Epidemiology

Schedule:

Friday, 25 May

9:30-11:00 – Session 1

Basic models and in epidemiology

11:30-13:00 – Session 2

Tuberculosis, pertussis, malaria

15:00-16:30 – Session 3

Multi-strain dynamics: the case of influenza

Types of models

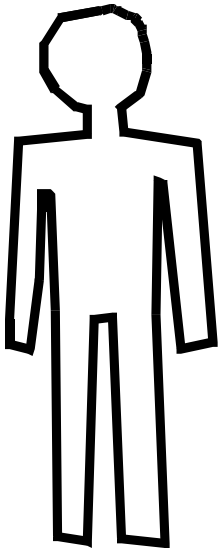
Mathematical models – simple and general:

Useful to explore general mechanisms, and to establish basic principles. Further complexity can be incorporated gradually. Traditional and common in biology.

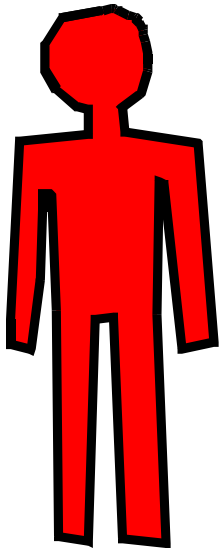
Computational models – complex and specific:

Attempt to describe every detail of the real system as accurately as possible. Weather prediction models are the best examples. Recent and increasingly common in biology.

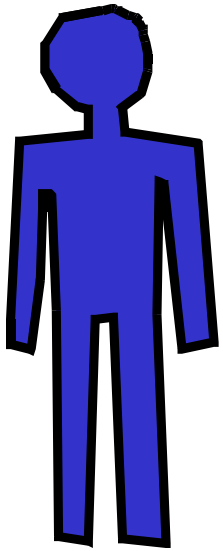
Host classification



Susceptible

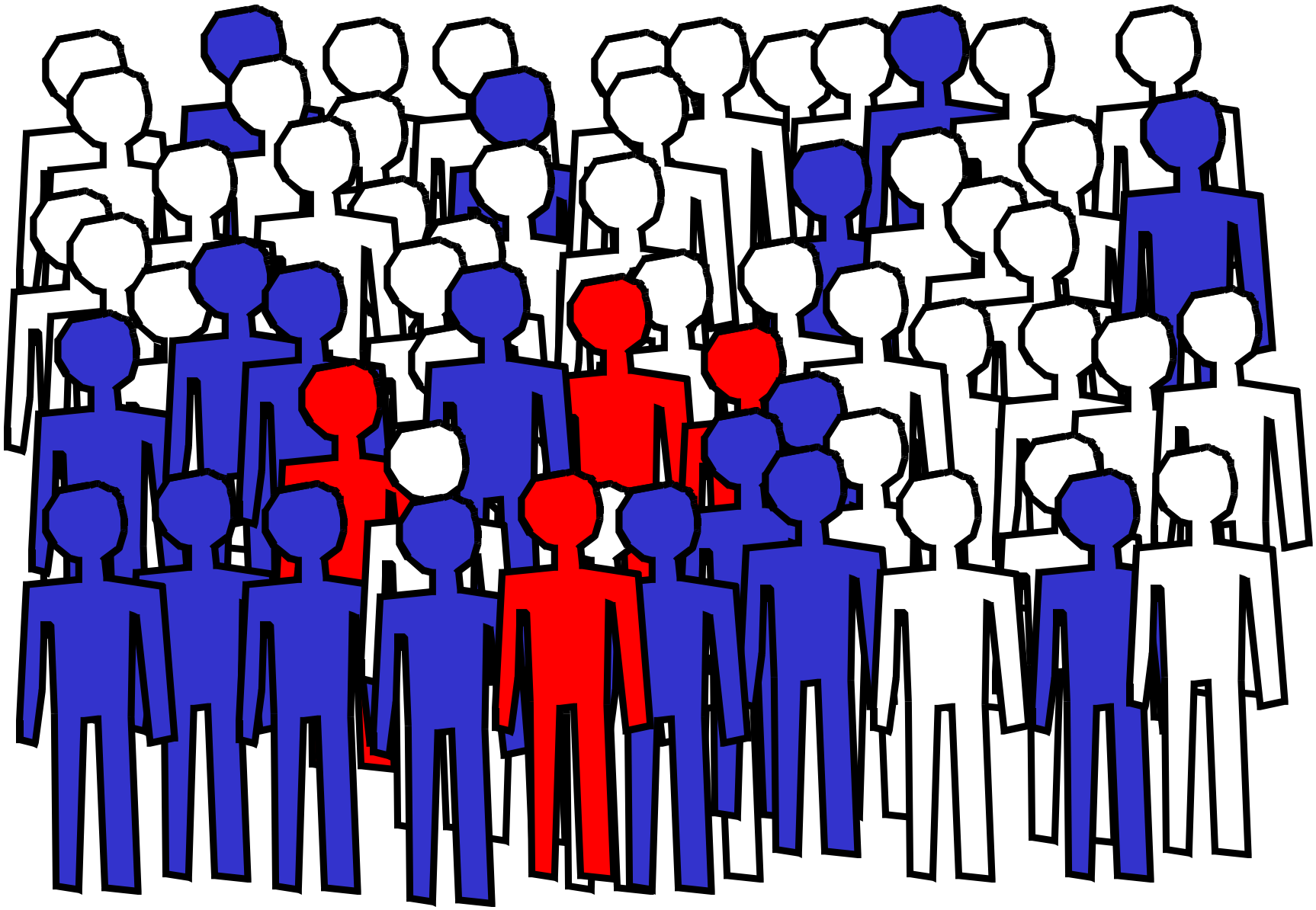


Infectious



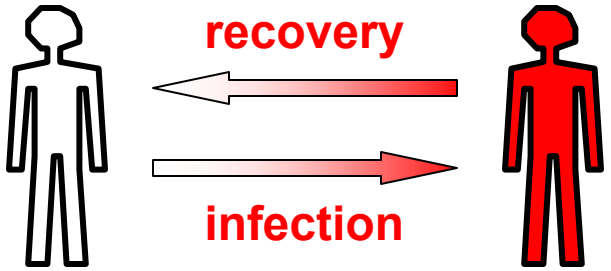
Recovered
(with immunity)

Host population



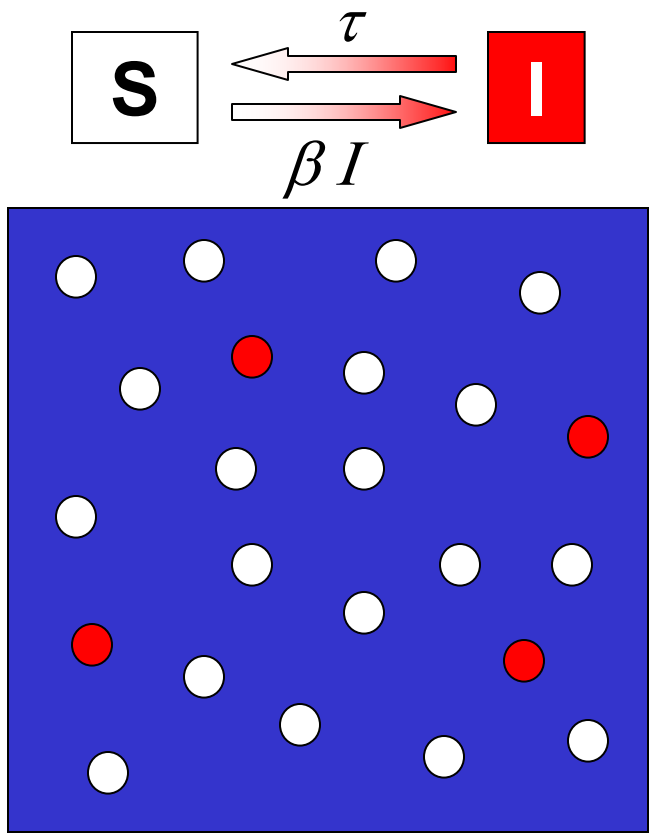
S/*S* model

Ronald Ross demonstrated that the parasite of malaria is transmitted by mosquitoes and in 1902, he received the Nobel Prize of Medicine. He developed mathematical models for malaria transmission, and was a pioneer in mathematical epidemiology.



SIS model

Appropriate for infections that induce no effective immunity (e.g. malaria).



$$\frac{dS}{dt} = -\beta IS + \tau I$$

$$\frac{dI}{dt} = \beta IS - \tau I$$

β – transmission coefficient

τ – recovery rate

SIS model

As $S + I = 1$, the model is one dimensional and represented by the equation

$$\frac{dI}{dt} = \beta(1-I)I - \tau I$$

This is a type of growth law known as *logistic growth*, and it appears commonly in population dynamics models in the form

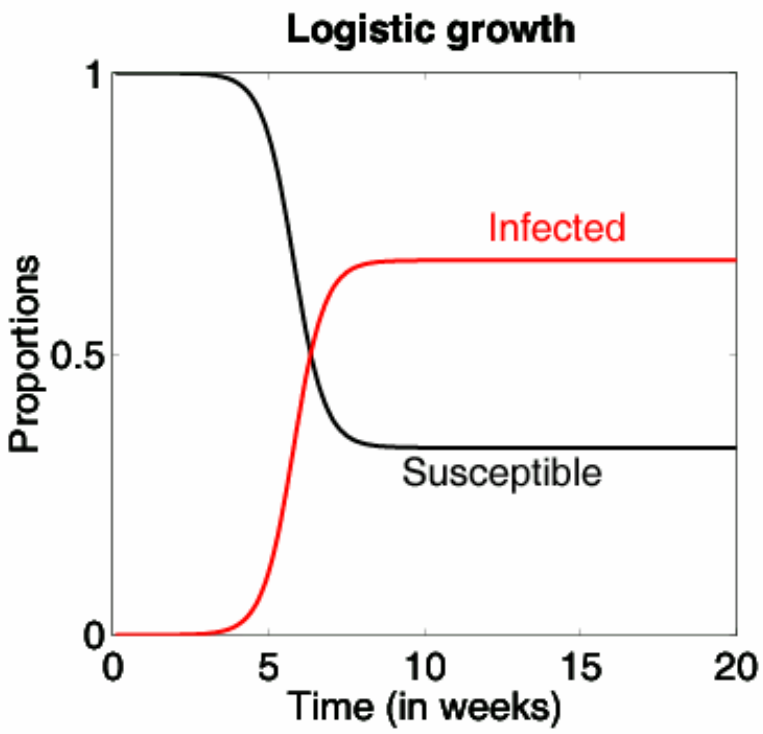
$$\frac{dI}{dt} = (\beta - \tau)\left(1 - \frac{I}{1-\tau/\beta}\right)I$$

The solution can be calculated to give

$$I(t) = \frac{I(0)(1-\tau/\beta)}{I(0) + (1-\tau/\beta - I(0))e^{-(\beta-\tau)t}}$$

SIS model

Given an *initial condition,* $I(0) = 10^{-6}$, the proportion of infectious individuals grows as



Parameters: $\beta = 3$, $\tau = 1$

Steady states:

1. Disease free equilibrium

$$I = 0, \quad S = 1$$

2. Endemic equilibrium

$$I = 1 - \frac{\tau}{\beta}, \quad S = \frac{\tau}{\beta}$$

The Basic Reproduction Number, R_0

The basic reproduction number is defined as

The average number of secondary cases produced by an average infectious individual in a totally susceptible population.

The basic reproduction number is calculated as

R_0 = (rate of transmission from an infectious individual) x (infectious period)

$= \beta \times (1 / \tau) = \beta / \tau$

R_0 is a nondimensional number, and depends on both the environment and the disease.

Disease	R_0
Smallpox	4
Measles	17
Rubella (England and Wales)	6
Rubella (Gambia)	15

Nondimensional *S*/*S* model

If time is measured in units of infectious period, ***D = 1 / τ***, then the *S*/*S* model becomes

$$\frac{dI}{dt} = R_0(1-I)I - I$$

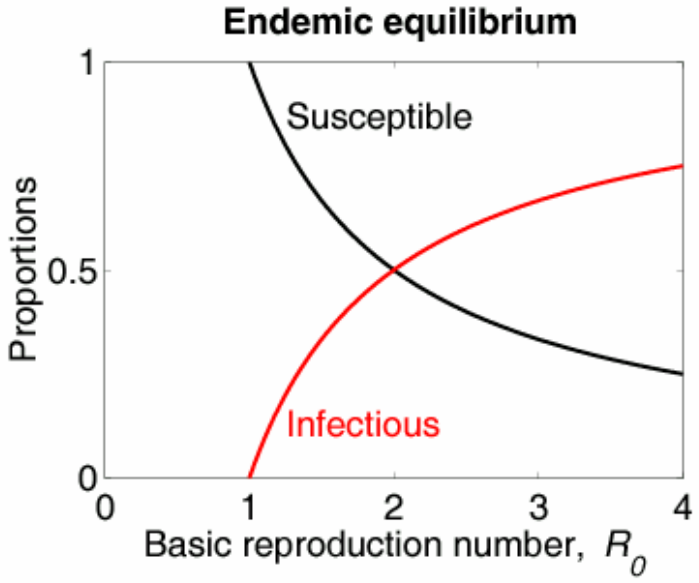
$$= R_0\left(1-\frac{1}{R_0}-I\right)I$$

The endemic equilibrium is rewritten as

$$I = 1-\frac{1}{R_0},\quad S = \frac{1}{R_0}$$

Epidemic threshold: Infection can invade a susceptible population iff

$$R_0 > 1$$



Stability of the *SIS* steady states

The *SIS* model is expanded as

$$\frac{dI}{dt} = \left(R_0 - 1\right)I - R_0 I^2$$

The stability of a steady state, I^* , is given by the sign of the linearisation

$$J(I^*) = R_0 - 1 - 2R_0 I^*$$

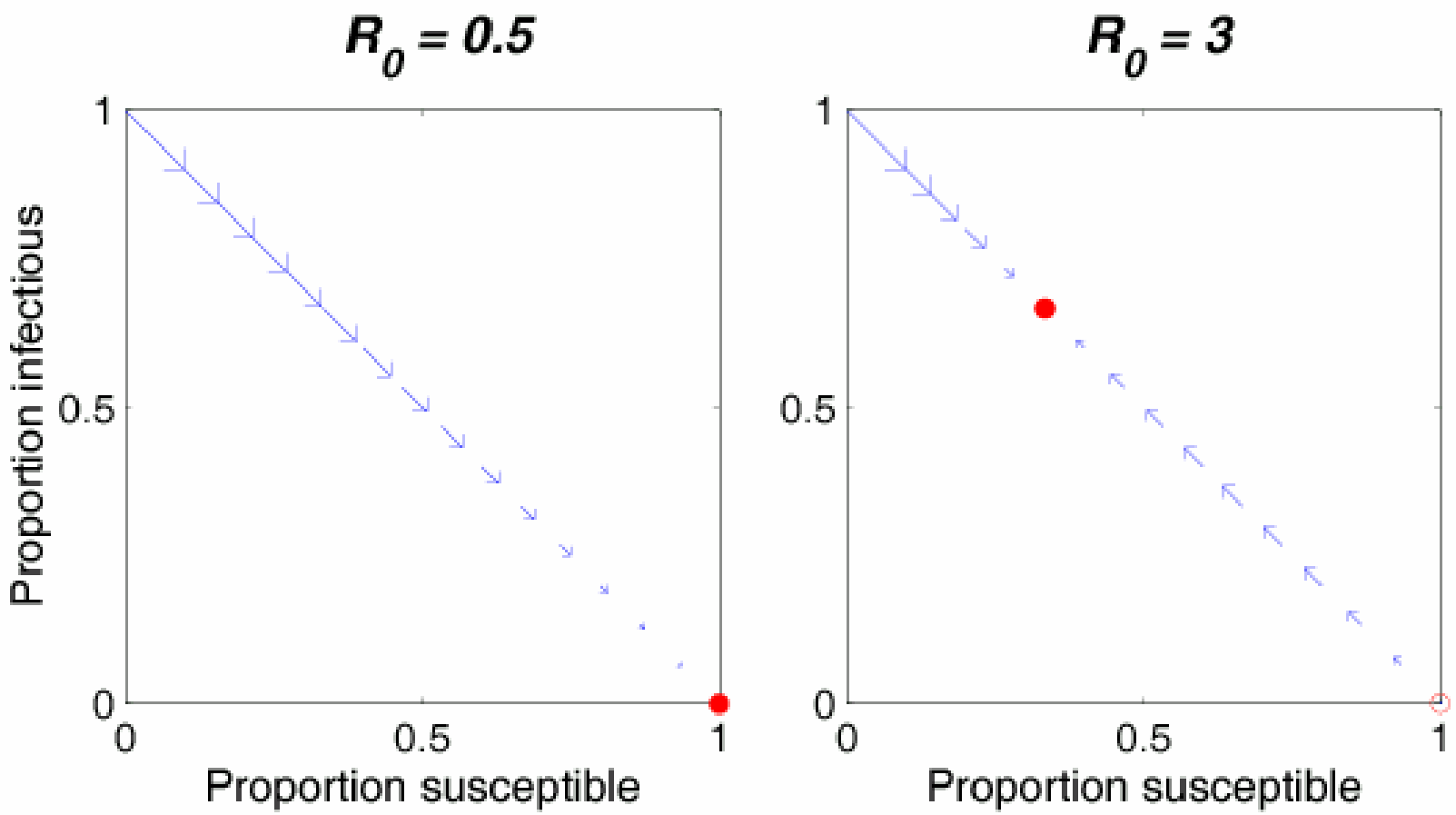
1. **Disease free equilibrium, $S = 1$, $I = 0$:**

$$J_1 = J(0) = R_0 - 1 \longrightarrow$$ **Stable if *R0 < 1***

2. **Endemic equilibrium, $S = 1/R_0$, $I = 1 - 1/R_0$:** $\longrightarrow$ **Possible if *R0 > 1***

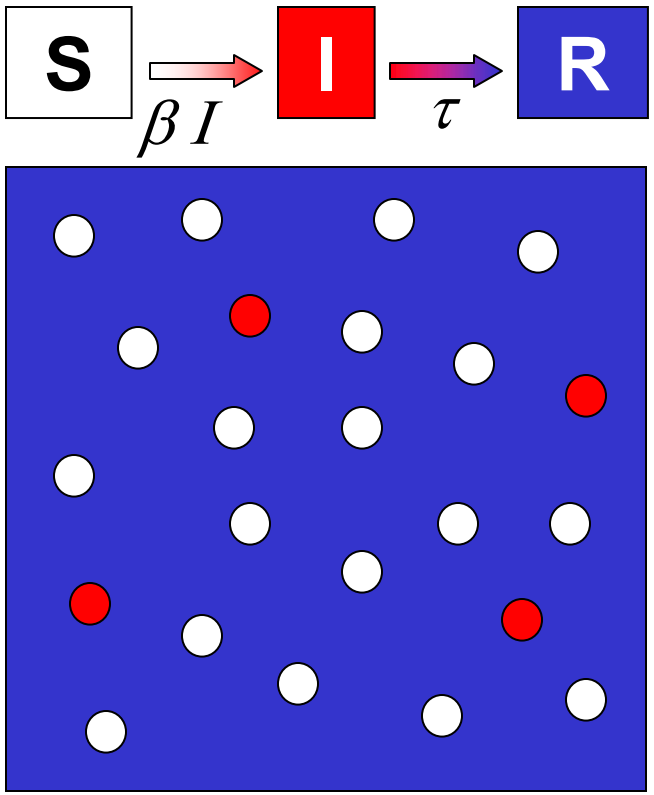
$$J_2 = J\left(1 - 1/R_0\right) = \left(R_0 - 1\right)^2 / R_0 \longrightarrow$$ **Stable**

Vector field for the *S/S* model



SIR model

Appropriate for infections that induce a highly effective immunity (e.g. measles, mumps, rubella).



$$\frac{dS}{dt} = -\beta IS$$

$$\frac{dI}{dt} = \beta IS - \tau I$$

$$\frac{dR}{dt} = \tau I$$

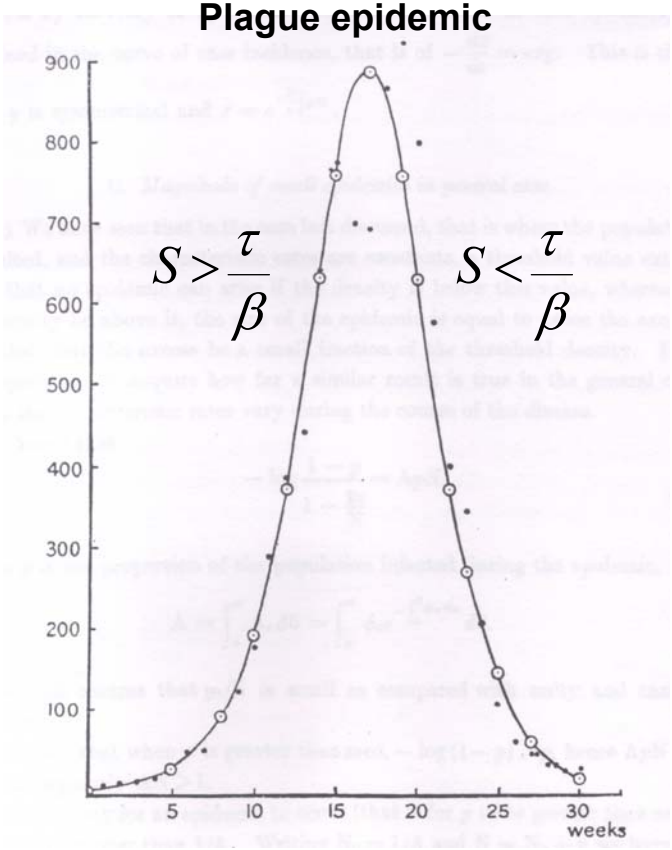
β – transmission coefficient

τ - recovery rate

Epidemic threshold

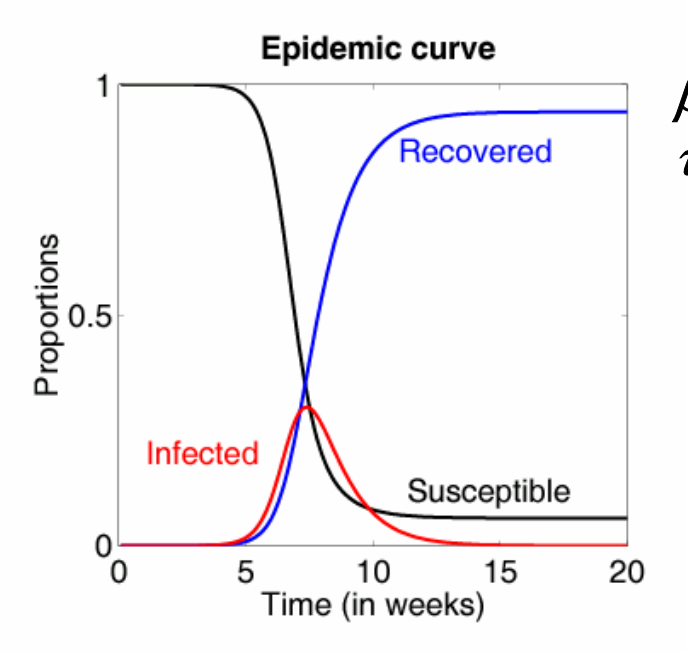
In 1927, Kermack e McKendrick fitted the model to various epidemic curves (in particular, the Bubonic plague). They established the theory of the **epidemic threshold**: the growth of an epidemic requires that, on average, an infected individual infects at least one susceptible. An epidemic falls when the density of susceptibles is below a threshold: $S < 1 / R_0$.

Plague epidemic



$$\frac{dS}{dt} = -\beta IS$$

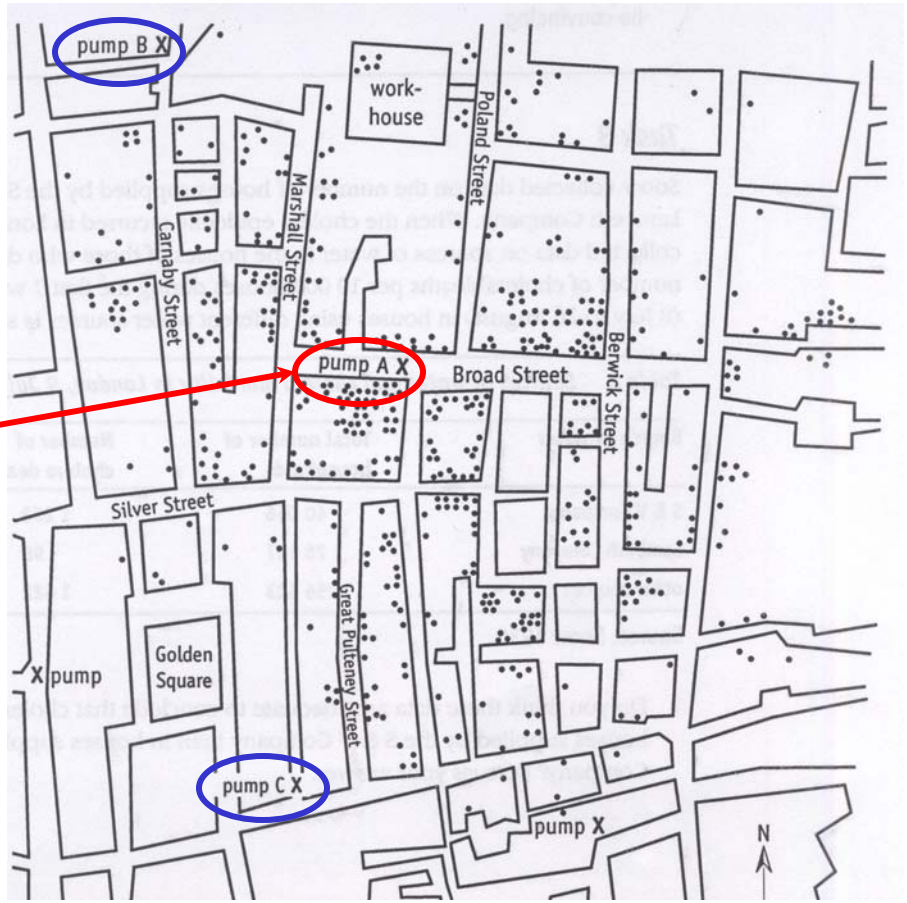
$$\frac{dI}{dt} = \beta IS - \tau I$$



Another example - Cholera

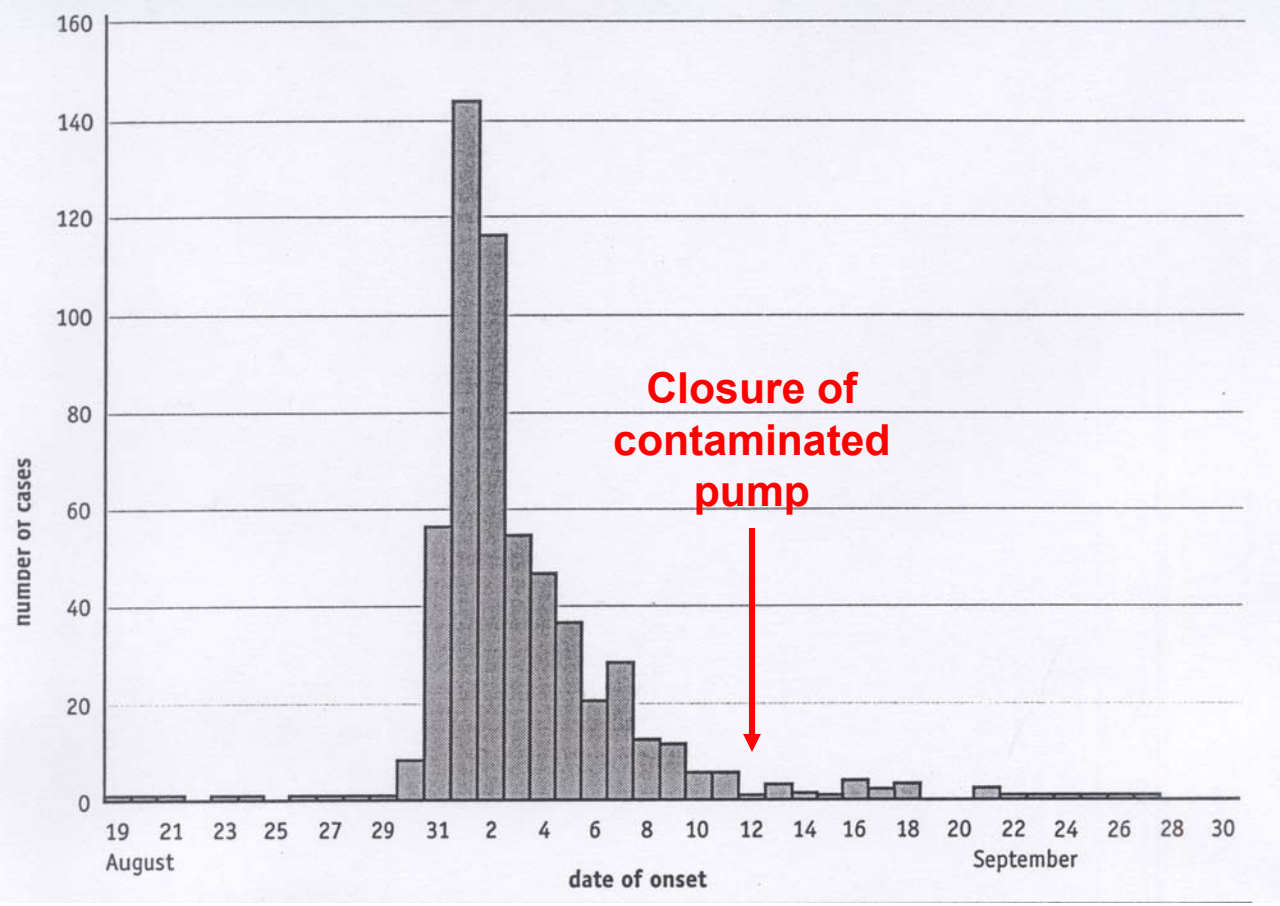
Cholera outbreak in London, 1854: Distribution of cases in a residential area.

Contaminated pump



Epidemic fad-out

The epidemic curve of cholera is typical of an infectious disease that induces protective immunity.



Nondimensional *SIR* model

If time is measured in units of infectious period, $D = 1/\tau$, then the *SIR* model becomes

$$\frac{dS}{dt} = -R_0 IS \quad \text{and} \quad \frac{dR}{dt} = I$$
$$\frac{dI}{dt} = R_0 IS - I$$

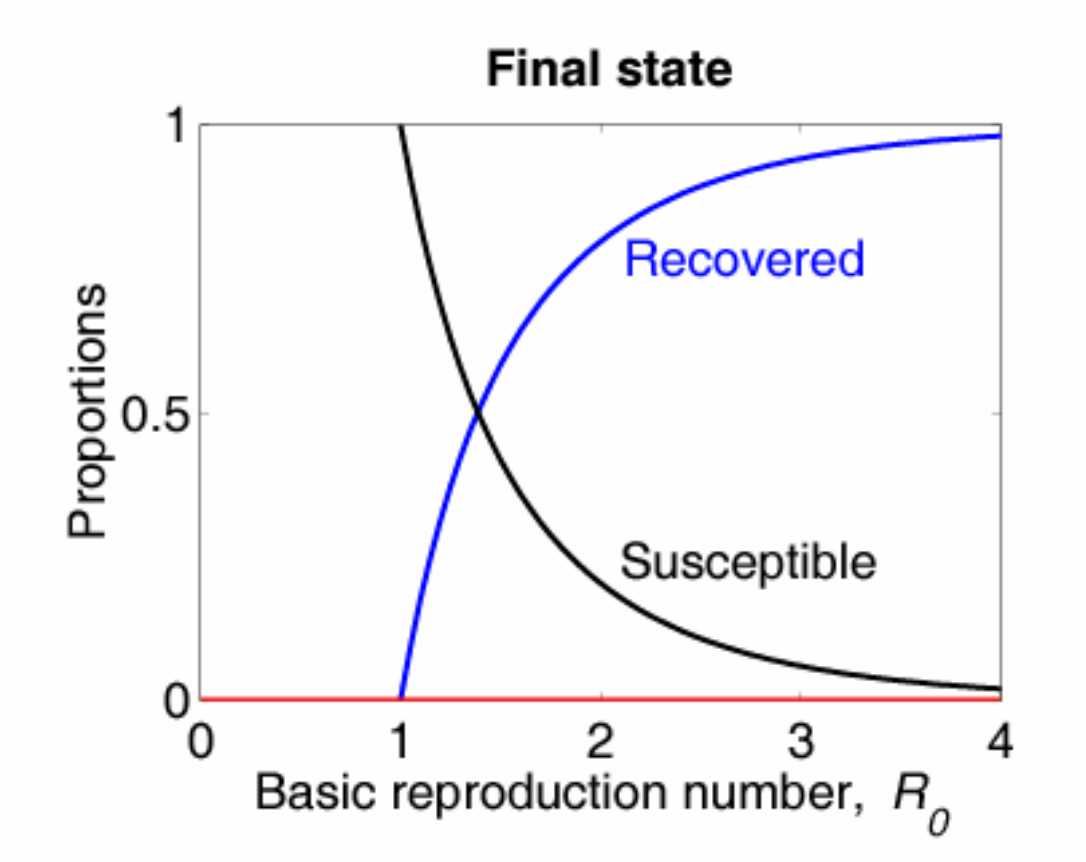
As individuals become immune, this system always approaches the disease free steady state, $I = 0$. As the epidemic progresses, the level of susceptibles decreases, and the level of recovered individuals increases. The important question is the final balance between these two classes – does the disease die out before all the susceptibles are exhausted?

$$\frac{dS}{dR} = -R_0 S \;\Rightarrow\; S = \exp\left(-R_0 R\right)$$

Using the fact that $S = 1 - I - R$, and at equilibrium $I = 0$, we get

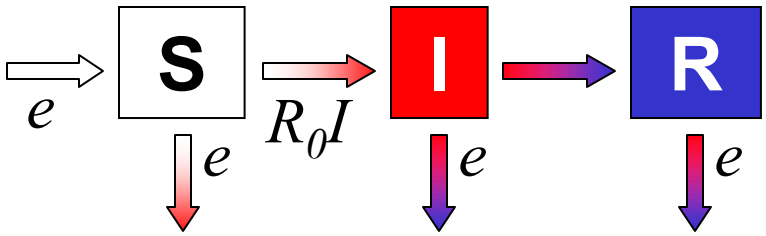
$$R^* = 1 - \exp\left(-R_0 R^*\right)$$

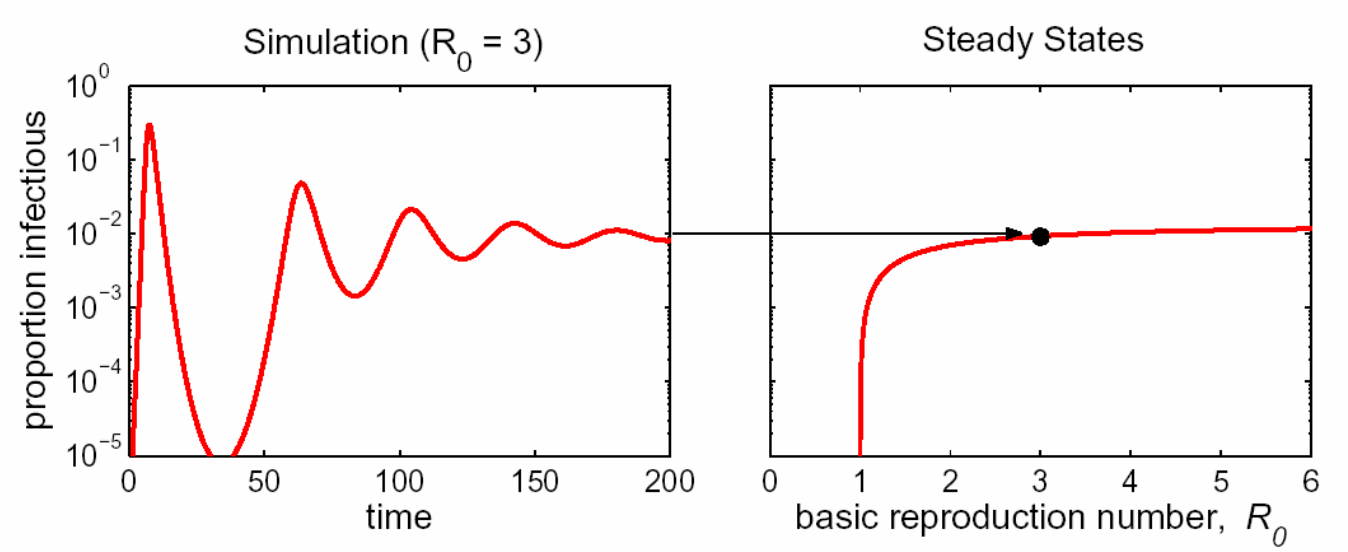
After epidemic – *SIR* steady state



Long-term *SIR* dynamics

In the long term, the susceptibility pool is replenished by births generating the conditions for new epidemics to occur.





SIR steady states

The new steady states are obtained from the model

$$\frac{dS}{dt} = e - R_0 IS - eS$$
$$\frac{dI}{dt} = R_0 IS - I$$

Steady states:

1. Disease free equilibrium: $I = 0,\ S = 1$

2. Endemic equilibrium: $I = e\left(1 - \frac{1}{R_0}\right),\ S = \frac{1}{R_0}$

The new parameter, **e**, represents the birth and death rate in units of infectious period. This is equivalent to ***D / L*** , where ***D*** is the average duration of infection and ***L*** is the life expectancy at birth. Assuming that ***D = 1 month***, and ***L = 70 years***, we get ***e = 0.0012***.

Stability of the *SIR* steady states

The linearisation of the *SIR* model is the Jacobian matrix

$$J(S^*, I^*) = \begin{pmatrix} -R_0 I^* - e & -R_0 S^* \\ R_0 I^* & R_0 S^* - 1 \end{pmatrix}$$

The stability of a steady state, (S^*, I^*), is given by the eigenvalues of the corresponding Jacobian matrix.

1. **Disease free equilibrium, $S = 1$, $I = 0$, eigenvalues:**

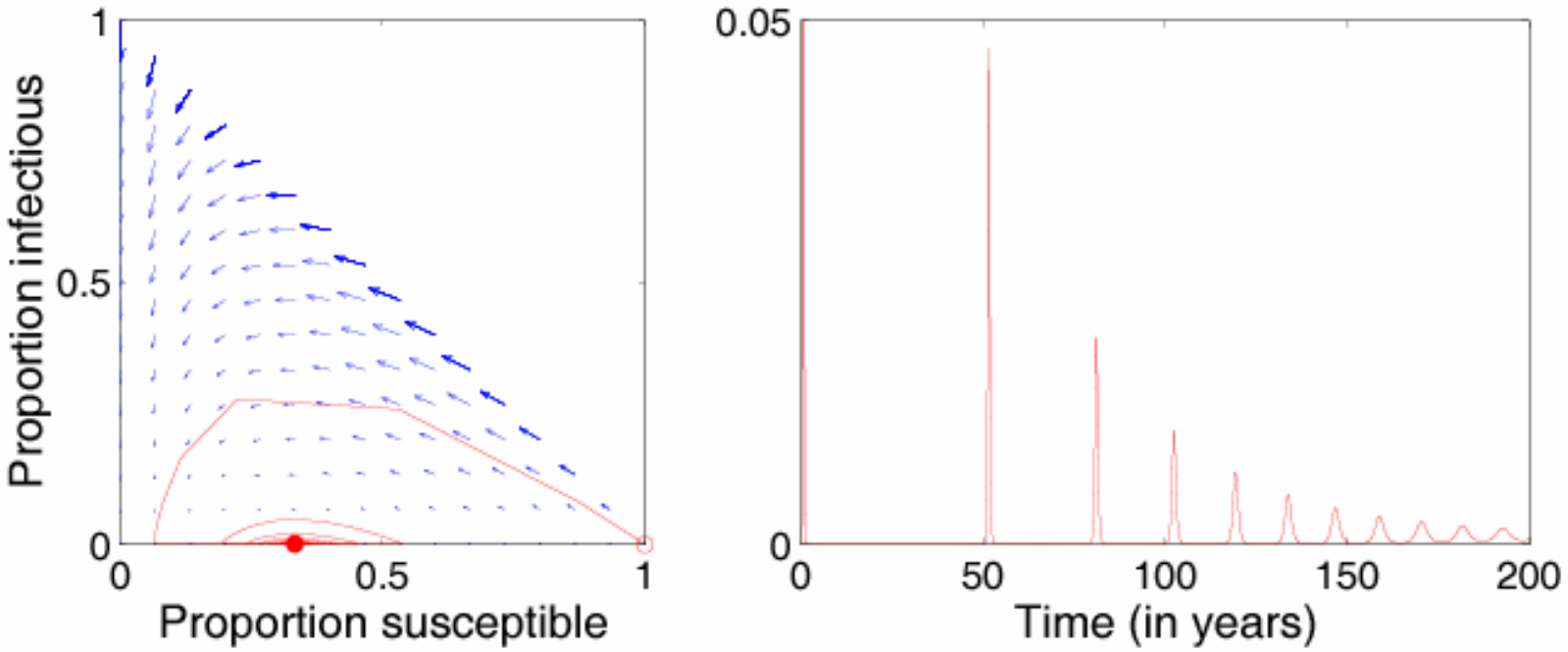
$$-e \quad \text{and} \quad R_0 - 1 \longrightarrow$$ **Stable if *R0 < 1***

2. **Endemic equilibrium, $S = 1/R_0$, $I = 1 - 1/R_0$, eigenvalues:**

$$-\frac{eR_0}{2} \pm \frac{1}{2}\sqrt{e^2 R_0^2 - 4e(R_0 - 1)} \longrightarrow$$ **Stable if *R0 > 1***

Vector field and simulation of the *SIR* model

$$R_0 = 3, \quad e = 0.0012$$

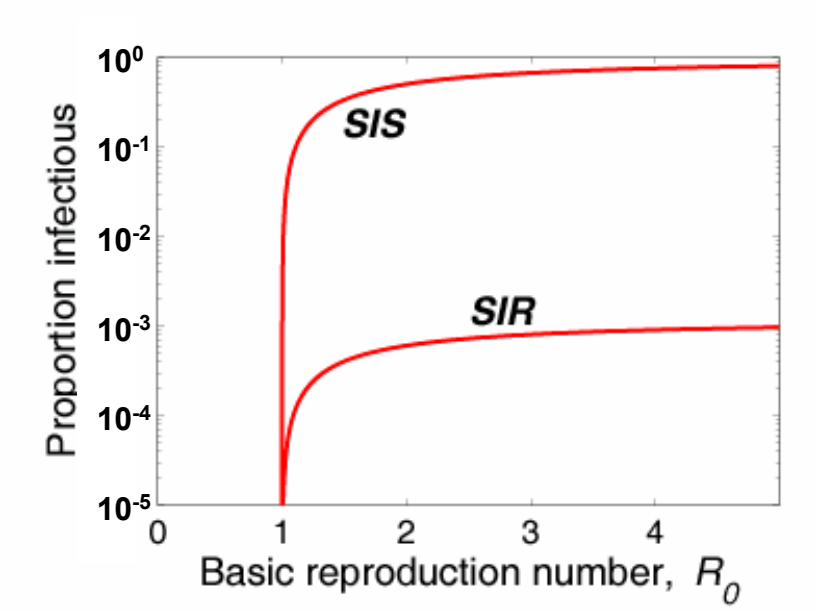


The inter-epidemic period near equilibrium is $\boldsymbol{T = 2\pi / \omega}$, where ω is the imaginary part of the eigenvalues of J_2, and this is

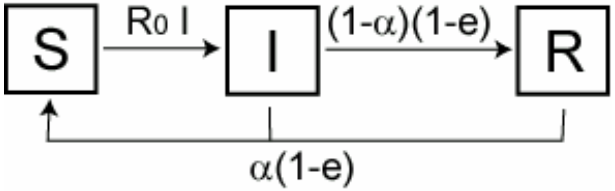
$$\omega = \frac{1}{2}\sqrt{4e\left(R_0 - 1\right) - e^2 R_0^2} \approx \sqrt{e\left(R_0 - 1\right)} \quad \Rightarrow \quad T = 2\pi \sqrt{\frac{L}{D\left(R_0 - 1\right)}}$$

Intermediate models

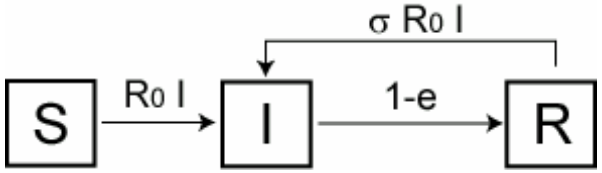
SIS and *SIR* steady states



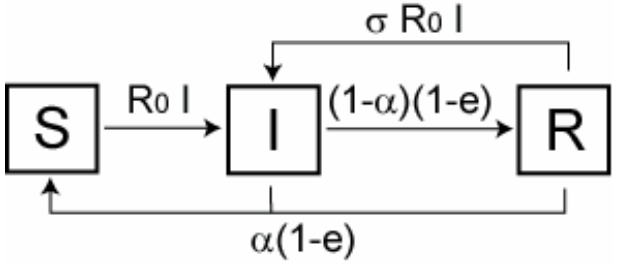
Temporary immunity



Partial immunity



Temporary-partial immunity



Temporary immunity and Partial immunity

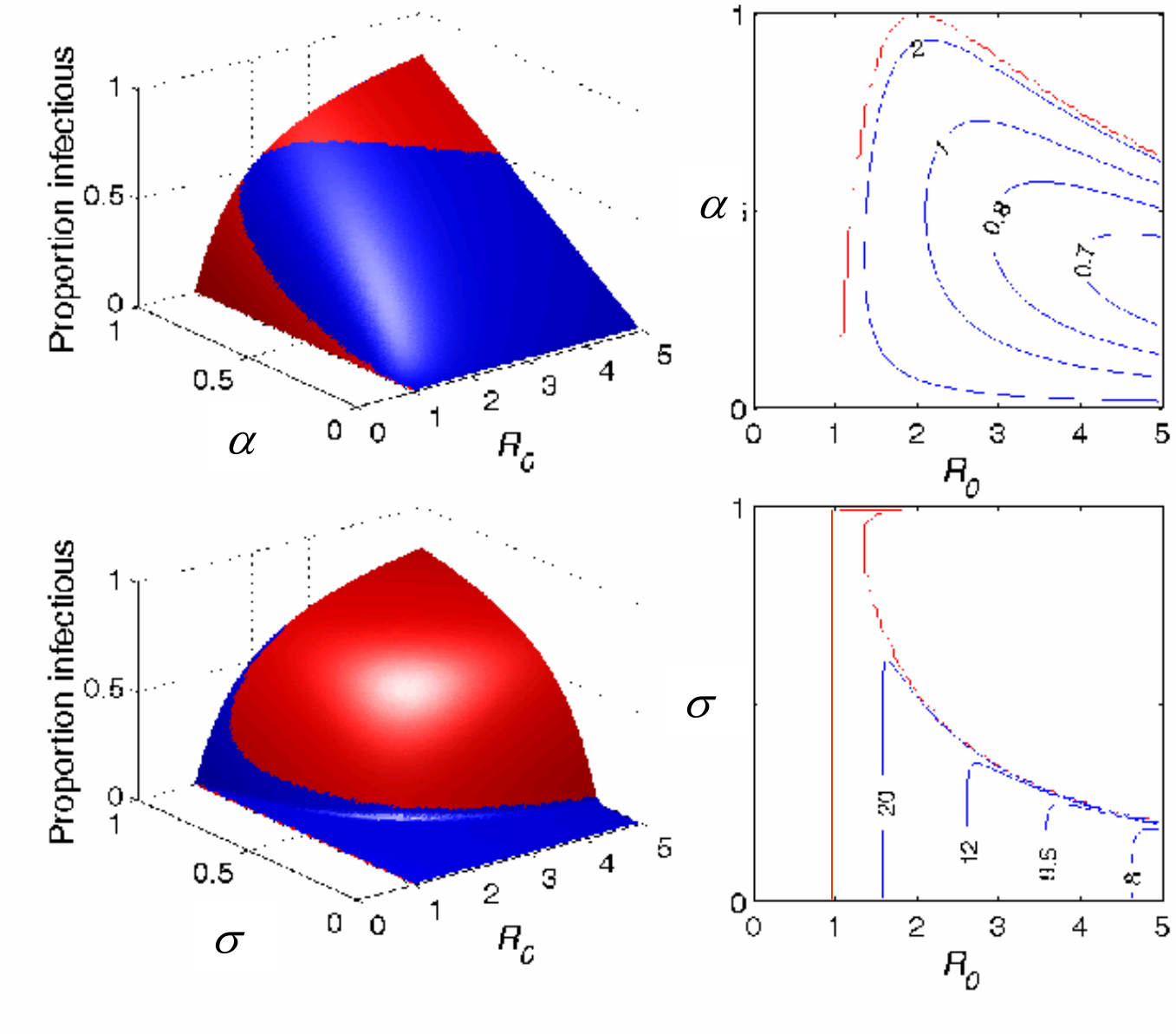
Temporary immunity: Decay of immunity over time appears to be an important factor in many diseases – for example, pertussis. In the extreme case, when immune efficacy drops from full protection to nothing at a given rate (parameterized by α), the model is

$$\frac{dS}{dt} = e - R_0 IS - eS + \alpha(1-e)(1-S)$$
$$\frac{dI}{dt} = R_0 IS - I$$

Partial immunity: Even more common is that immunity is not fully protective, but rather reduces the risk of further infections by some factor (σ) – for example, tuberculosis. This is represented by the model

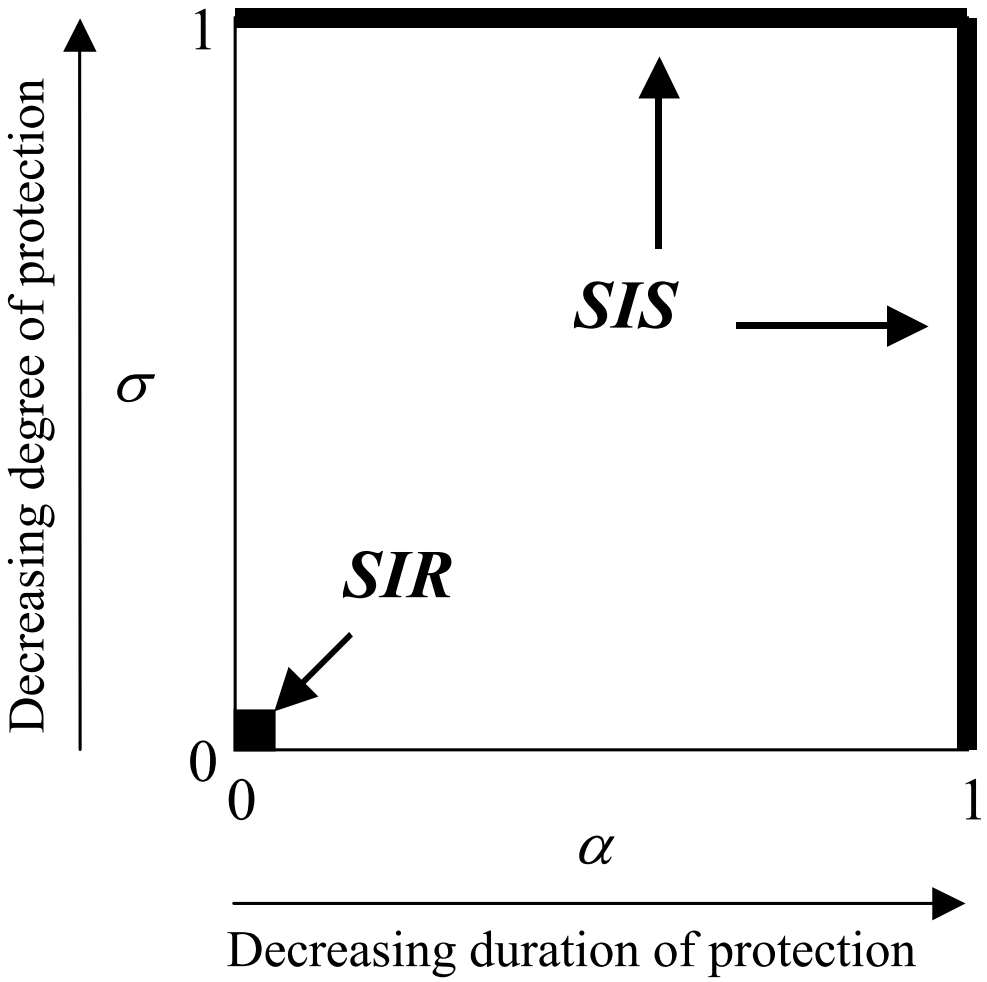
$$\frac{dS}{dt} = e - R_0 IS - eS$$
$$\frac{dI}{dt} = R_0 I\left(S + \sigma(1-S-I)\right) - I$$

Steady states and inter-epidemic period



Temporary-Partial immunity

When immunity is not fully protective, it is likely to accommodate a specific combination of both temporary (α) and partial (σ) factors.

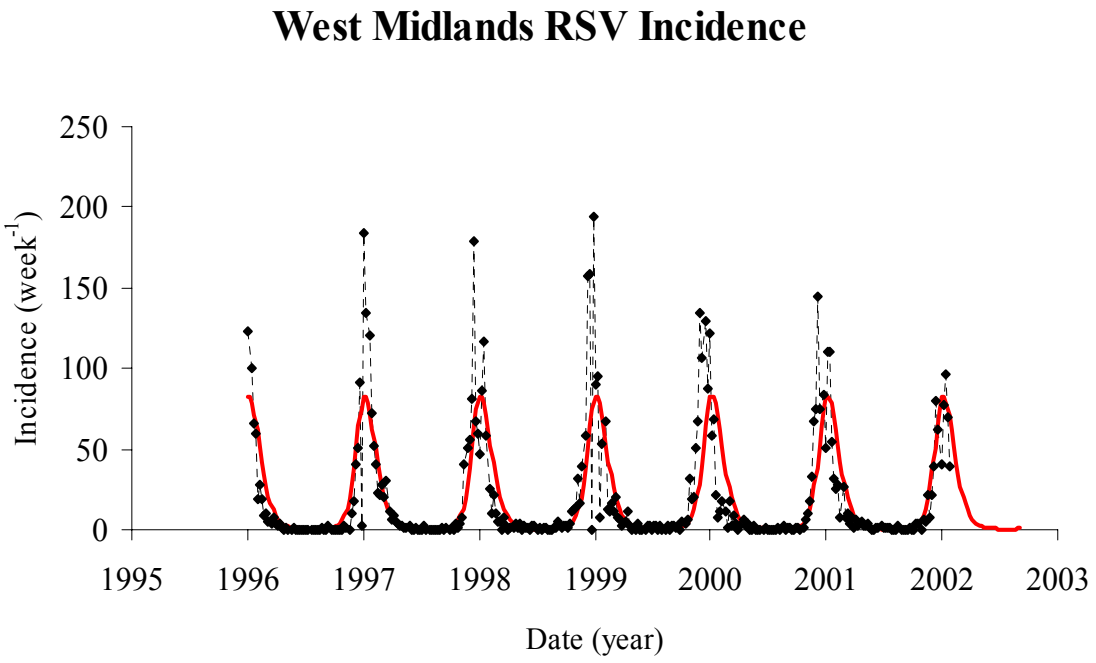


Temporary-Partial immunity model

The combined model is represented as

$$\frac{dS}{dt} = e - R_0 IS - eS - \alpha(1-e)(1-S)$$
$$\frac{dI}{dt} = R_0 I\left(S + \sigma(1-S-I)\right) - I$$

Having both α and σ allows better fitting to data sets.



Vaccination

Smallpox: Immunity is a very old popular concept – people who survive certain diseases, acquire protection, and will not get the disease again.

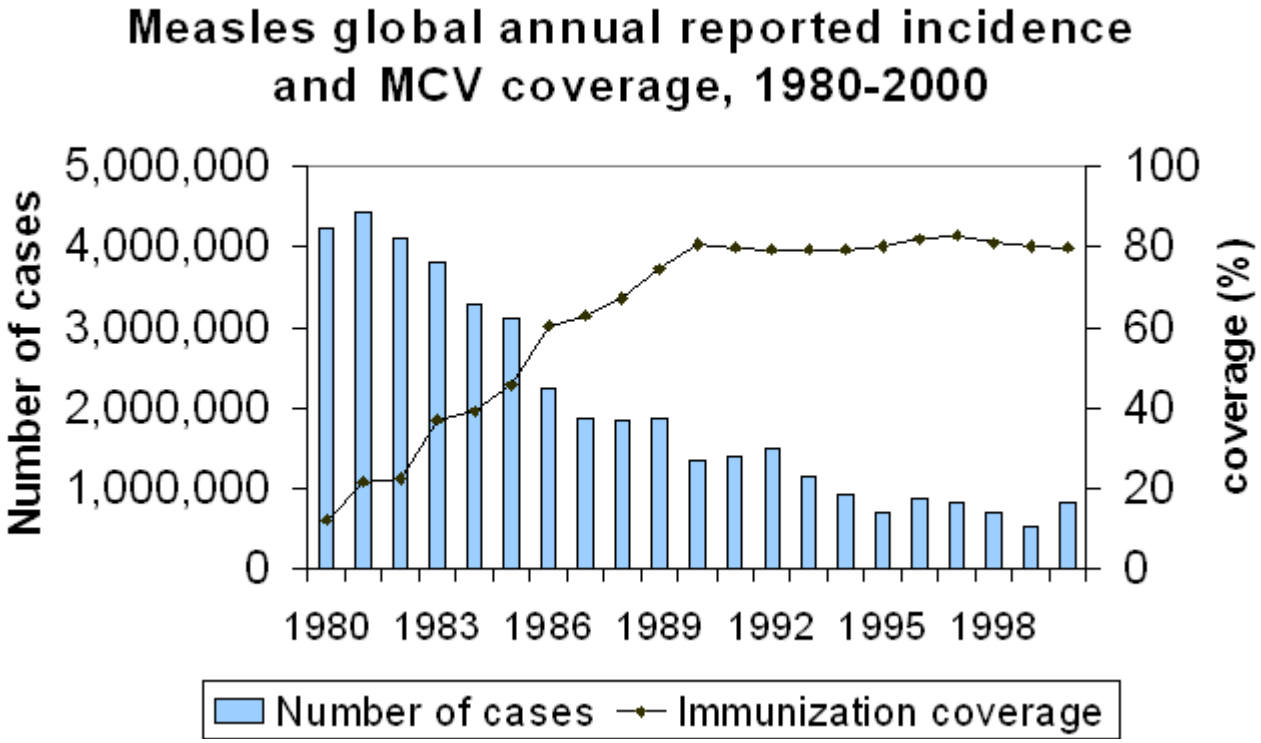
It was realised how the same protection could be induced – variolation protected against smallpox. In 1760, Daniel Bernoulli initiated the development of mathematical techniques to assess the efficacy of such interventions.

In 1796, Edward Jenner noticed that cowpox caused a less severe disease on people, and also resulted in protection against smallpox. In few years, the new technique of vaccination became very popular.

Smallpox was declared eradicated from the world in 1979.

Vaccination

Measles:



Vaccination

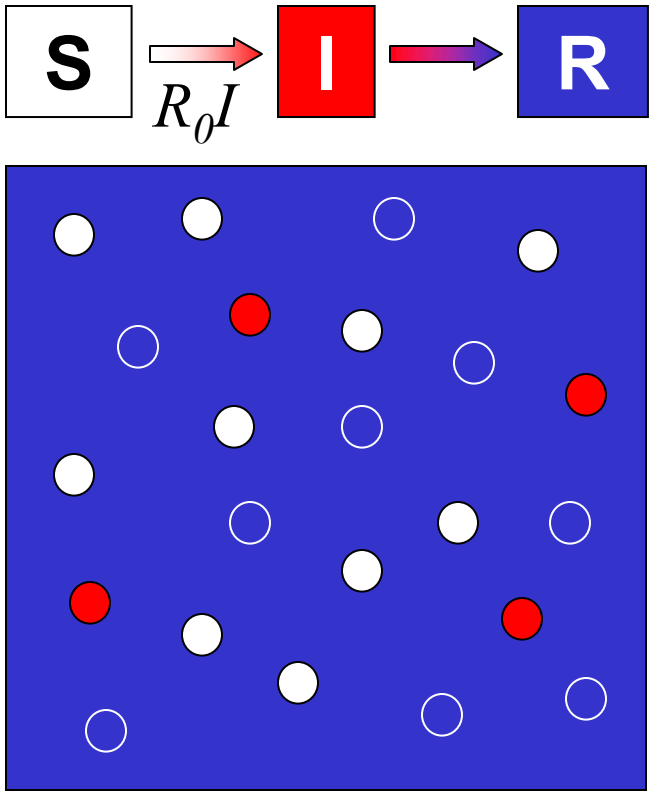
Many diseases preventable by vaccination:

- Smallpox
- Measles
- Mumps
- Rubella
- Diphtheria
- Whopping cough
- Meningitis (*Hib*)
- Meningitis (*Neisseria meningitidis*)
- Tetanus
- Poliomyelitis
- Hepatitis B
- Yellow fever
- Tuberculosis (BCG)
- Influenza

And many more are in development.

Vaccination – *SIR* model

The collective effect of a vaccination programme is to reduce the pool of susceptible individuals.



Vaccination – *SIR* model

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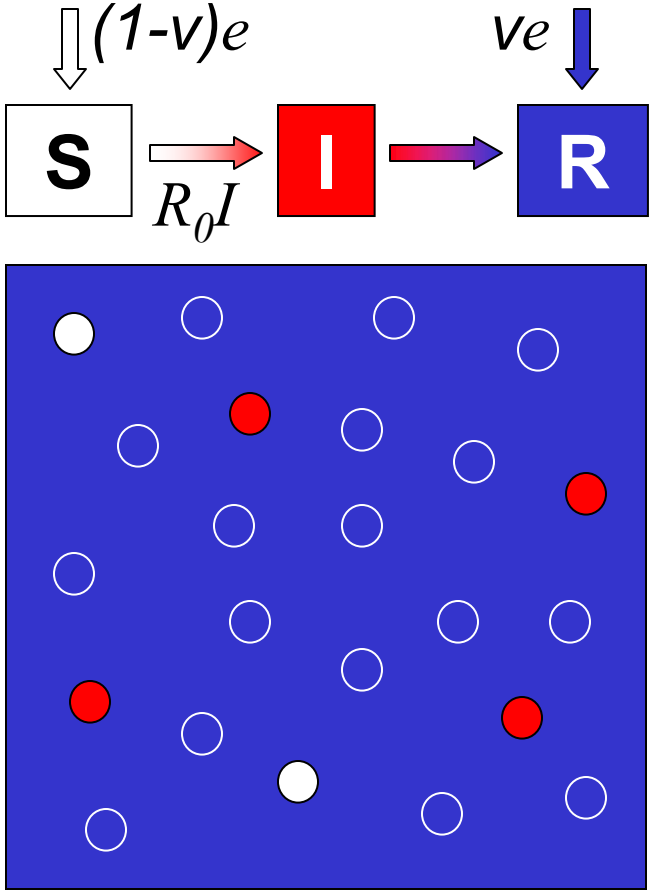
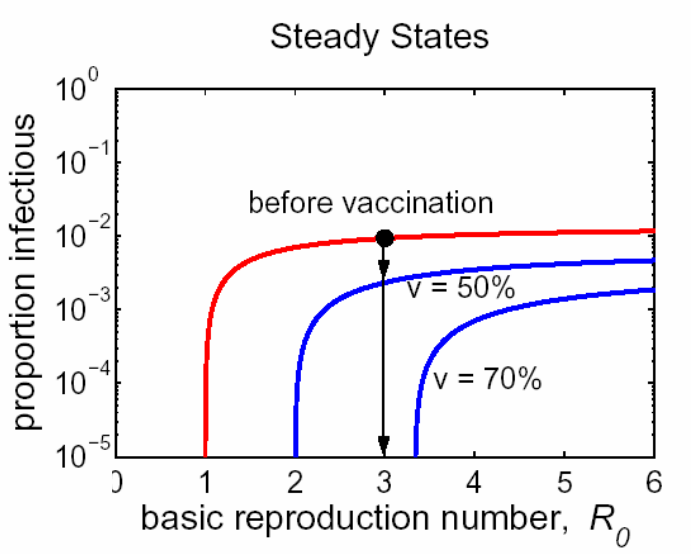
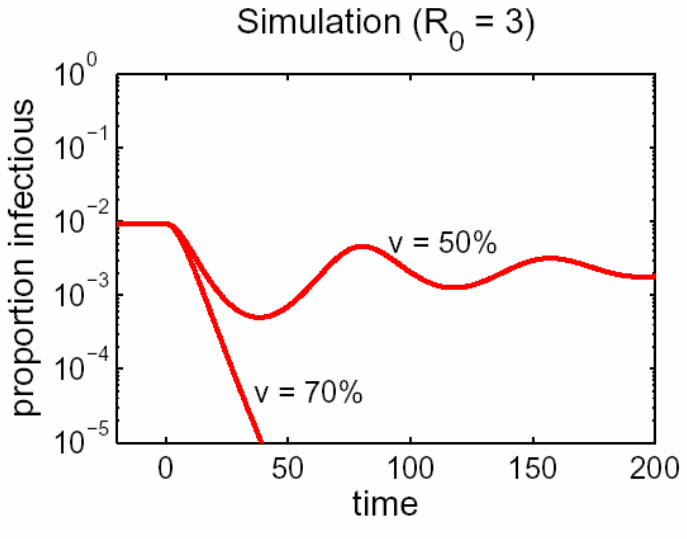


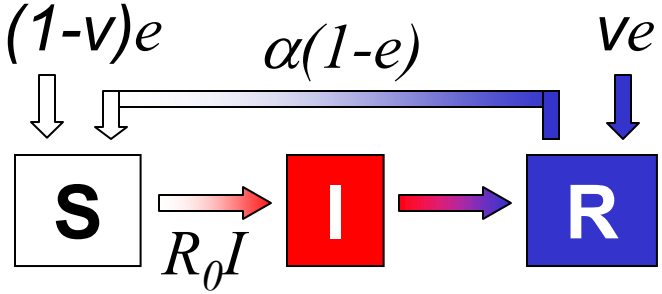
***v*: vaccination coverage**

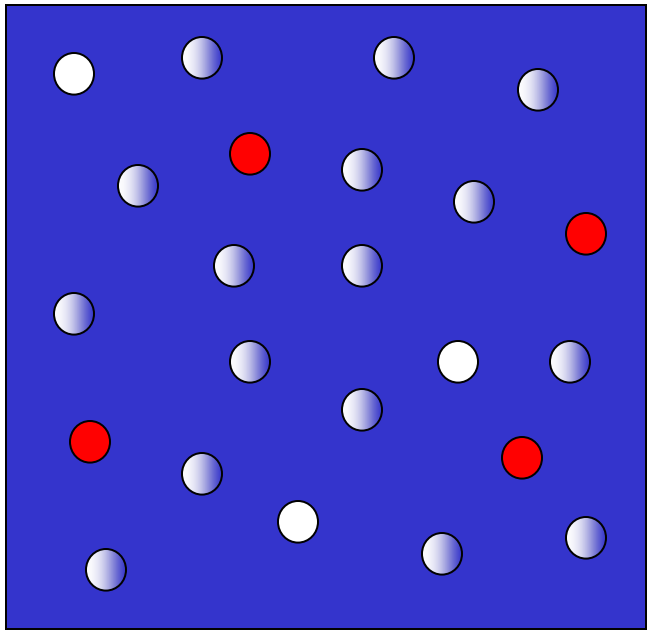


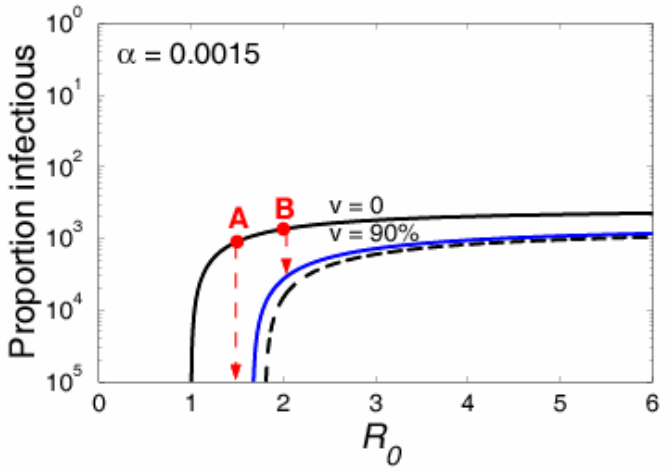


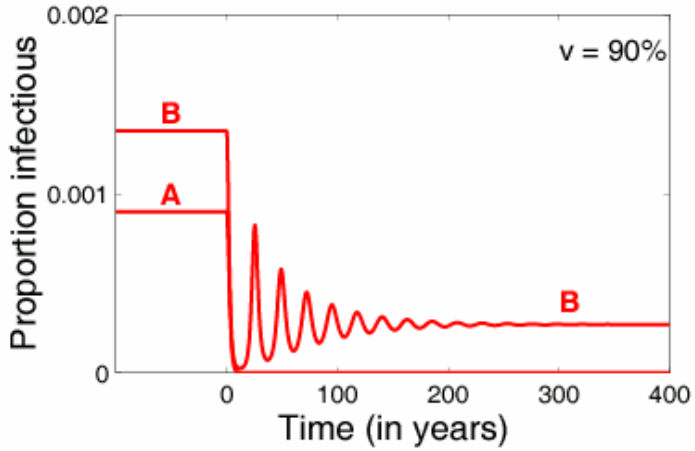
Vaccination – Temporary immunity model

Waning of immunity poses a major obstacle on disease eradication.





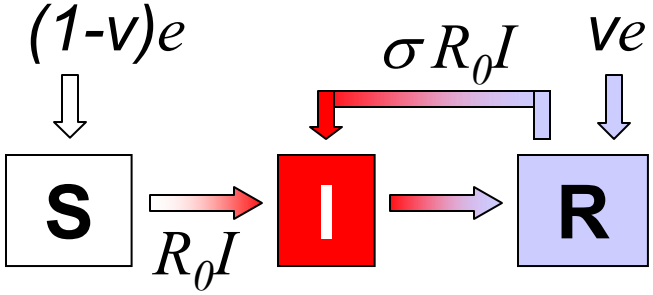


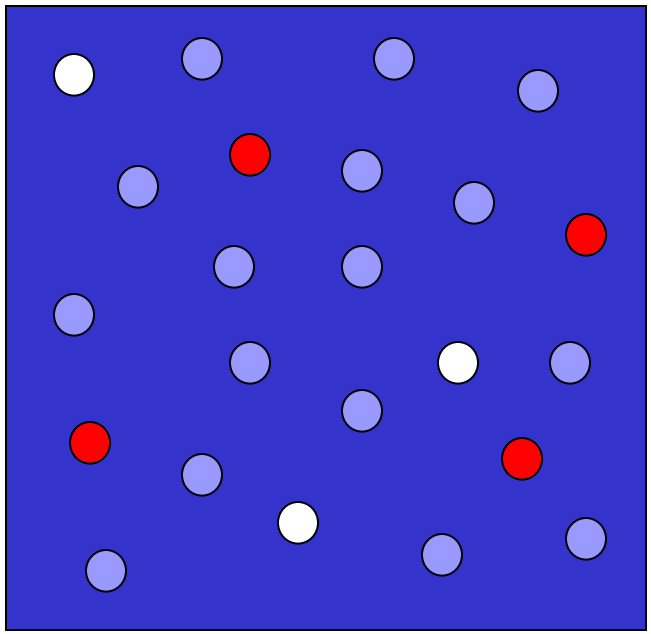


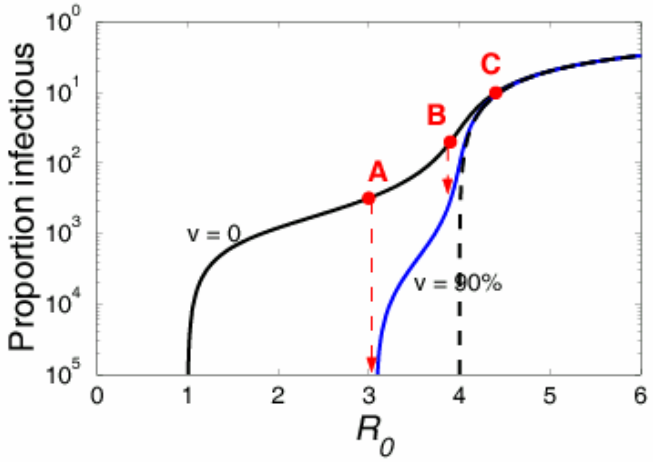
σ: susceptibility reduction factor

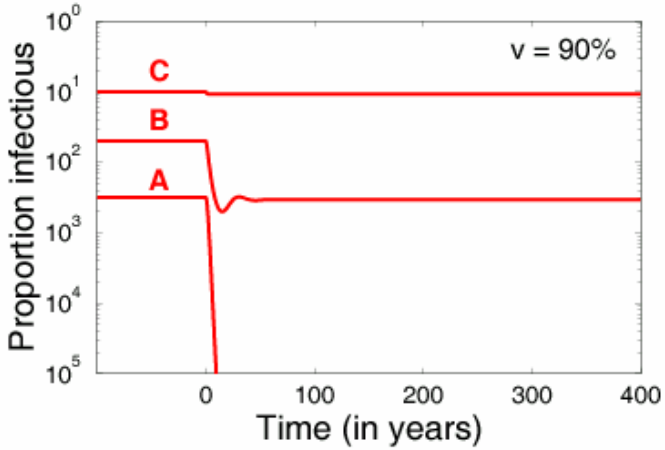
Vaccination – Partial immunity model

Partial immunity creates a **reinfection threshold**, $R_0 = 1 / \sigma$, above which the prevalence of infection is insensitive to vaccination.



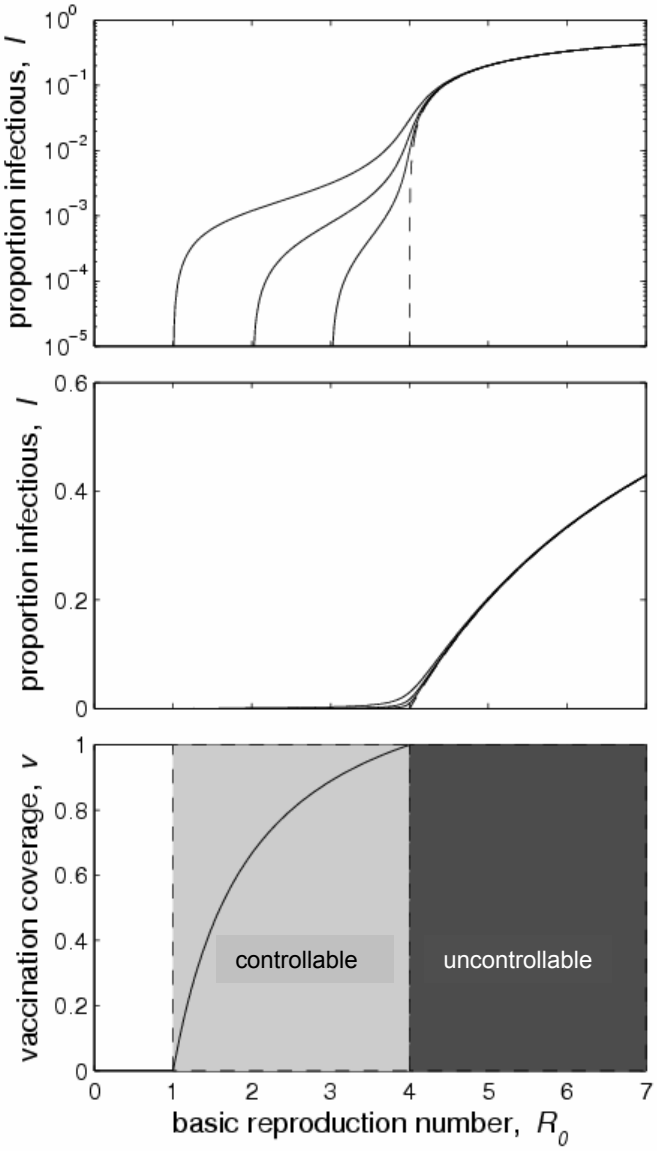






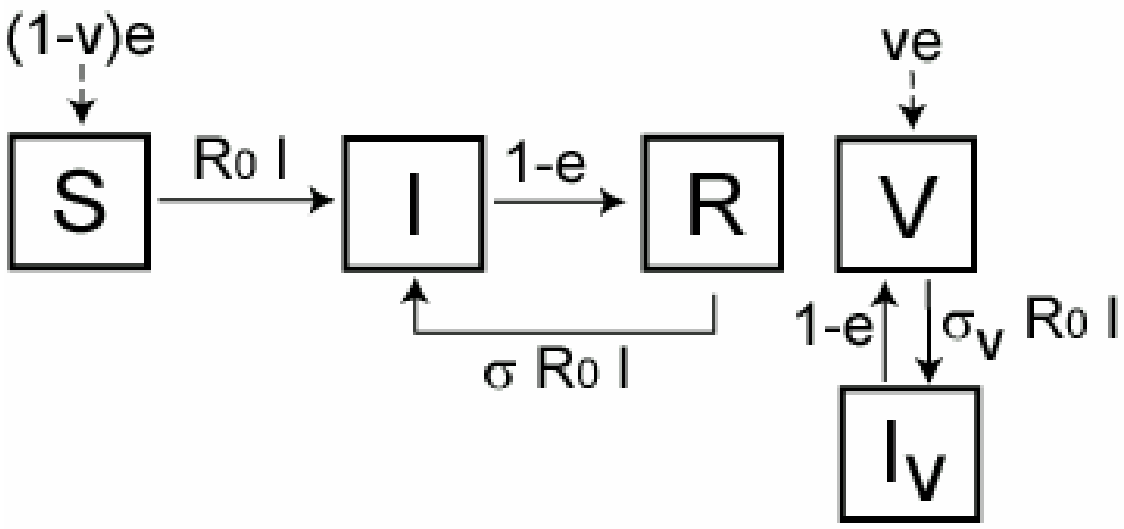
σ: susceptibility reduction factor

Reinfection threshold



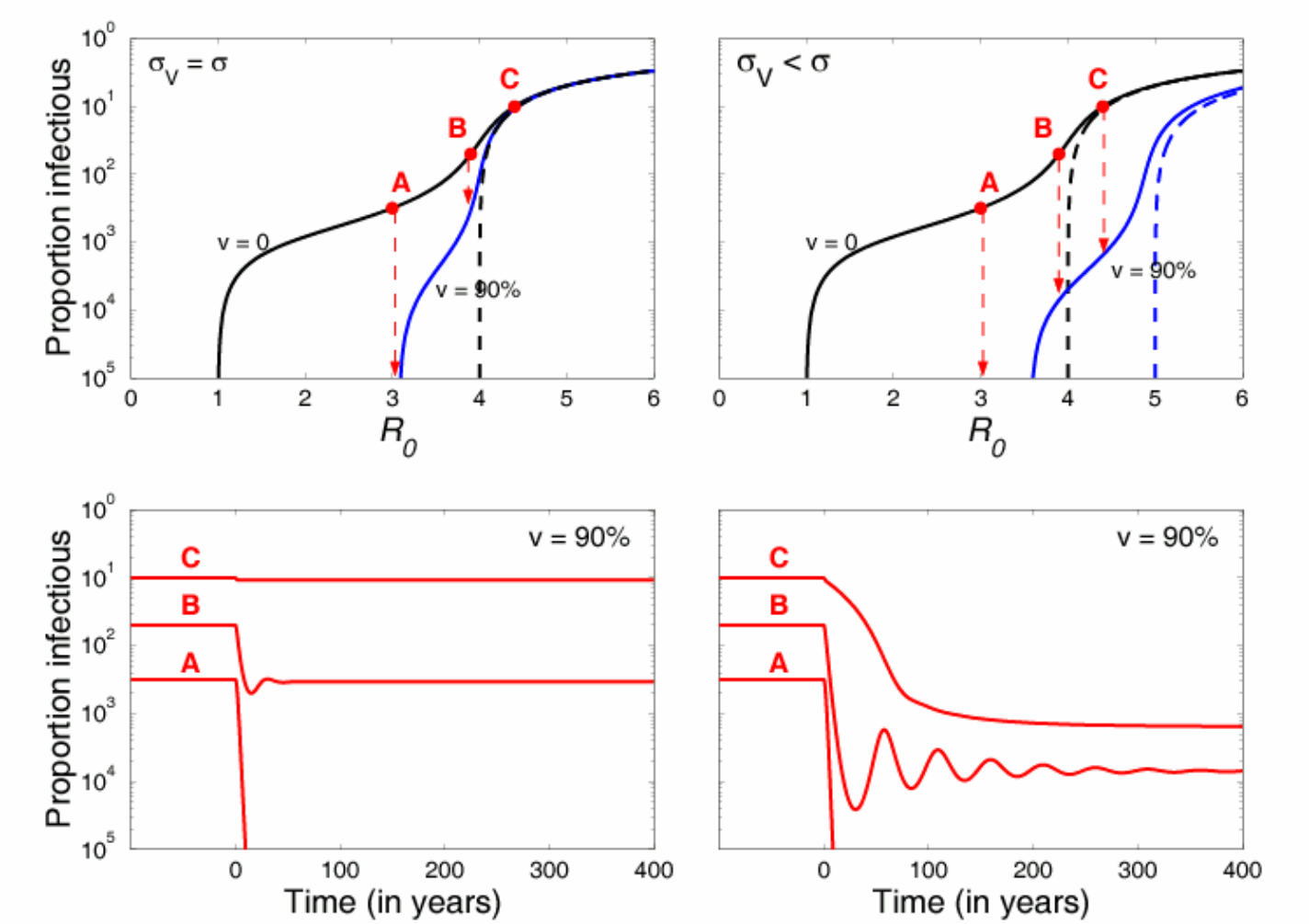
Vaccine more protective than natural immunity

No existing vaccine confers a level protection that is superior than that induced by natural infection. However, this is a prime goal in vaccine development research. In order to predict the epidemiological impact of such vaccine we need an extention to the partial immunity model.

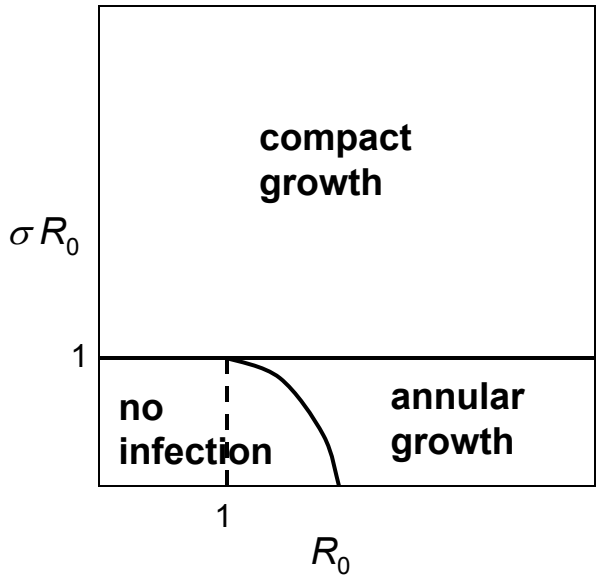


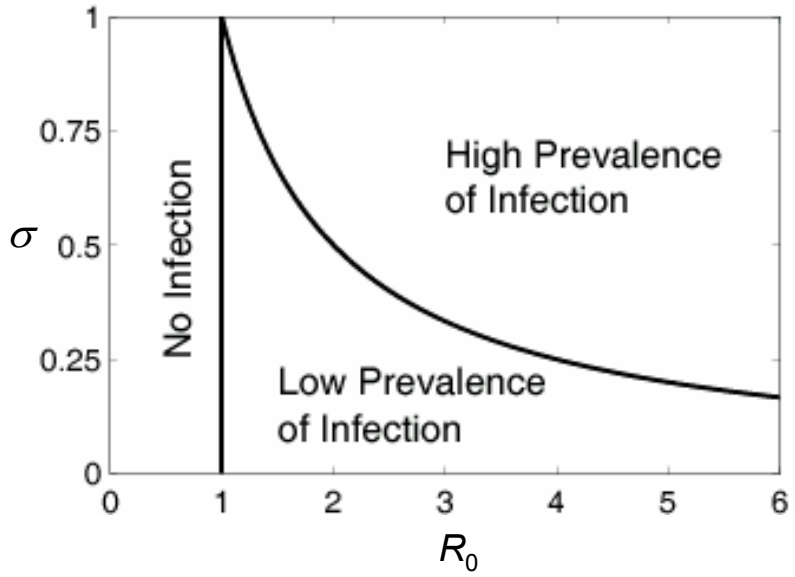
The vaccine is more potent than natural infection iff $\sigma_V < \sigma$.

Vaccine more protective than natural immunity



Back to Grassberger et al.





Grassberger, Chaté, Rousseau (1997) Spreading in media with long-time memory. Phys. Rev. E 55, 2488-2495.

Stollenwerk N, Gökaydin D, Hilker FM, van Noort SP, Gomes MGM 2007 The reinfection threshold is the mean field version of the transition between annular and compact growth in spatial models (submitted).

Gomes MGM, White LJ, Medley GF (2004) Infection, reinfection, and vaccination under suboptimal immune protection: epidemiological perspectives. *J. Theor. Biol.* 228, 539-549.

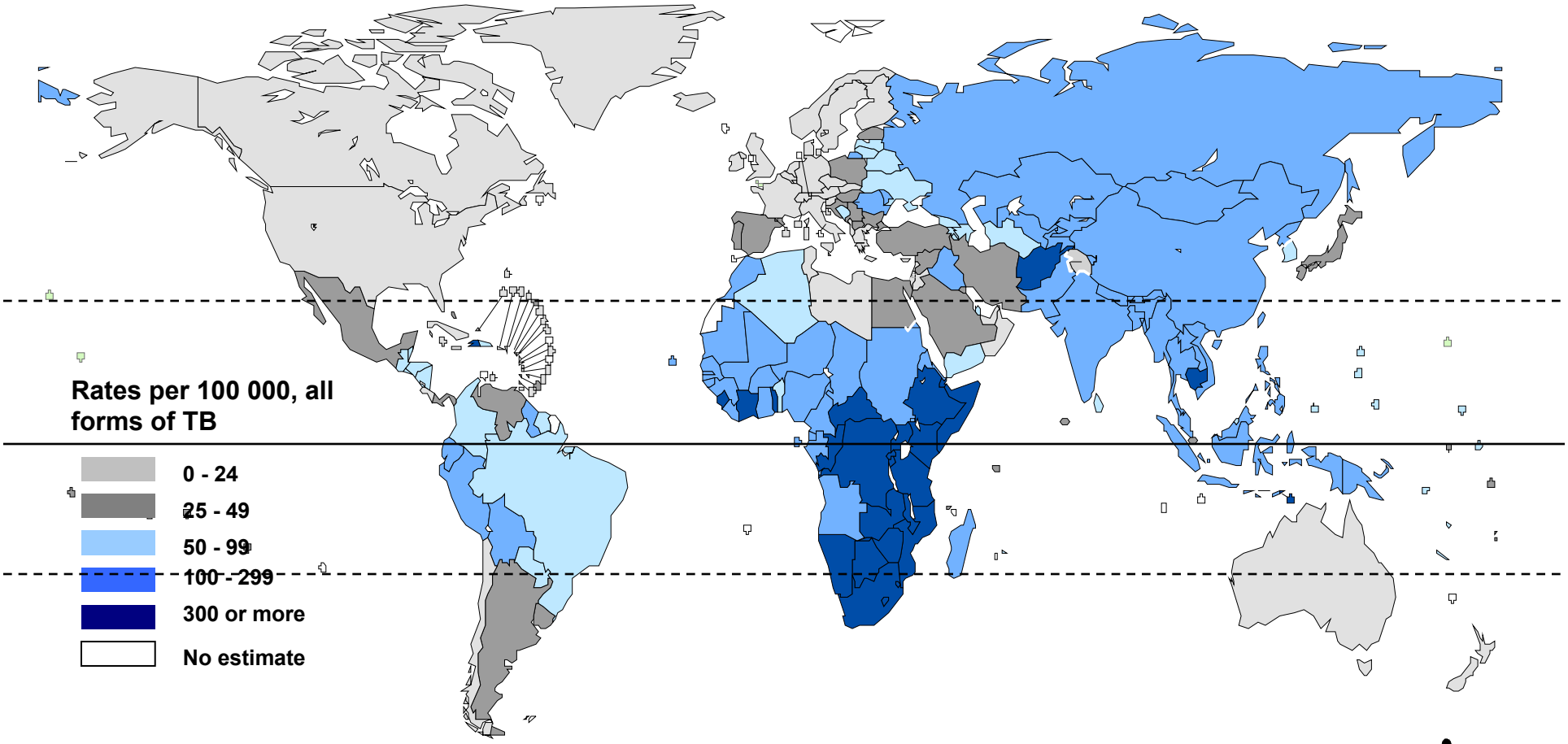
Breban R, Blower S (2005) The reinfection threshold does not exist. *J. Theor. Biol.* 235, 151-152.

Gomes MGM, White LJ, Medley GF (2005) The reinfection threshold. *J. Theor. Biol.* 236, 111-113.


Break

Tuberculosis

Estimated TB incidence rate, 2003



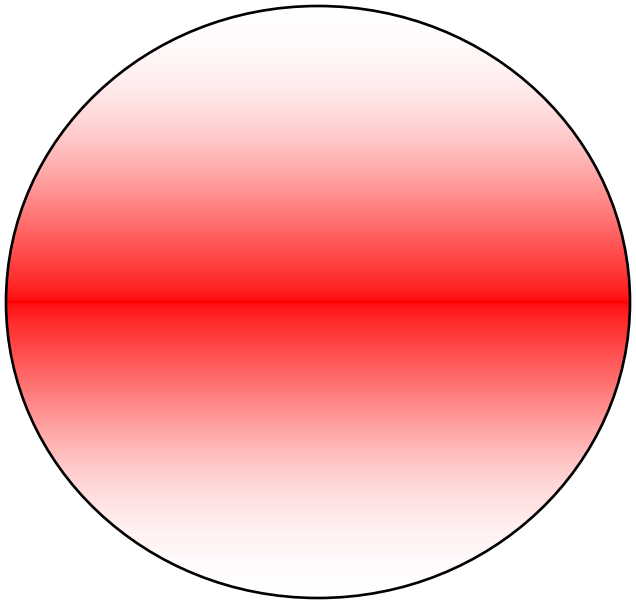
The designations employed and the presentation of material on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. White lines on maps represent approximate border lines for which there may not yet be full agreement.

The BCG paradox – variable efficacy

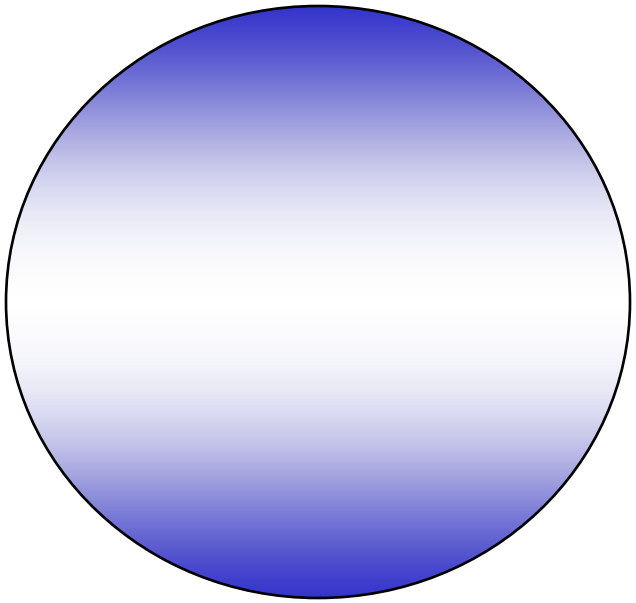
BCG was introduced in the global immunisation programme in 1973, and it is today one of the mostly widely used vaccines.

Estimates of its efficacy vary from 0% to 80%, generating great controversy.

TB incidence

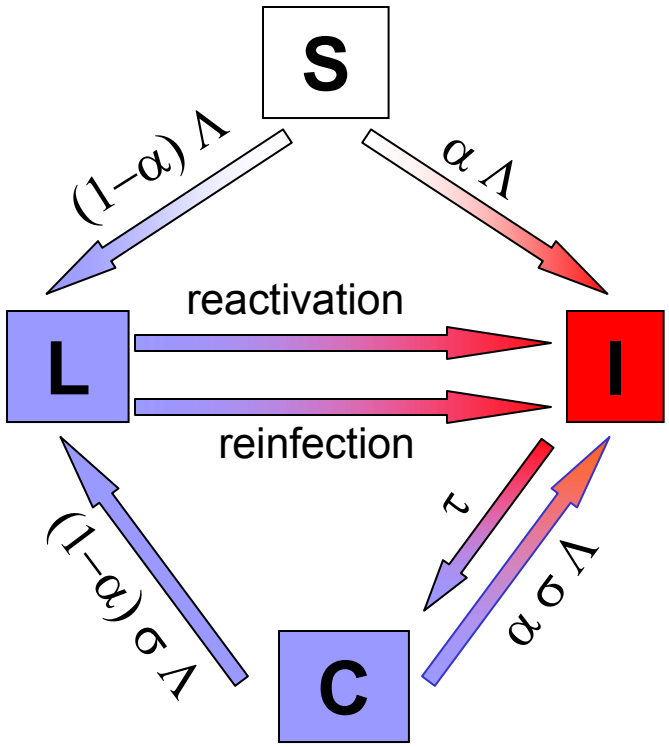


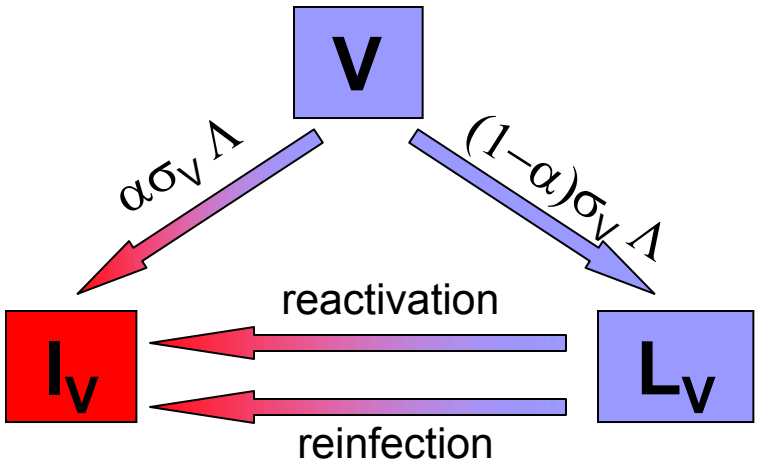
BCG efficacy



A mathematical model

Paula Rodrigues, IGC





Λ : rate of infection ($\Lambda = \beta\ (I + I_V)$)

α : proportion progressing to active TB in less than 2 years

ω : rate of reactivation of latent TB

A mathematical model

$$\frac{dS}{dt} = (1-v)\mu - \varepsilon\Lambda S - \mu S$$

$$\frac{dI}{dt} = \phi\Lambda\left(\varepsilon S + \sigma\left(C + L\right)\right) + \omega L - \left(\tau + \mu\right)I$$

$$\frac{dL}{dt} = \left(1-\phi\right)\Lambda\left(\varepsilon S + \sigma C\right) - \phi\sigma\Lambda L - \left(\omega + \mu\right)L$$

$$\frac{dC}{dt} = \tau I - \left(\sigma\Lambda + \mu\right)C.$$

Non vaccinated

Vaccinated

$$\frac{dV}{dt} = v\mu - \sigma_V \Lambda V - \mu V$$

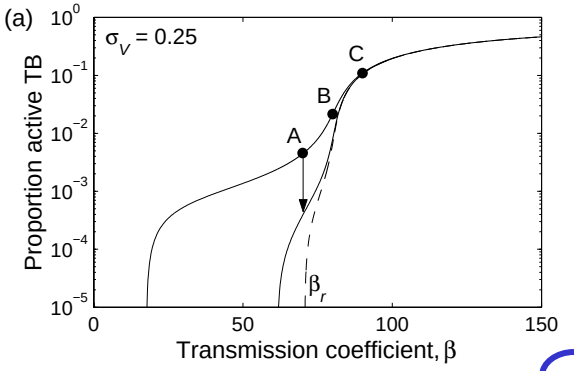
$$\frac{dI_V}{dt} = \phi\sigma_V \Lambda\left(V + L_V\right) + \omega L_V - \left(\tau + \mu\right)I_V$$

$$\frac{dL_V}{dt} = \left(1-\phi\right)\sigma_V \Lambda V - \phi\sigma_V \Lambda L_V - \left(\omega + \mu\right)L_V.$$

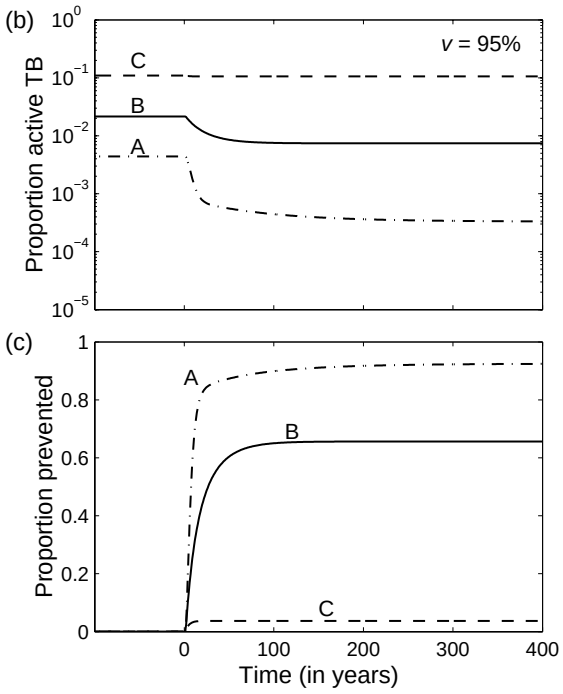
Model predicts variable efficacy

Simulation of a vaccination programme in 3 regions: **A**, **B**, **C**.

Endemic equilibrium



Simulations

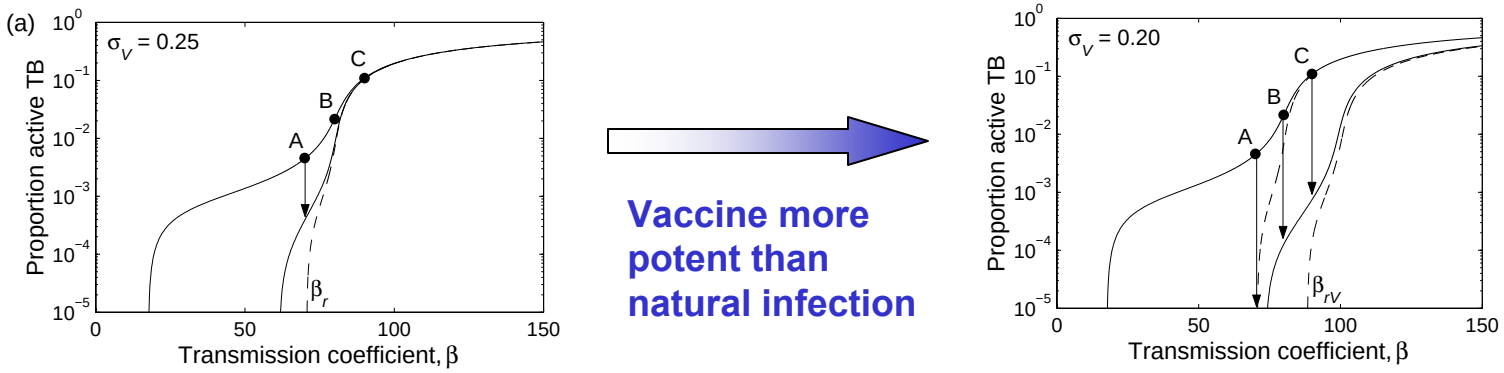


Effectiveness of the same vaccination programme in the 3 regions

The vaccine is highly effective where incidence is low, but it has no effect where incidence is high.

Perspectives for control

A major focus of TB research is the development of more potent vaccines. Mathematical models play an important role in the definition of a “good vaccine” and a “good intervention”, from the view point of global control.



Alternative control measures are detection and treatment of both active and latent TB cases, but variable efficacy is also expected. The globalisation of planning is essential.

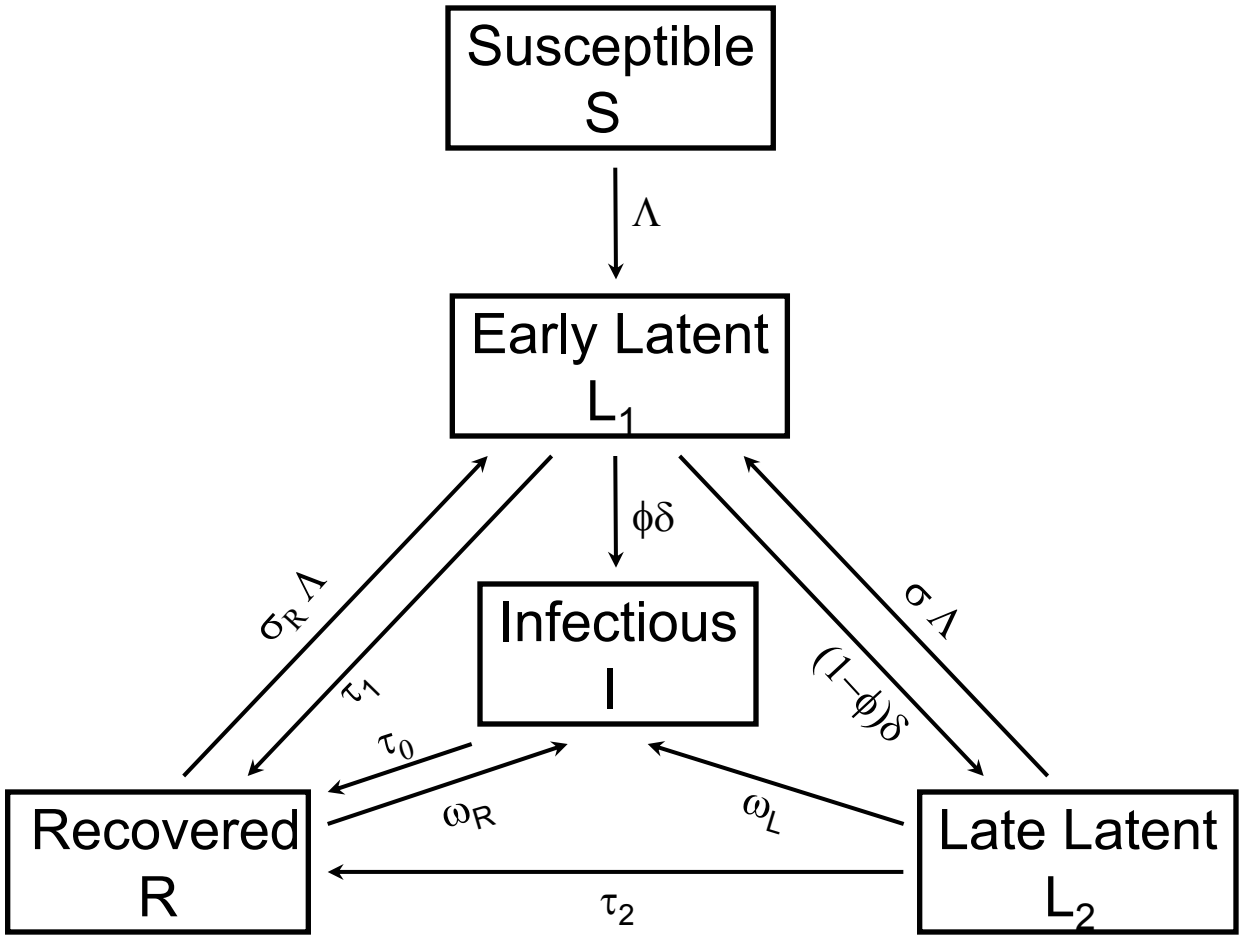
The potential of post-exposure interventions

• 1/3 of the world population (~10^9 individuals) is infected, the majority in latent form;

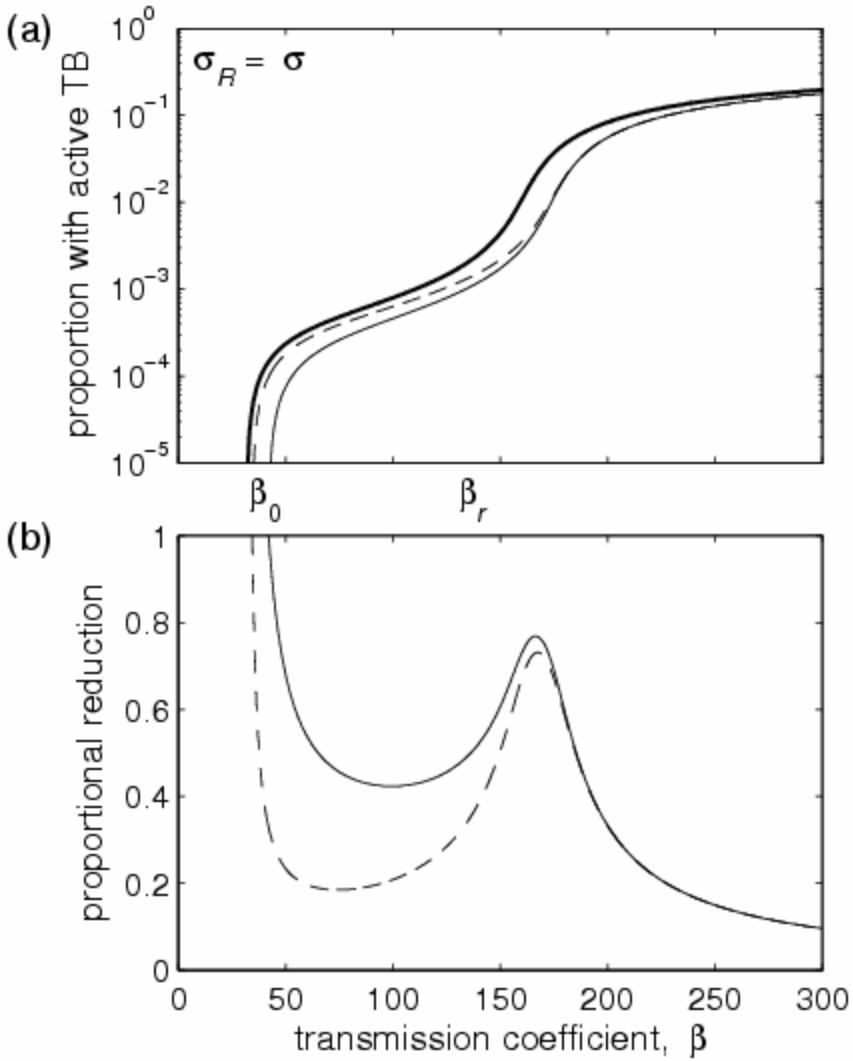
• It is estimated that 10% (~10^8 individuals) will develop pulmonary tuberculosis;

• This immense reservoir can only be controlled by post-exposure interventions: chemoprophylaxis or prophylactic vaccines.

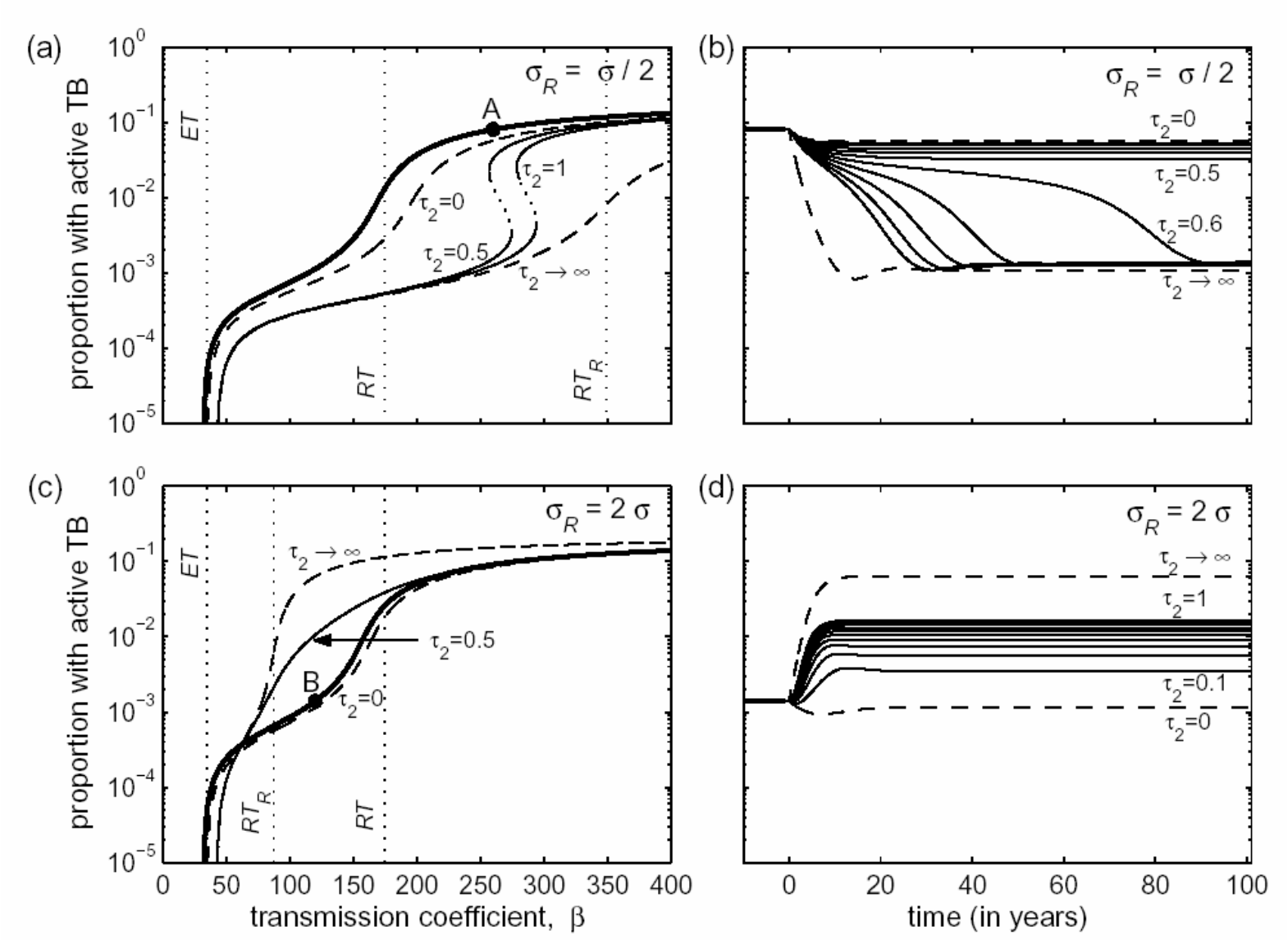
Treatment of latent infection



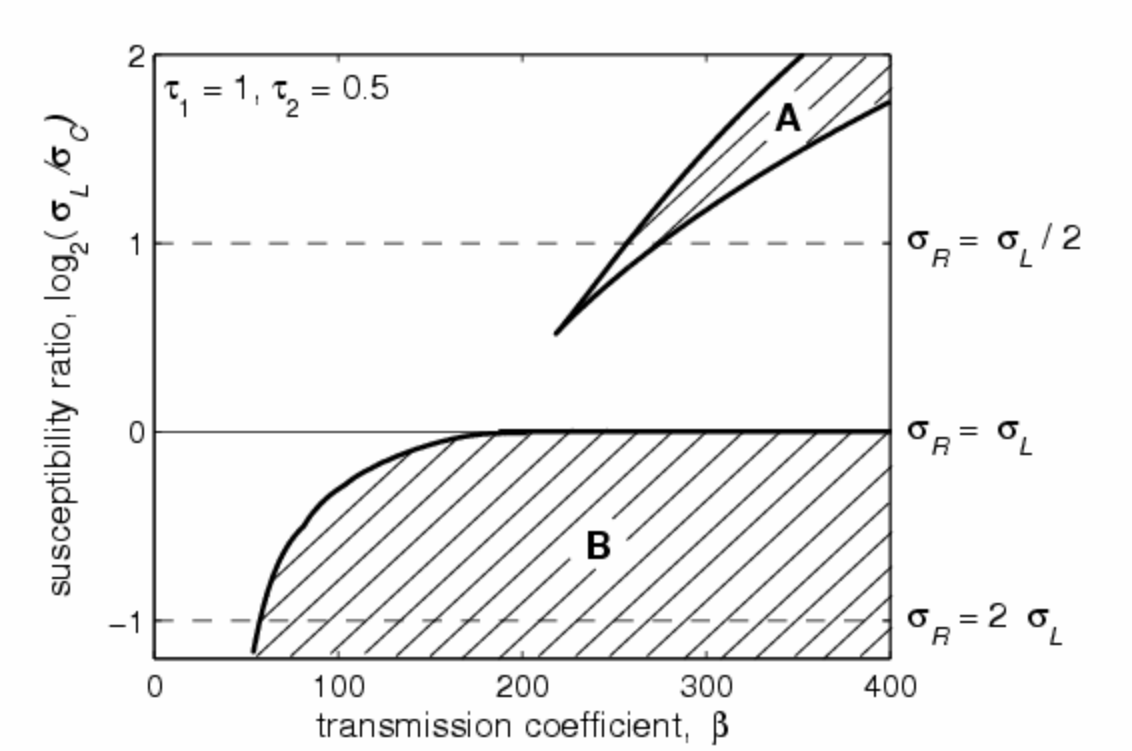
Widespread treatment of latents does not benefit all populations



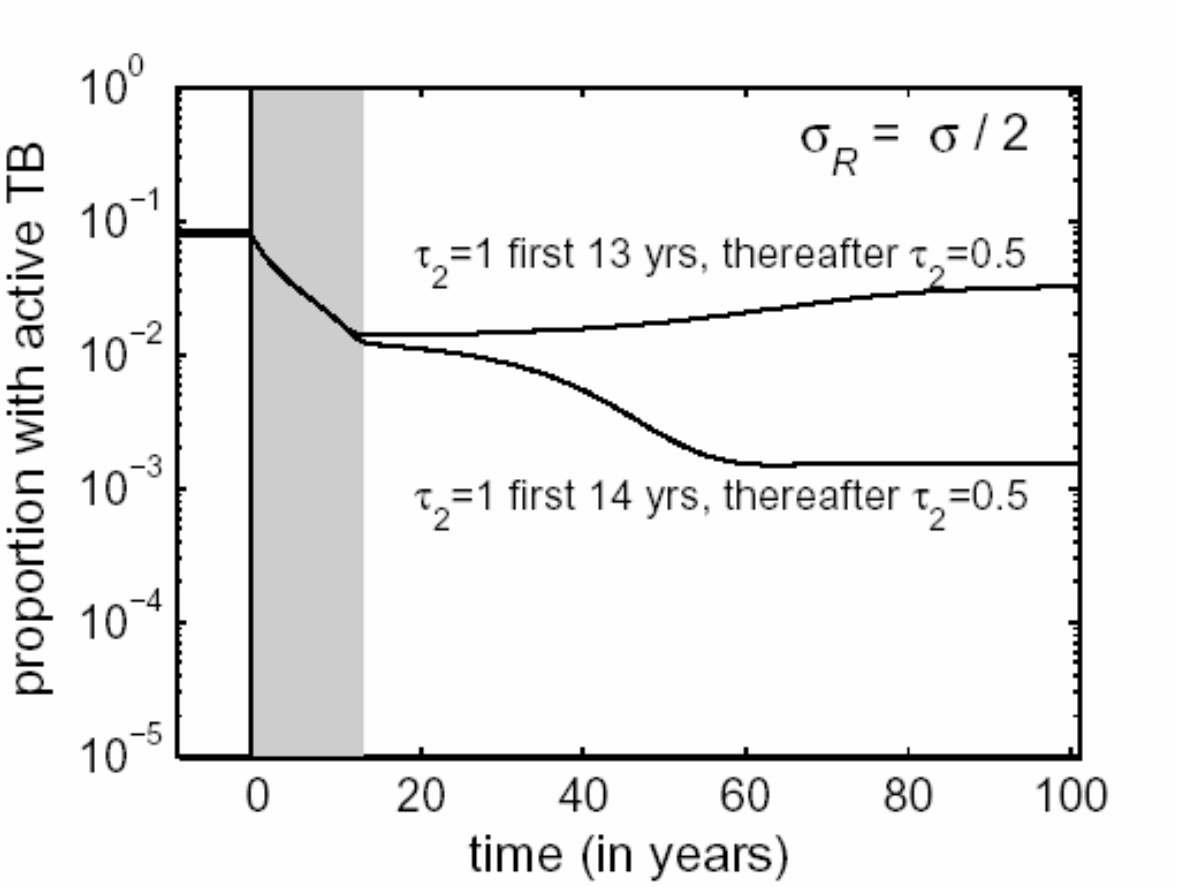
Altered susceptibility after treatment



Summary


$\tau_1 = 1, \tau_2 = 0.5$
A
B
$\sigma_R = \sigma_L / 2$
$\sigma_R = \sigma_L$
$\sigma_R = 2\ \sigma_L$
susceptibility ratio, $\log_2(\sigma_L / \sigma_C)$
transmission coefficient, β
2
1
0
−1
0
100
200
300
400

Intervention planning



Summary

1. Partial immunity induces a threshold in transmission above which reinfection is high enough to overcome natural immunity;

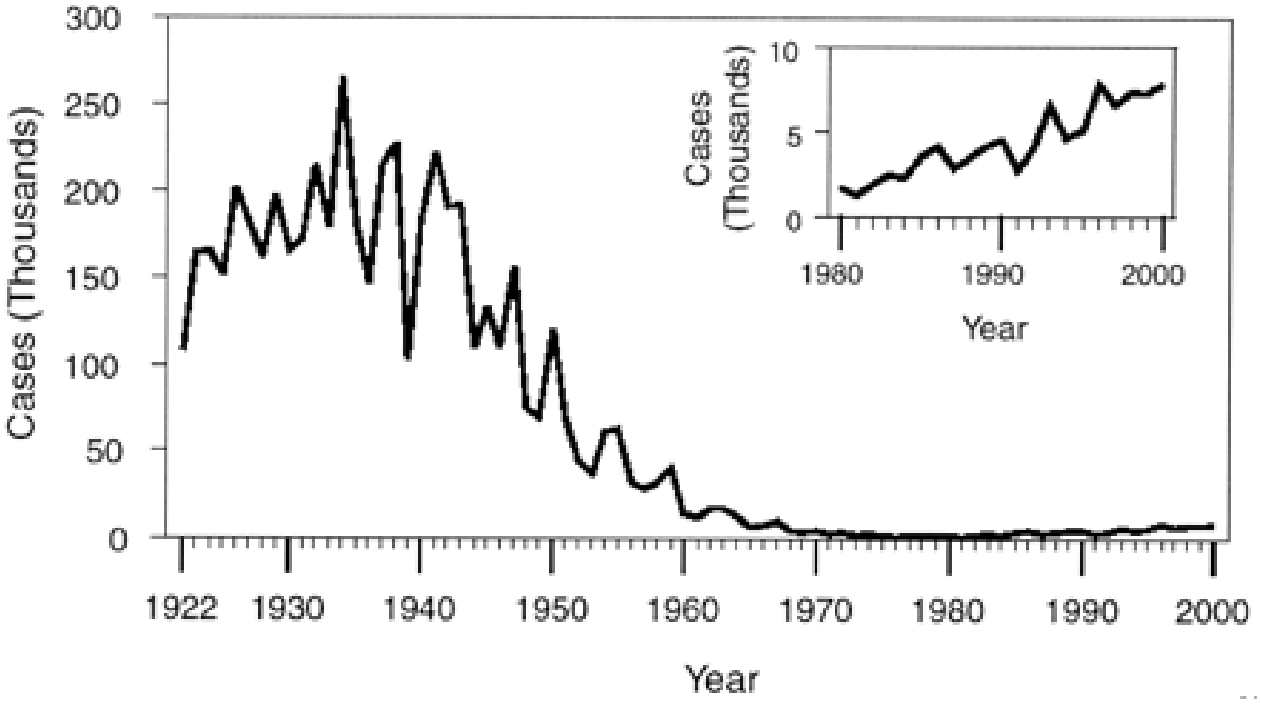
2. A vaccine will be ineffective above the reinfection threshold unless it does better than naturally acquired immunity;

3. Post-exposure interventions can have a wide range of outcomes, making it very important to characterise their mode of action;

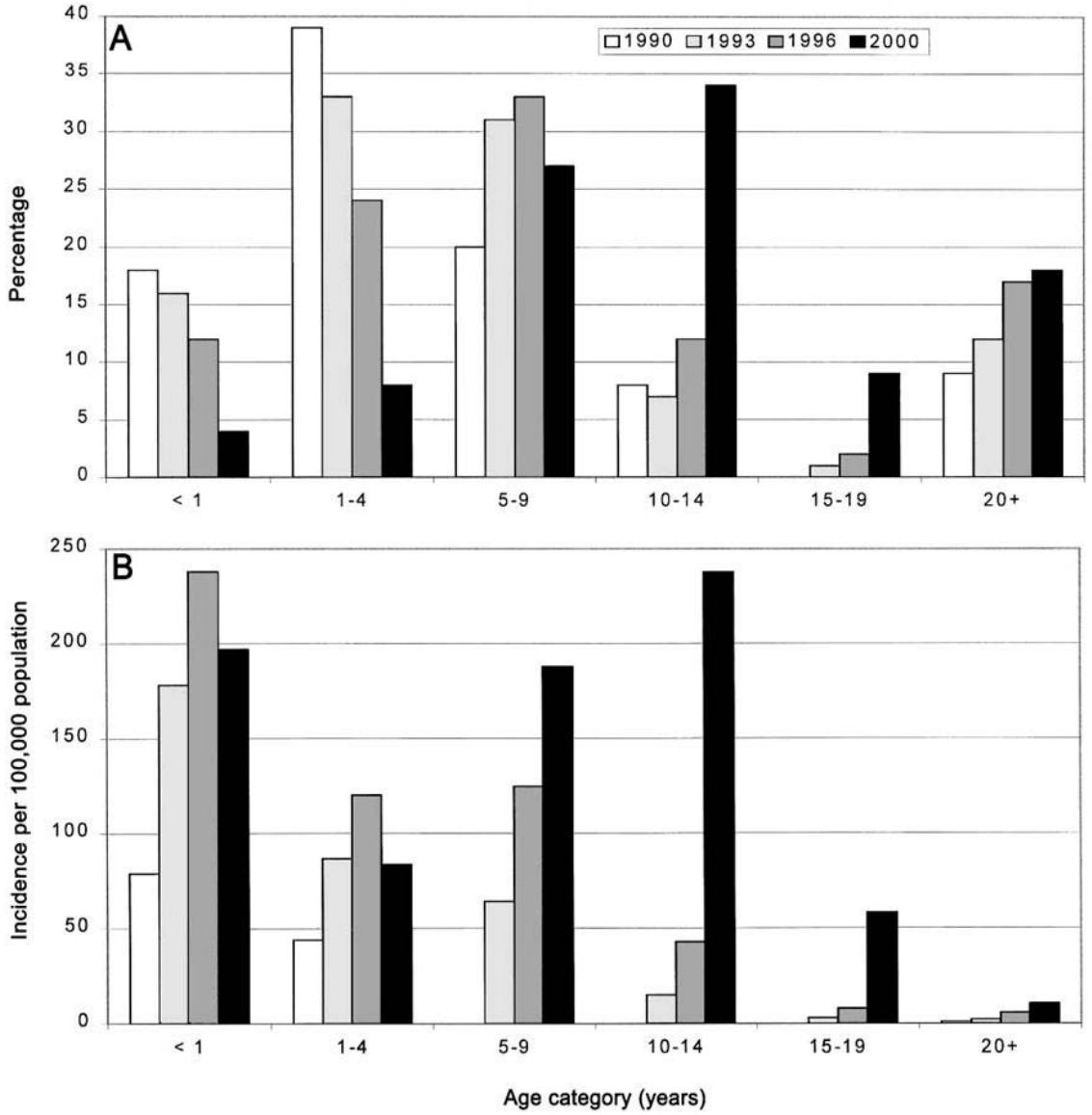
4. Post-exposure interventions that reduce both the risk of reactivation and the risk of reinfection can have minor of major effects depending on the design of the control programme.

Pertussis

Pertussis – resurgence

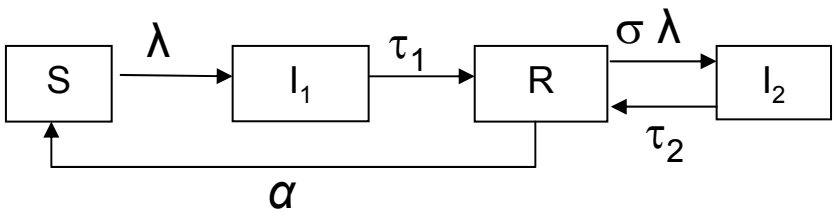


Increasing age at infection



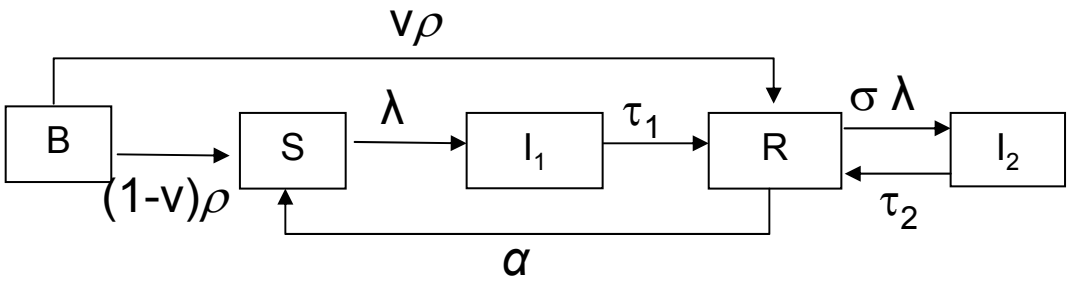
Basic model

Ricardo Águas, IGC

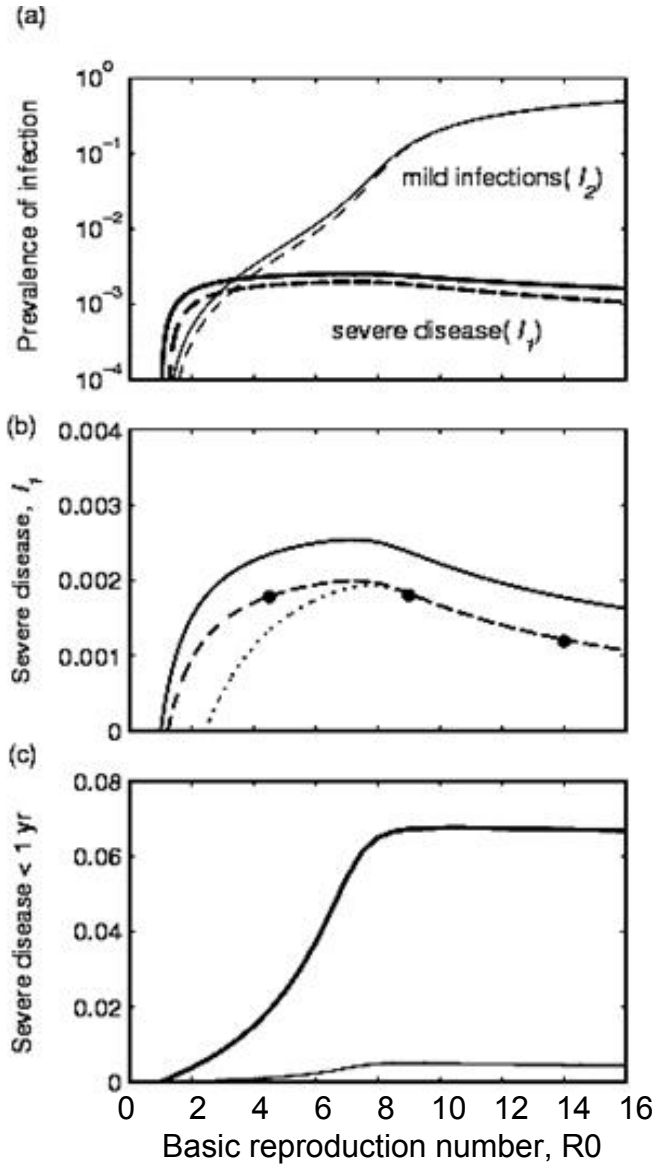


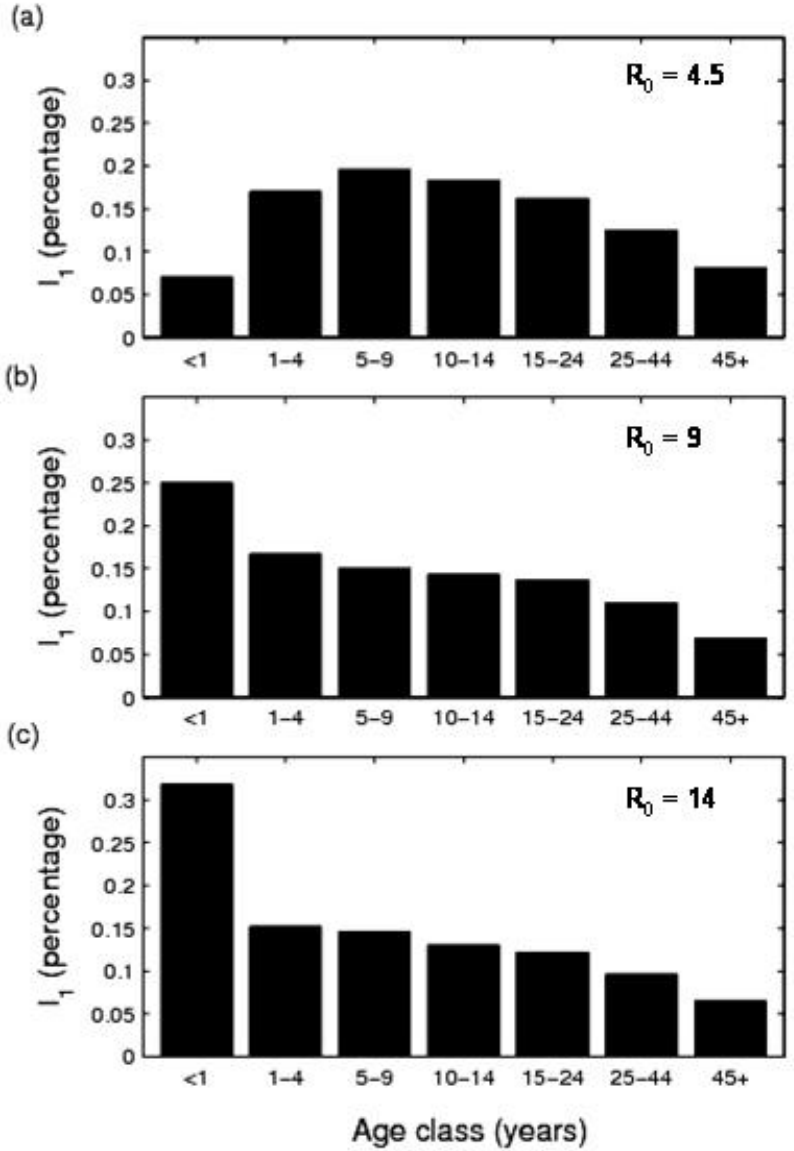
Basic model

Ricardo Águas, IGC

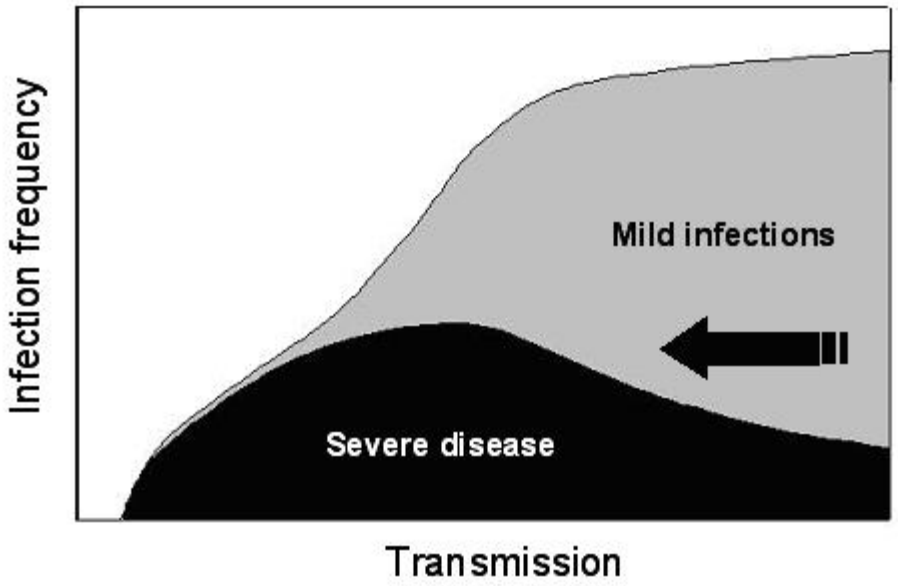


Pertussis – Endemic stability





Increasing disease with decreasing transmission



Model equations

$$\frac{dS_0}{dt} = (1 - v_0)\mu + \alpha R - S_0(\lambda + \mu)$$

$$\frac{dR}{dt} = v_0\mu + \tau_1 I_1 + \tau_2 I_2 - R(\sigma\lambda + \alpha + \mu)$$

$$\frac{dI_1}{dt} = \lambda S_0 - I_1(\tau_1 + \mu)$$

$$\frac{dI_2}{dt} = \sigma\lambda R - I_2(\tau_2 + \mu)$$

Age and time – equations

$$\frac{\partial S_0}{\partial t} + \frac{\partial S_0}{\partial a} = \alpha R - S_0(\lambda + v_0\mu + \mu)$$

$$\frac{\partial R}{\partial t} + \frac{\partial R}{\partial a} = v_0\mu + \tau_1 I_1 + \tau_2 I_2 - R(\sigma\lambda + \alpha + \mu)$$

$$\frac{\partial I_1}{\partial t} + \frac{\partial I_1}{\partial a} = \lambda S_0 - I_1(\tau_1 + \mu)$$

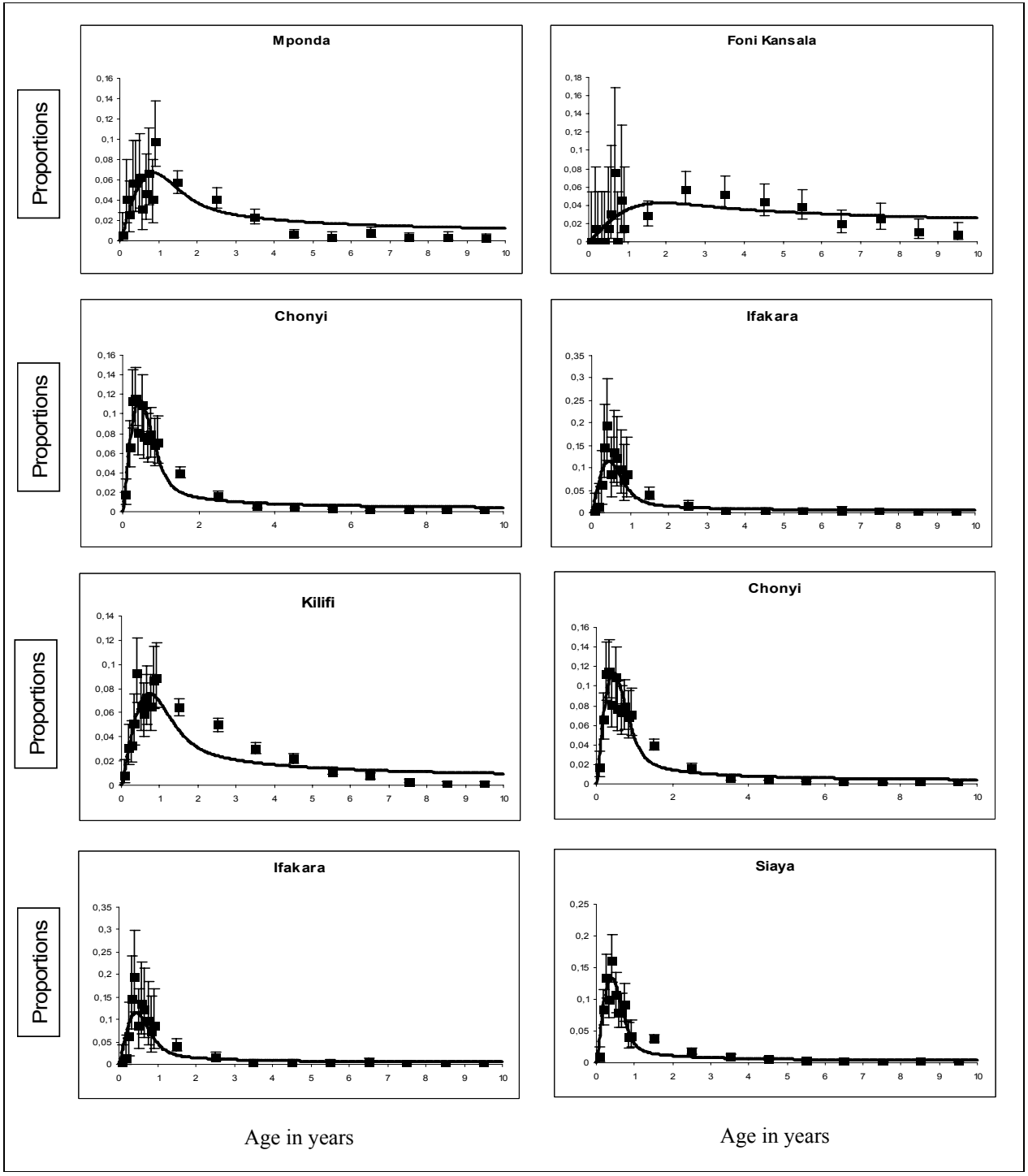
$$\frac{\partial I_2}{\partial t} + \frac{\partial I_2}{\partial a} = \sigma\lambda R - I_2(\tau_2 + \mu)$$

Boundary conditions:

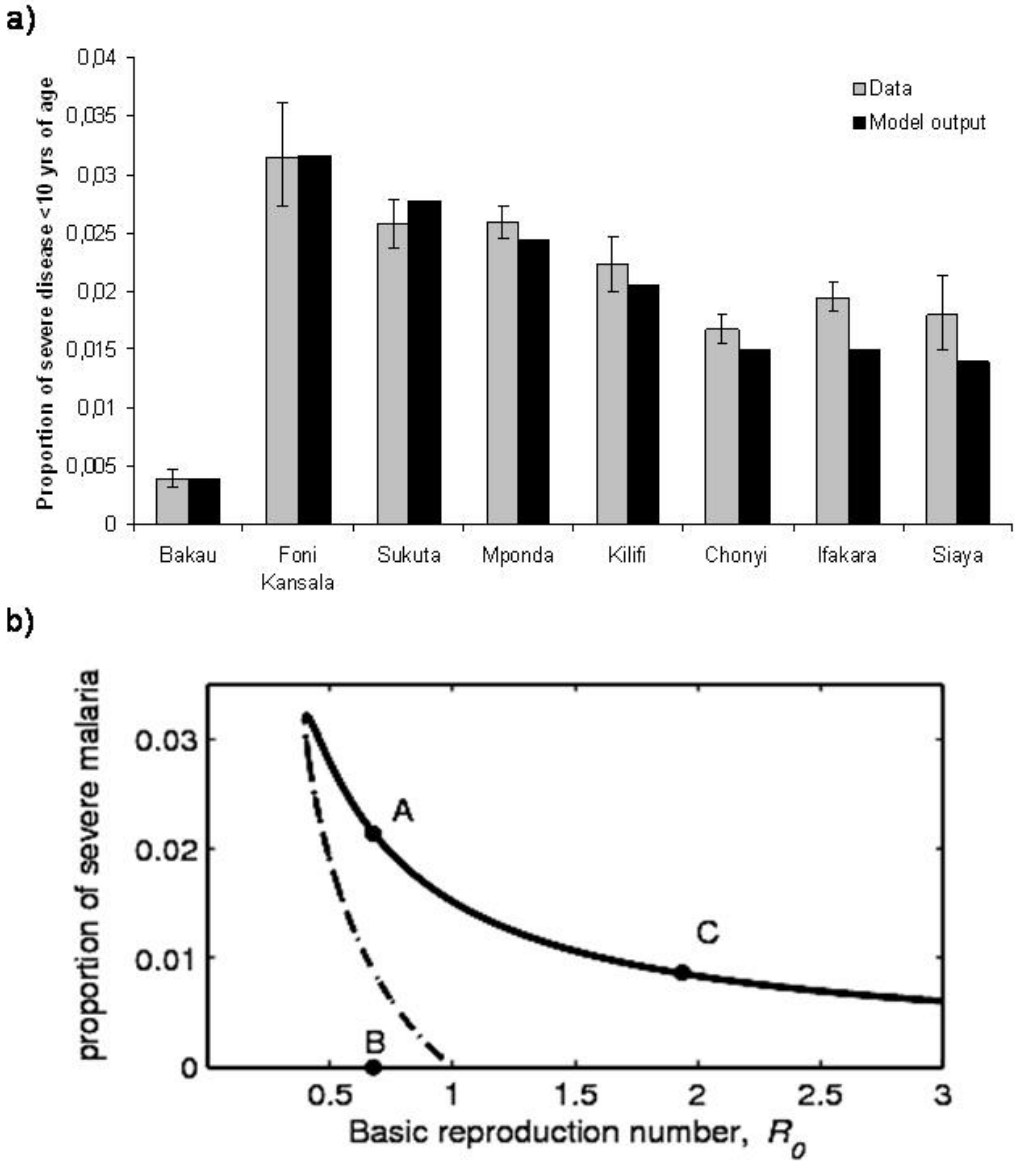
$$S_0(\mathrm{t},0) = \mu \qquad R(\mathrm{t},0) = I_1(\mathrm{t},0) = I_2(\mathrm{t},0) = 0$$

Malaria

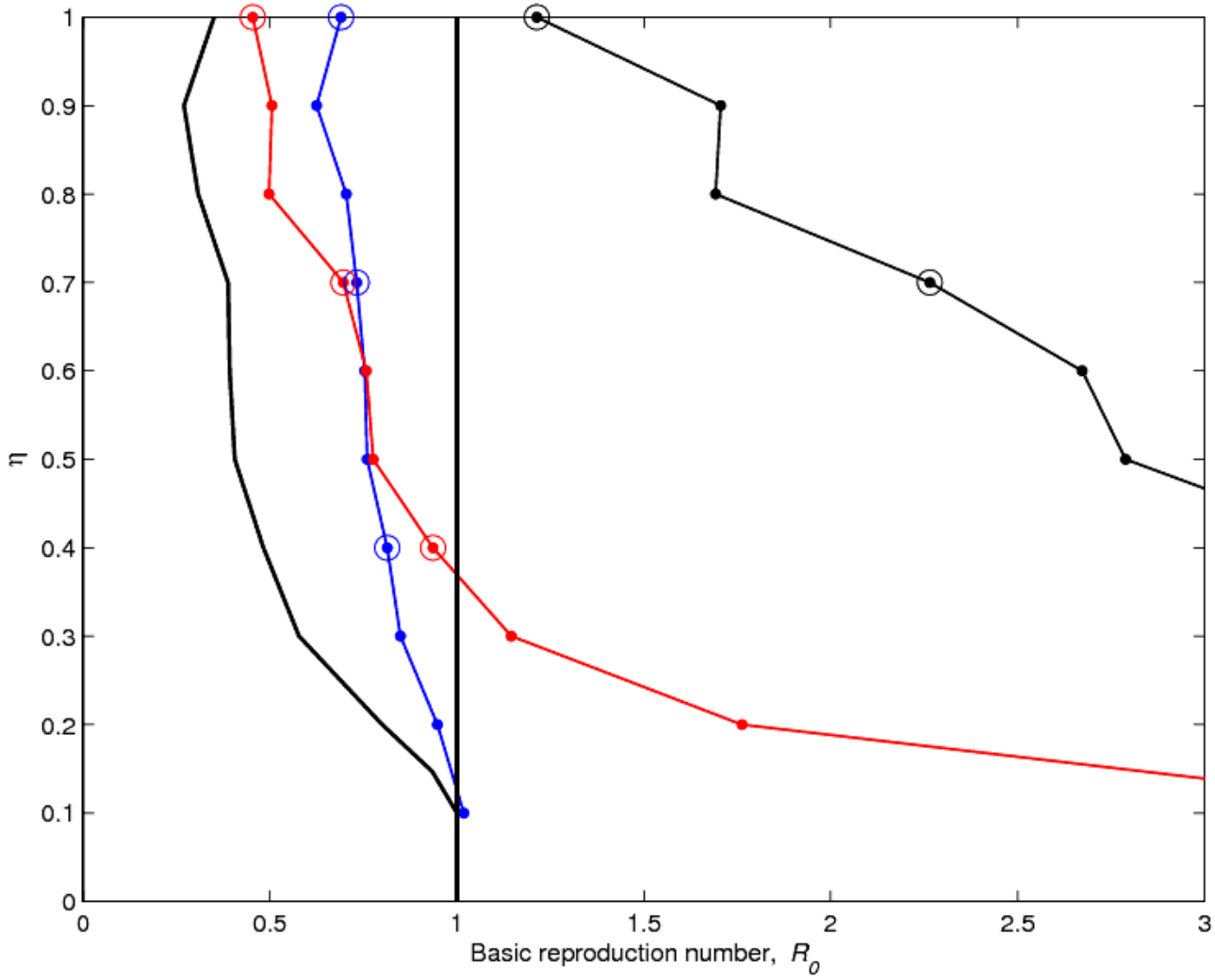
Malaria: Data from Sub-Saharan Africa



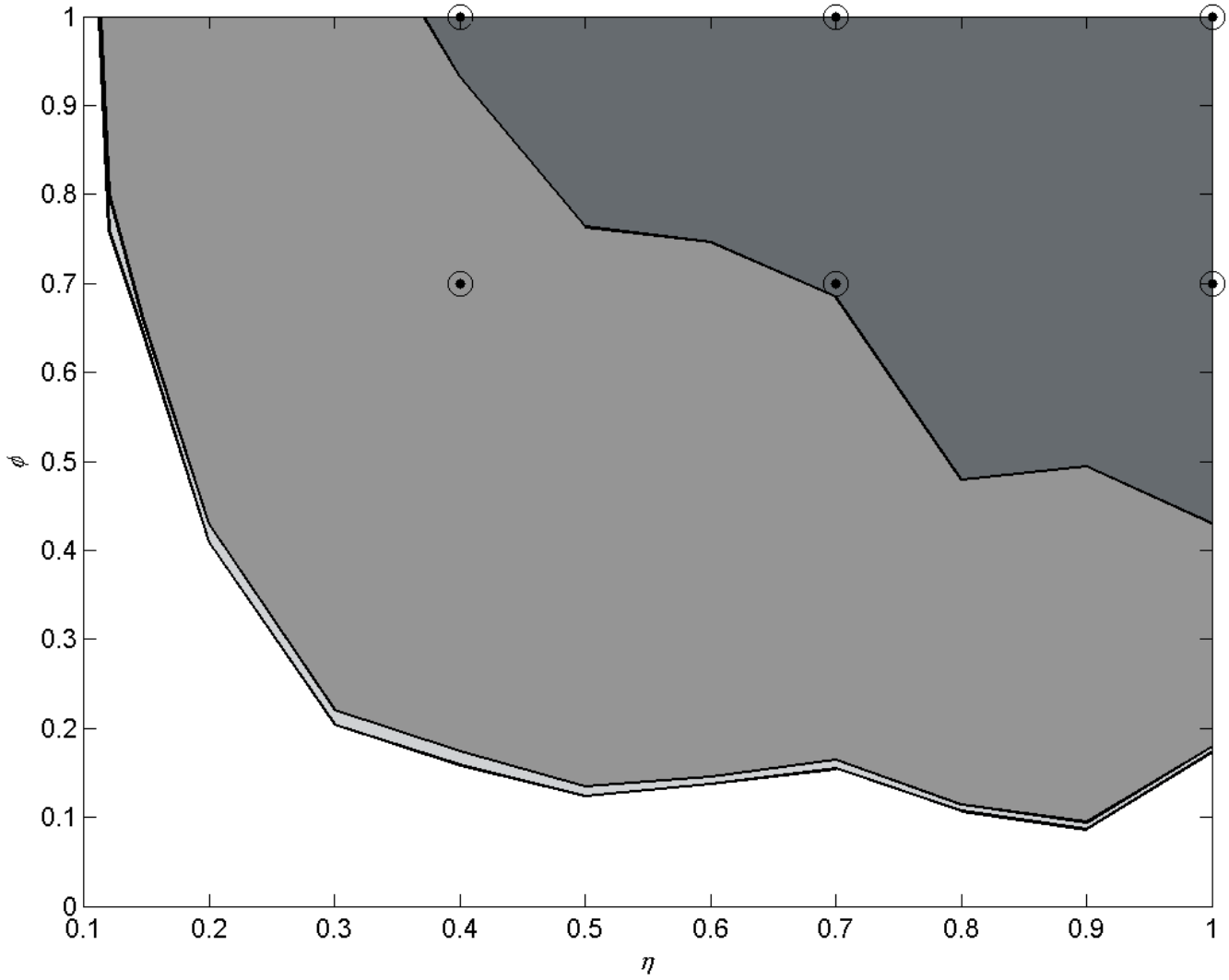
Malaria – endemic stability



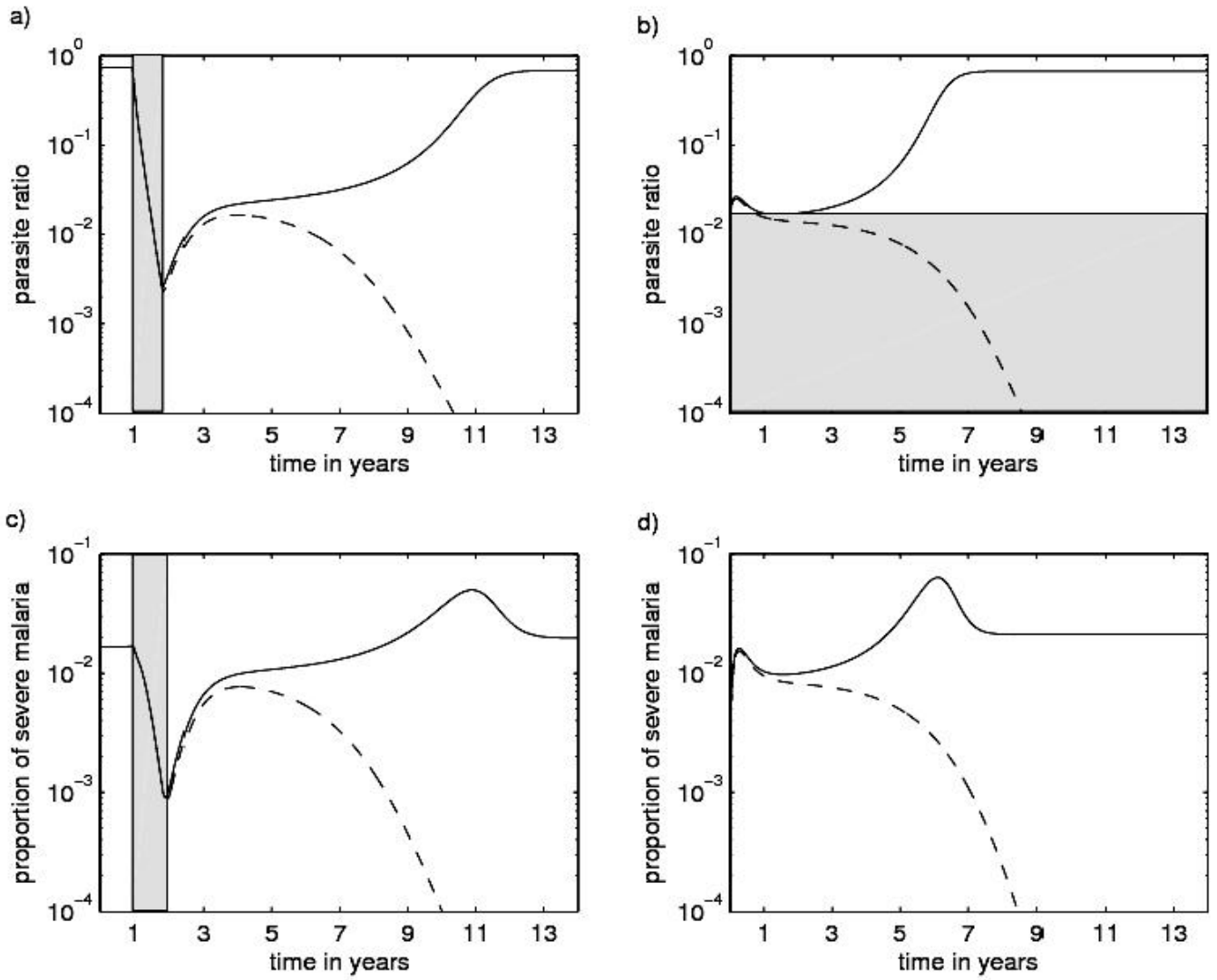
Malaria – sensitivity to reporting rate



Malaria – sensitivity to reduced infectivity

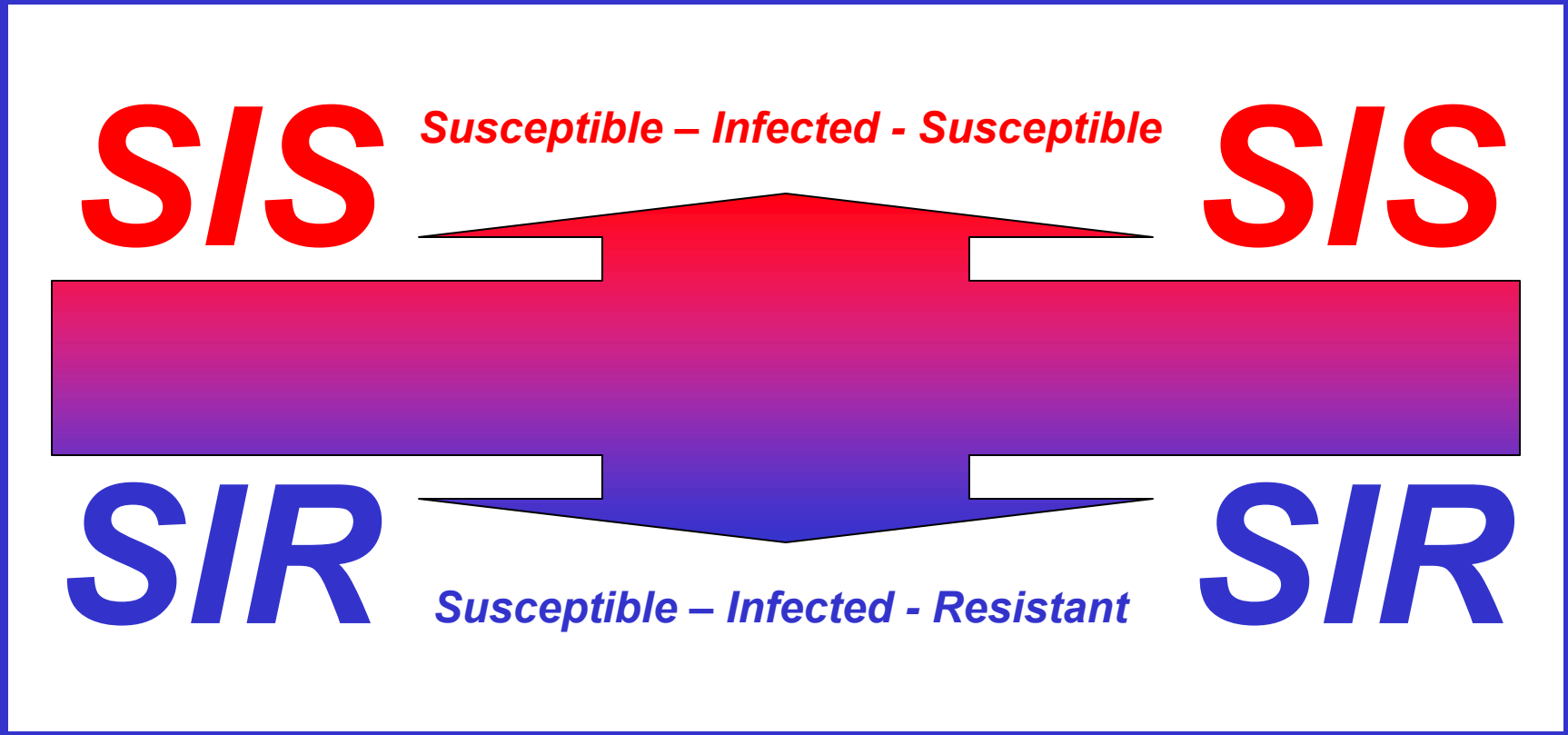


Malaria – intervention design



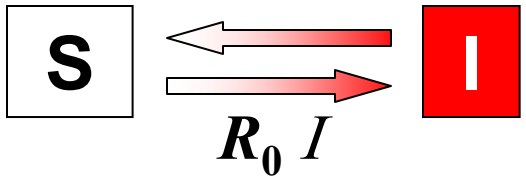

Break

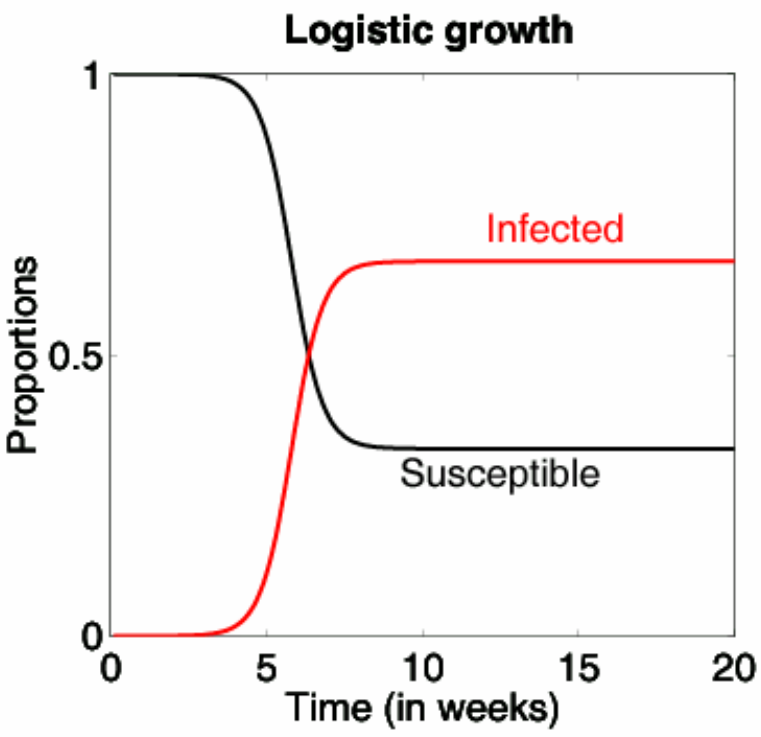
Multi-strain dynamics: the case of influenza



SIS model

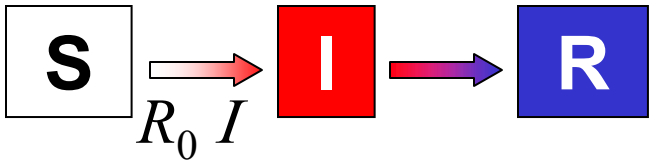
Appropriate for infections that induce no effective immunity (e.g. malaria).

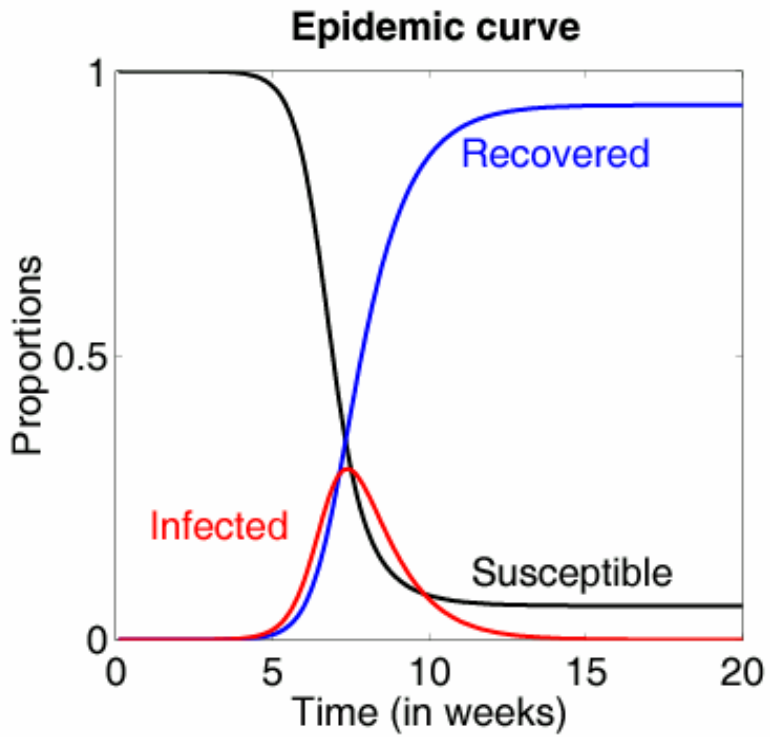




SIR model

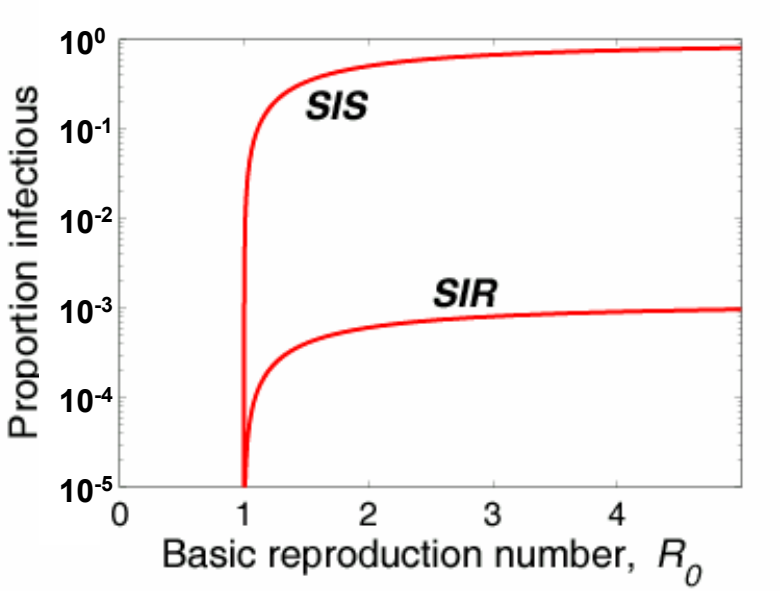
Appropriate for infections that induce a highly effective immunity (e.g. measles, mumps, rubella).



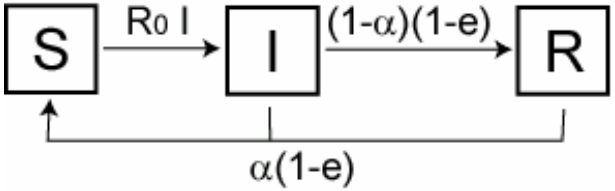


Intermediate models

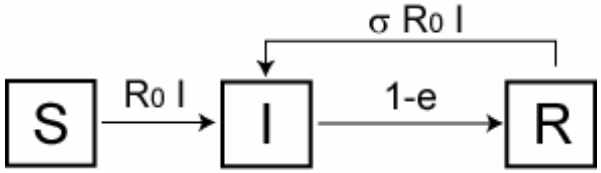
SIS and *SIR* steady states



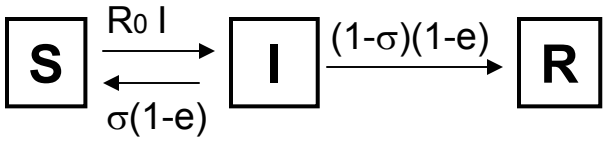
Temporary immunity



Partial immunity



Polarised immunity



Partial immunity and Polarised immunity

Partial immunity:

$$\dot{S} = e - R_0 IS - eS$$

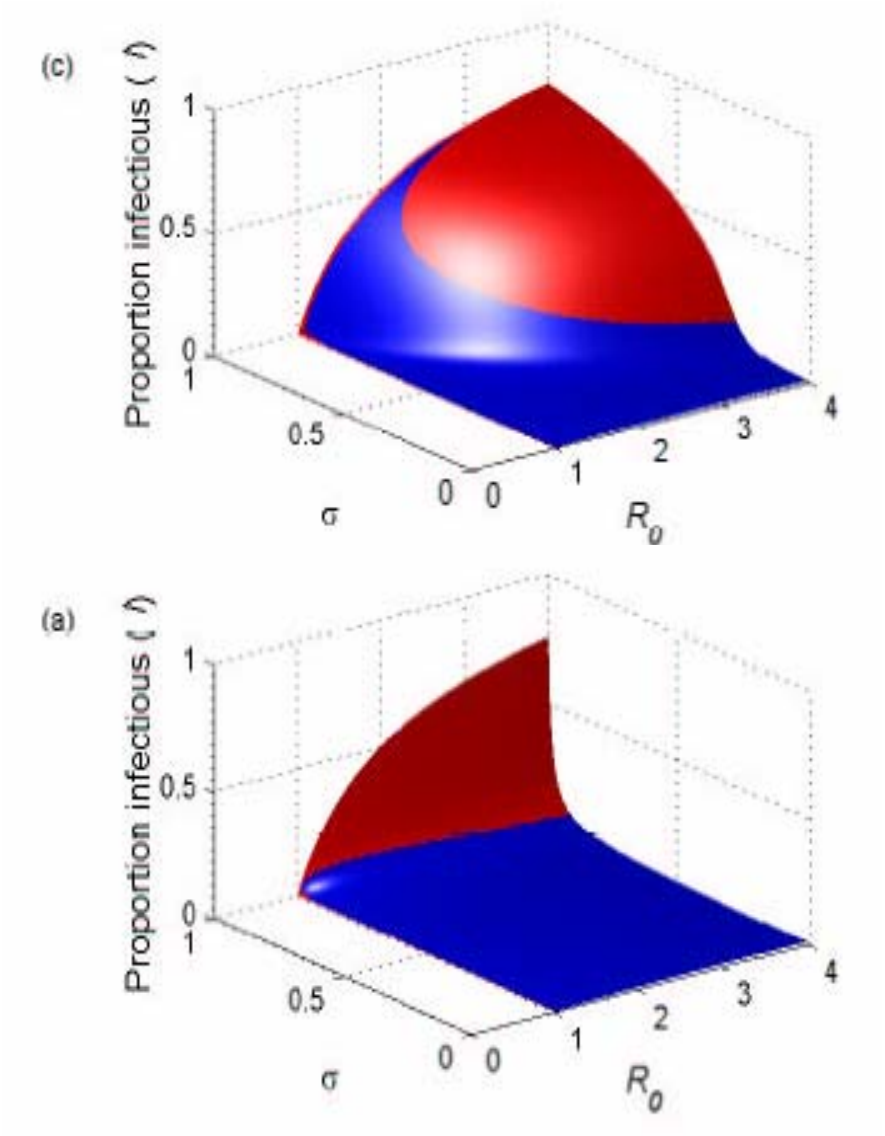
$$\dot{I} = R_0 I\big(S + \sigma(1 - S - I)\big) - I$$

Polarised immunity:

$$\dot{S} = e - R_0 IS - eS + \sigma(1 - e)I$$

$$\dot{I} = R_0 IS - I$$

Steady states

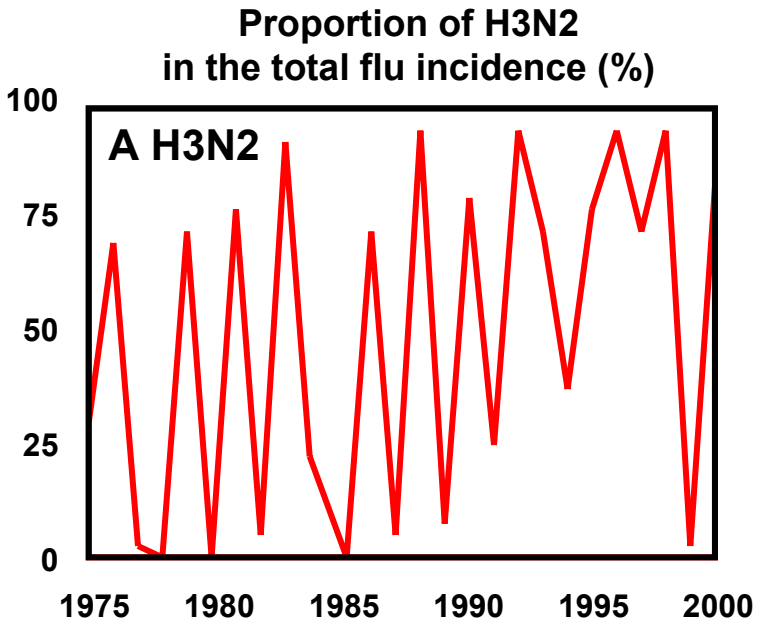


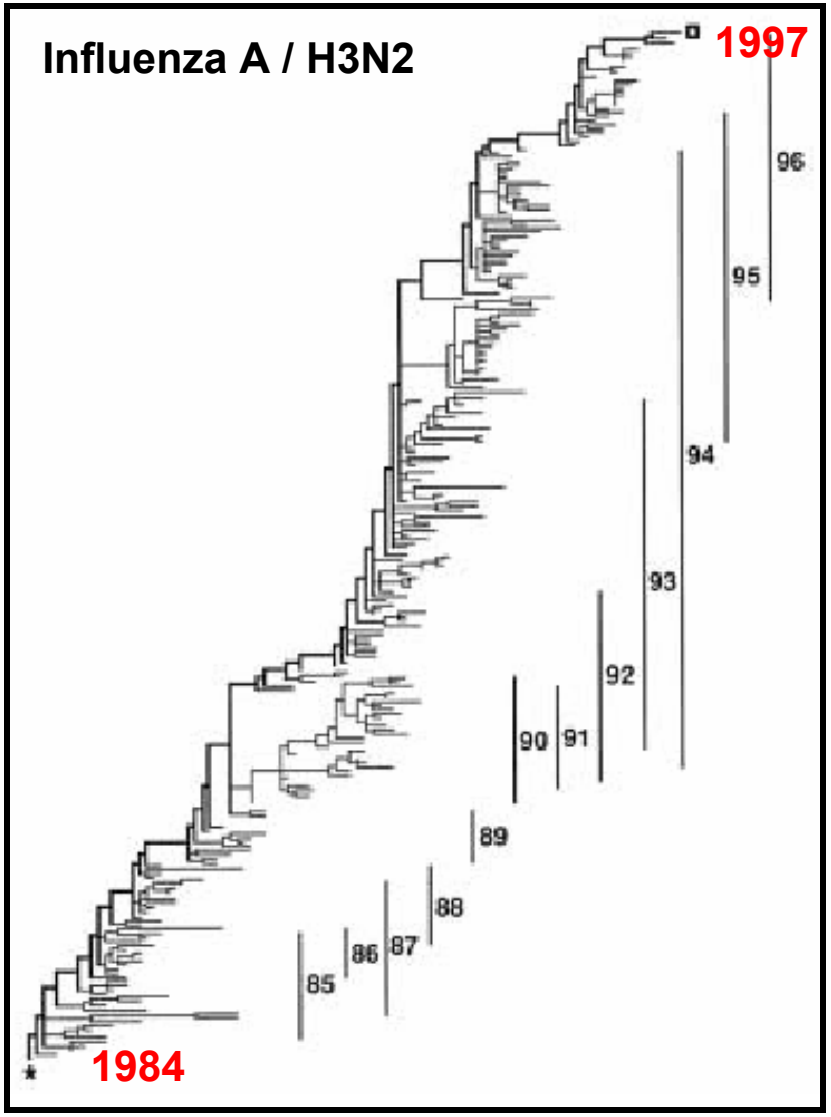
Partial immunity

Polarised immunity

Pathogen diversity and disease epidemiology

Combining the epidemiology and evolution of infectious diseases.





Why flu is a favourite model system

1) Evolutionary and Epidemic time scales coincide.

2) Global surveillance provides both epidemic and evolutionary data.

3) Important recurrent disease – major cause of morbidity and mortality.

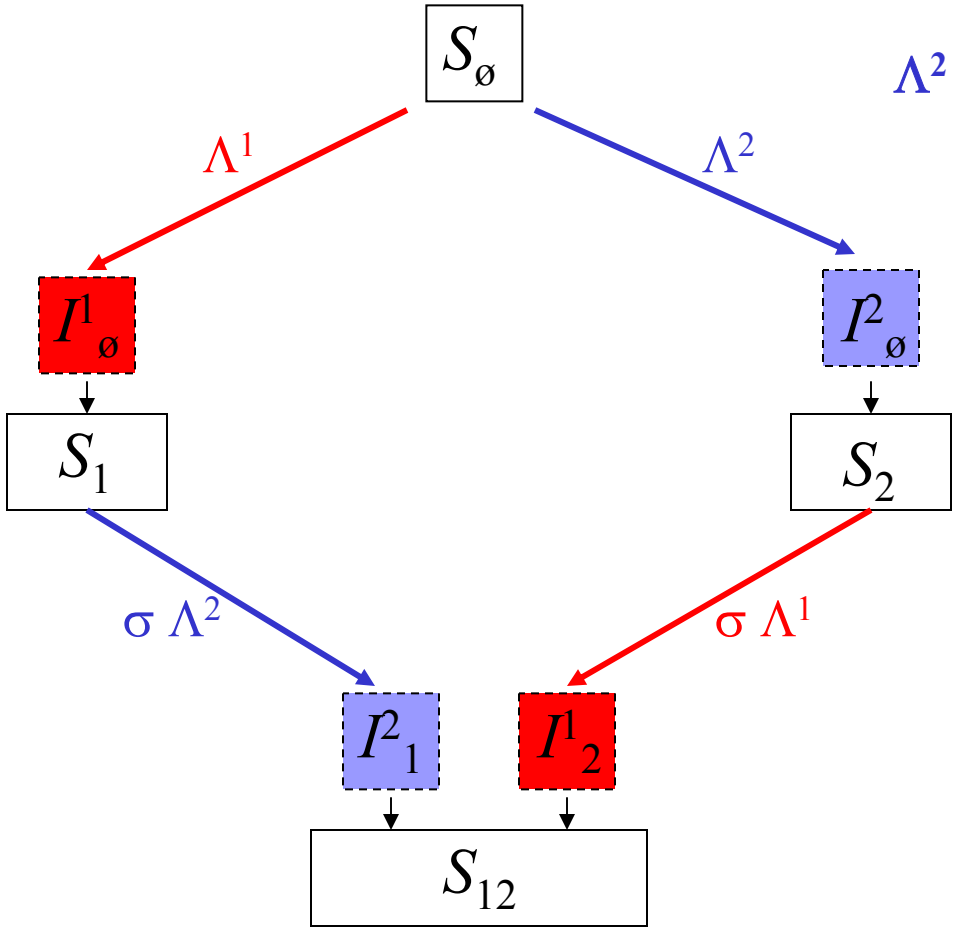
2 strains with partial cross-immunity

Viggo Andreasen, Roskilde

Force of infection:

$$\Lambda^1 = R_0 (I^1_{\varnothing} + I^1_2)$$

$$\Lambda^2 = R_0 (I^2_{\varnothing} + I^2_1)$$



2 strains with partial cross-immunity

$$\dot{S}_{\emptyset} = e - \left(\Lambda^1 + \Lambda^2\right) S_{\emptyset} - eS_{\emptyset}$$
$$\dot{S}_1 = (1-e) I^1{}_{\emptyset} - \sigma \Lambda^2 S_1 - eS_1$$
$$\dot{S}_2 = (1-e) I^2{}_{\emptyset} - \sigma \Lambda^1 S_2 - eS_2$$
$$\dot{S}_{12} = (1-e)\left(I^1{}_2 + I^2{}_1\right) - eS_{12}$$

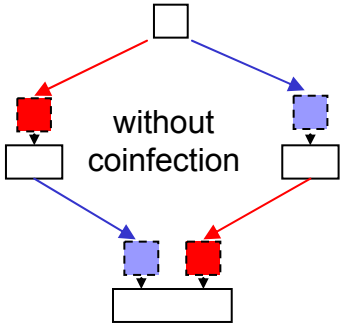
2^n susceptible classes
(in case of n strains)

$$\dot{I}^1{}_{\emptyset} = \Lambda^1 S_{\emptyset} - I^1{}_{\emptyset}$$
$$\dot{I}^1{}_2 = \Lambda^1 \sigma S_2 - I^1{}_2$$
$$\dot{I}^2{}_{\emptyset} = \Lambda^2 S_{\emptyset} - I^2{}_{\emptyset}$$
$$\dot{I}^2{}_1 = \Lambda^2 \sigma S_1 - I^2{}_1$$

$n2^{n-1}$ infected classes
(in case of n strains)

$$S_{\emptyset} + S_1 + S_2 + S_{12} + I^1{}_{\emptyset} + I^1{}_2 + I^2{}_{\emptyset} + I^2{}_1 = 1$$

2 strains with partial cross-immunity and coinfection

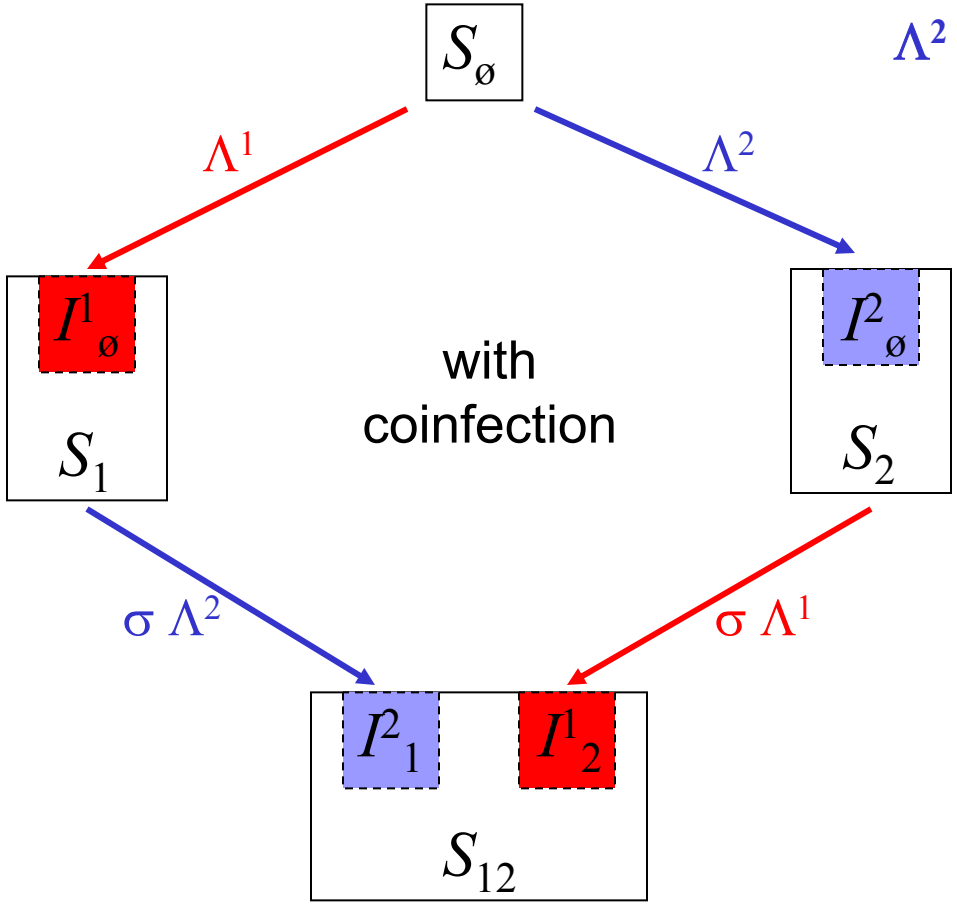


with Graham Medley & James Nokes
Warwick

Force of infection:

$\Lambda^1 = R_0 (I^1_{\varnothing} + I^1_2)$

$\Lambda^2 = R_0 (I^2_{\varnothing} + I^2_1)$



2 strains with partial cross-immunity and coinfection

$$\dot{S}_{\varnothing} = e - \left(\Lambda^1 + \Lambda^2\right) S_{\varnothing} - eS_{\varnothing}$$

$$\dot{S}_1 = \Lambda^1 S_{\varnothing} - \sigma\Lambda^2 S_1 - eS_1$$

$$\dot{S}_2 = \Lambda^2 S_{\varnothing} - \sigma\Lambda^1 S_2 - eS_2$$

$$\dot{S}_{12} = \sigma\left(\Lambda^1 S_2 + \Lambda^2 S_1\right) - eS_{12}$$

$$\dot{I}^1{}_{\varnothing} = \Lambda^1 S_{\varnothing} - I^1{}_{\varnothing}$$

$$\dot{I}^1{}_2 = \Lambda^1 \sigma S_2 - I^1{}_2$$

$$\dot{\Lambda}^1 = R_0 \Lambda^1 \left(S_{\varnothing} + \sigma S_2\right) - \Lambda^1$$

$$\dot{I}^2{}_{\varnothing} = \Lambda^2 S_{\varnothing} - I^2{}_{\varnothing}$$

$$\dot{I}^2{}_1 = \Lambda^2 \sigma S_1 - I^2{}_1$$

$$\dot{\Lambda}^2 = R_0 \Lambda^2 \left(S_{\varnothing} + \sigma S_1\right) - \Lambda^2$$

2 strains with partial cross-immunity and coinfection

$$\dot{S}_{\varnothing} = e - \left(\Lambda^1 + \Lambda^2\right) S_{\varnothing} - e S_{\varnothing}$$
$$\dot{S}_1 = \Lambda^1 S_{\varnothing} - \sigma \Lambda^2 S_1 - e S_1$$
$$\dot{S}_2 = \Lambda^2 S_{\varnothing} - \sigma \Lambda^1 S_2 - e S_2$$

} 2^n susceptible classes

$$\dot{\Lambda}^1 = R_0 \Lambda^1 \left(S_{\varnothing} + \sigma S_2\right) - \Lambda^1$$
$$\dot{\Lambda}^2 = R_0 \Lambda^2 \left(S_{\varnothing} + \sigma S_1\right) - \Lambda^2$$

} n infected classes

n strains with partial cross-immunity and coinfection

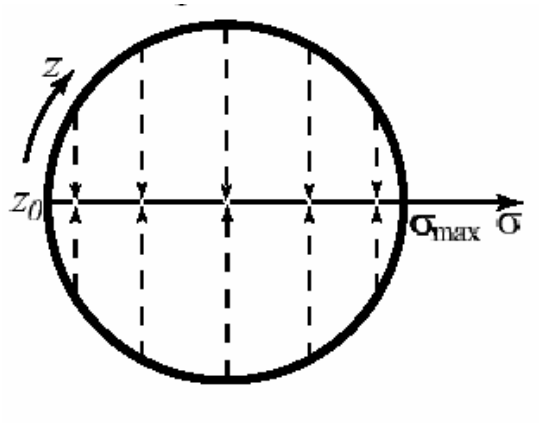
Variants indexed by the set $N = \{1, 2, \ldots, n\}$ and ordered by similarity.
Variants compete for hosts and interact through cross-reactive immunity.
The dynamics of n strains are described by a system of $2^n + n$ equations.

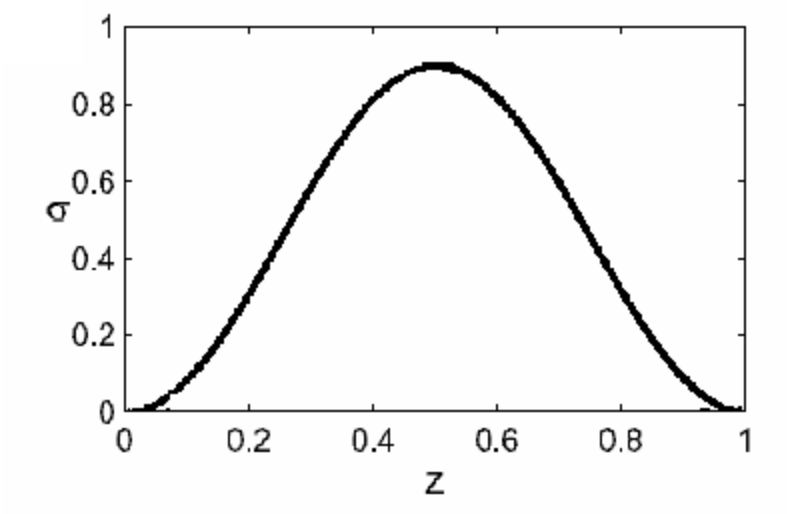
$$\dot{S}_{\varnothing} = e - \sum_{i \in N} \sigma^i_{\varnothing} \Lambda^i S_{\varnothing} - e S_{\varnothing}$$

$$\dot{S}_J = \sum_{i \in J} \sigma^i_{J \setminus i} \Lambda^i S_{J \setminus i} - \sum_{i \notin J} \sigma^i_J \Lambda^i S_J - e S_J$$

$$\dot{\Lambda}^i = R_0 \sum_{J \subseteq N} \sigma^i_J \Lambda^i S_J - \Lambda^i$$

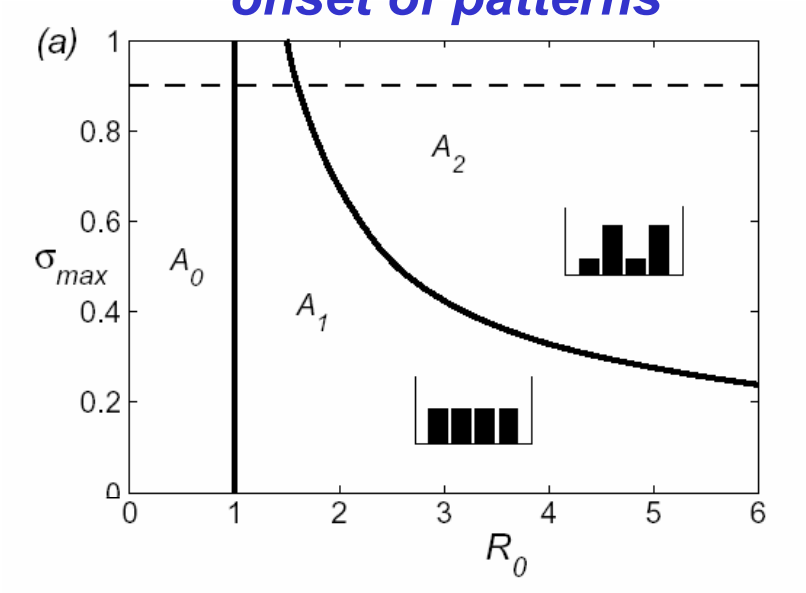
1-D strain space



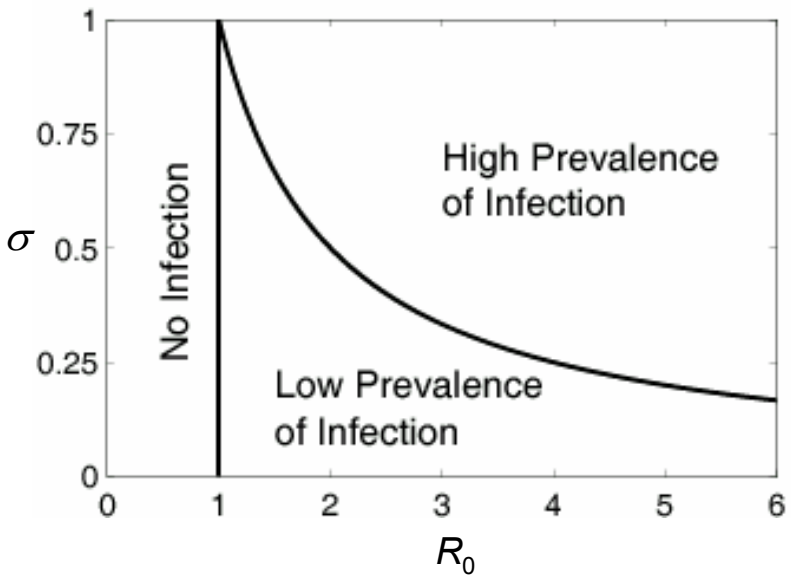


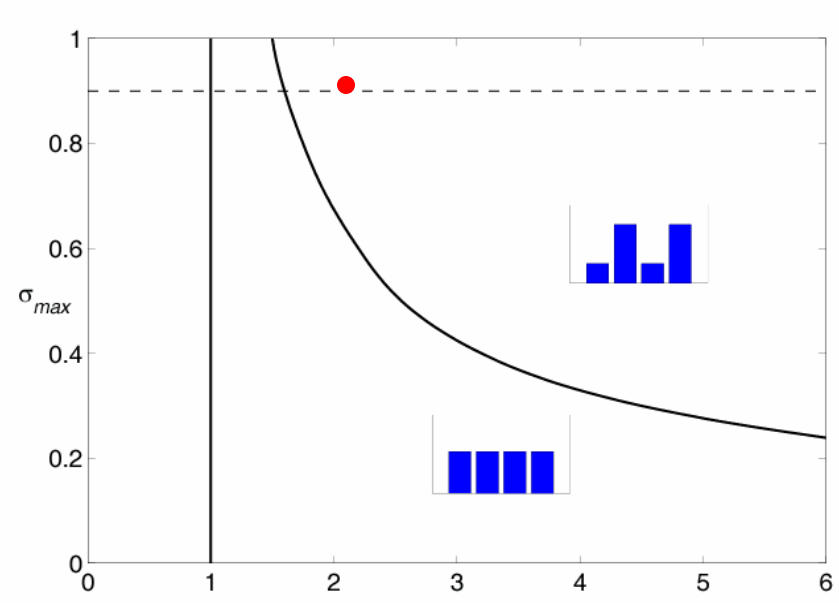
1-D strain space

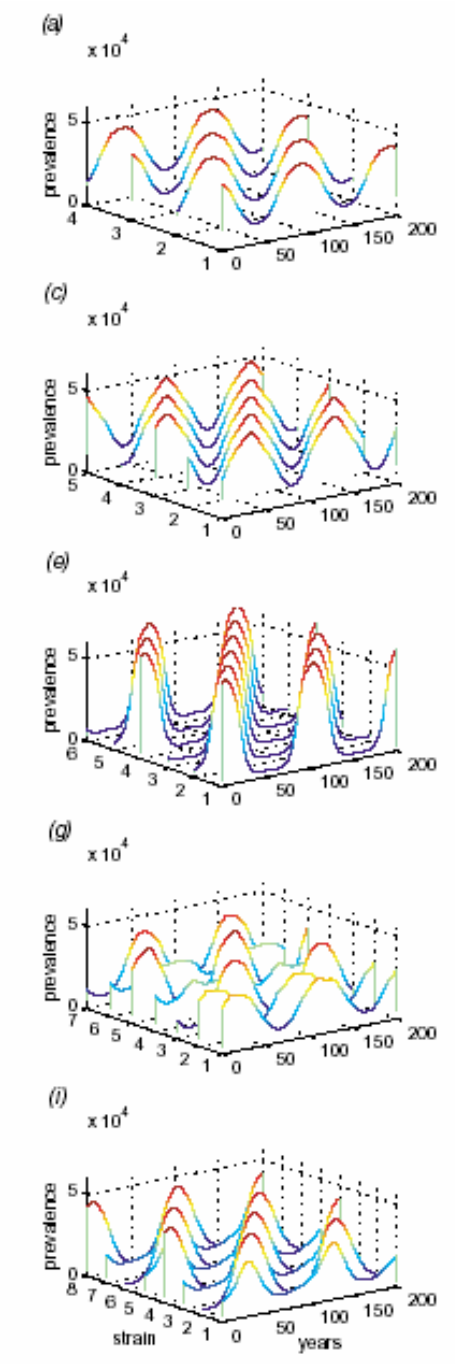
onset of patterns



reinfection threshold



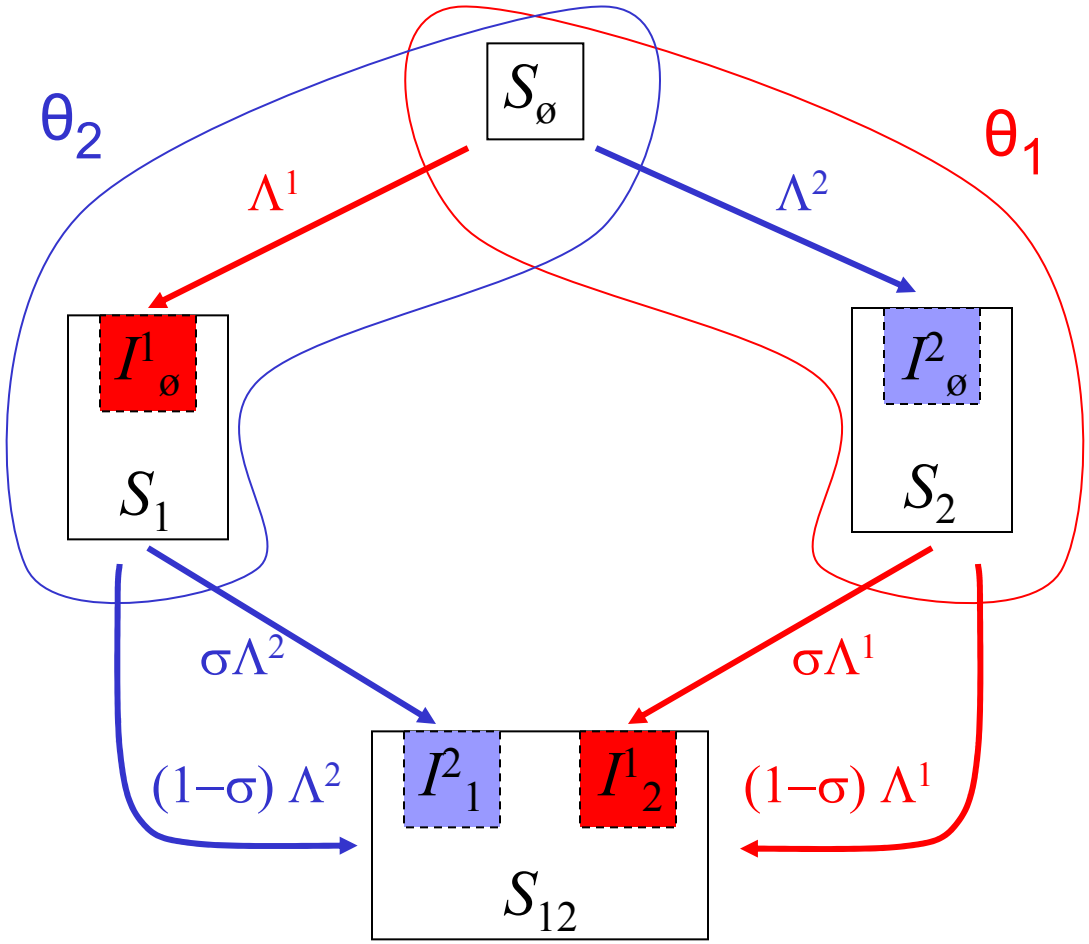

1
0.8
0.6
0.4
0.2
0
σmax
0
1
2
3
4
5
6


(a)
(c)
(e)
(g)
(i)
x 10^4
prevalence
strain
years
50
100
150
200

2 strains with polarised cross-immunity and coinfection

... and reduced transmission

Julia Gog, Cambridge



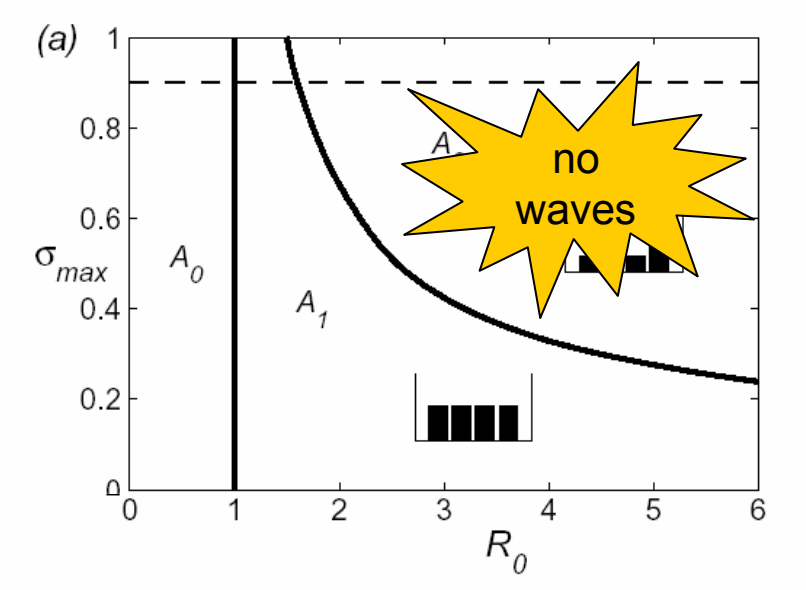
2 strains with polarised cross-immunity and coinfection

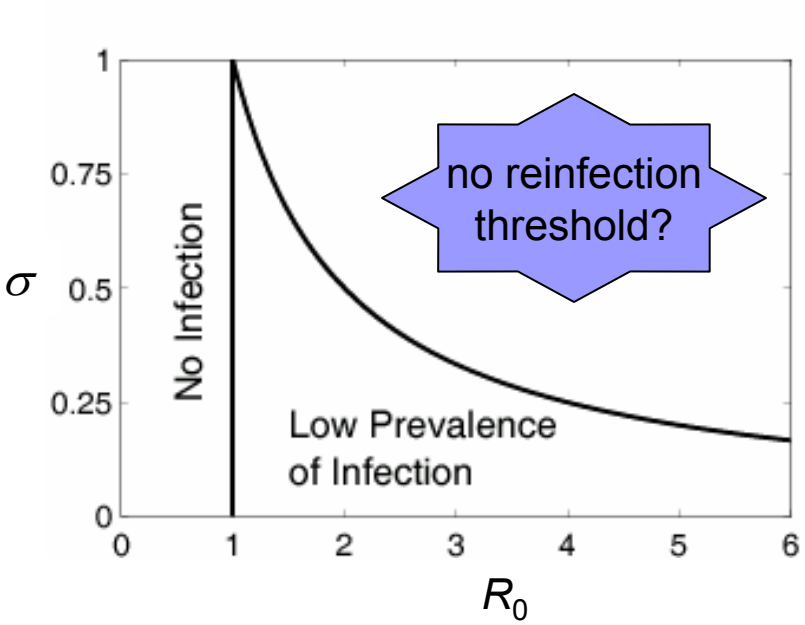
$$\theta_1 = S_\varnothing + S_2, \quad \theta_2 = S_\varnothing + S_1$$

$$\left.\begin{aligned} \dot{\theta}_1 &= e - \Lambda^1\theta_1 - (1-\sigma)\Lambda^2\theta_1 - e\theta_1 \\ \dot{\theta}_2 &= e - \Lambda^2\theta_2 - (1-\sigma)\Lambda^1\theta_2 - e\theta_2 \end{aligned}\right\}$$ n susceptible classes

$$\left.\begin{aligned} \dot{\Lambda}^1 &= R_0\Lambda^1\theta_1 - \Lambda^1 \\ \dot{\Lambda}^2 &= R_0\Lambda^2\theta_2 - \Lambda^2 \end{aligned}\right\}$$ n infected classes

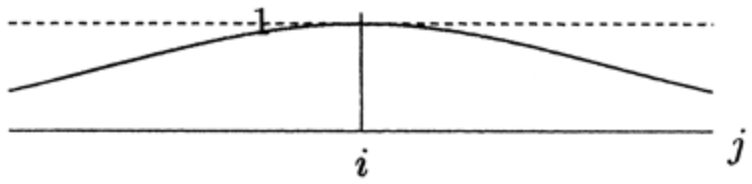
More tractable, but different…



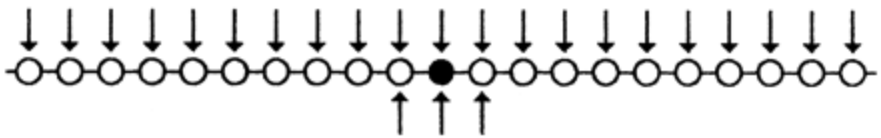


Polarised cross-immunity and mutation

$$\sigma_{ij} = e^{-(\frac{i-j}{d})^2}$$

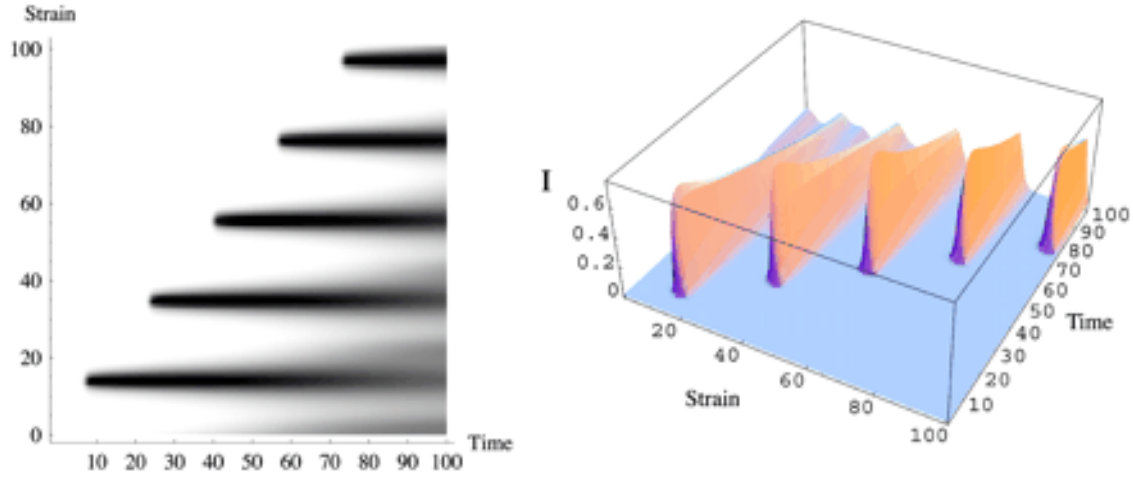


Cross-immunity to nearby strains

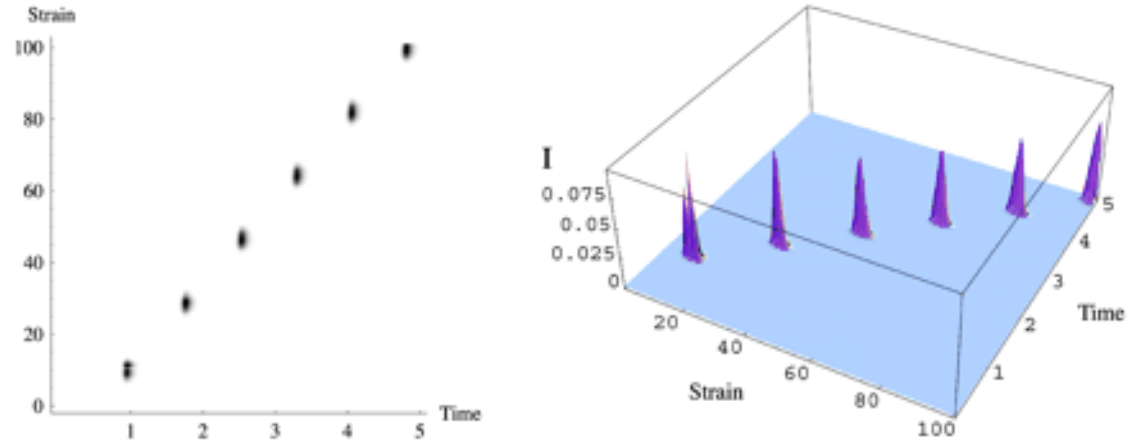


Mutation to adjacent strains

Polarised cross-immunity and mutation

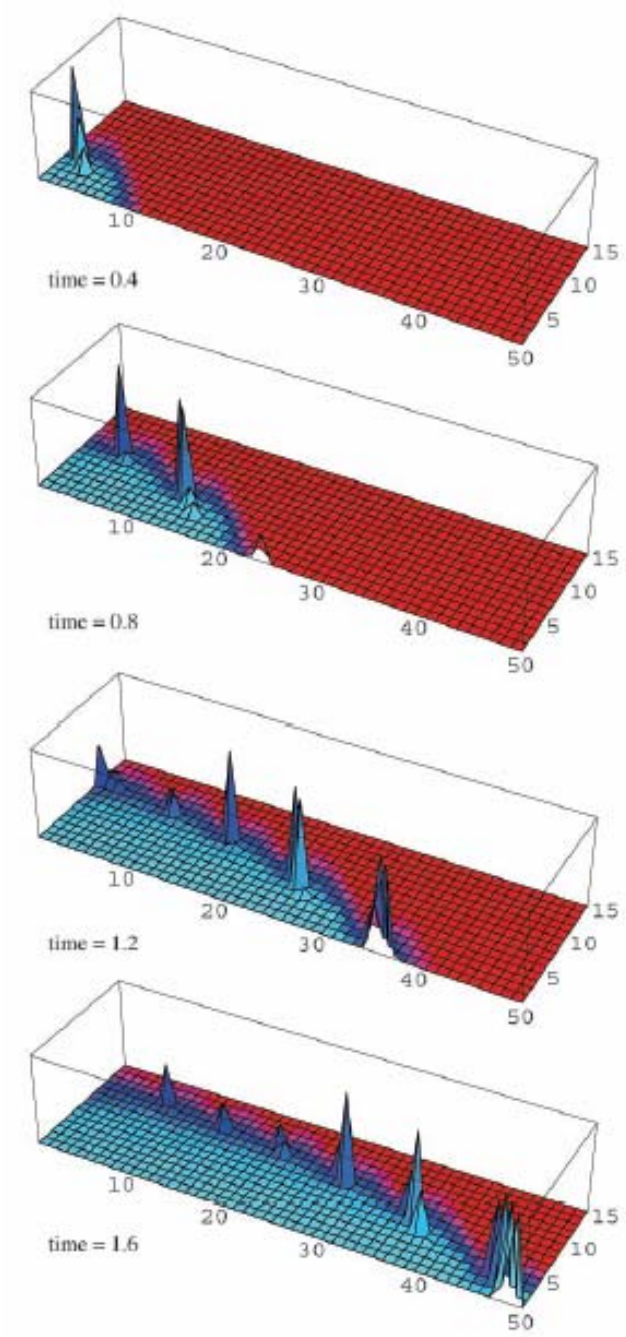


a Long infection



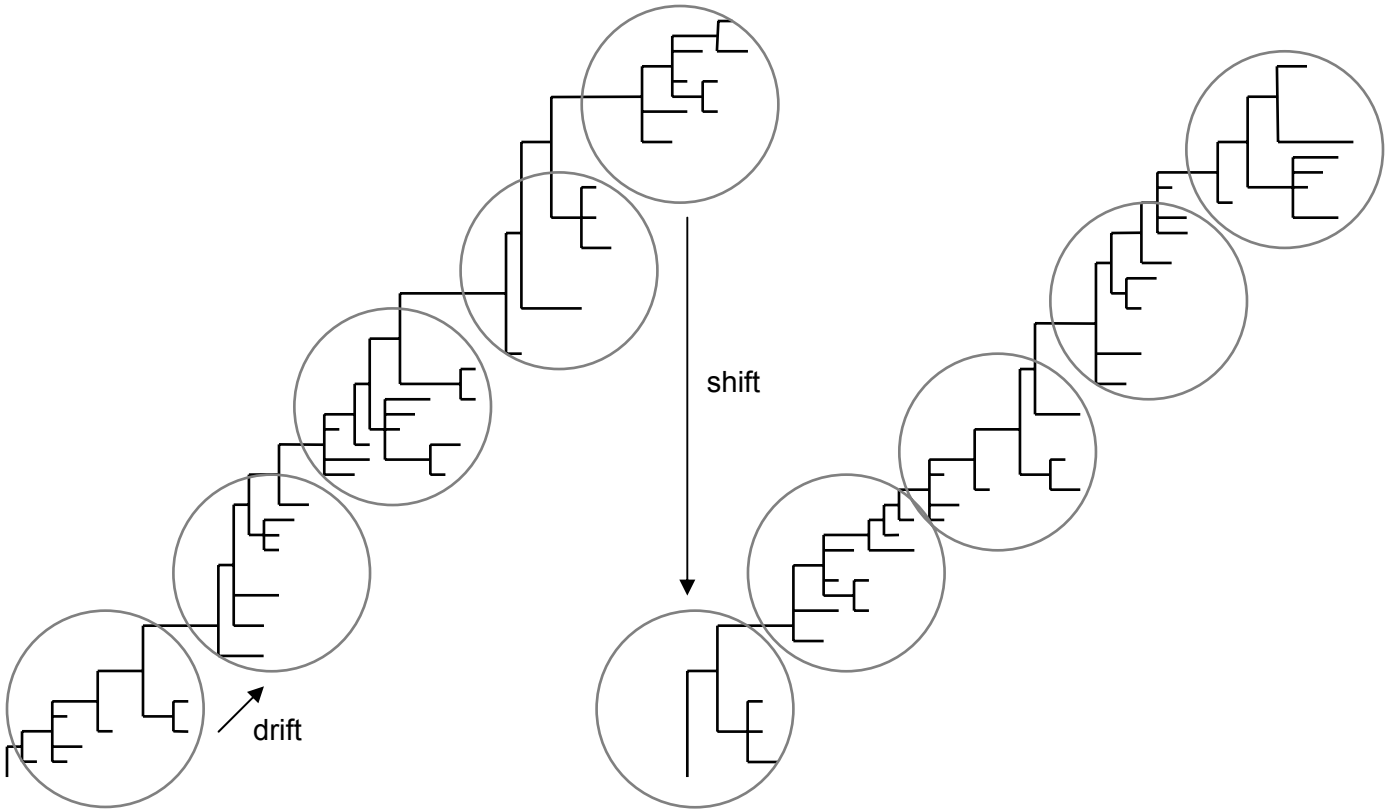
b Short infection

2-D strain space



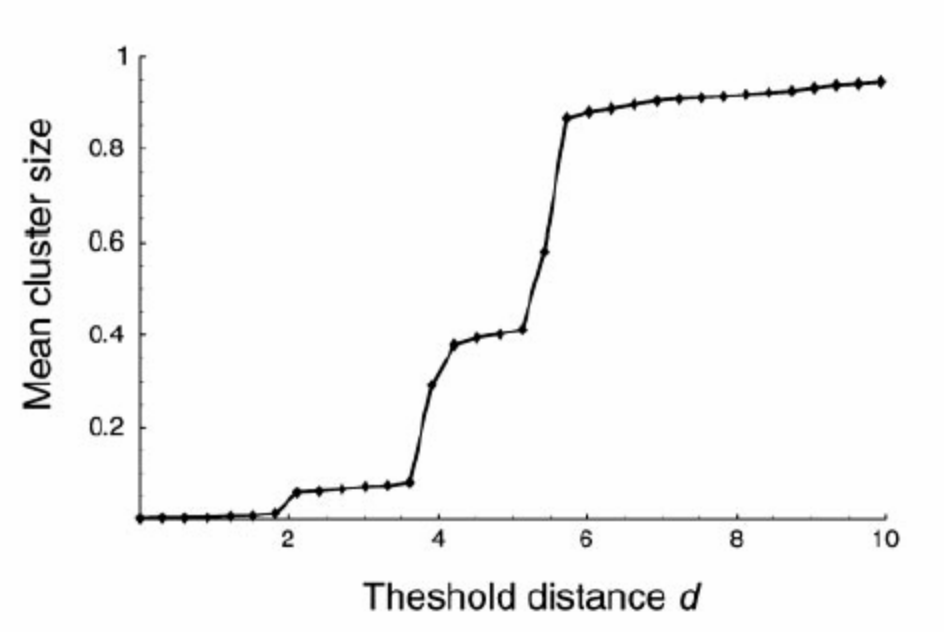
Cluster as the modelling unit

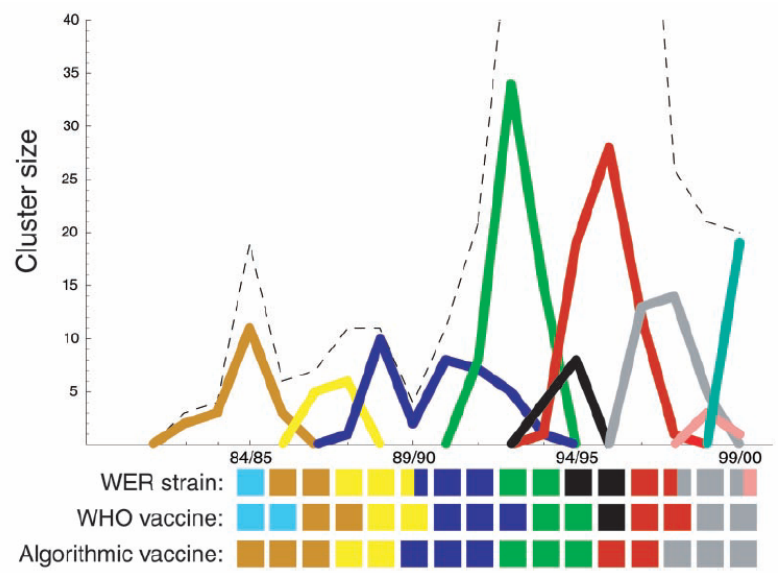
But despite all differences between models, the cluster appears as a natural modelling unit...



Clusters of influenza A virus

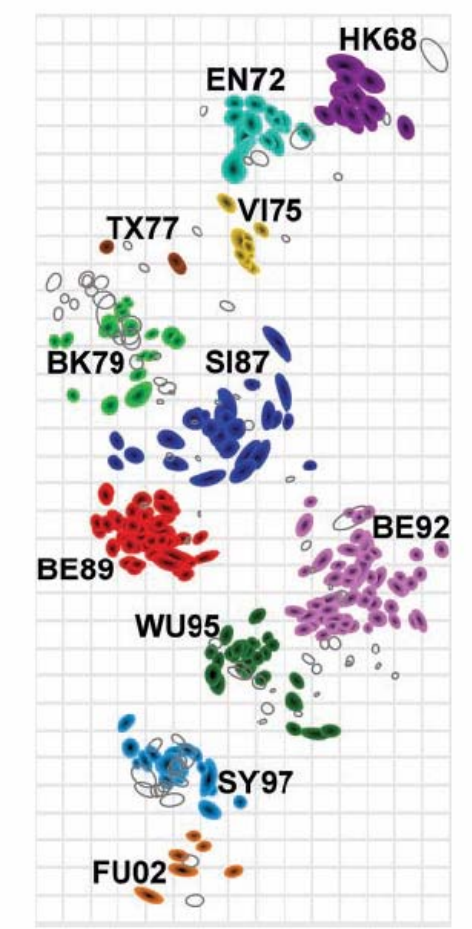
Plotkin, Dushoff, Levin, Princeton



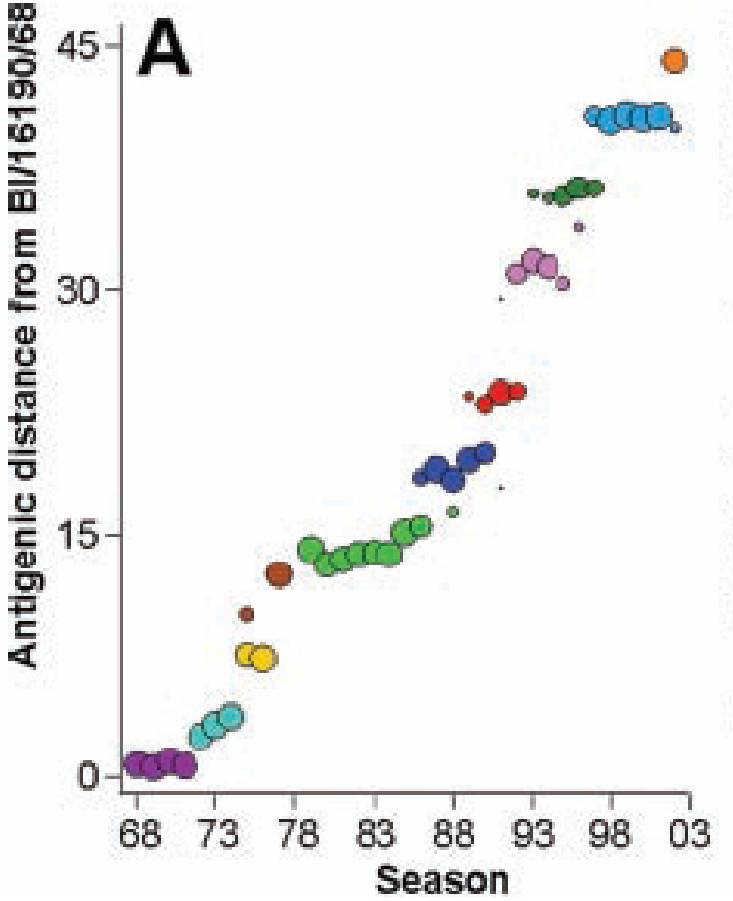


Clusters of influenza A virus

Derek Smith, Cambridge

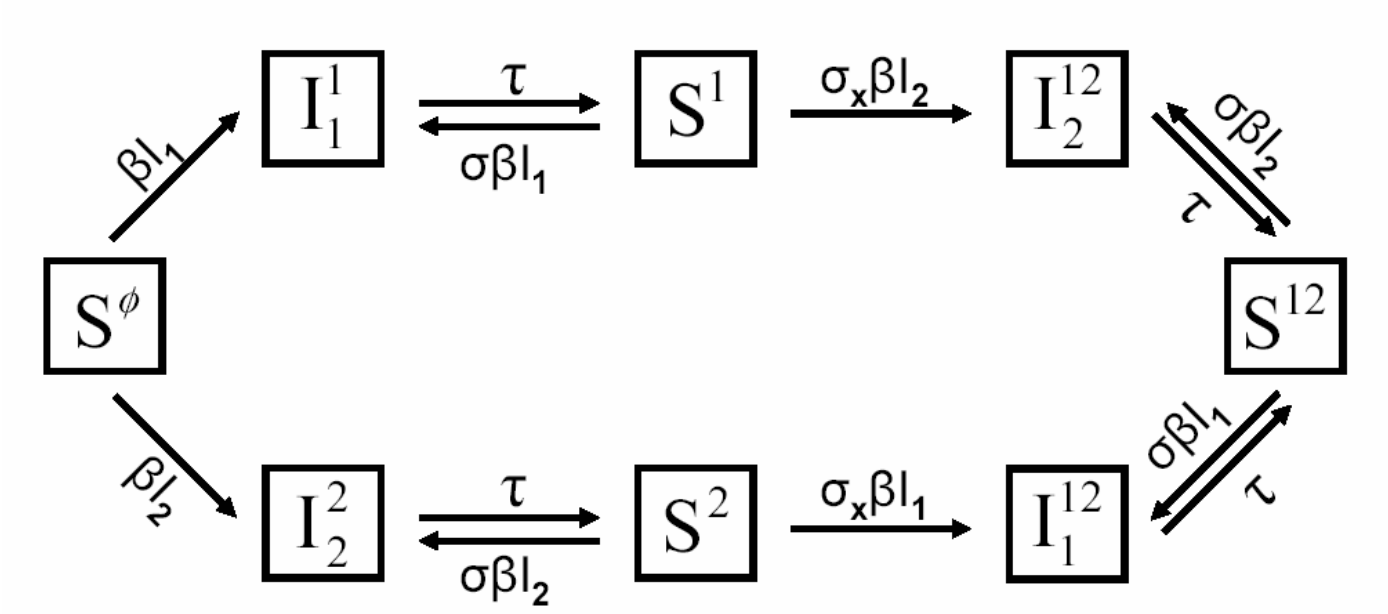


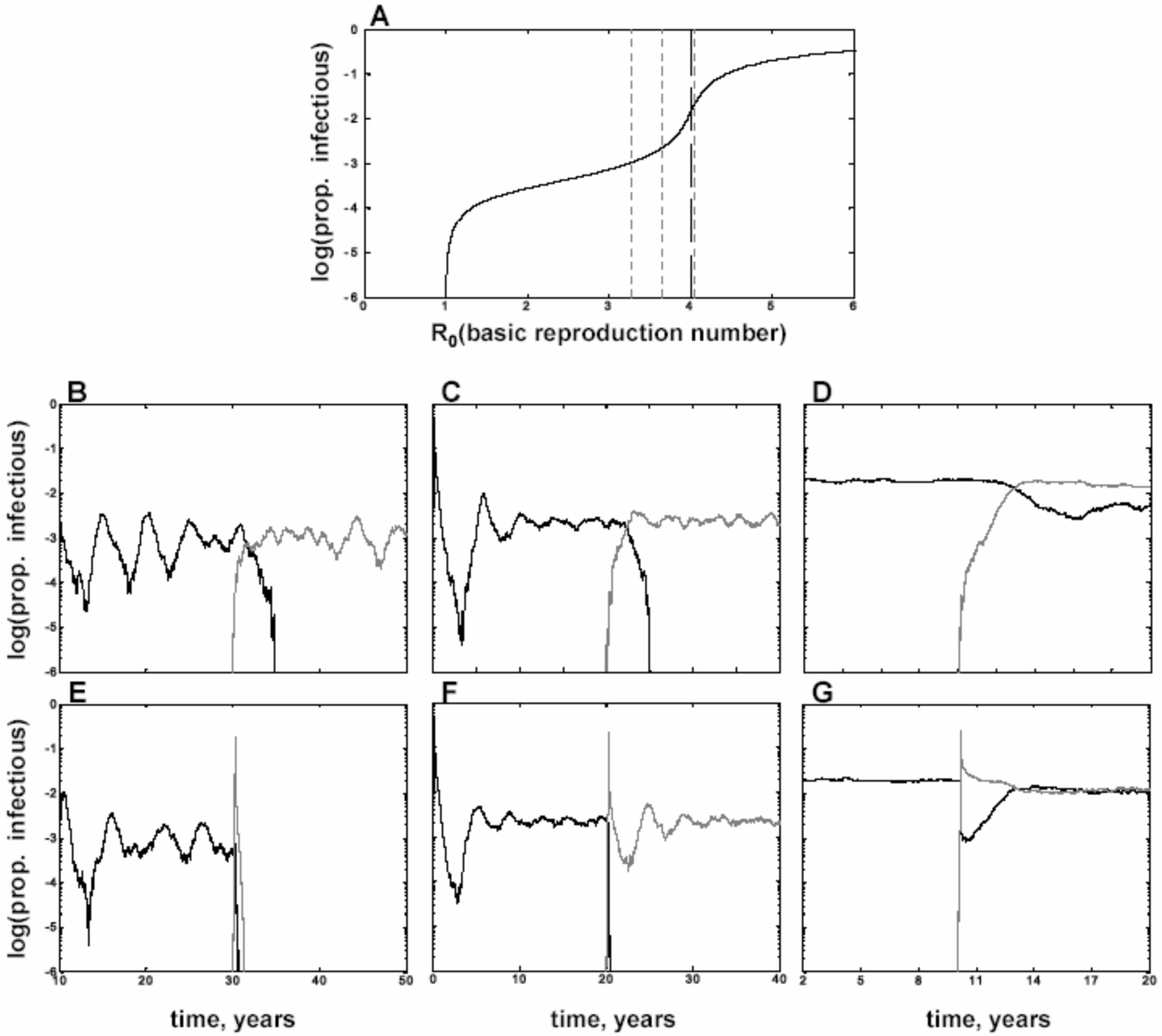
Antigenic map of influenza

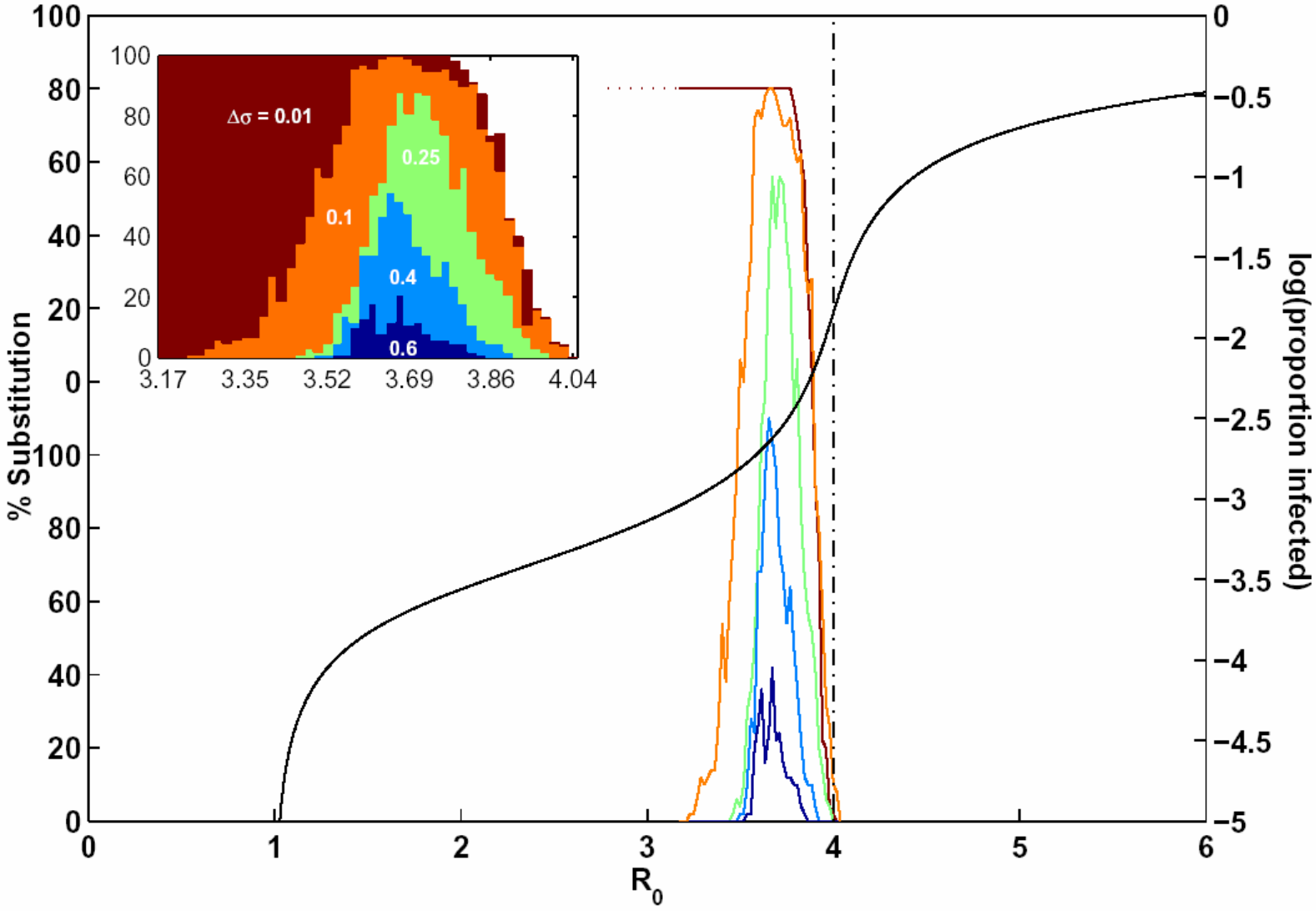


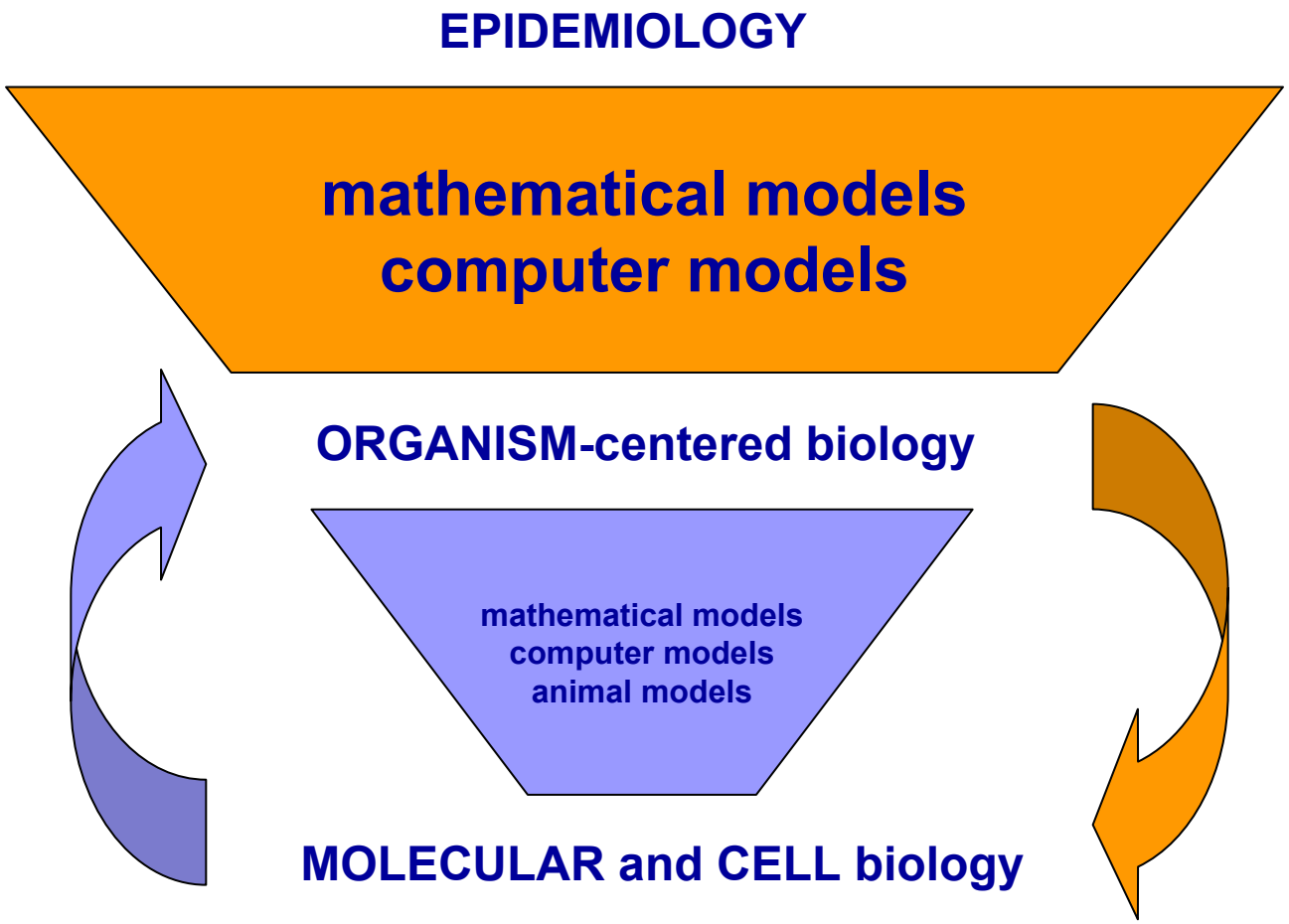
Model structure

Dinis Gökaydin, IGC




A
log(prop. infectious)
R_0(basic reproduction number)
B
C
D
E
F
G
log(prop. infectious)
log(prop. infectious)
time, years
time, years
time, years

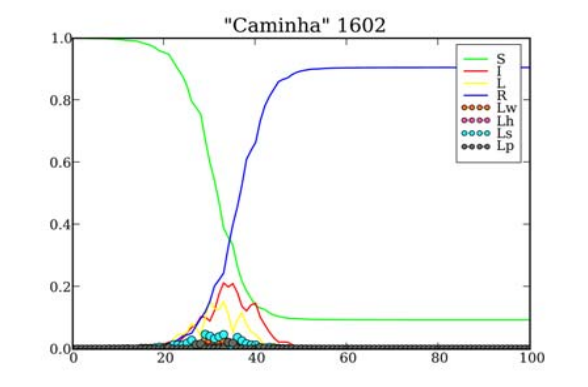

% Substitution
log(proportion infected)
R0
Δσ = 0.01
0.1
0.25
0.4
0.6
100
80
60
40
20
0
3.17
3.35
3.52
3.69
3.86
4.04
0
1
2
3
4
5
6
−0.5
−1
−1.5
−2
−2.5
−3
−3.5
−4
−4.5
−5

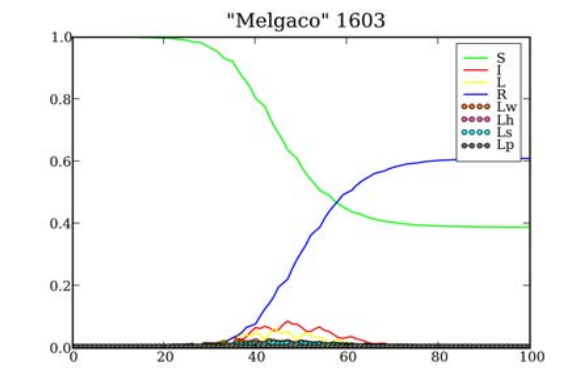

EPIDEMIOLOGY
mathematical models
computer models
ORGANISM-centered biology
mathematical models
computer models
animal models
MOLECULAR and CELL biology

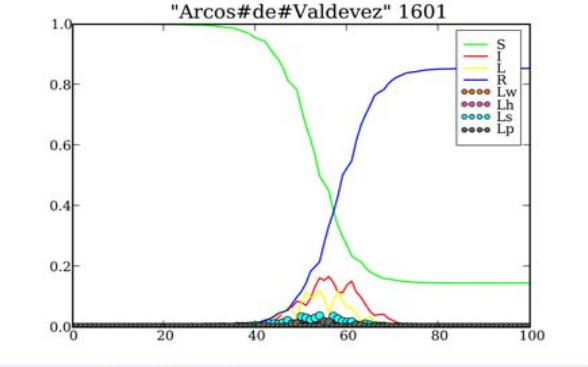
FluSpread

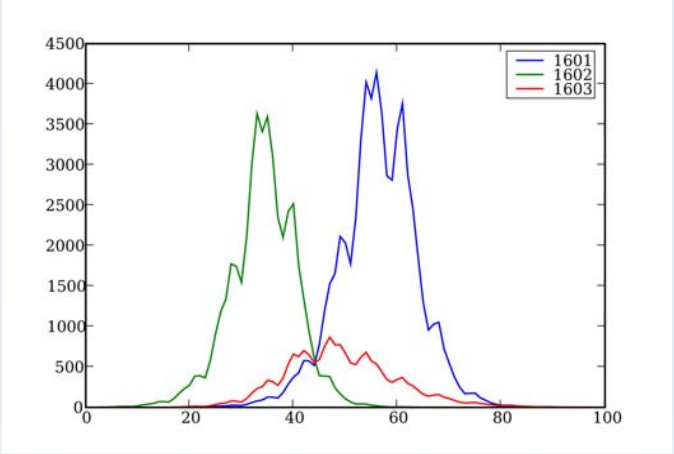
A tool for public health policy making

José Lourenço, IGC

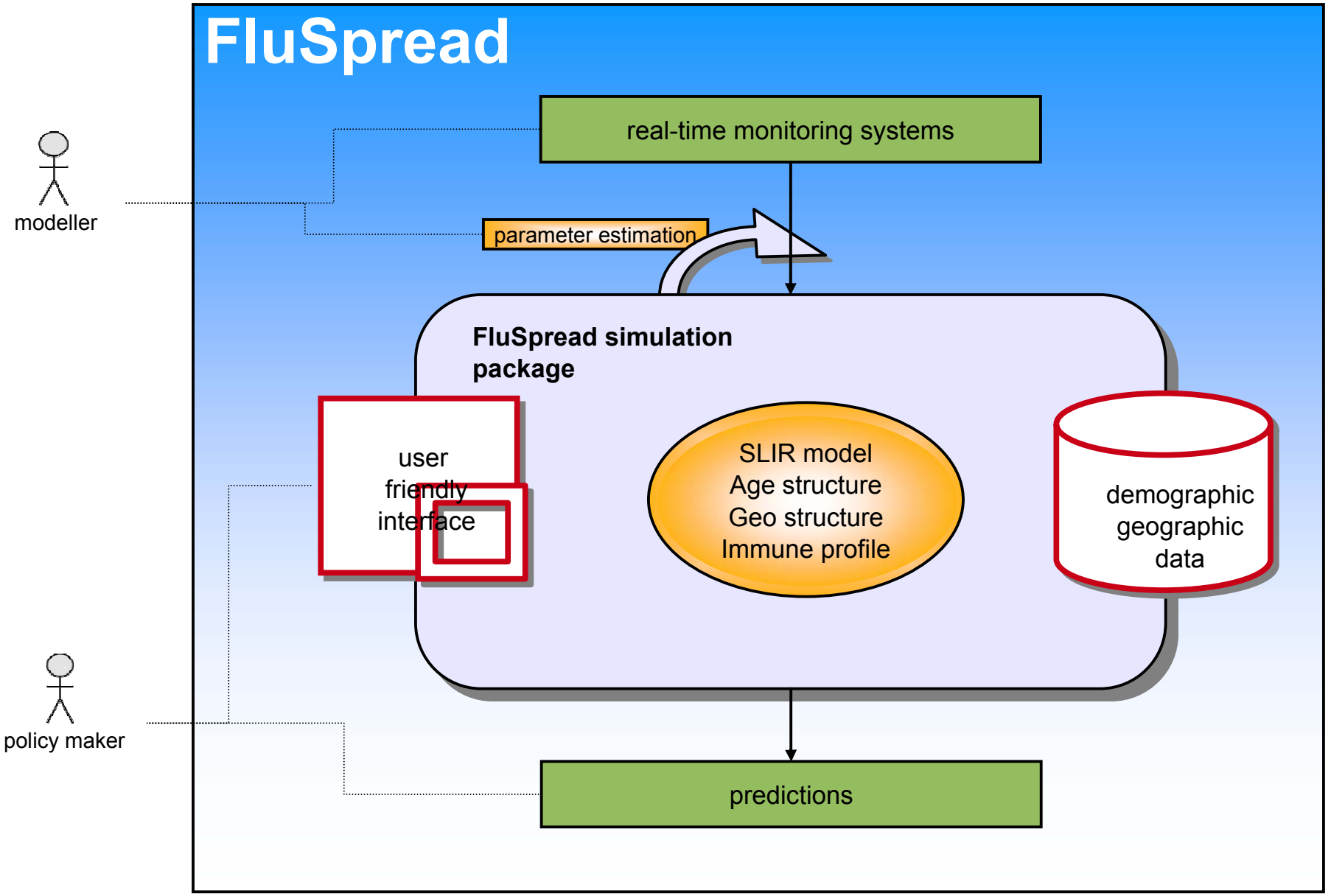








Demographic and Geographical Information


FluSpread
real-time monitoring systems
modeller
parameter estimation
FluSpread simulation package
user friendly interface
SLIR model
Age structure
Geo structure
Immune profile
demographic geographic data
policy maker
predictions