IGC

FIOCRUZ

Mathematical models and control strategies in infectious diseases

Gabriela Gomes

Lecture 1

Epidemiological Thresholds and Control Strategies I: field

4000 years of mathematics

Arithmetics

Pure mathematics

Renaissance

2000 BC | 1000 BC | 1000 AD | 2000 AD

Babylon
Egipt
India
China

Greece

Arabia

Europe

First mathematical model for malaria transmission (Ross)

Ronald Ross
1857-1932

Discovery mosquitoes transmit malaria (Ross – Nobel Prize 1902)

China

Rome

China

2000 AD | 1000 AD | 1000 BC | 2000 BC

Discovery of the parasite in blood of patient (Laveran – Nobel Prize 1907)

Medicinal plants

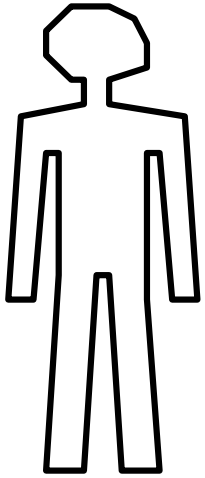
Association between malaria and swamps

First reports of malaria symptoms

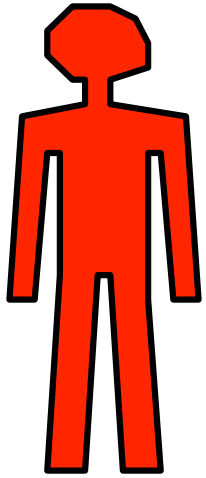
DDT Global Eradication Campaign 1955-1978

4000 years of malaria

Host classification

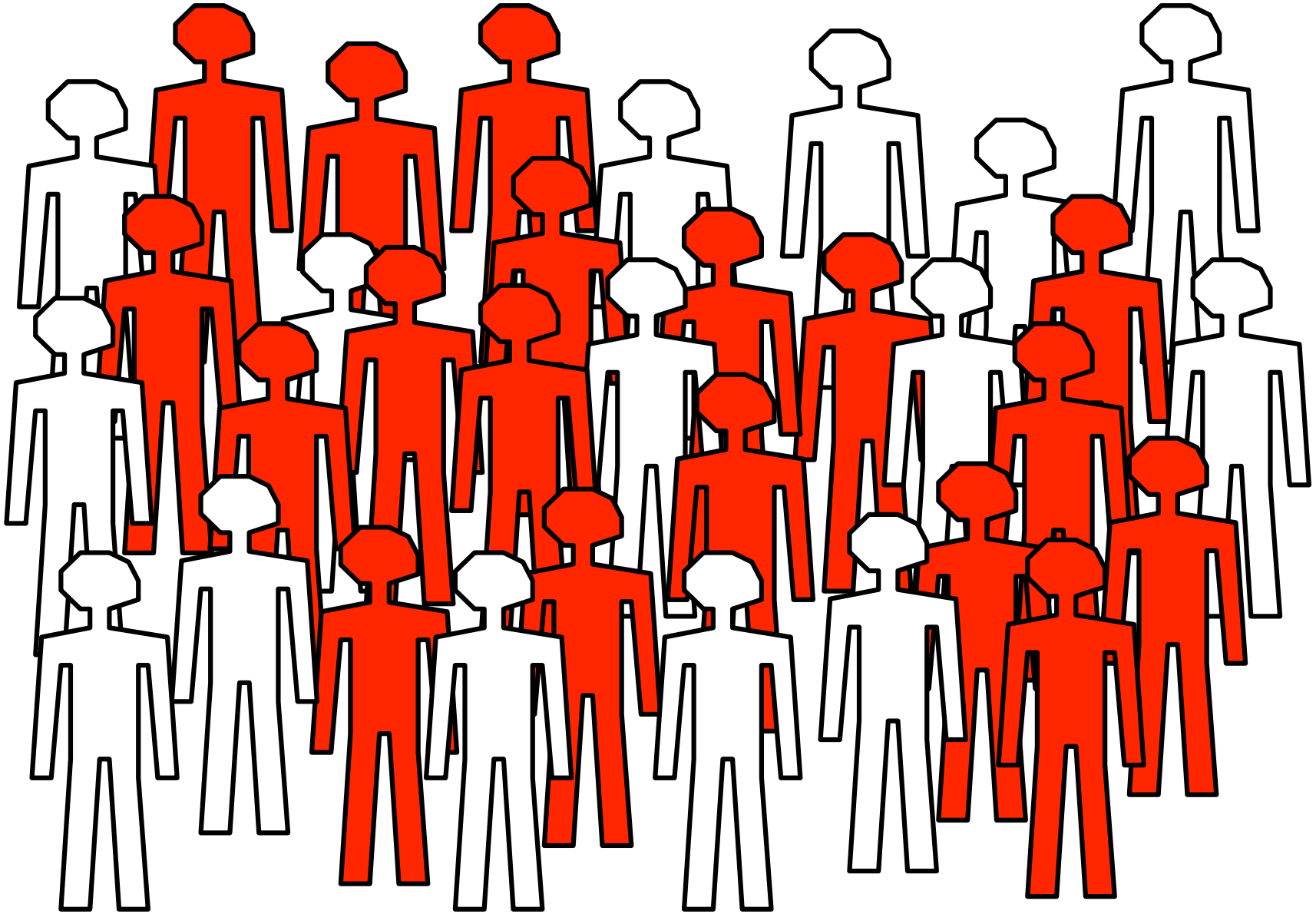


Susceptible



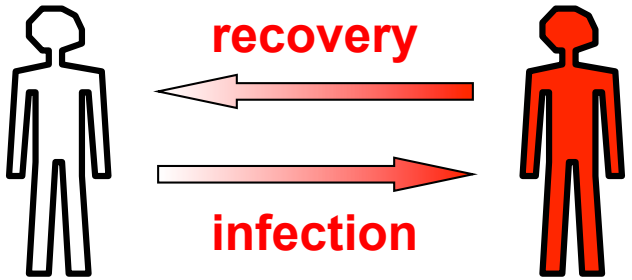
Infectious

Host population



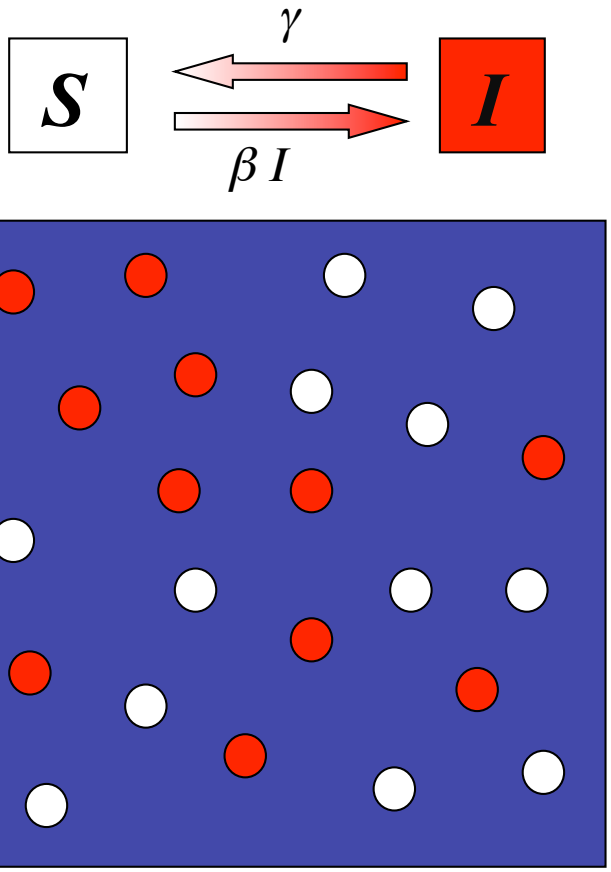
SIS model

Sir 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).



$$\frac{dS}{dt} = -\beta I S + \gamma I$$

$$\frac{dI}{dt} = \beta I S - \gamma I$$

β – transmission coefficient

γ – recovery rate

SIS model

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

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

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

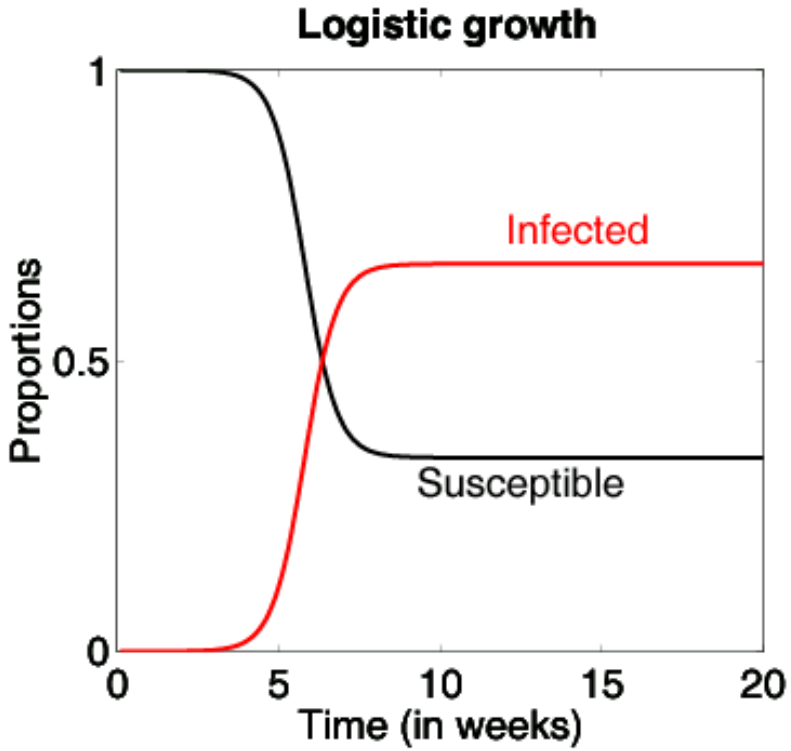
$$\frac{dI}{dt} = (\beta-\gamma)\left(1-\frac{I}{1-\gamma/\beta}\right) I$$

The solution can be obtained analytically

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

SIS model

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



Steady states:

1. Disease free equilibrium

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

2. Endemic equilibrium

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

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

Basic reproduction number, R_0

The basic reproduction number is defined as the

average number of secondary infections produced by an average infectious individual, during its entire infectious period, in a totally susceptible population

The basic reproduction number is calculated as

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

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

R_0 is a nondimensional number, and depends on both the environment (physical and social) and the disease.

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

Nondimensional SIS model

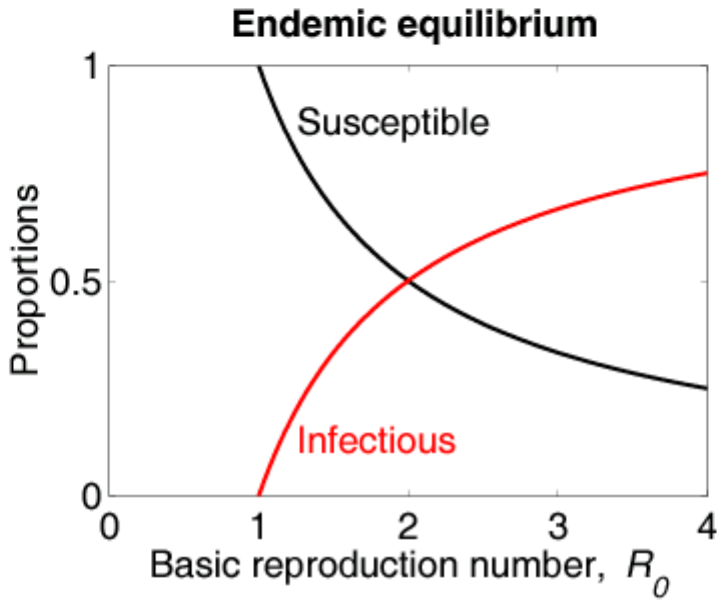
If time is measured in units of infectious period, $D = 1/\gamma$, then the SIS model becomes

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

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

The endemic equilibrium is rewritten as

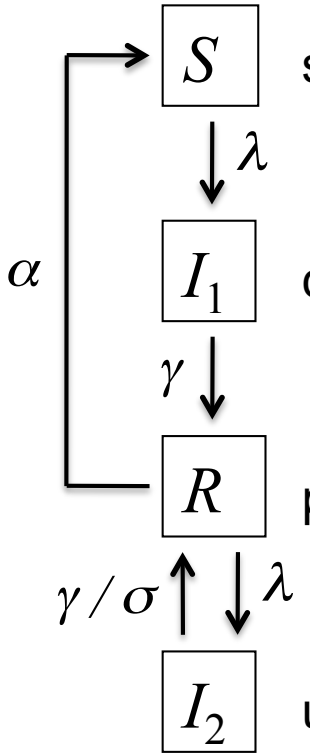
$$I = 1-\frac{1}{R_0}, \quad S = \frac{1}{R_0}$$



Epidemic threshold: Infection can invade a totally susceptible population if and only if

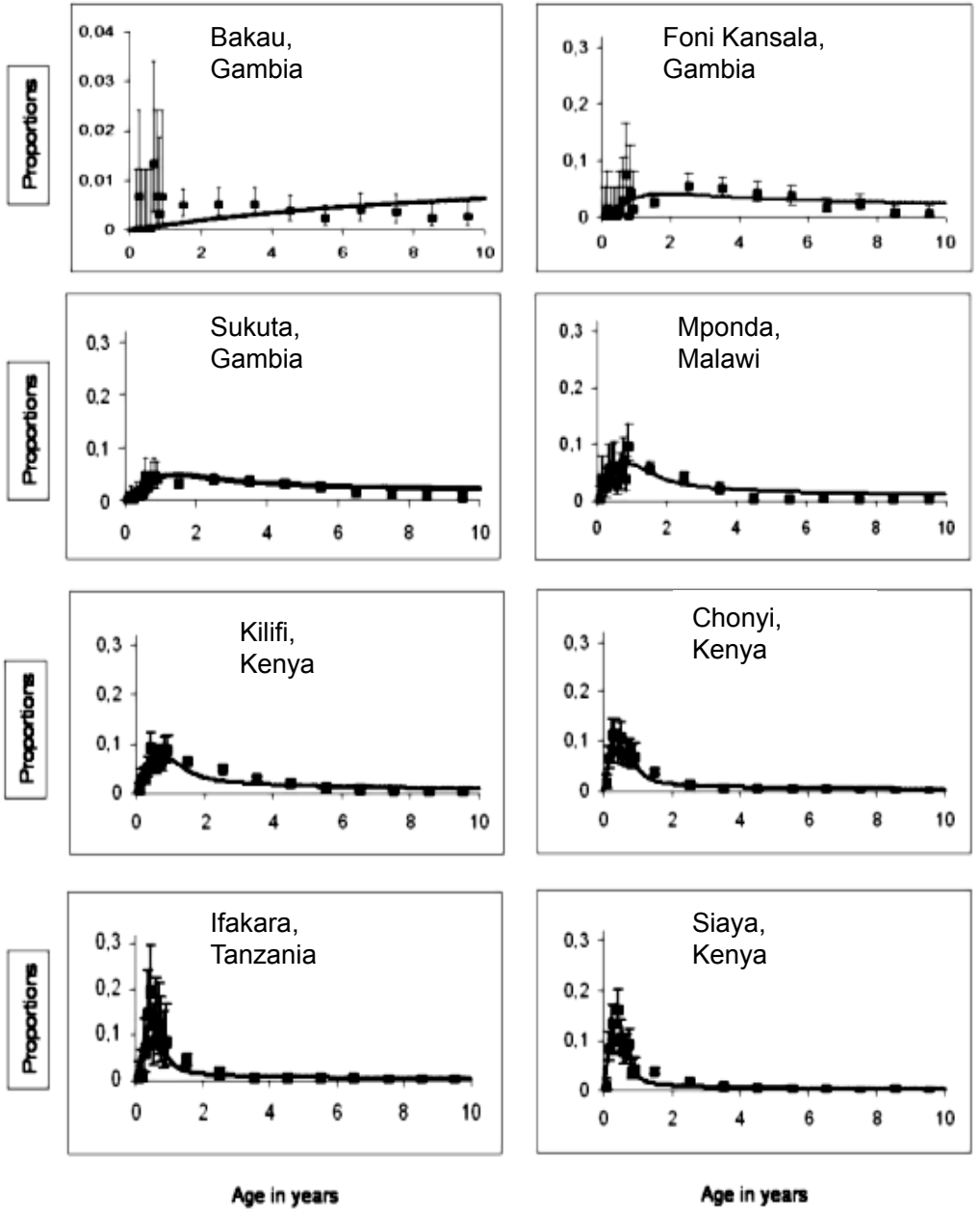
$$R_0 > 1$$

Field data: clinical malaria by age



Force of infection:

$$\lambda = \beta\left(I_1 + I_2\right)$$



System of partial differential equations (SIRI-like for malaria)

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

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

$$\frac{\partial R}{\partial t} + \frac{\partial R}{\partial a} = \gamma\left(I_1 + \frac{1}{\sigma} I_2\right) - R(\lambda + \alpha + \mu)$$

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

Boundary conditions:

$$S(t,0) = \mu \qquad R(t,0) = I_1(t,0) = I_2(t,0) = 0$$

Model fitting and parameter estimation for malaria

Global parameters:

average duration of clinical malaria ~ 1 month
$[\gamma = 14.12\ \mathrm{yr}^{-1}]$

average duration of uncomplicated malaria ~ 6 month
$[\sigma = 6.33]$

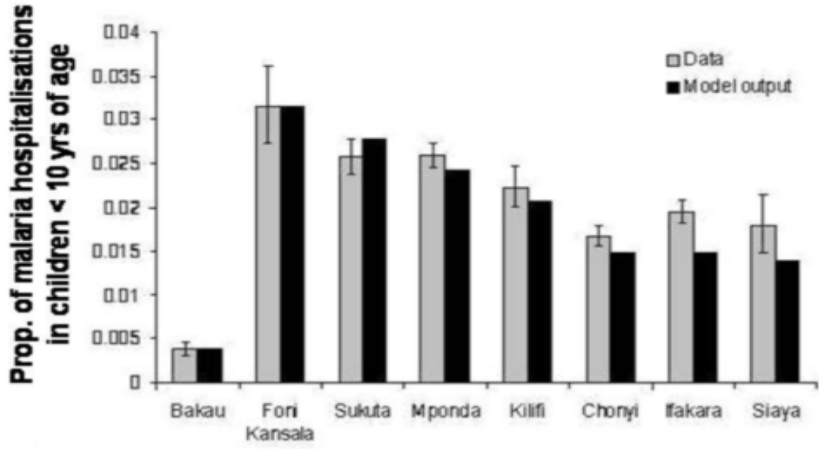
average duration of partial immunity ~ 12 month
$[\alpha = 1.07\ \mathrm{yr}^{-1}]$

Local parameters:

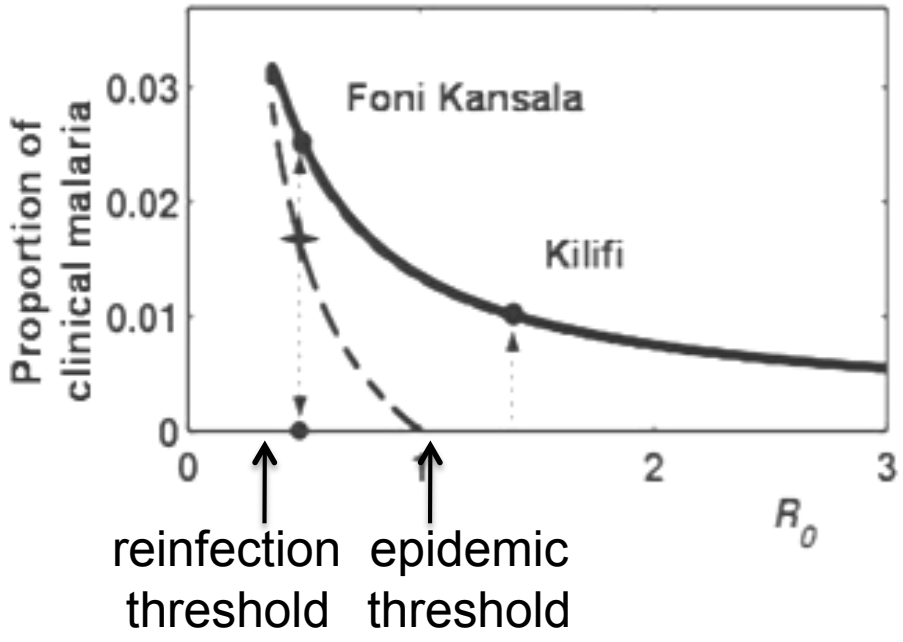
Region	λ_o (95% c.i.)	Λ	β	R_0
Bakau	0.14 (−0.09–0.37)	0.12	*NA*	*NA*
Foni Kansala	4.86 (4.63–5.09)	4.26	6.99	0.49
Sukuta	6.70 (6.47–6.93)	5.87	8.48	0.60
Mponda	14.96 (14.73–15.19)	13.10	15.52	1.10
Kilifi	19.87 (19.64–20.10)	17.40	19.77	1.40
Chonyi	47.21 (46.98–47.44)	41.35	43.66	3.08
Ifakara	50.16 (49.93–50.40)	43.94	46.25	3.27
Siaya	71.02 (70.79–71.25)	62.21	64.53	4.56

$$R_0 = \beta/\gamma$$

Multi-population malaria trends

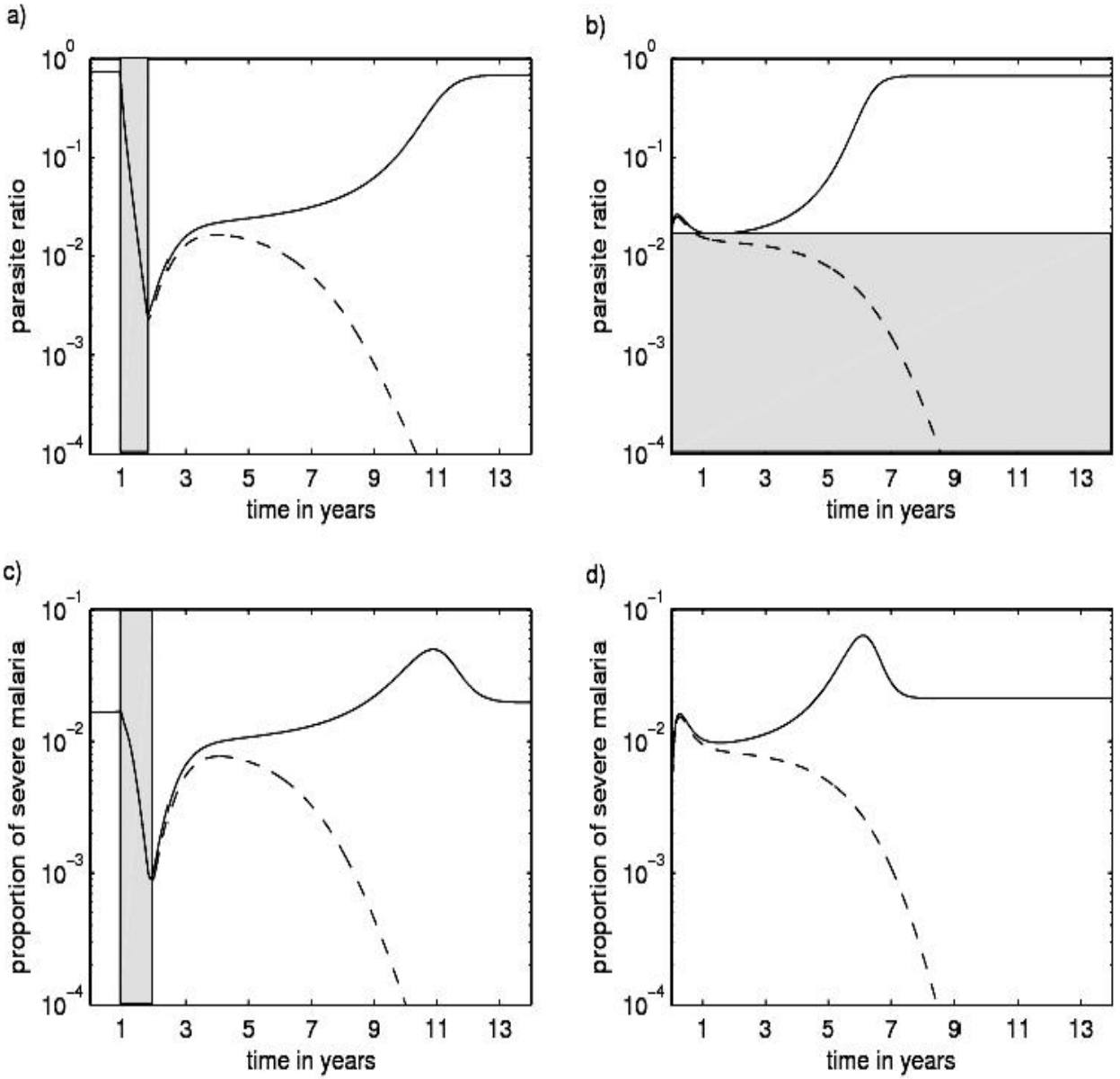


Decreasing disease with increasing transmission



Sustainable transmission for $R_0 < 1$ (hysteresis)

Bistable regime with implications for malaria elimination and resurgence



Epidemiological thresholds of the SIRI model

Epidemic threshold: Infection can invade a population where every individual is “totally susceptible” if and only if

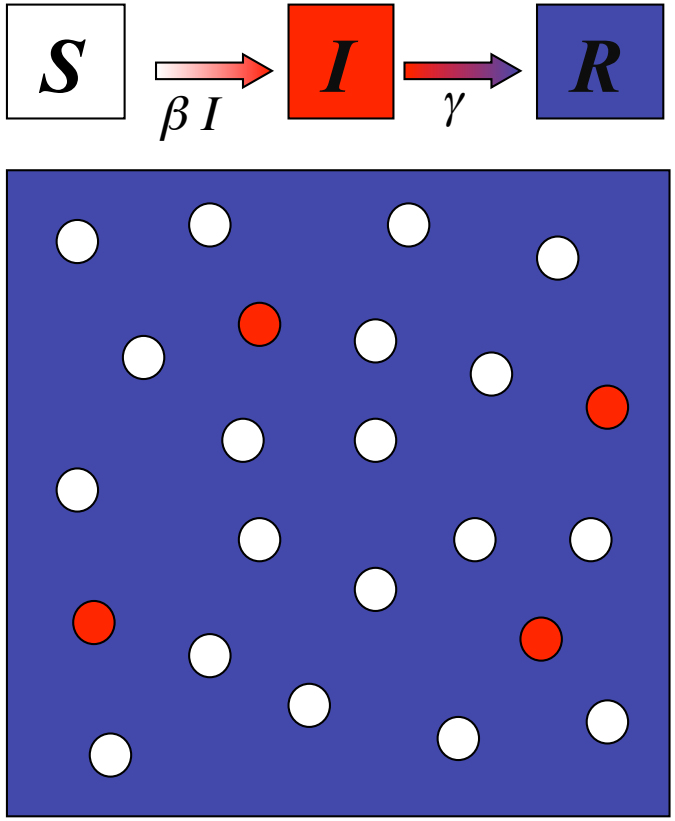
$$R_0 > 1$$

Reinfection threshold: Infection can invade a population where every individual is “partially immune” if and only if

$$R_0 > \frac{1}{\sigma}$$

SIR model

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



$$\frac{dS}{dt} = -\beta I S$$

$$\frac{dI}{dt} = \beta I S - \gamma I$$

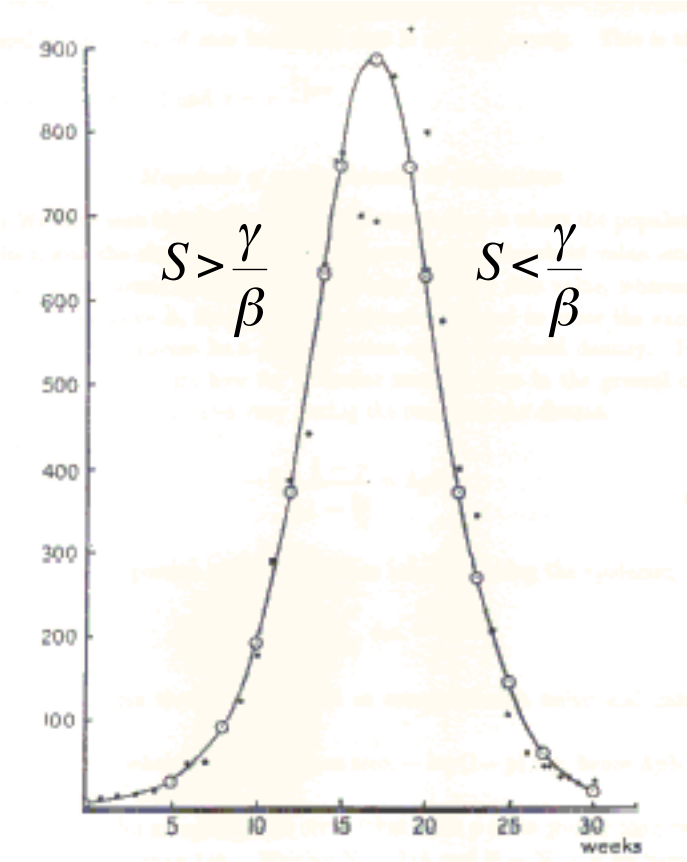
$$\frac{dR}{dt} = \gamma I$$

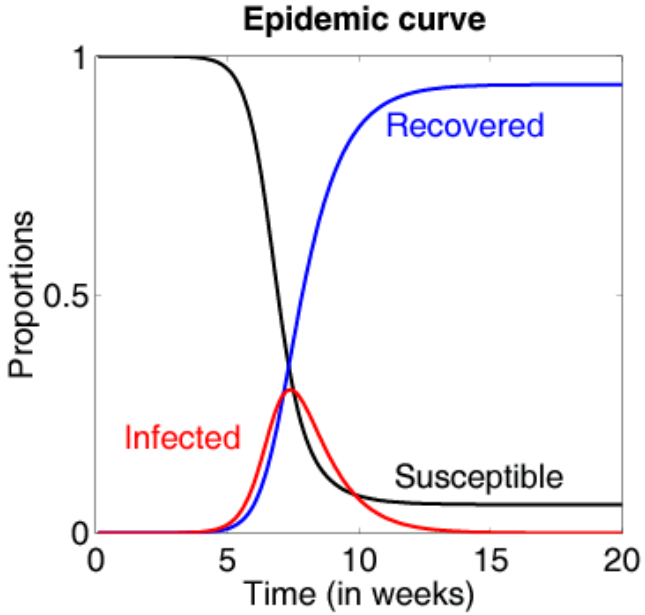
β – transmission coefficient

γ – recovery rate

SIR model fitted to a plague epidemic in Bombay 1906

In 1927, Kermack e McKendrick fitted the model to various epidemic curves. They established the notion of the epidemic threshold, under a slightly different formulation: 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: $S < 1 / R_0$.





$\beta = 3$

$\gamma = 1$

Nondimensional SIR model

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

$$\frac{dS}{dt} = -R_0 I S \qquad \text{and} \qquad \frac{dR}{dt} = I$$
$$\frac{dI}{dt} = R_0 I S - I$$

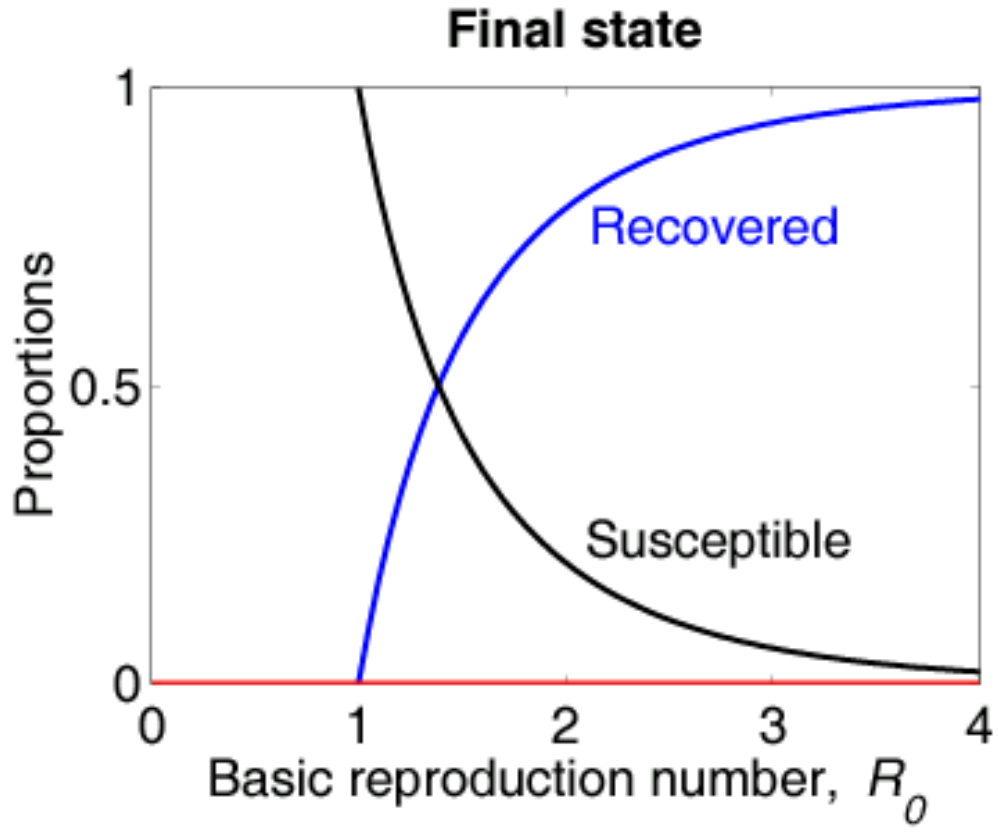
As individuals become immune, this system always approaches the disease free steady state, $I = 0$. As the epidemic progresses, the level of susceptibles decreases, and the level of recovered individuals increases. The important question is the final balance between these two classes – does the disease 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 $R = 1 - I - S$, and at equilibrium $I = 0$, we get

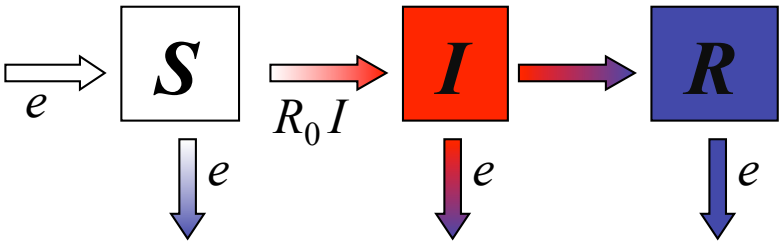
$$R^* = 1 - \exp\left(-R_0 R^*\right)$$

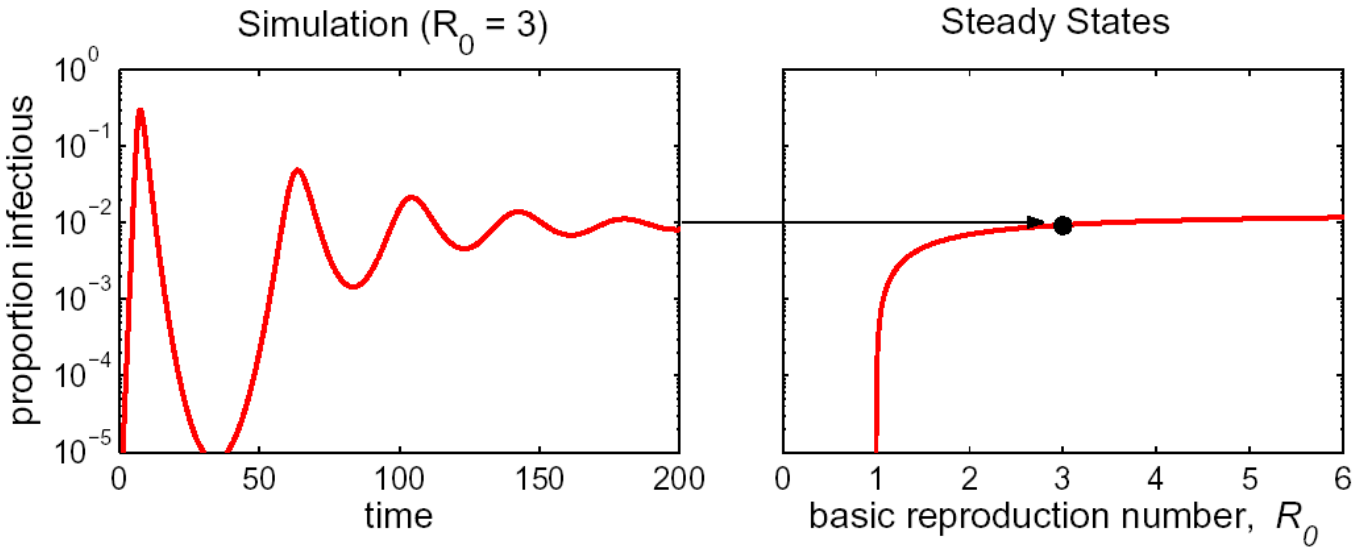
Final epidemic size



SIR with host demography

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





SIR with host demography

The new steady states are obtained from the model

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

Steady states:

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

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

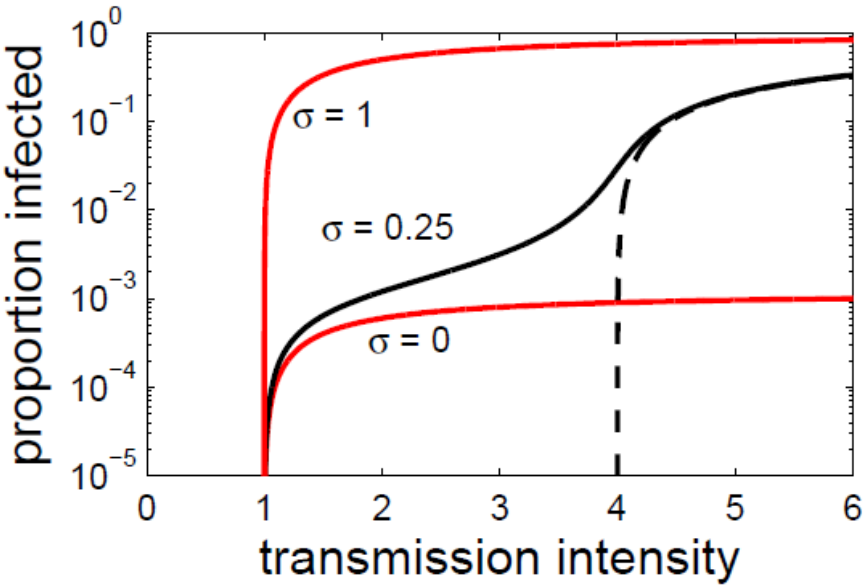
The new parameter, e, represents the birth and death rate in units of infectious period. This is equivalent to D / L, where D is the average duration of infection and L is the life expectancy at birth. Assuming that $D = 1$ month, and $L = 70$ years, we get $e = 0.0012$.

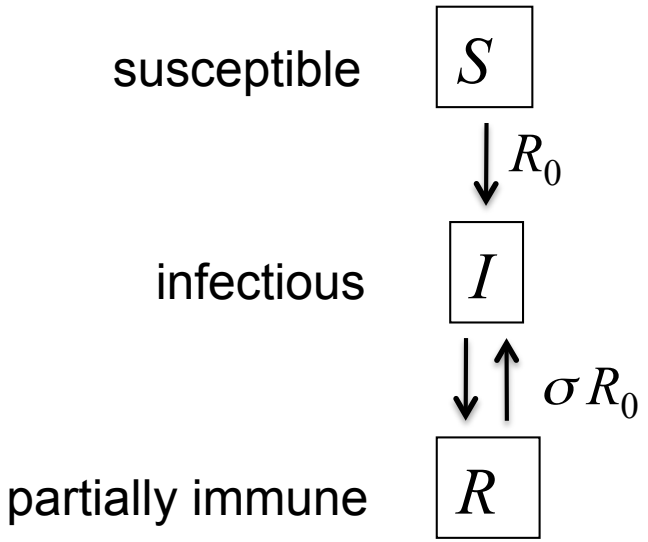
Partial immunity SIRI model

A common scenario is that immunity is not fully protective, but reduces the risk of further infections by some factor (e.g. tuberculosis).

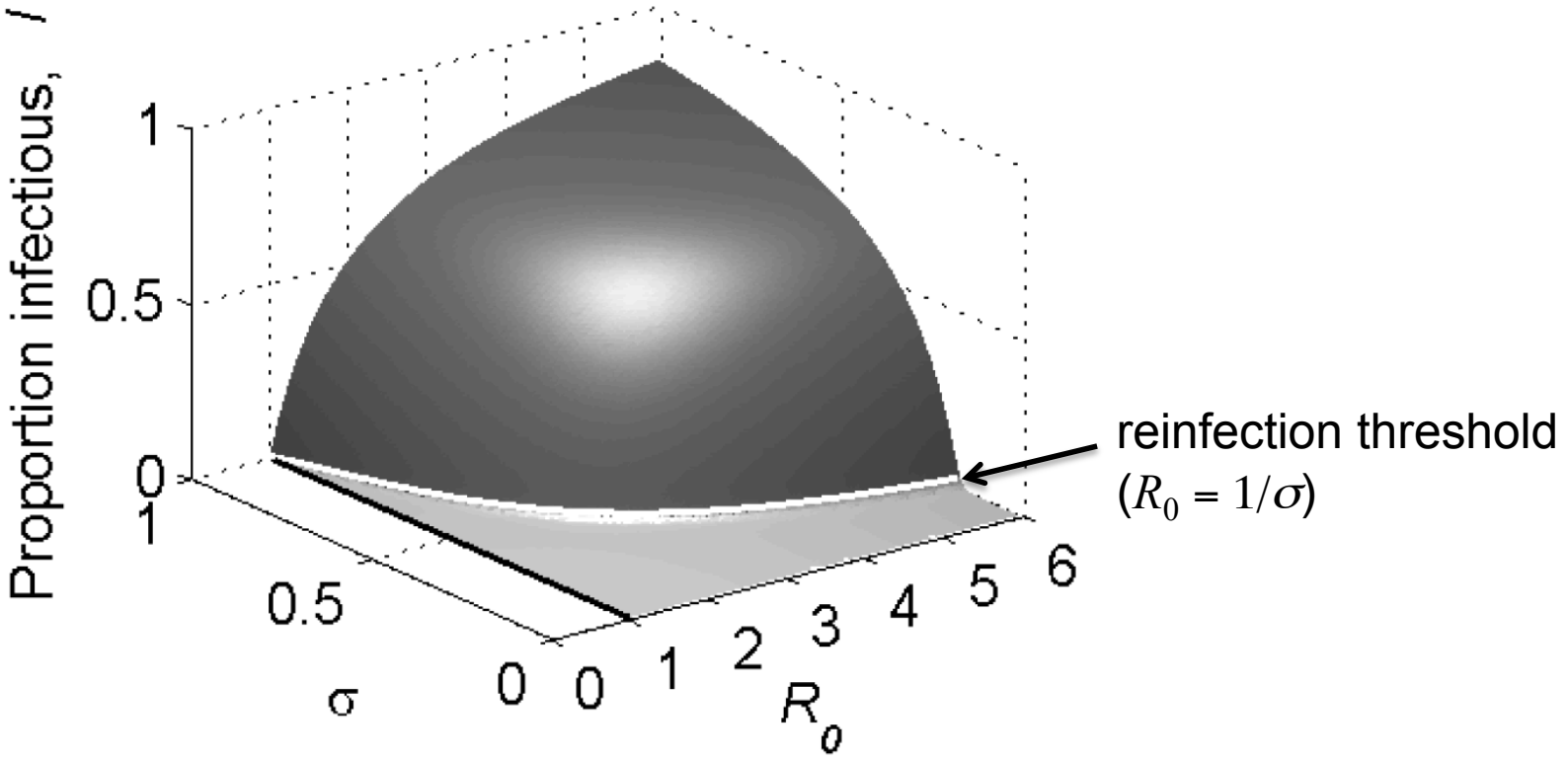
$$\frac{dS}{dt} = e - R_0 I S - eS$$

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



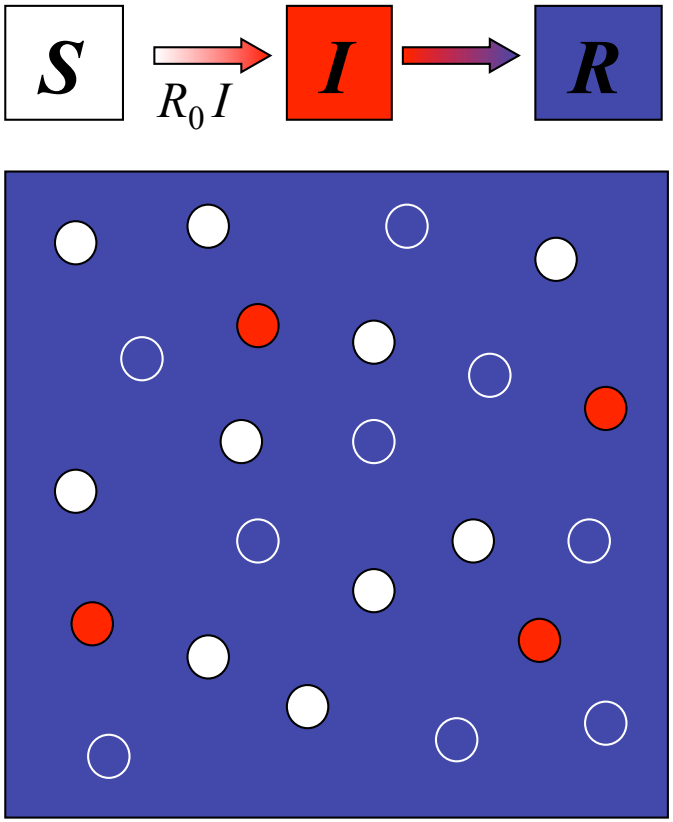


Partial immunity SIRI model



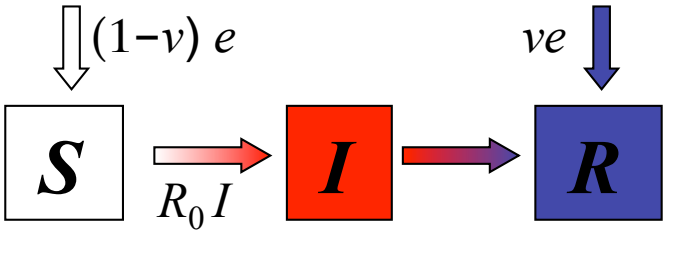
Vaccination in SIR model

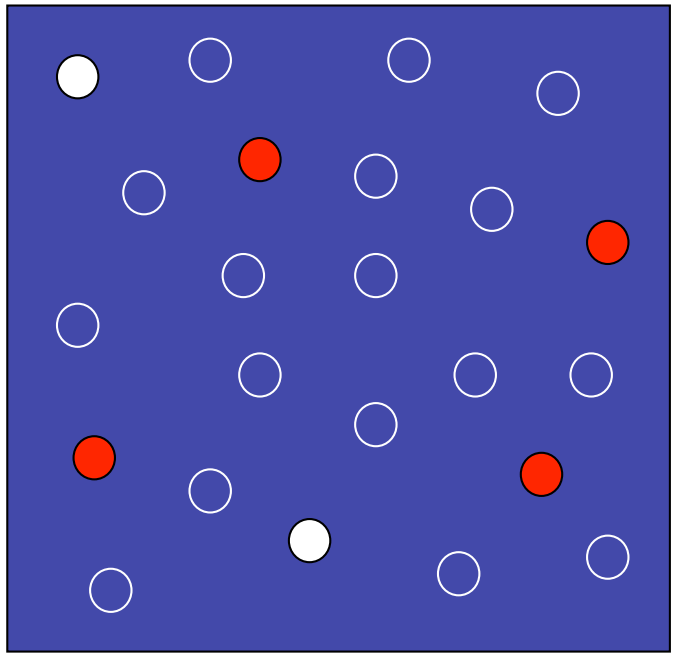
The collective effect of a vaccination programme is to reduce the pool of susceptible individuals.



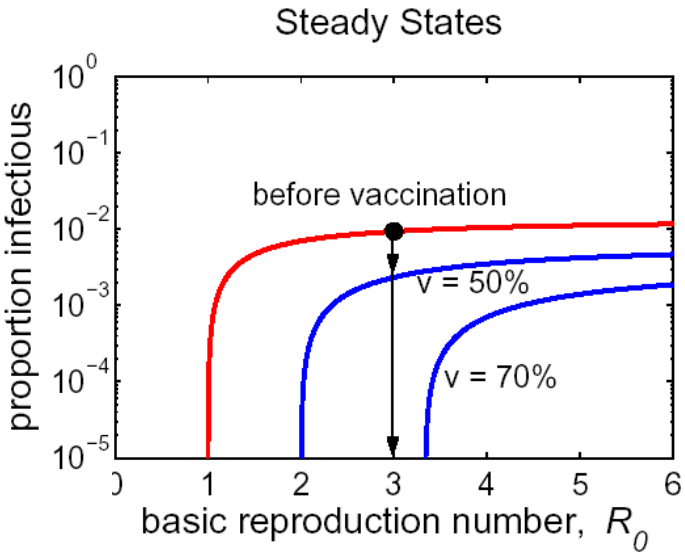
Vaccination in SIR model

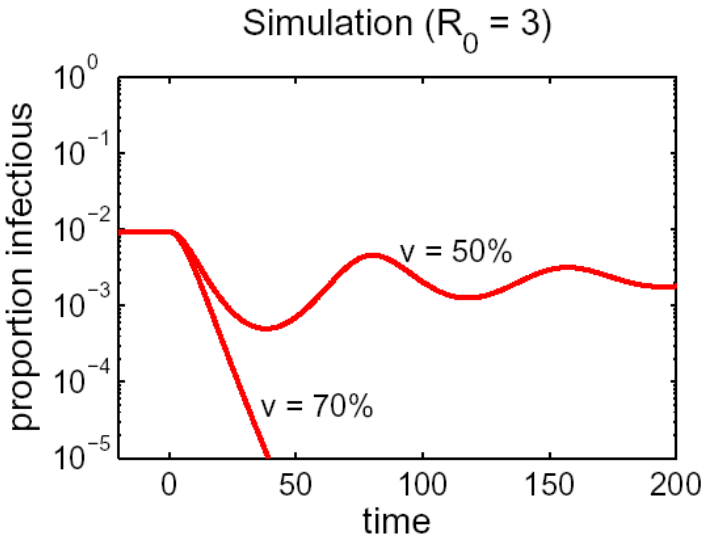
The collective effect of a vaccination programme is to reduce the pool of susceptible individuals.





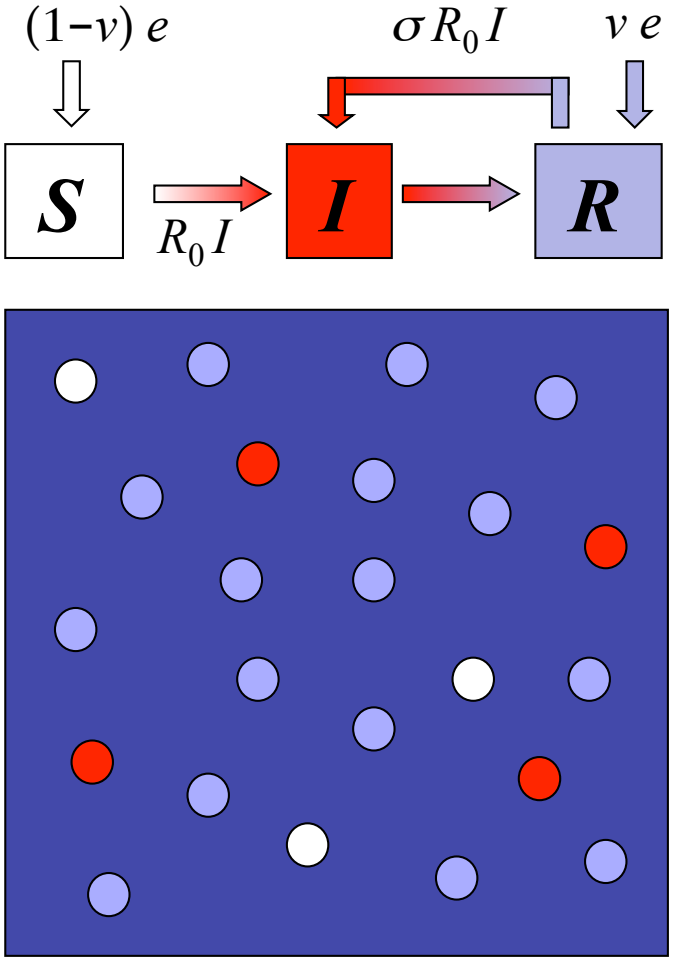
v: vaccination coverage



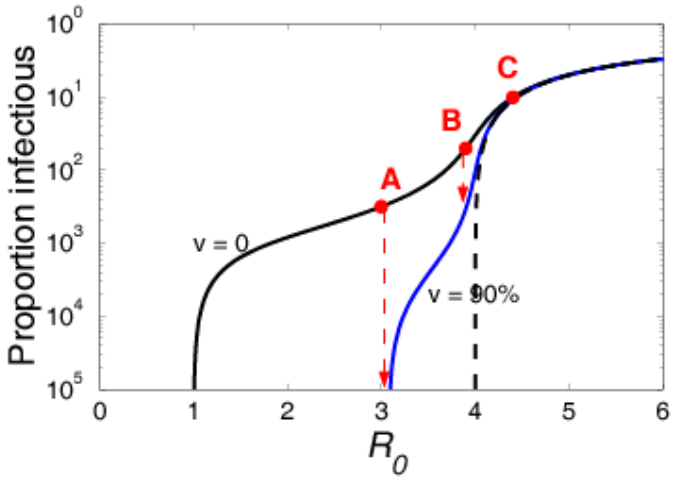


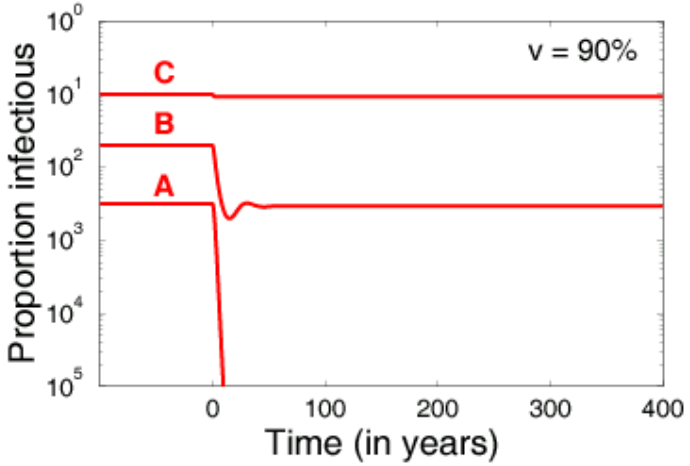
Vaccination in SIRI model

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

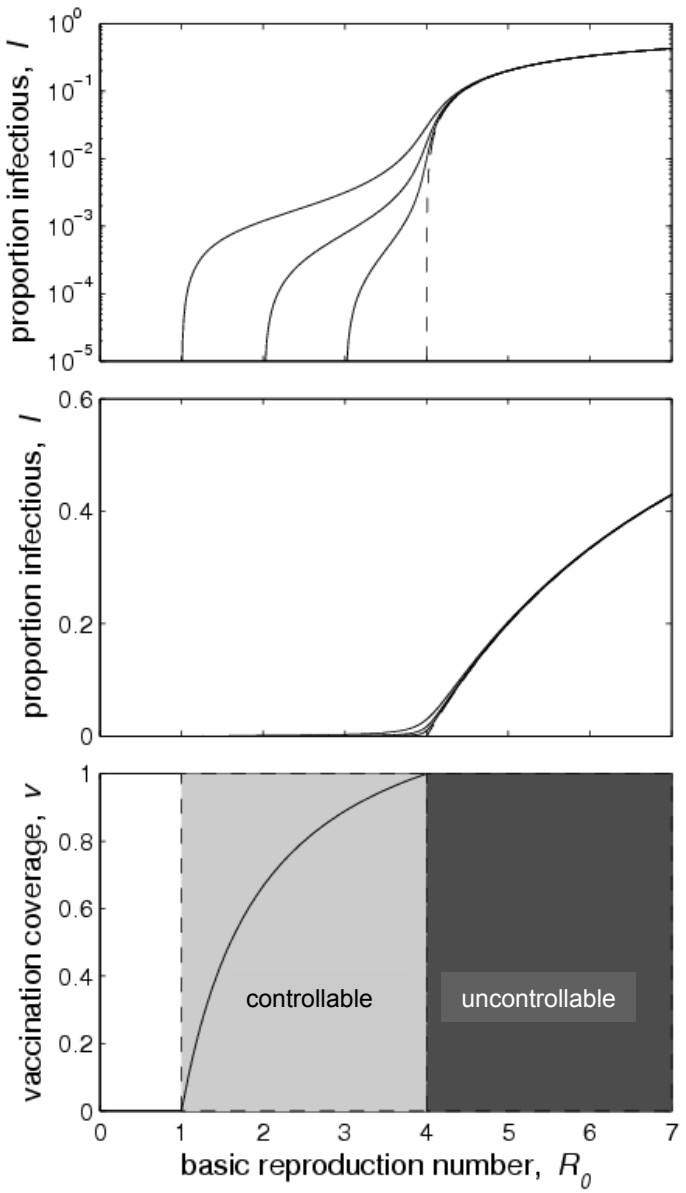


σ: susceptibility reduction factor



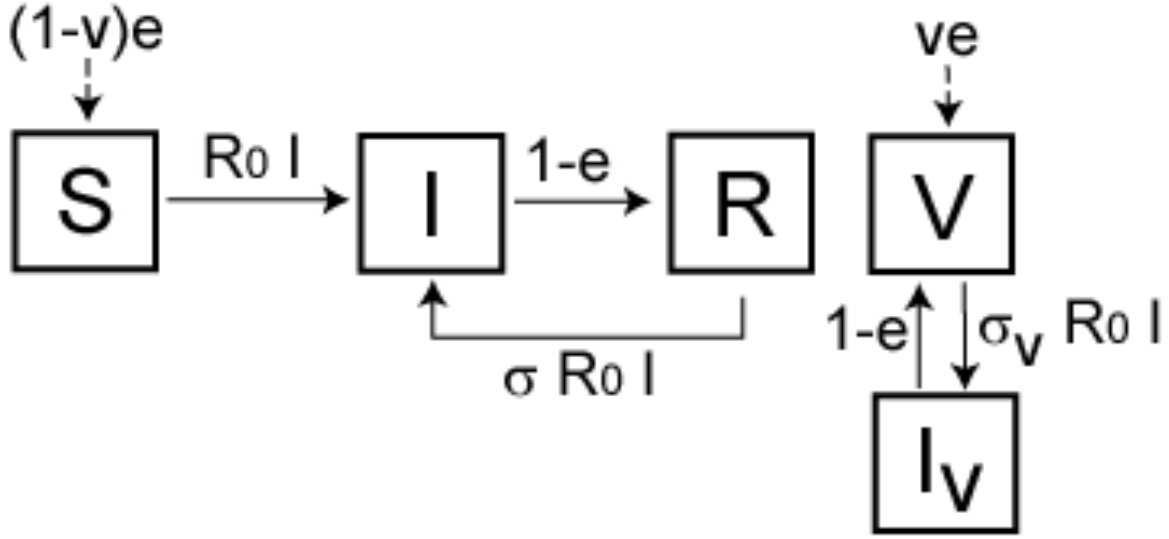


Reinfection threshold and effectiveness of vaccination programs



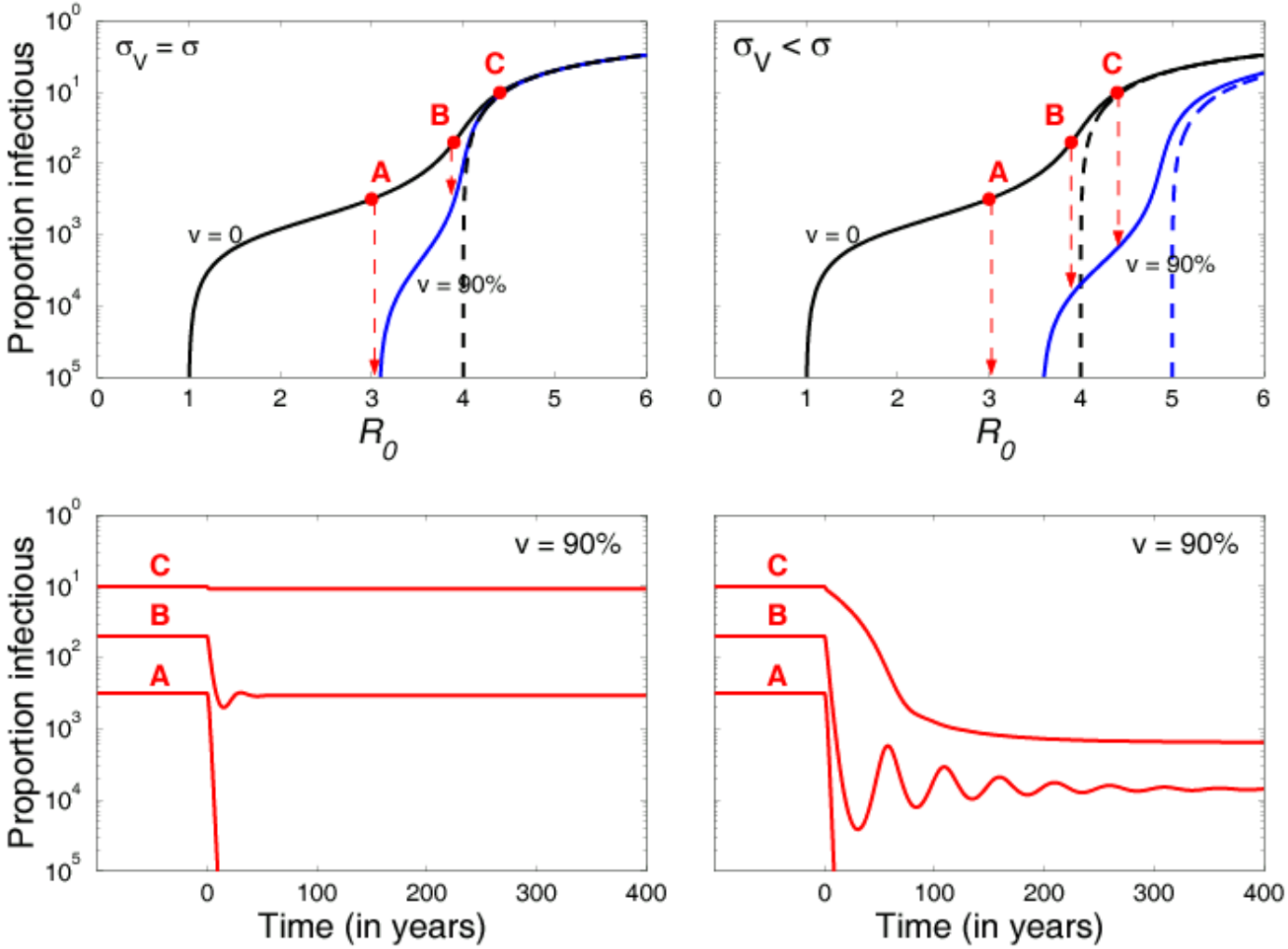
Defining effications vaccines

Typically vaccines do not confer a level protection superior to that induced by natural infection. However, this is a prime goal in vaccine research. In order to predict the epidemiological impact of such vaccine we need an extension to the partial immunity model.

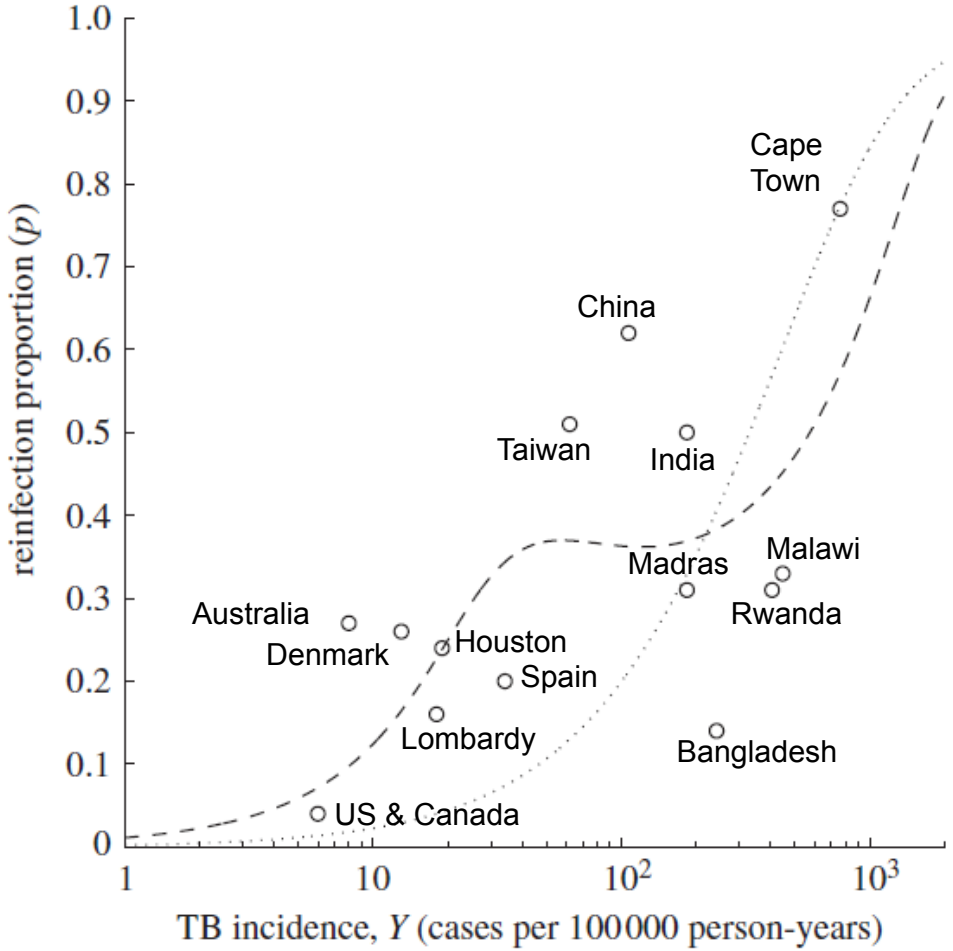


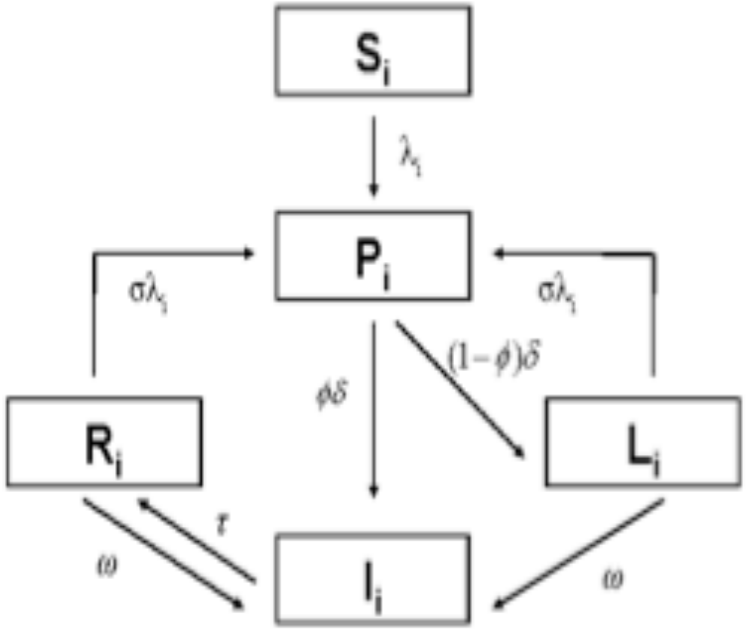
The vaccine is more potent than natural infection if and only of $\sigma_V < \sigma$.

Defining effications vaccines



Field data: tuberculosis reinfection





System of ordinary differential equations (SIRI-like for tuberculosis)

$$\frac{dS_i}{dt} = \mu p_i - \left(\lambda_i + \mu\right) S_i$$

$$\frac{dP_i}{dt} = \lambda_i S_i + \sigma \lambda_i \left(L_i + R_i\right) - \left(\delta + \mu\right) P_i$$

$$\frac{dI_i}{dt} = \phi \delta P_i + \omega \left(L_i + R_i\right) - \left(\gamma + \mu\right) I_i$$

$$\frac{dL_i}{dt} = \left(1 - \phi\right) \delta P_i - \left(\sigma \lambda_i + \omega + \mu\right) L_i$$

$$\frac{dR_i}{dt} = \gamma I_i - \left(\sigma \lambda_i + \omega + \mu\right) R_i$$

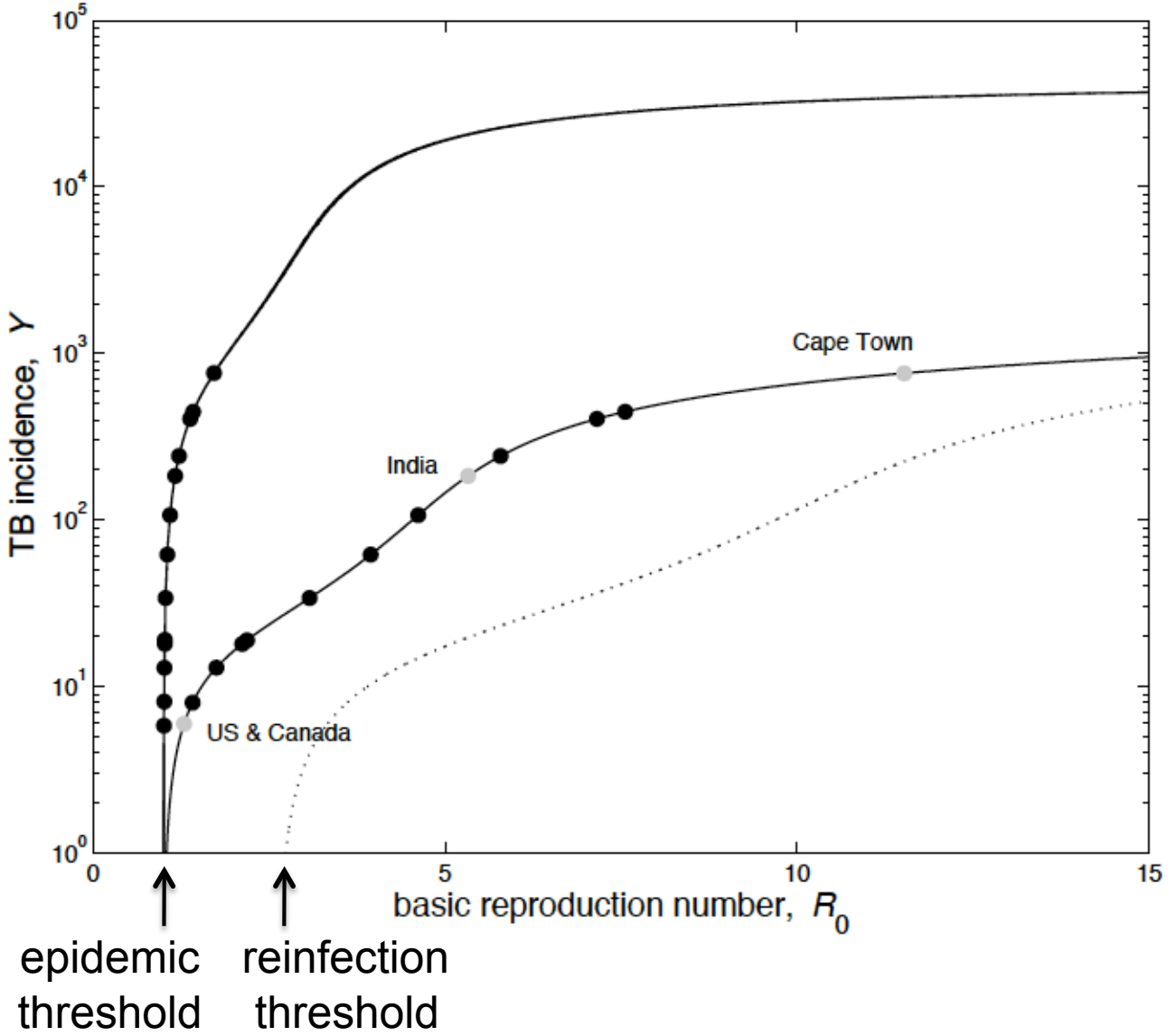
$$\lambda_i = \alpha_i \lambda$$

Model fitting and parameter estimation for tuberculosis

Global parameters

Parameter	Heterogeneous model	Homogeneous model
p	0.98 [0.95, 1.00]	NA
α	0.15 [0.00, 0.56]	NA
σ	0.51 [0.00, 2.37]	3.87 [1.61, 7.79]
RSS	0.30	0.74
SEE	0.16	0.24
F test	8.12 (0.007)	NA
Log-likelihood test	12.70 (0.002)	NA

Multi-population tuberculosis trends



Estimates of R_0 may be very sensitive to heterogeneity in host susceptibility

Bibliography

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

Gomes MGM, Franco AO, Gomes MC, Medley GF (2004) The reinfection threshold promotes variability in tuberculosis epidemiology and vaccine efficacy. *Proc R Soc Lond* B 271: 617-623.

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

Águas R, White LJ, Snow RW, Gomes MGM (2008) Prospects for malaria eradication in sub-Saharan Africa. *PLoS ONE* 3(3): e1767.

Gomes MGM, Águas R, Lopes JS, Nunes MC, Rebelo C, Rodrigues P, Struchiner CJ (2012) How host selection governs tuberculosis reinfection. *Proc R Soc Lond* B 279: 2473-2478.