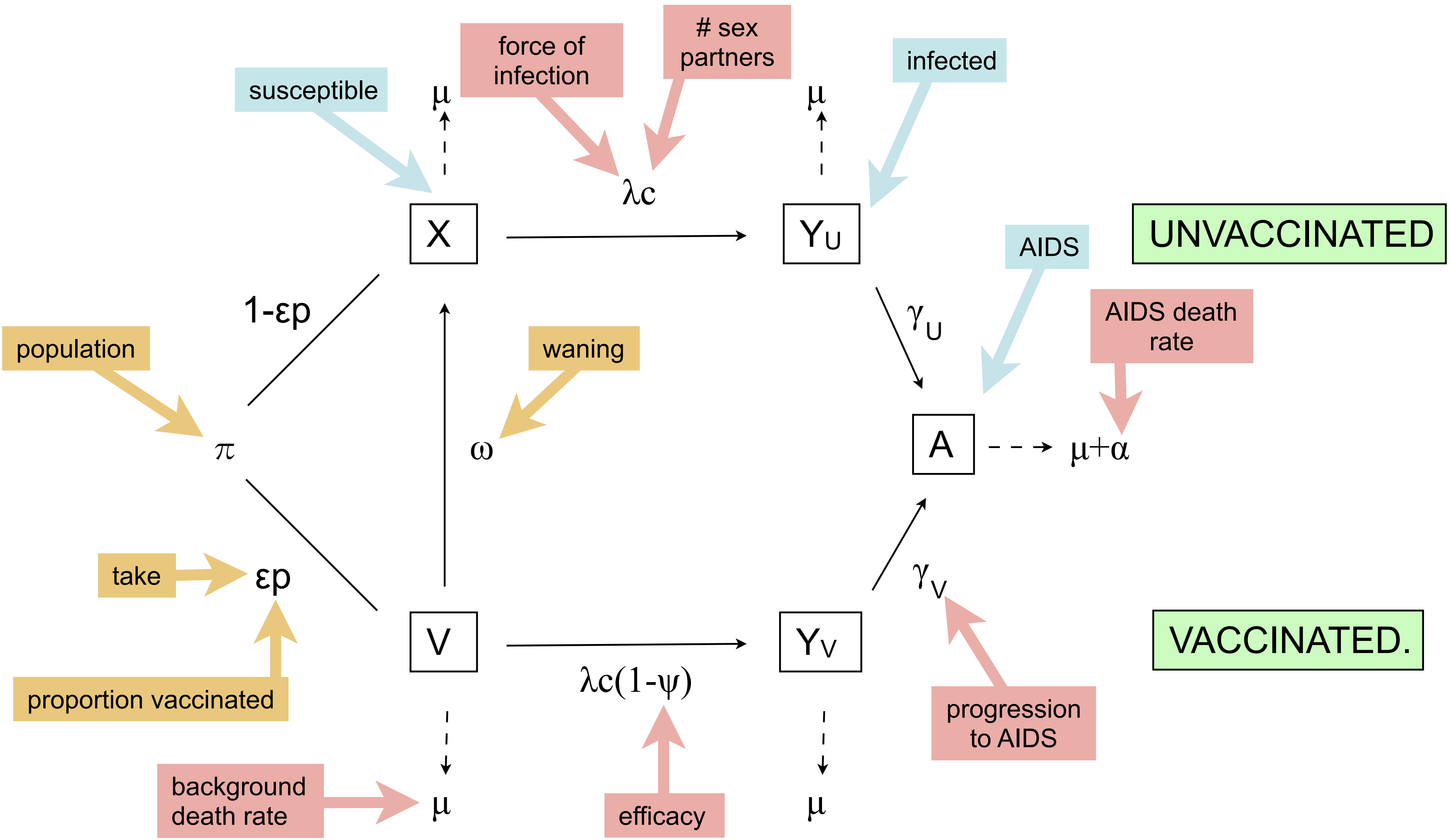
- allow you to become infected
- reduce your viral load
- lower your transmissability
- slow your progression to AIDS.

Efficacy

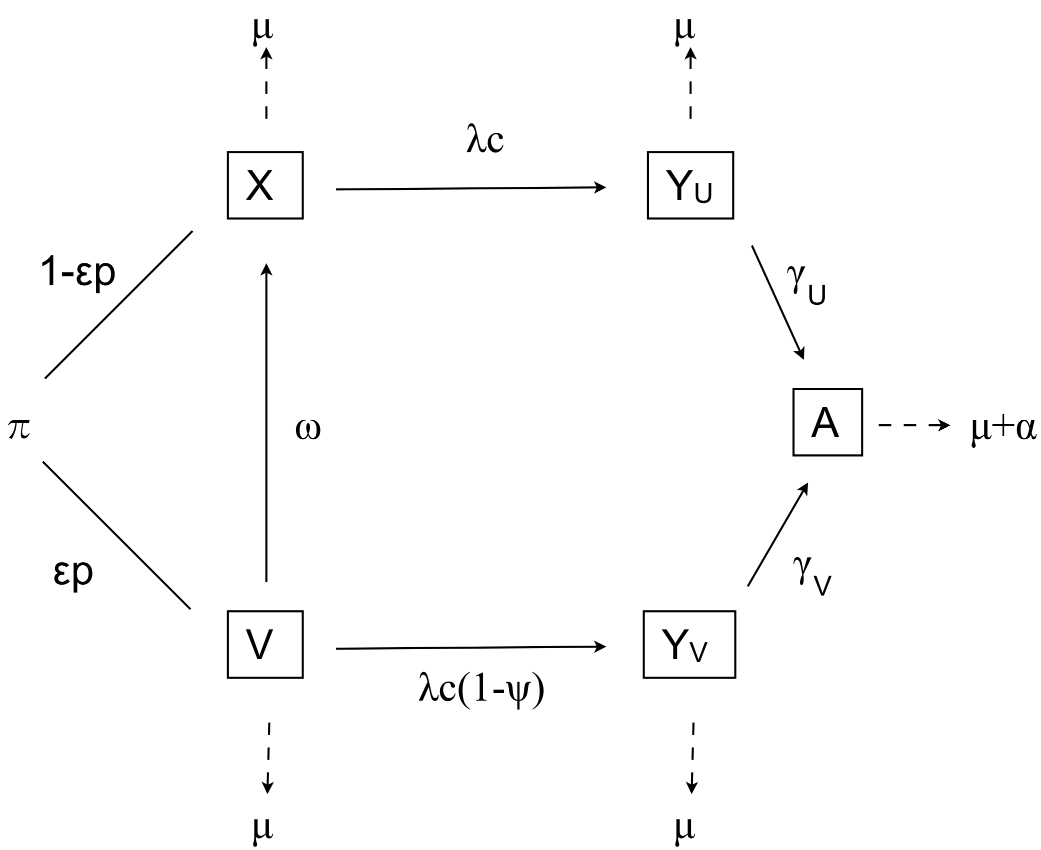
A disease-modifying vaccine with 35% efficacy would:

- stop infection 35% of the time
- permit infection the remaining 65% of the time
- lower your viral load once you became infected.

The model


susceptible
μ
force of infection
sex partners
μ
infected
λc
X
Yᵤ
UNVACCINATED
AIDS
1-εp
γᵤ
AIDS death rate
population
waning
π
ω
A
μ+α
take
εp
γᵥ
V
Yᵥ
VACCINATED.
λc(1-ψ)
proportion vaccinated
progression to AIDS
background death rate
μ
efficacy
μ

The ODEs



$$\frac{dX}{dt} = (1-\epsilon p)\pi - \mu X - \lambda c X + \omega V$$

$$\frac{dV}{dt} = \epsilon p \pi - \mu V - \omega V - (1-\psi) c \lambda V$$

$$\frac{dY_U}{dt} = \lambda c X - (\mu + \gamma_U) Y_U$$

$$\frac{dY_V}{dt} = \lambda c (1-\psi) V - (\mu + \gamma_V) Y_V$$

$$\frac{dA}{dt} = \gamma_U Y_U + \gamma_V Y_V - (\mu + \alpha) A$$

$\lambda = \beta_U (Y_U/N) + \beta_V (Y_V/N)$ is the force of infection, where N is the total population.

Basic reproductive numbers

- The average number of secondary HIV infections caused by an infected unvaccinated individual is R_0
- The average number of secondary HIV infections caused by an infected vaccinated individual is R_V.

Fitness ratio

- The relationship between R_0 and R_V can be defined by the fitness ratio *f*, where $f = R_V / R_0$
- Sufficiently high values of *f* may lead to *perversity*

  (*i.e.* the epidemic gets worse because of the vaccine).

R_0=*reproductive number (unvaccinated)*
R_V=*reproductive number (vaccinated)*

Unvaccinated R_0

$R_0 = \beta_U c / (\mu + \gamma_U)$, where

- β_U = transmission probability for unvaccinated individuals
- c = number of sex partners
- μ = background death rate
- γ_U = rate of progression to AIDS for unvaccinated individuals

A similar formula holds for R_V.

(See HIV Vaccination Notes)

R_0=reproductive number (unvaccinated)

Population reproductive number

- The total number of secondary infections caused by a single individual is

$$R_p = S(1-\psi)R_V + (1-S)R_0$$

(See HIV Vaccination Notes)

- S = proportion "successfully" vaccinated
- ψ = efficacy of the vaccine.

R_0=reproductive number (unvaccinated)
R_V=reproductive number (vaccinated)

A condition for perversity

- In the absence of behavioural changes, perversity will occur if $R_p > R_0$; *i.e.*

$$S(1-\psi)R_V + (1-S)R_0 > R_0$$

$$S(1-\psi)\, f\, R_0 - SR_0 > 0$$

$$(1-\psi)f - 1 > 0.$$

perversity=epidemic gets worse
f=fitness ratio
ψ=*vaccine efficacy*
S=proportion succcessfully vaccinated
R_0=*reproductive number (unvaccinated)*
R_V=*reproductive number (vaccinated)*
R_p=*population reproductive number*

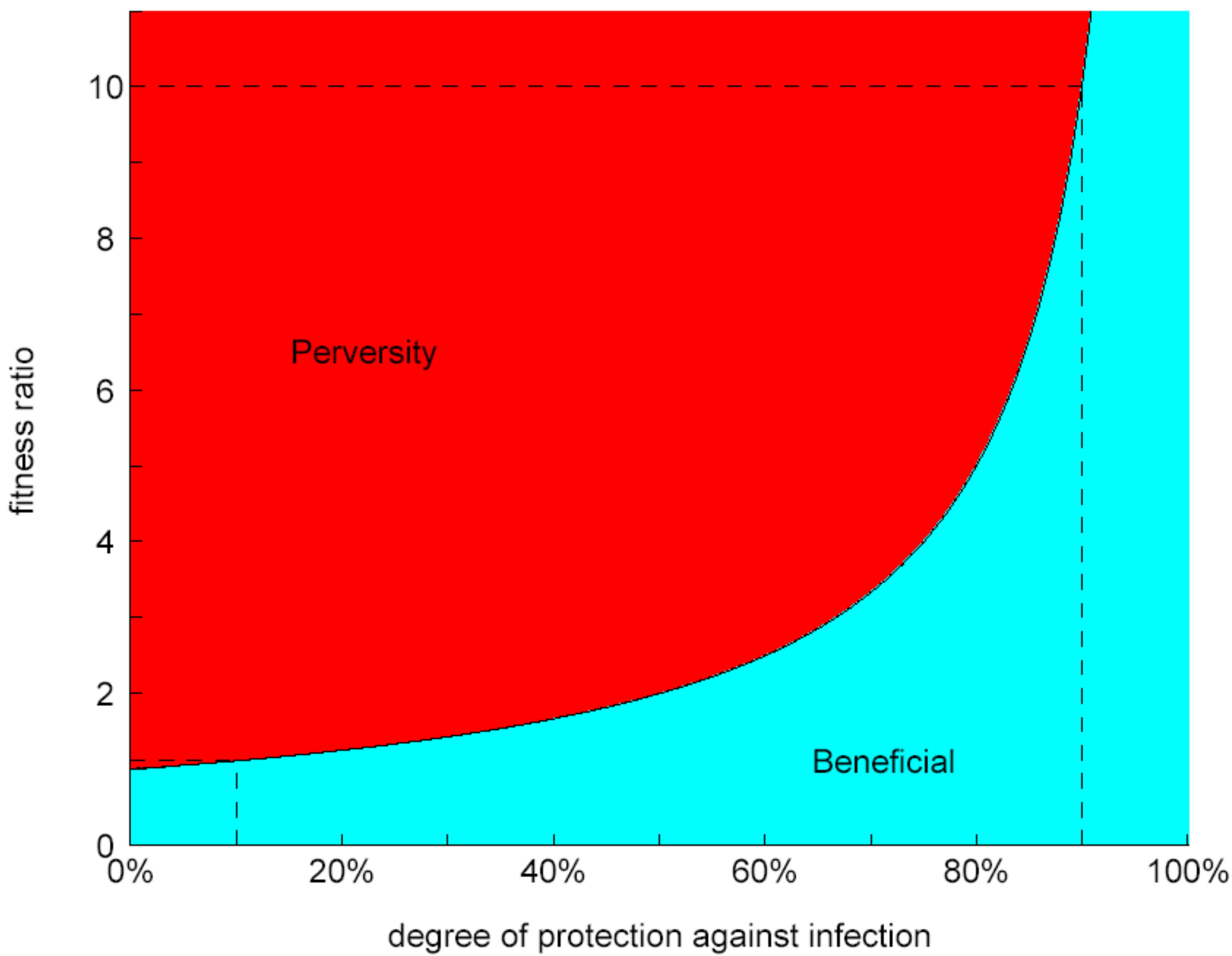
Efficacy is crucial

- Thus, perversity will occur if

$$f > 1/(1-\psi)$$

- This creates a threshold that depends on the efficacy.

perversity=epidemic gets worse
f=fitness ratio
ψ=vaccine efficacy


Perversity
Beneficial
fitness ratio
0
2
4
6
8
10
0%
20%
40%
60%
80%
100%
degree of protection against infection

Low efficacy vaccines

- For low efficacy vaccines, perversity is roughly equivalent to $f > 1$
- That is, if there are more infections due to the vaccine than currently
- This may occur simply due to longer-lived patients, even without behaviour changes.

perversity=epidemic gets worse
f=fitness ratio

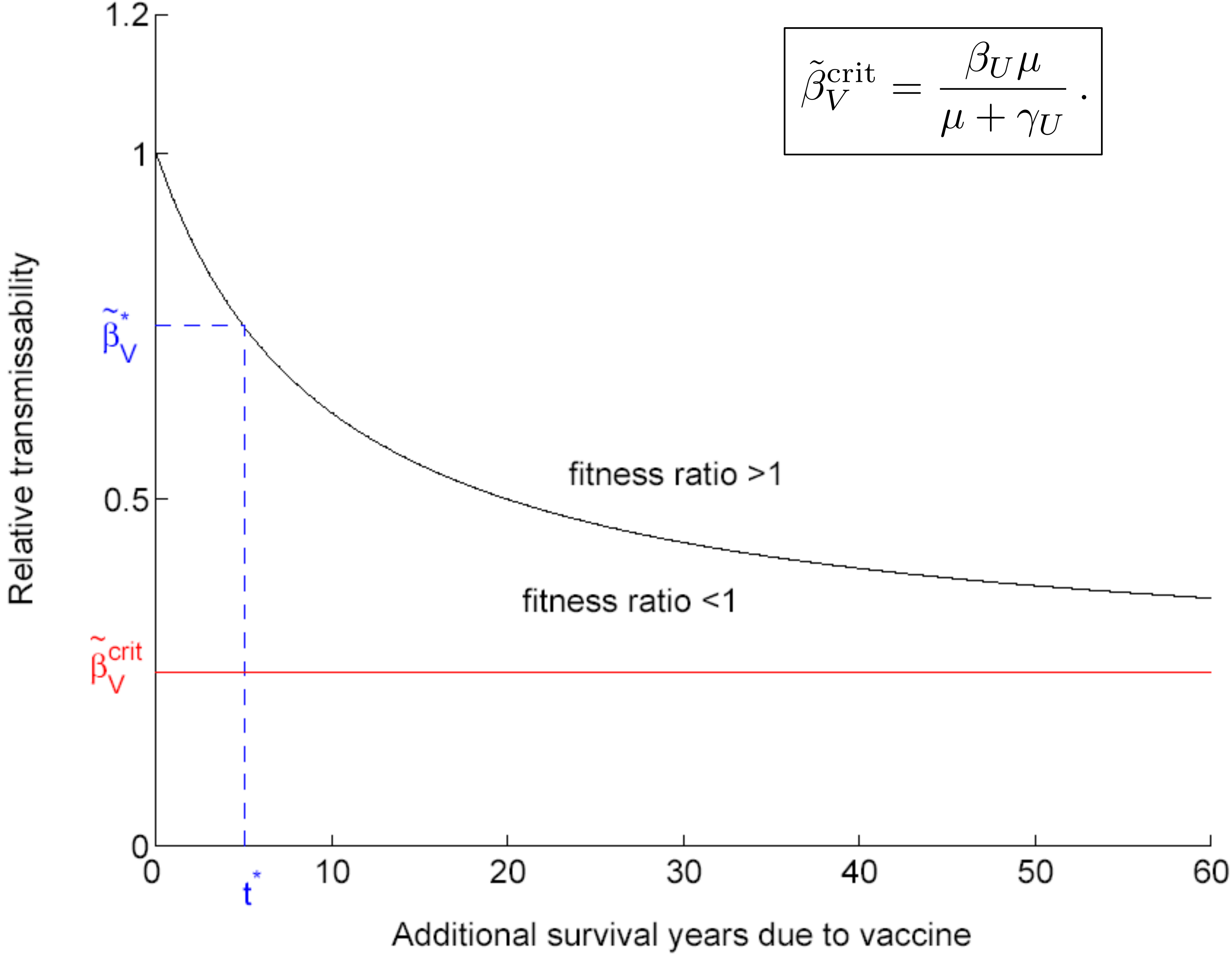
An explicit formula for f

- Recall that $R_0 = \beta_U c/(\mu+\gamma_U)$ and $R_V = \beta_V c/(\mu+\gamma_V)$
- Thus

$$f = R_V/R_0$$
$$= \beta_V(\mu+\gamma_U)/\beta_U(\mu+\gamma_V)$$

- This depends on the relative transmission probability (β_V/β_U) and the number of additional years of life ($1/\gamma_V - 1/\gamma_U$).

R_0=reproductive number (unvaccinated)
R_V=reproductive number (vaccinated)
f=fitness ratio μ=background death rate
β_j=transmission probability
γ_j=progression to AIDS

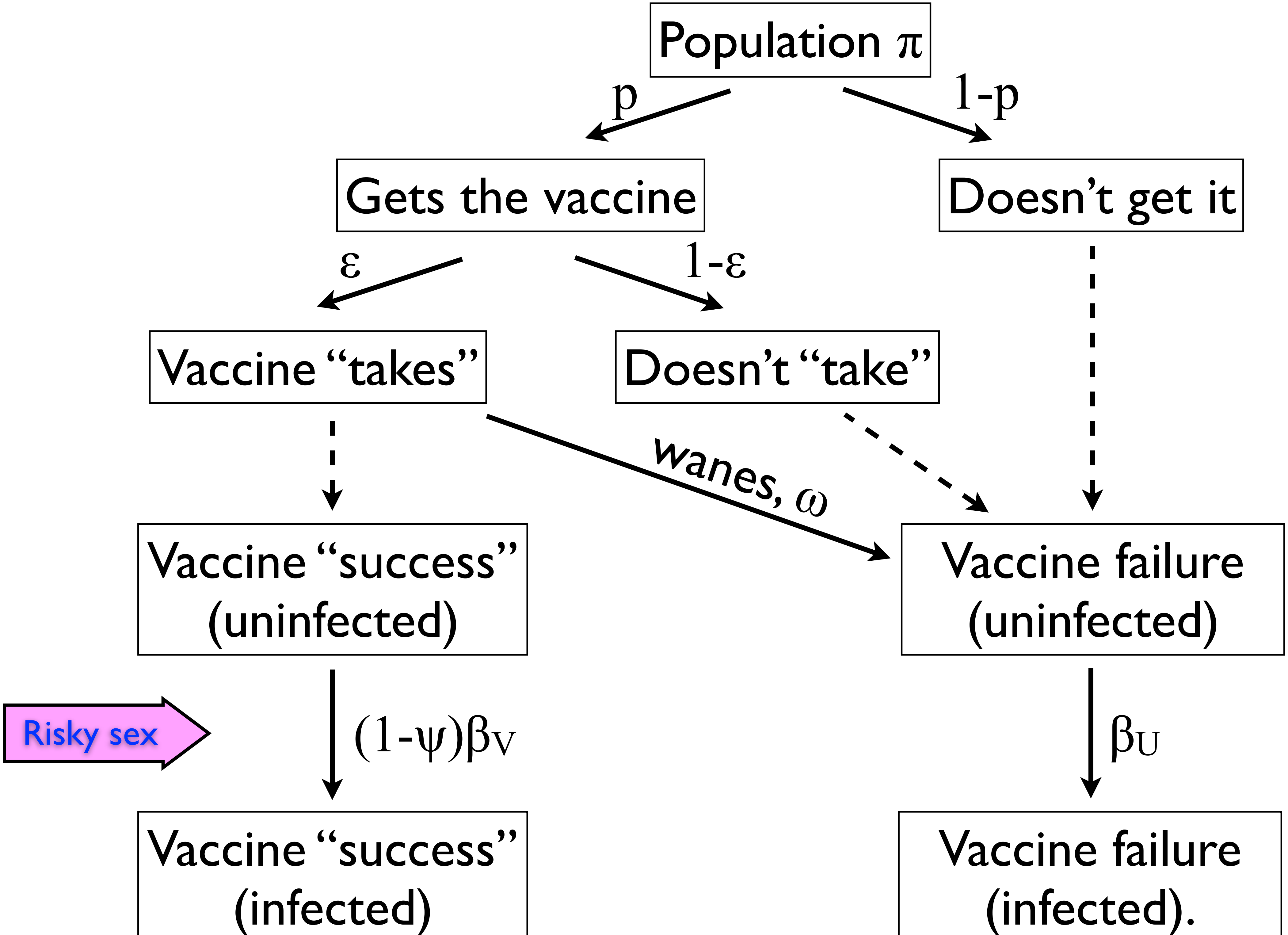


$\tilde{\beta}_V^{\text{crit}} = \frac{\beta_U \mu}{\mu + \gamma_U}$.
1.2
1
0.5
0
$\tilde{\beta}_V^*$
$\tilde{\beta}_V^{\text{crit}}$
Relative transmissability
fitness ratio >1
fitness ratio <1
0
10
20
30
40
50
60
t^*
Additional survival years due to vaccine

Implications

- Reducing the transmission probability is crucial

- If the transmission probability is reduced by 75% or more, the fitness ratio is always less than 1.


Population π
p
1-p
Gets the vaccine
Doesn't get it
ε
1-ε
Vaccine "takes"
Doesn't "take"
wanes, ω
Vaccine "success" (uninfected)
Vaccine failure (uninfected)
Risky sex
(1-ψ)βV
βU
Vaccine "success" (infected)
Vaccine failure (infected).

Four groups

For any vaccine, there are four groups:

a) those who never received the vaccine;
b) those who received the vaccine but the vaccine did not take;
c) those who received the vaccine, the vaccine took, but the vaccine waned over time; and
d) those who received the vaccine, the vaccine took and for whom the vaccine did not wane over time.

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Risky behaviour

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

- ‘Vaccinated’ individuals = group (d)

- Risky behaviour may increase or decrease for individuals in all groups.

Behaviour changes

- m_U = behaviour changes in the infected unvaccinated
- m_V = behaviour changes in the infected vaccinated.

Perversity with risky behaviour

- Perversity with behaviour changes will occur if $R_p > R_0$; *i.e.*

$$S(1-\psi)R_V m_V + (1-S)R_0 m_U > R_0$$

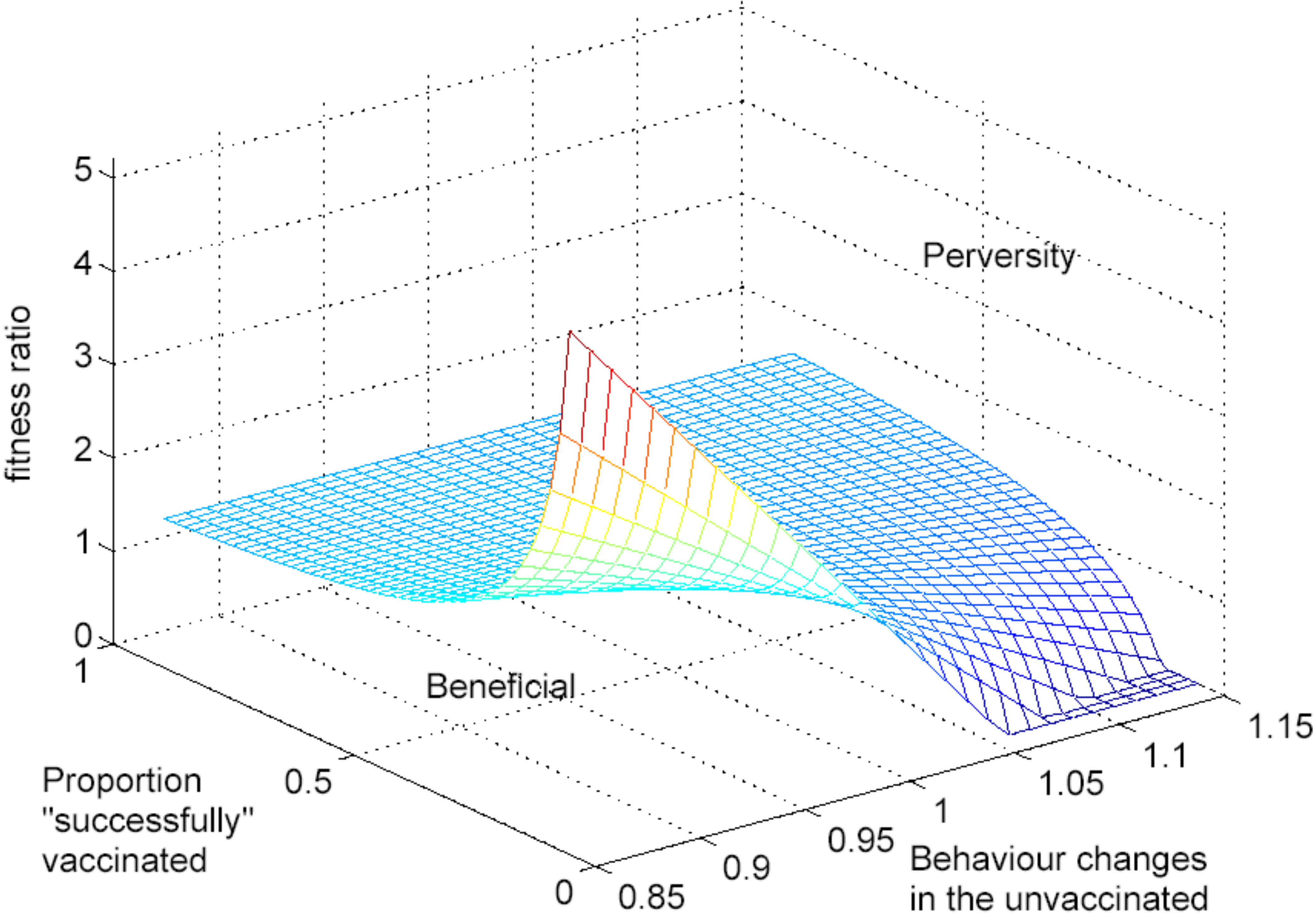
$$S(1-\psi)\, f\, m_V + (1-S)\, m_U > 1.$$

perversity=epidemic gets worse
f=fitness ratio
ψ*=vaccine efficacy*
S=proportion succcessfully vaccinated
R_0*=reproductive number (unvaccinated)*
R_V*=reproductive number (vaccinated)*

Threshold surface

- The perversity threshold is now a surface
- For a given efficacy ψ, the surface depends on *f*, *S*, m_U and m_V
- A beneficial outcome will only occur if *f* is below the surface.

perversity=epidemic gets worse
f=fitness ratio
S=proportion succcessfully vaccinated
m_U*=behaviour changes (unvaccinated)*
m_V*=behaviour changes (vaccinated)*



When risky behaviour in the vaccinated decreases by 15%

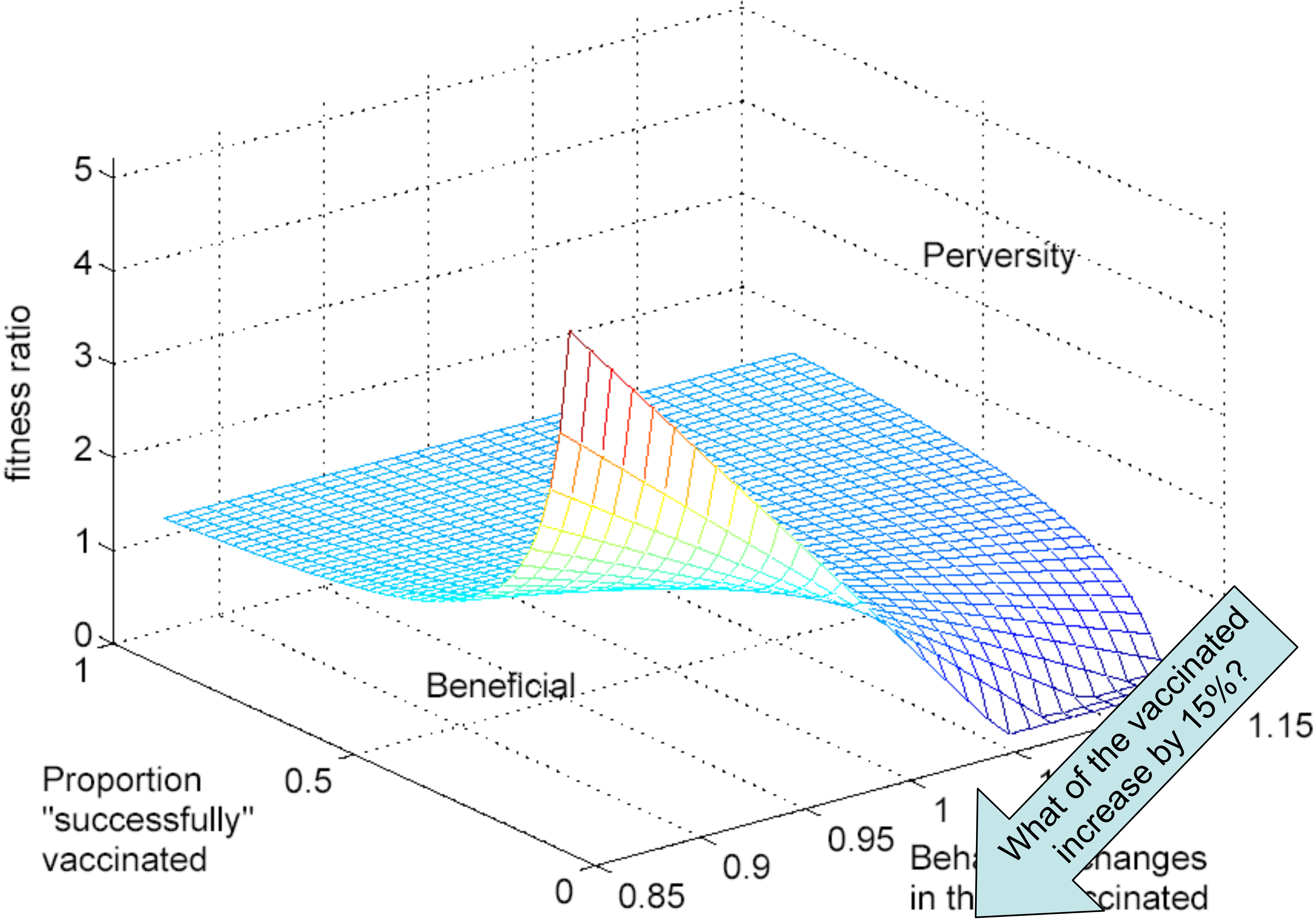
Implications

- (*f* could increase if coverage levels are low and the unvaccinated decrease their risky behaviour, but this is an unlikely situation)

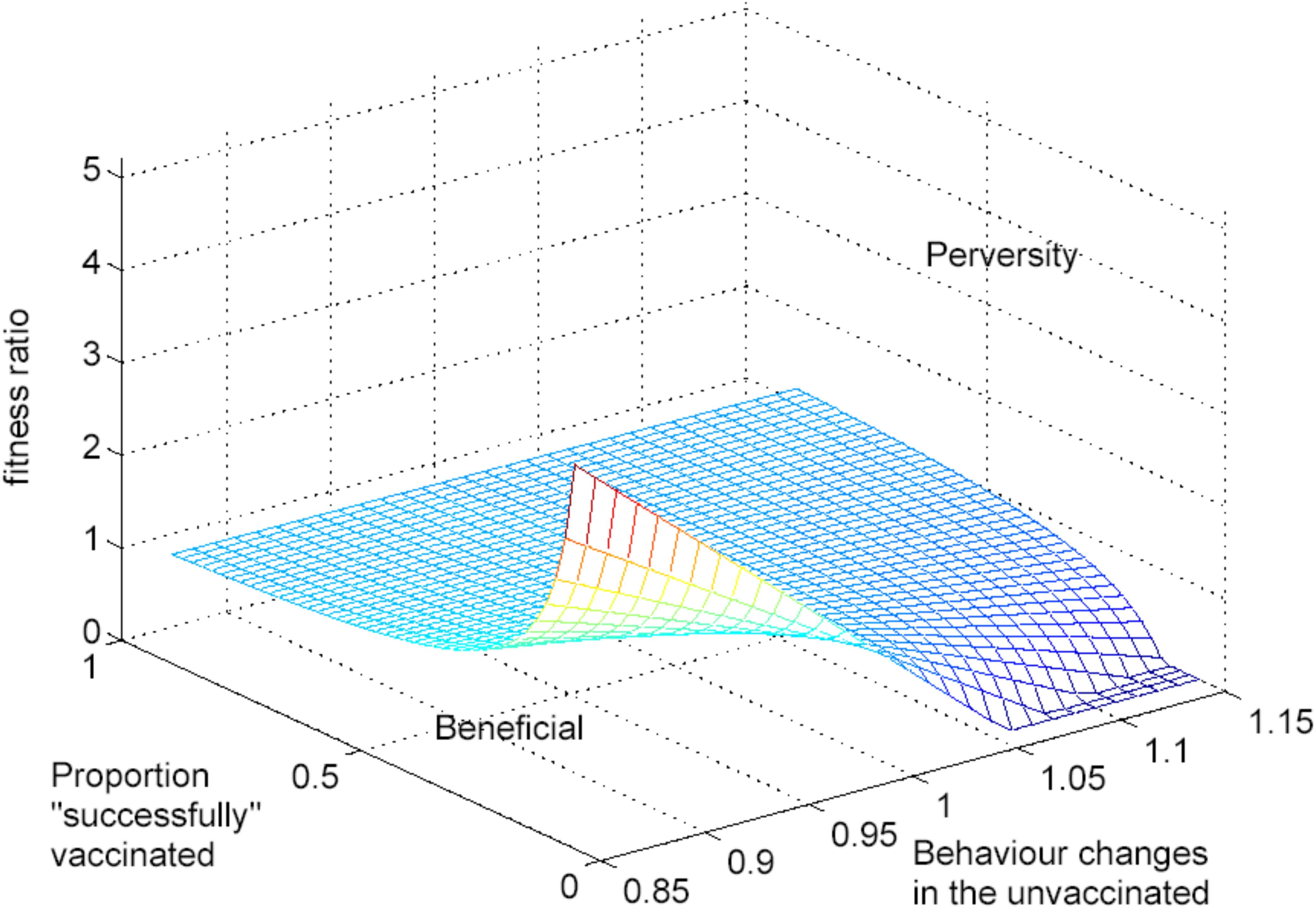
- If the unvaccinated increase their risky behaviour, it is imperative that vaccination coverage be maximised

- Otherwise, perversity occurs for $f \sim 1$, as before.

f=fitness ratio



When risky behaviour in the vaccinated decreases by 15%



When risky behaviour in the vaccinated increases by 15%

The outcome depends on the uninfected

- If the vaccinated increase their risky behaviour, the control strategies are unchanged

- The outcome is significantly more dependent on the behaviour changes in the unvaccinated than the vaccinated

(See HIV Vaccination Notes).

Strategies

- Effective behavioural intervention strategies should be tightly linked with vaccination programs
- Before a disease-modifying vaccine is introduced, the population-level impact should be carefully assessed
- This is critical for low-efficacy vaccines.