Modeling Infectious Diseases Using R: An Introduction

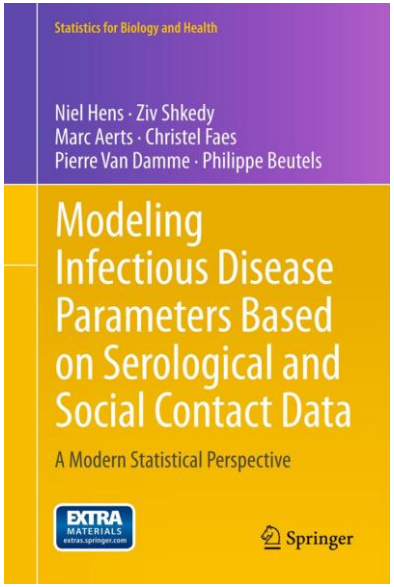
Prof. Dr. Ziv Shkedy
Center for Statistics, Hasselt University, Belgium

SUSAN-SSACAB 2019 Conference, 8 - 11 September 2019, Cape Town, South Africa

Topics

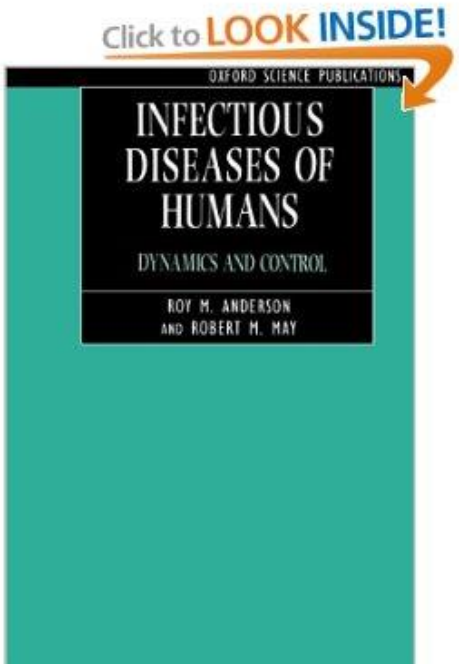
- Introduction:
  - Example tour and terminology
  - The modeling framework.
  - Transmission and Transmission models.
- The SIR model:
  - Incidence Data &
    SIR transmission model in R.
  - The SIR model in time homogeneity setting.
  - More about modeling.
- Multiple populations:
  - Understanding contact/mixing patterns in the population.
  - Age structured population.
- Vaccination: Intervention and Control.
- Case studies:
  - Transmission model for HIV/AIDS.
  - Transmission models for HCV among injecting drug users.

Reference



All programs for all book chapters are available at:

http://www.simid.be/



Materials from the first 9 chapters.

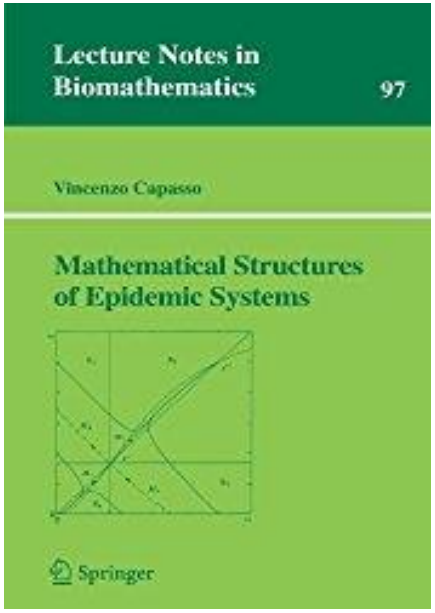


Illustration of some models.

Software

- R package: `deSolve`.
- R programs for practical sessions.

Example tour and terminology

Example: outbreak of Ebola virus 2015

- Ebola virus disease (EVD), formerly known as Ebola haemorrhagic fever, is a severe, often fatal illness in humans.

- The virus is transmitted to people from wild animals and spreads in the human population through human-to-human transmission.

- The average EVD case fatality rate is around 50%. Case fatality rates have varied from 25% to 90% in past outbreaks

Transmission

- Human-to-human transmission occurs only via direct contact with blood or bodily fluids from an infected person who is showing signs of infection.
- By contact with objects recently contaminated by an actively ill infected person.
- Airborne transmission has not been documented during Ebola outbreaks
- The time interval from infection with the virus to onset of symptoms is two to twenty-one days.
- Because dead bodies are still infectious, the handling of the bodies of Ebola victims can only be done while observing proper barrier/ separation procedures.

The first cases ?

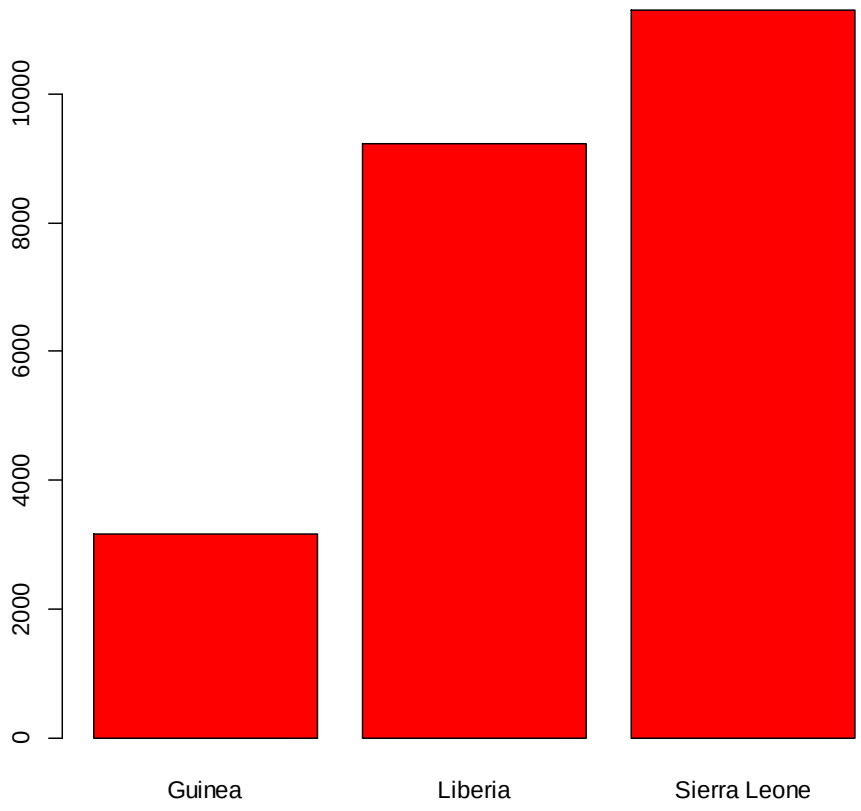
- Outbreak 2014.
- Researchers generally believe that a year-old boy, later identified as Emile Ouamouno, who died in December 2013 in the village of Meliandou, Guéckédou Prefecture, Guinea, was the index case of the current Ebola virus disease epidemic.

March 2014

- On 25 March 2014, the Guinea's Ministry of Health had reported an outbreak of Ebola virus disease in four southeastern districts, with suspected cases in the neighbouring countries of Liberia and Sierra Leone being investigated.

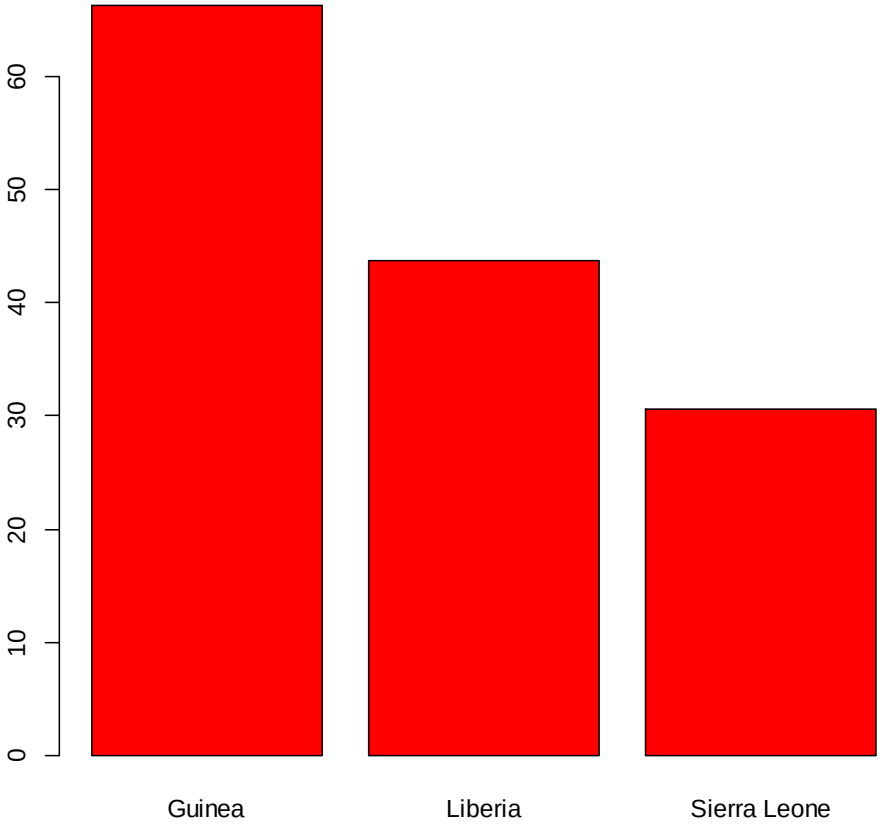
- In Guinea, a total of 86 suspected cases, including 59 deaths had been reported as of 24 March

Number of cases 06/03/2015



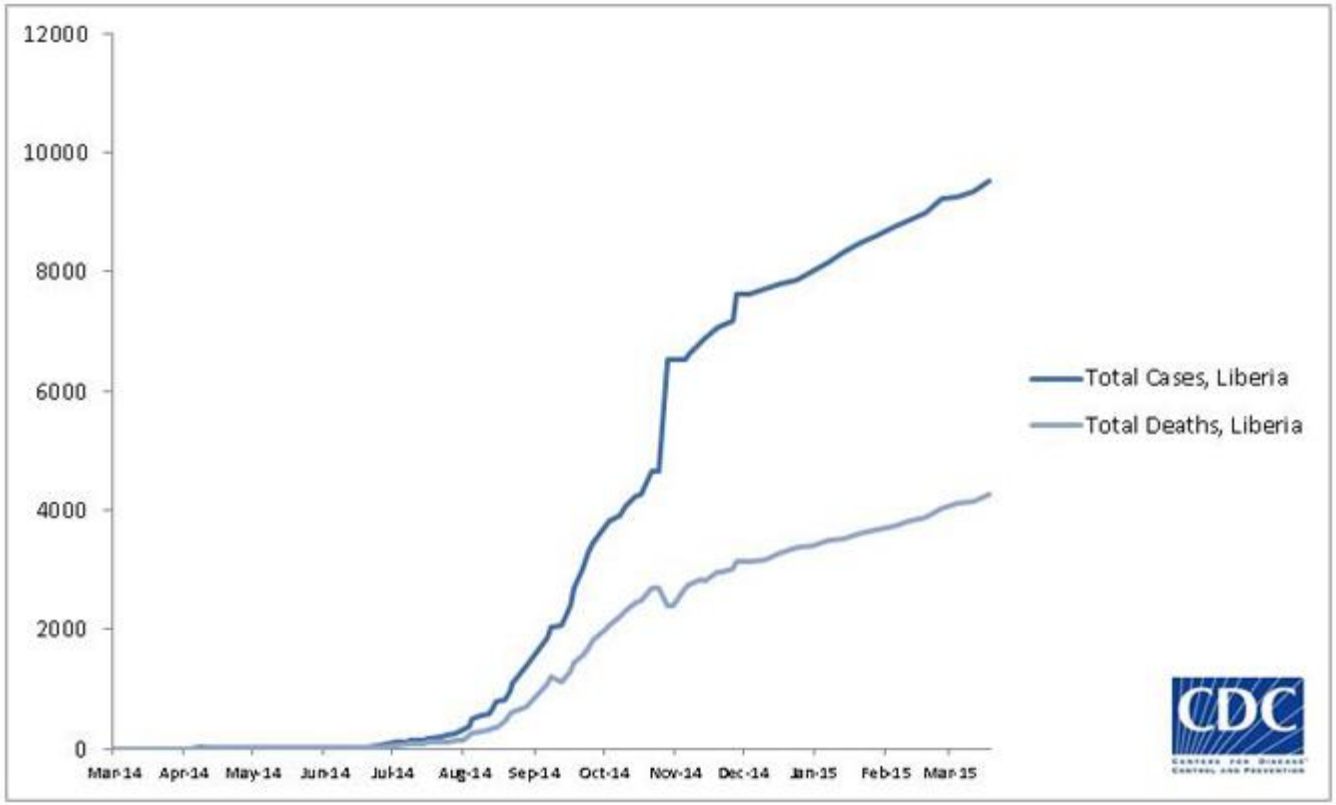
Number of cases in Guinea (3155), Liberia (9238), and Sierra Leone (11301).

Death rate 06/03/2015



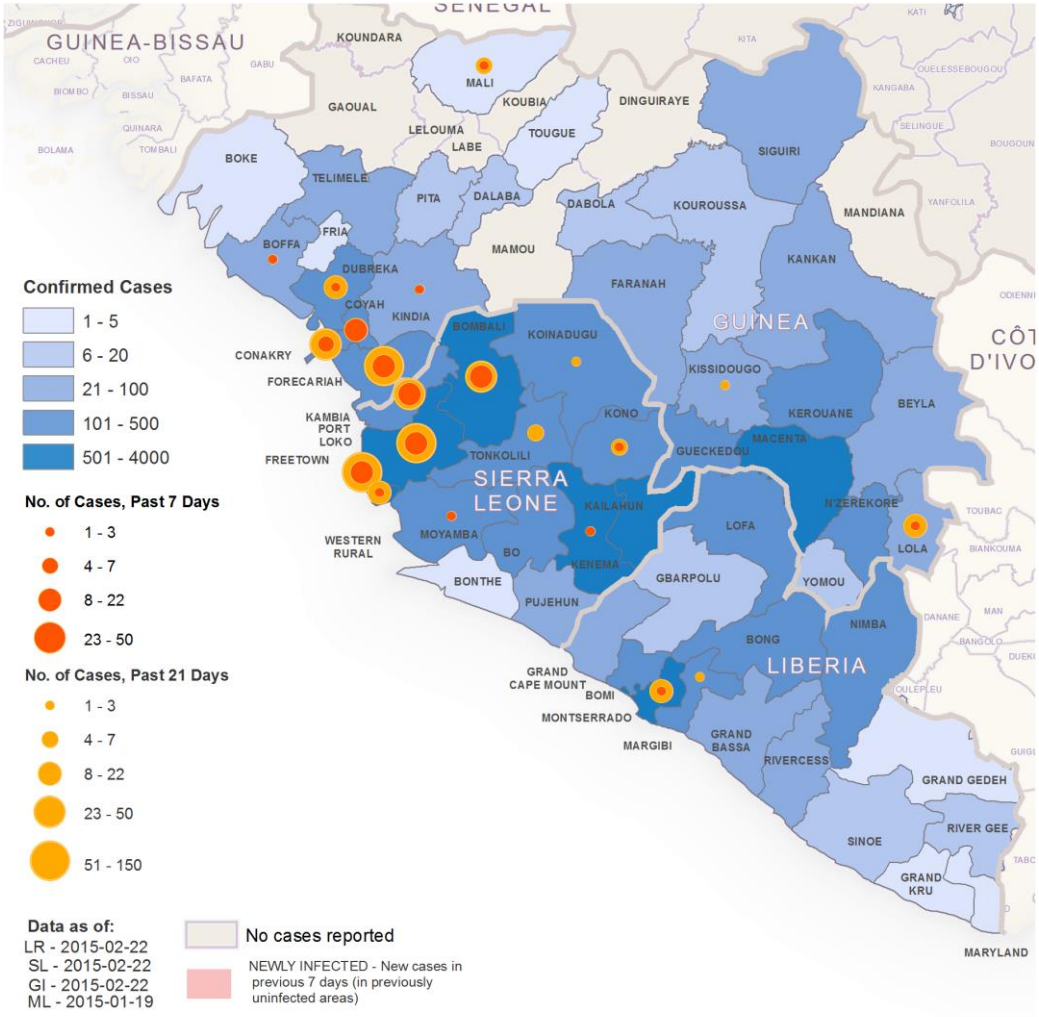
Guinea : 0.66
Liberia :0.43
Sierra Leone:0.30

Death rate 18/03/2015, Liberia

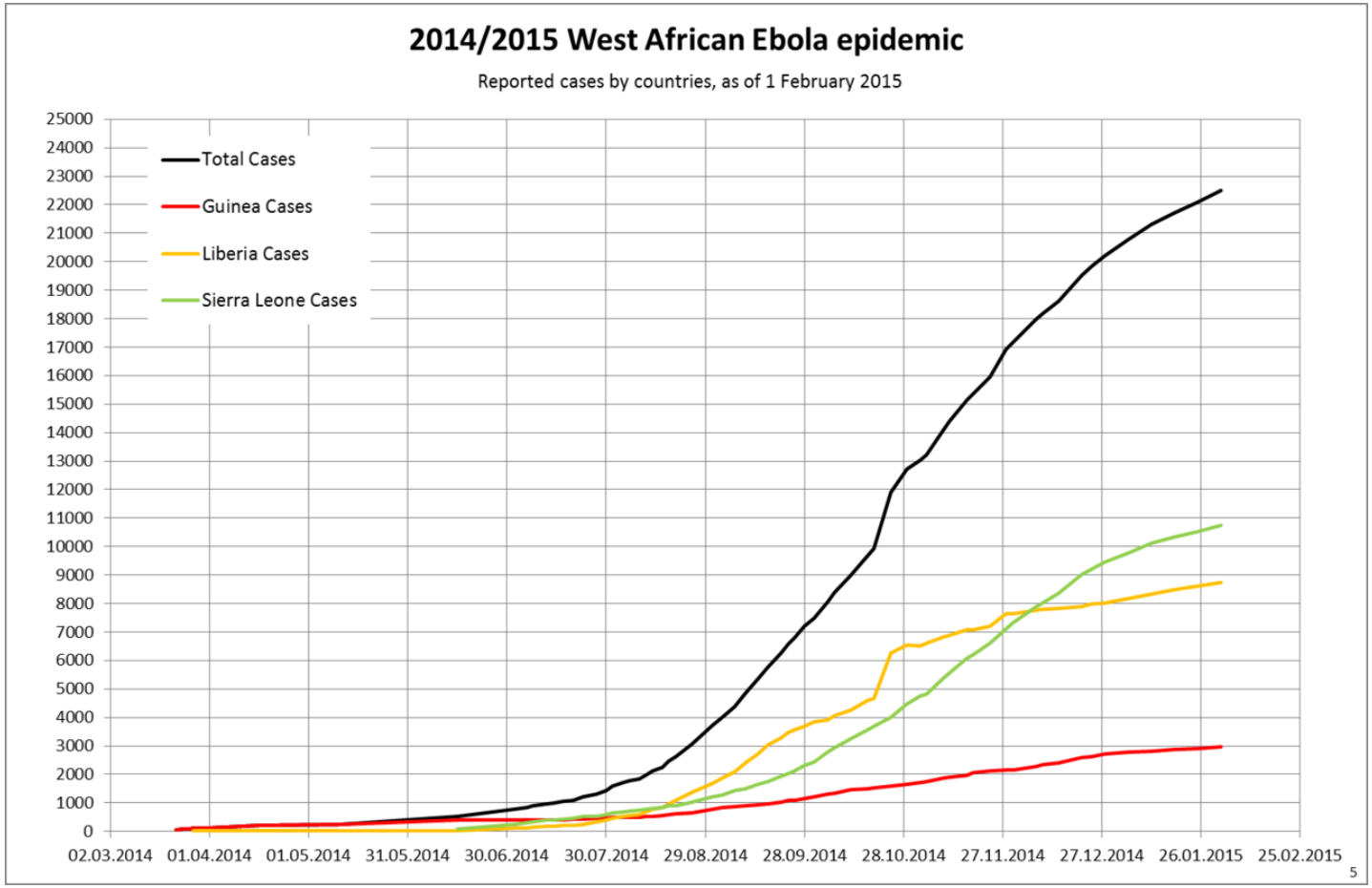


Infected	9526
Death	4264
%	44.76%

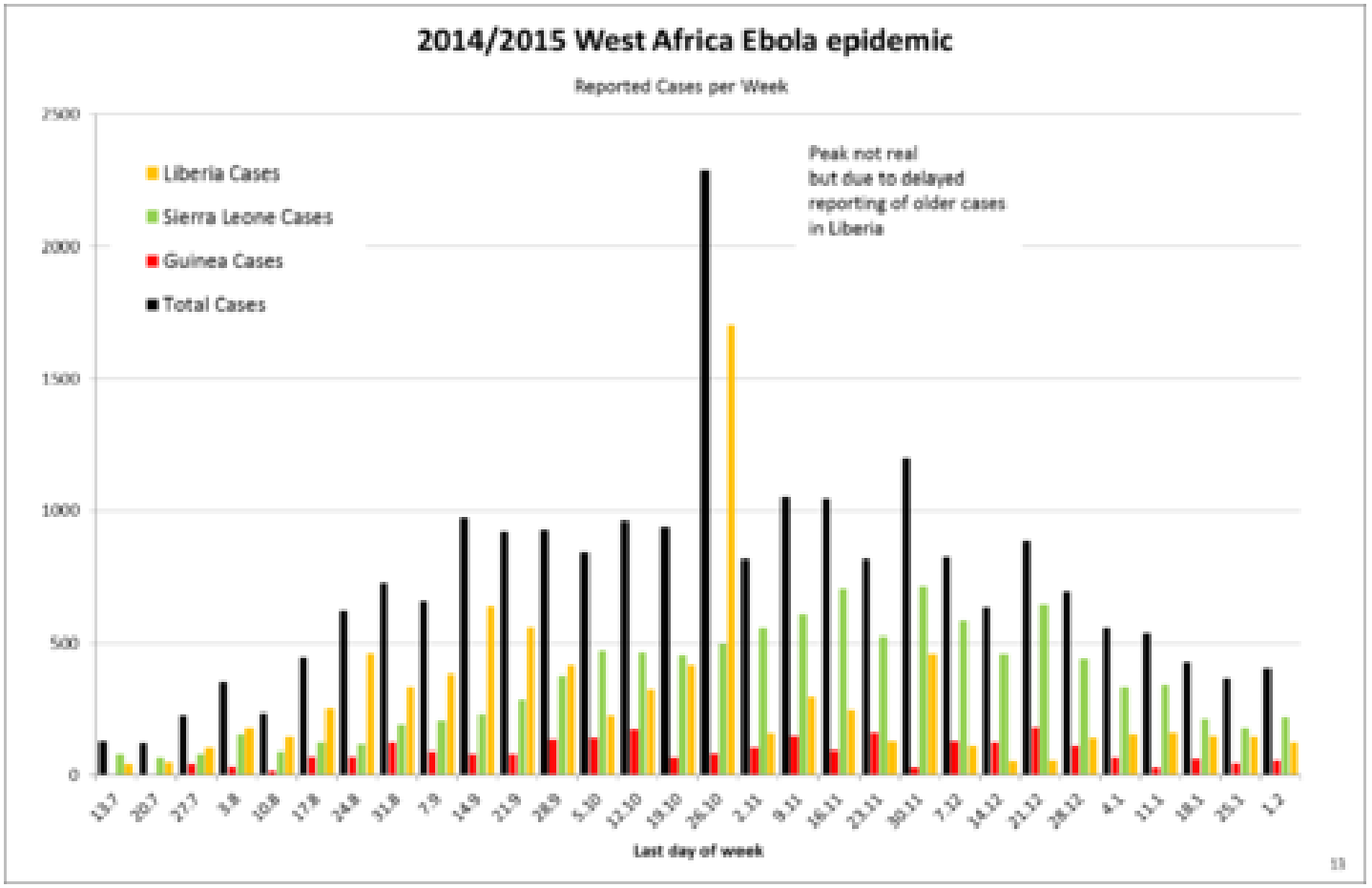
Number of new cases 06/03/2015



Cumulative number of new cases 02/2015



Weekly number of cases 02/2015



Example: outbreak of Zika virus disease - 2016

- Zika virus disease is caused by a virus transmitted by *Aedes* mosquitoes.
- People with Zika virus disease usually have symptoms that can include mild fever, skin rashes, conjunctivitis, muscle and joint pain, malaise or headache. These symptoms normally last for 2-7 days.
- There is no specific treatment or vaccine currently available.
- The best form of prevention is protection against mosquito bites.
- The virus is known to circulate in Africa, the Americas, Asia and the Pacific

http://www.cdc.gov/zika/

This year (2016): Zika virus disease

Spread of Zika virus in 2016 in America

BBC NWES: Brazil Zika virus- New link to microcephaly in babies

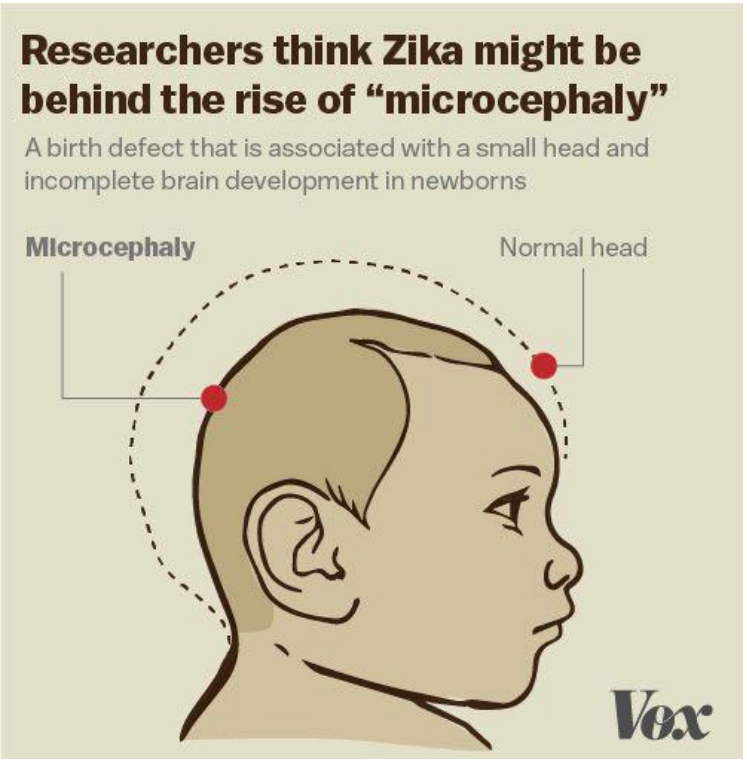
- The team at the PUC-Parana University discovered the virus in the brains of two babies who only lived for 48 hours.

- The mosquito-borne virus is thought to cause microcephaly in babies, who are born with damaged brains and abnormally small heads.

- Brazil has about 460 confirmed cases of microcephaly, and is investigating about 3,850 suspected case.

http://www.bbc.com/news/world-latin-america-35584953

Microcephaly in babies



Possible Association Between Zika Virus Infection and Microcephaly — Brazil, 2015

- Schuler-Faccini et al CDC*Weekly* / January 29, 2016 / 65(3);59–62
- In early 2015, an outbreak of Zika virus, a flavivirus transmitted by *Aedes* mosquitoes, was identified in northeast Brazil.
- By September, reports of an increase in the number of infants born with microcephaly in Zika virus-affected areas began to emerge.
- Zika virus RNA was identified in the amniotic fluid of two women whose fetuses had been found to have microcephaly by prenatal ultrasound.

http://www.cdc.gov/mmwr/volumes/65/wr/mm6503e2.htm#T1_down

Possible Association Between Zika Virus Infection and Microcephaly — Brazil, 2015

- Among a cohort of 35 infants with microcephaly born during August–October 2015 in eight of Brazil's 26 states and reported to the registry.

- The mothers of all 35 had lived in or visited Zika virus-affected areas during pregnancy.

- 25 (71%) infants had severe microcephaly (head circumference >3 SD below the mean for sex and gestational age).
- 17 (49%) had at least one neurologic abnormality, and among 27 infants who had neuroimaging studies, all had abnormalities.

Brazil may have fewer Zika-related microcephaly cases than previously reported

- The Washington post, January 29.

- On Wednesday, Brazil's Ministry of Health said 4,180 cases of Zika-related microcephaly had been reported since October.

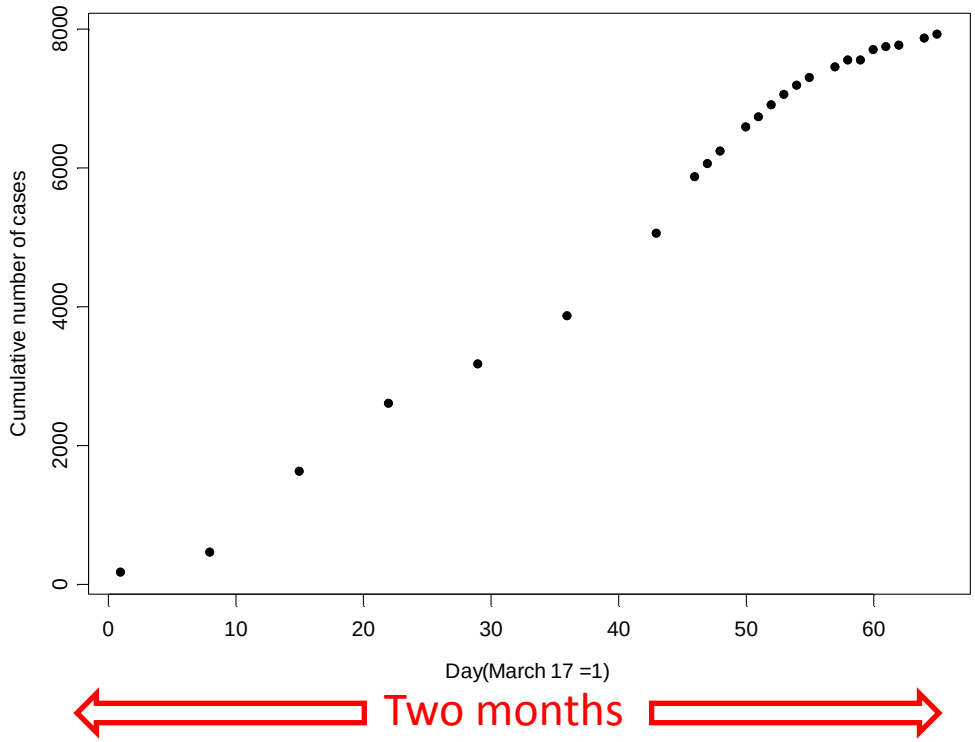
- After experts scrutinized 732 of the cases they found that more than half either weren't microcephaly, or weren't related to Zika

Example : outbreak of SARS

- Severe acute respiratory syndrome (SARS) is a viral respiratory illness caused by a coronavirus, called SARS-associated coronavirus (SARS-CoV).
- SARS was first reported in Asia in February 2003.
- Over a period of few months, the illness spread to more than two dozen countries in North America, South America, Europe, and Asia. The SARS global
- outbreak of 2003 was contained; however, it is possible that the disease could re-emerge.
- Depends on age, the death rate is between 6% to 50%.

Outbreak of SARS

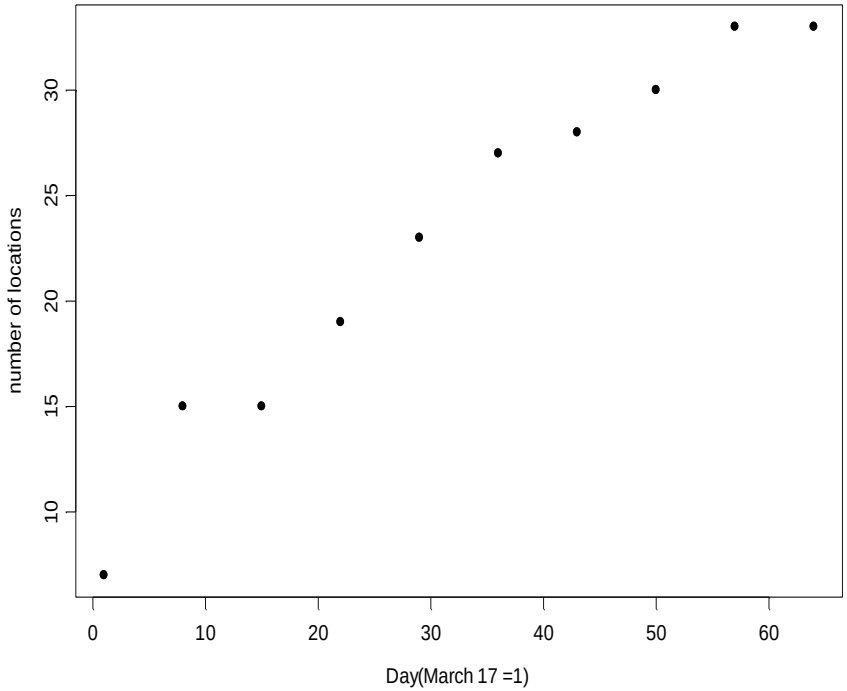
- The cumulative number of reported SARS cases, In March, 17, 2003 the number of reported cases was 167 and it increased to 7919 in May, 20, 2003.



Spread of SARS Over the World

- The rapid spread of SARS can also be seen in the figure which shows the number of countries with at least 1 reported case of SARS.
- In March 17, 2003,

  the number of countries is 7 and it increased to 31 by May, 20, 2003.

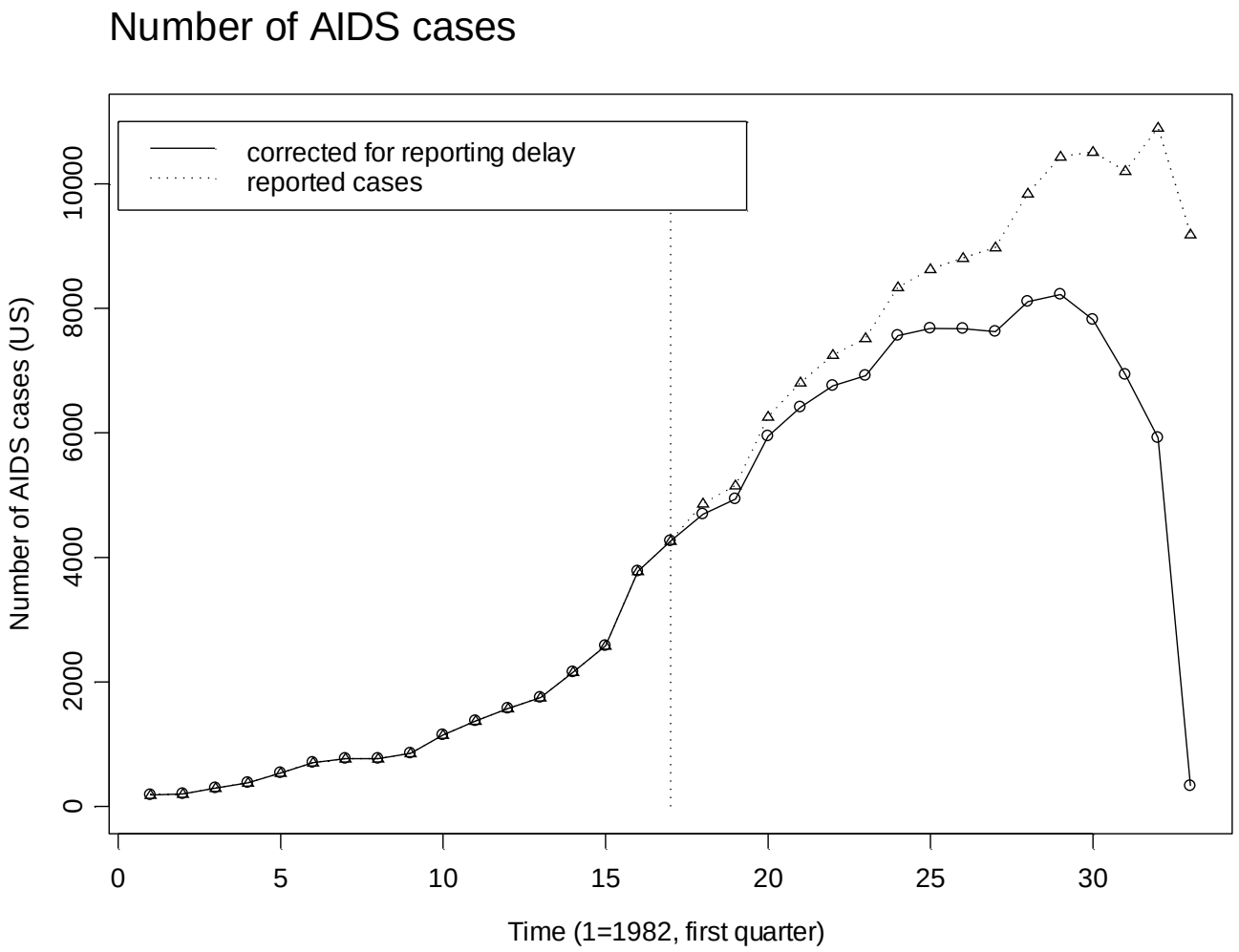


www.cdc.gov/ncidod/sars/ and www.who.int/csr/sars

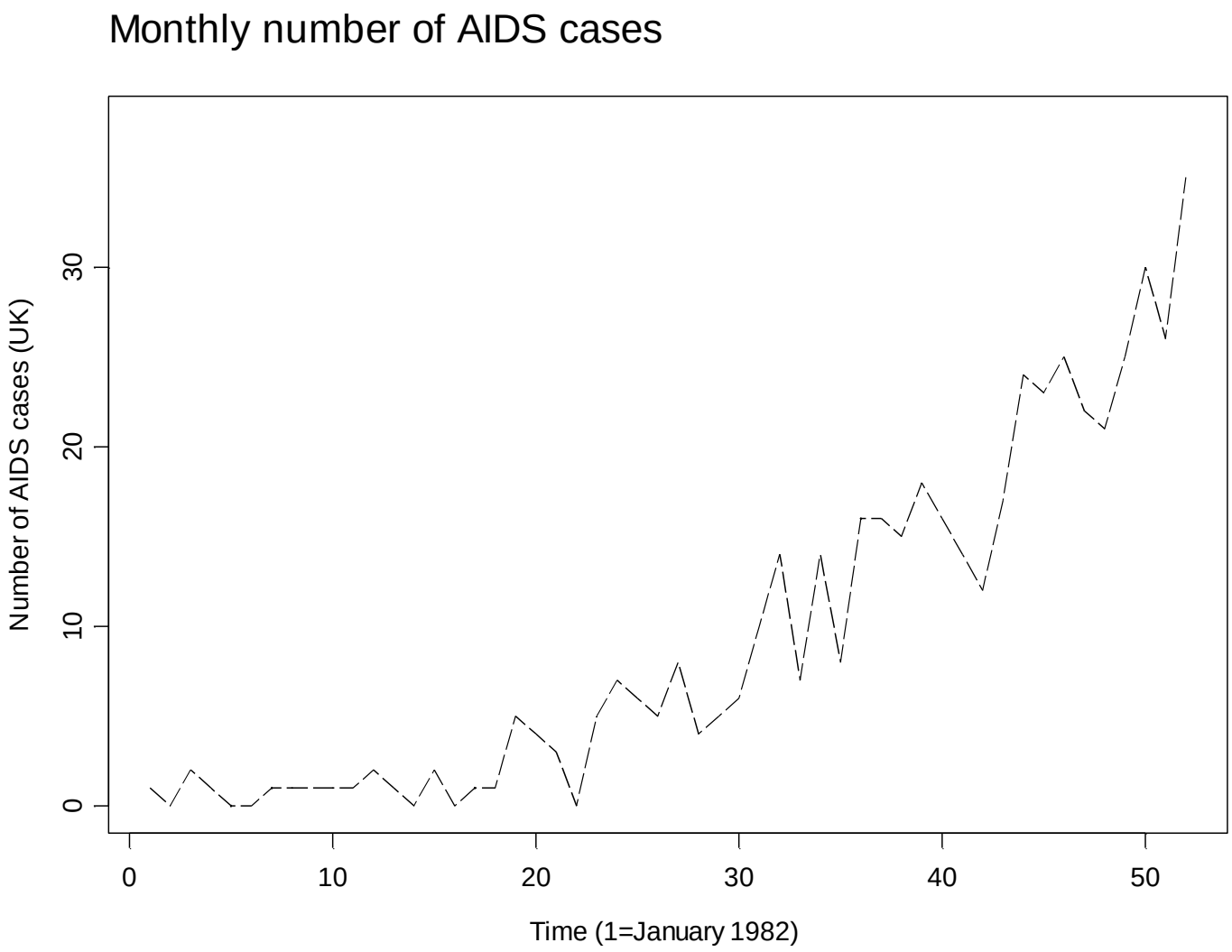
Example: Outbreak of AIDS in US

- Up to December 1992, the centers for disease control in USA (CDC) has reported on 249199 cases of AIDS in USA (Hay and Wolak, 1994) and 169623 AIDS related deaths.
- The Figure (solid line) shows the quarterly number of reported cases AIDS in USA.
- The decline in number of cases in the last few quarters is due to underreporting.

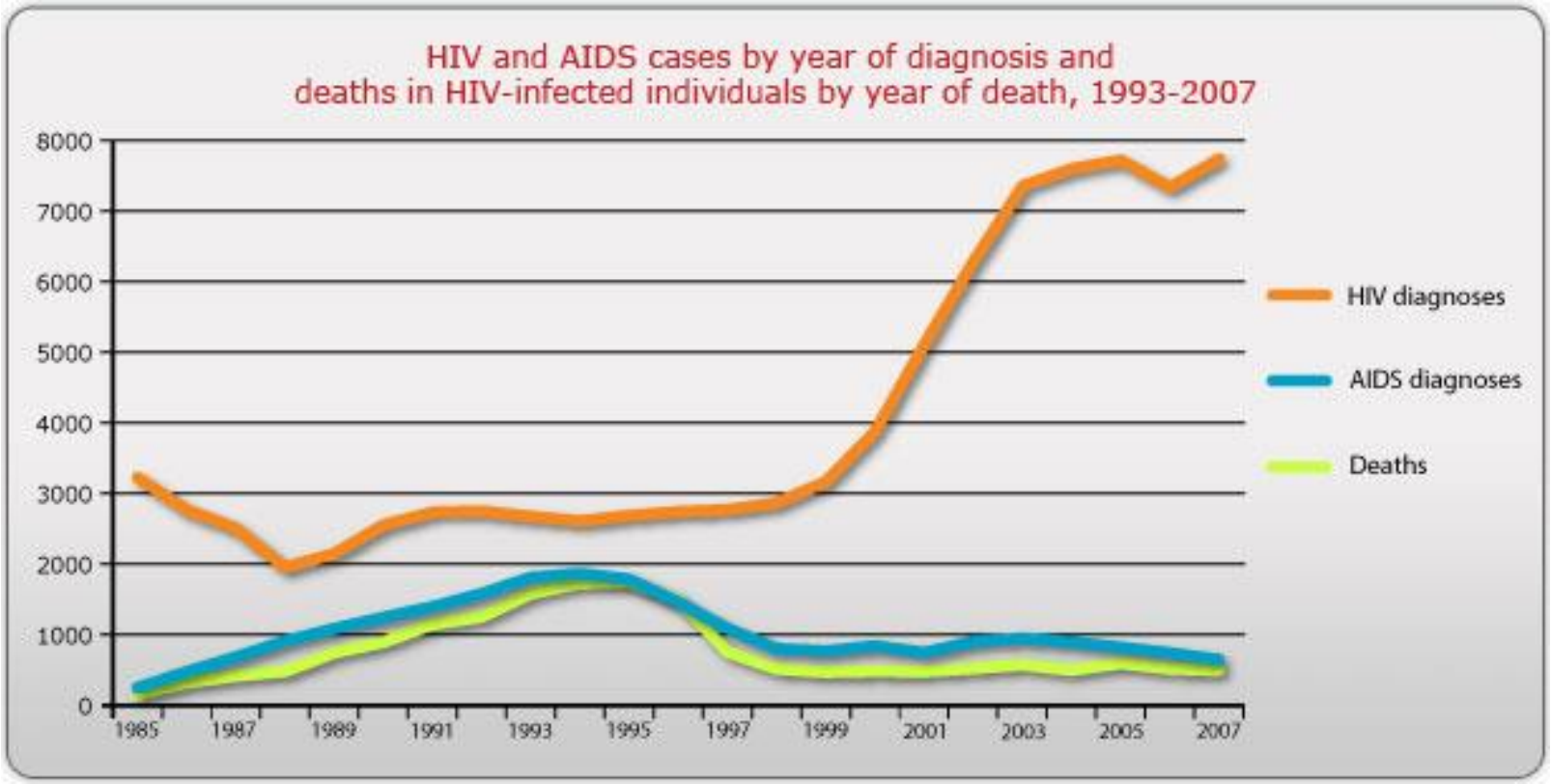
Outbreak of AIDS in US



Monthly number of cases in UK

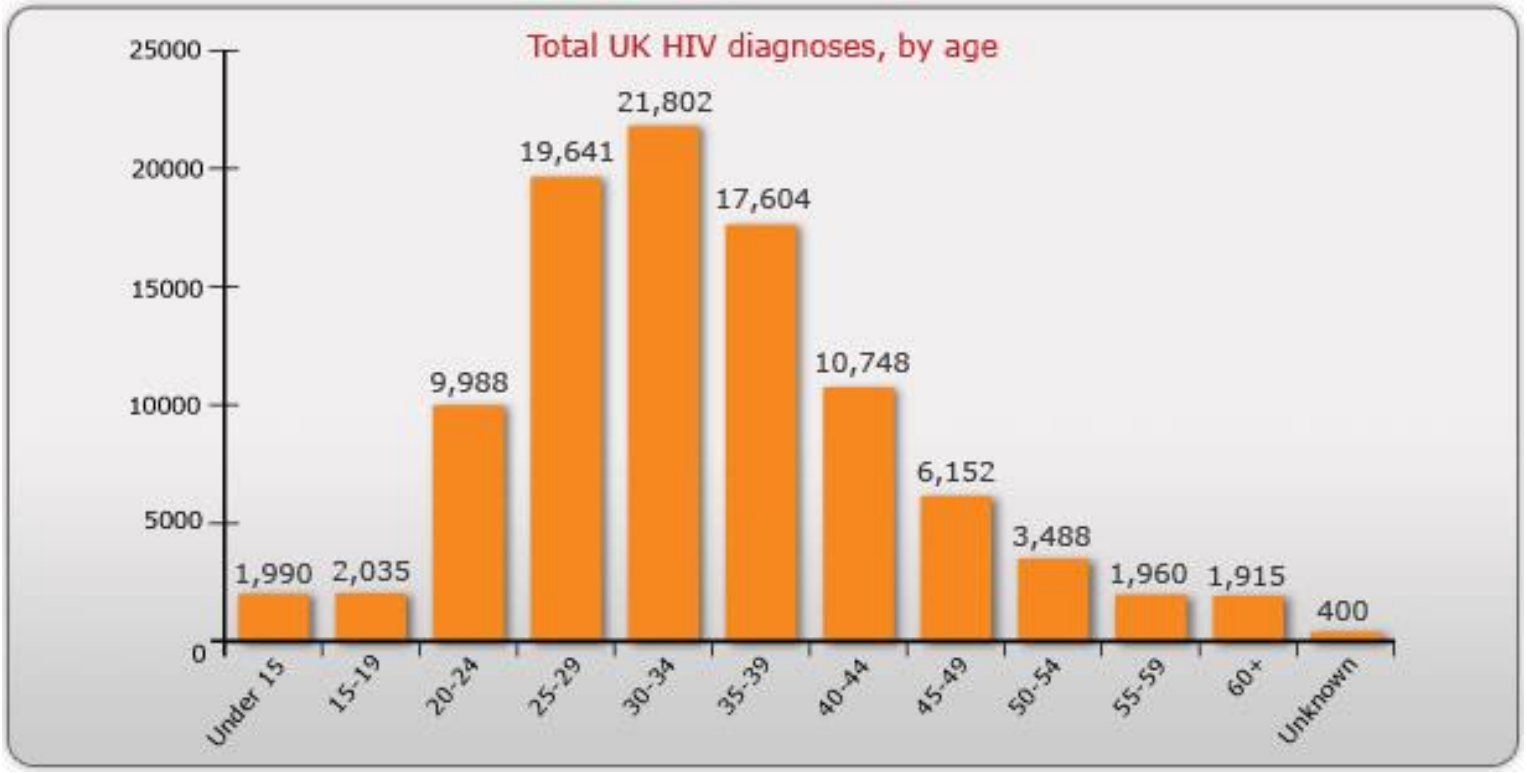


Is the HIV epidemic under control ?
The Number of HIV/AIDS cases in UK



http://www.avert.org/uk-statistics.htm

Population at risk: Age dependent Transmission



http://www.avert.org/uk-statistics.htm

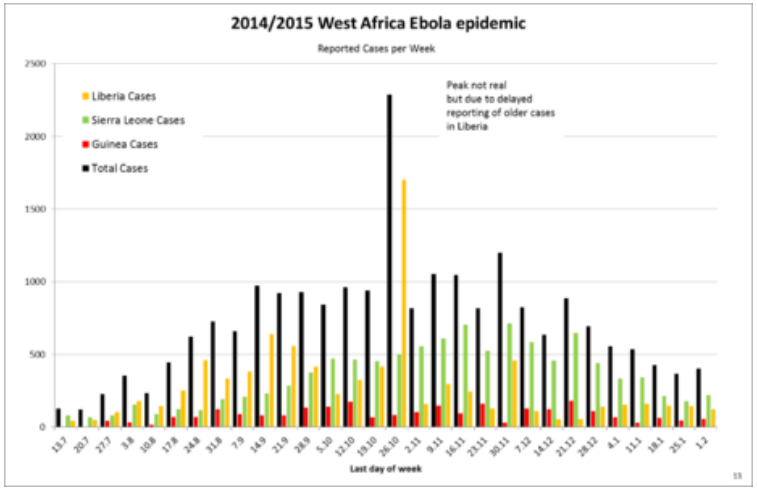
Transmission

Transmission

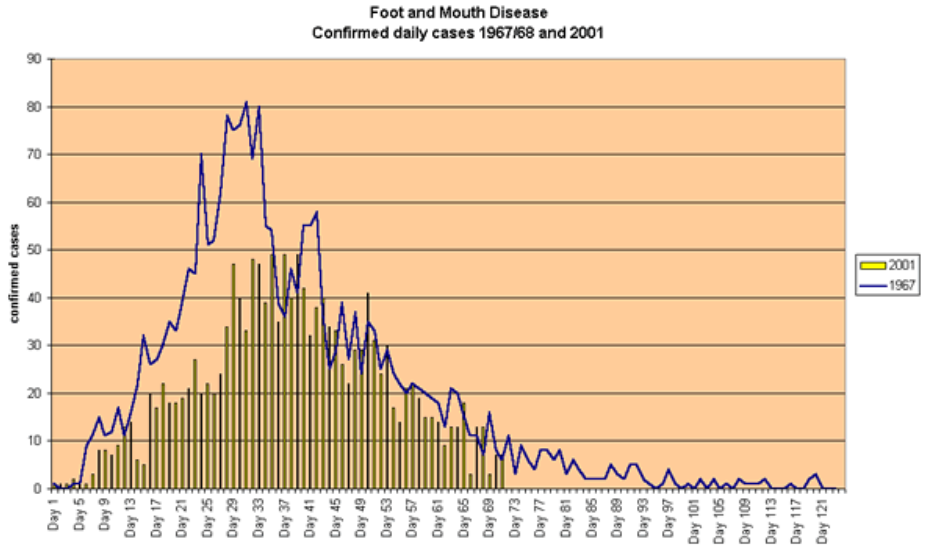
- How does an infectious disease speared ?
- Will the disease die out or continue to spread ?
- A general framework for modeling ?

Weekly number of cases

EVD

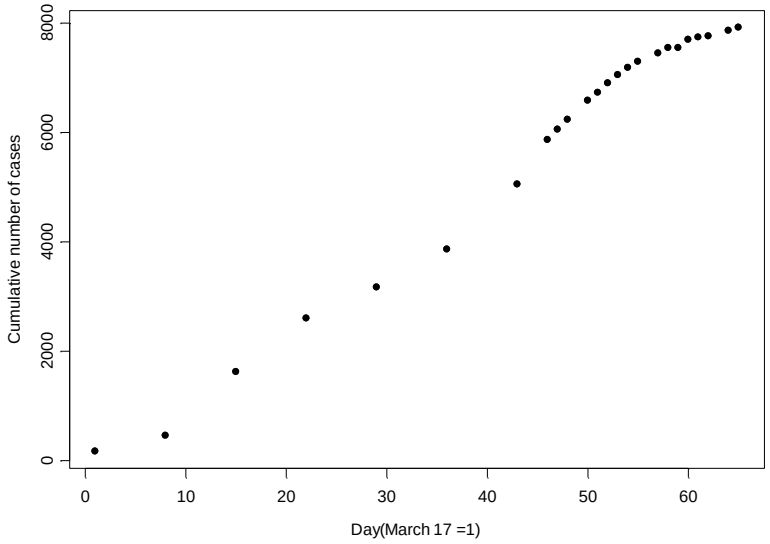


FMD

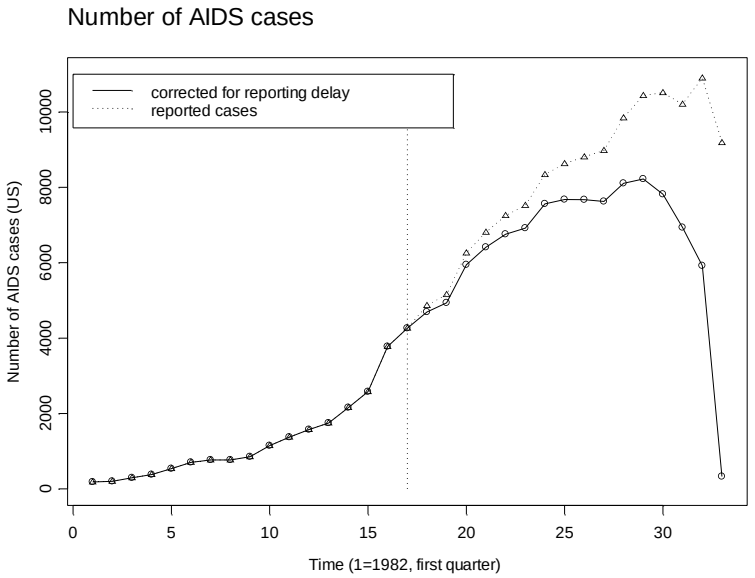


Number of cases

SARS



HIV/AIDS



The modeling framework (I):
A very short “history”: The priori and posteriori models

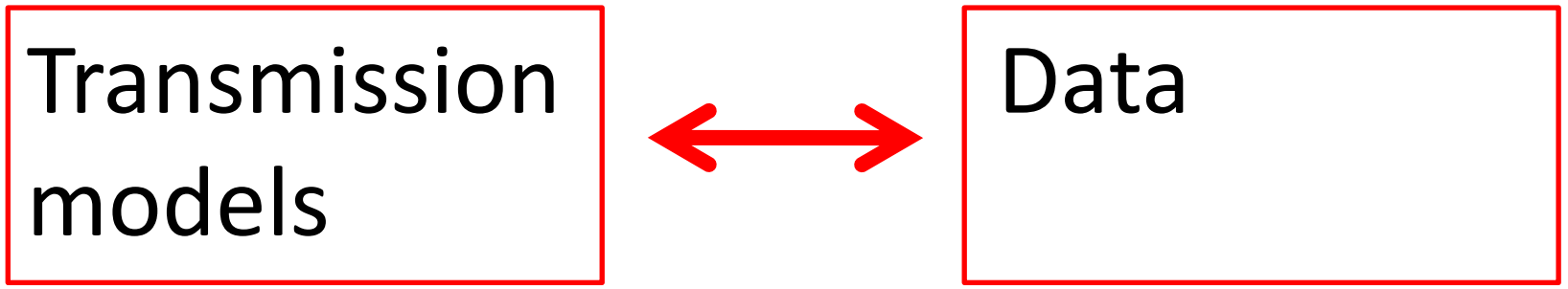
A priori and a posteriori methods

Sir Ronald Ross (1857-1932)

Ross, (July 15, 1915), An application of the theory of probability to the study of a priori pathometry. (Page 205)

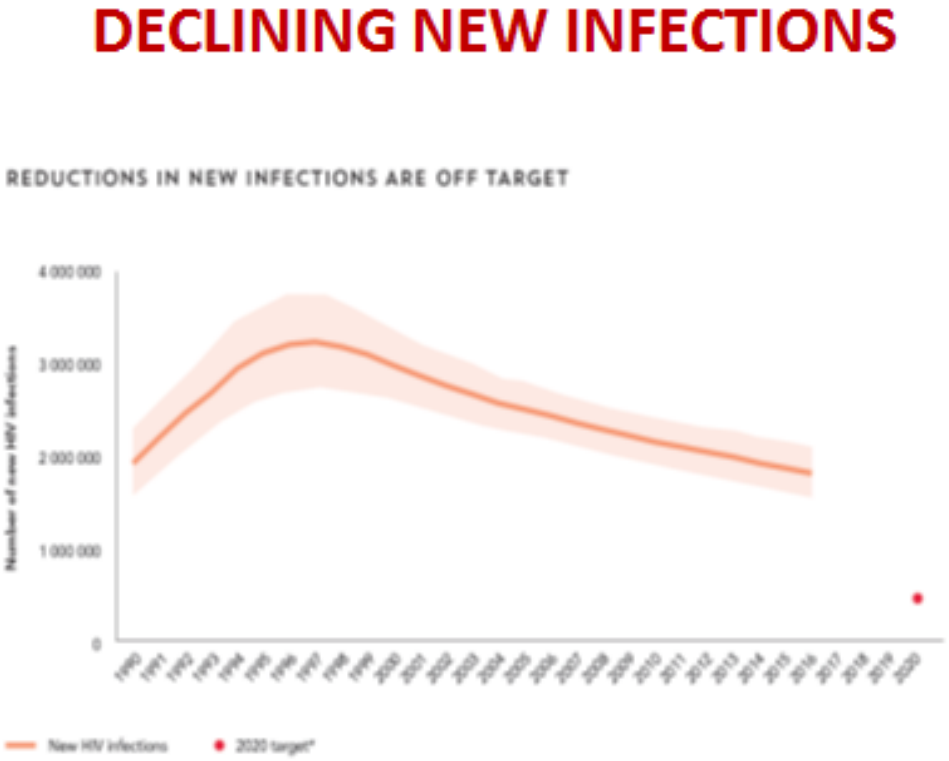
"The whole subject is capable of study by **two distinct methods** which are used in other branches of science, which are complementary of each other, and which would converge towards the same results – the a posteriori and the a priori methods. In the former we commence with observed statistics….fit analytical laws to them and so work backwards to the underlying cause…..and in the latter we assume a knowledge of causes, construct our diffential equations on that supposition….and finally test the calculated results by comparing them with the observed statistics."

A priori and a posteriori methods



How can we relate the transmission models to the data ?

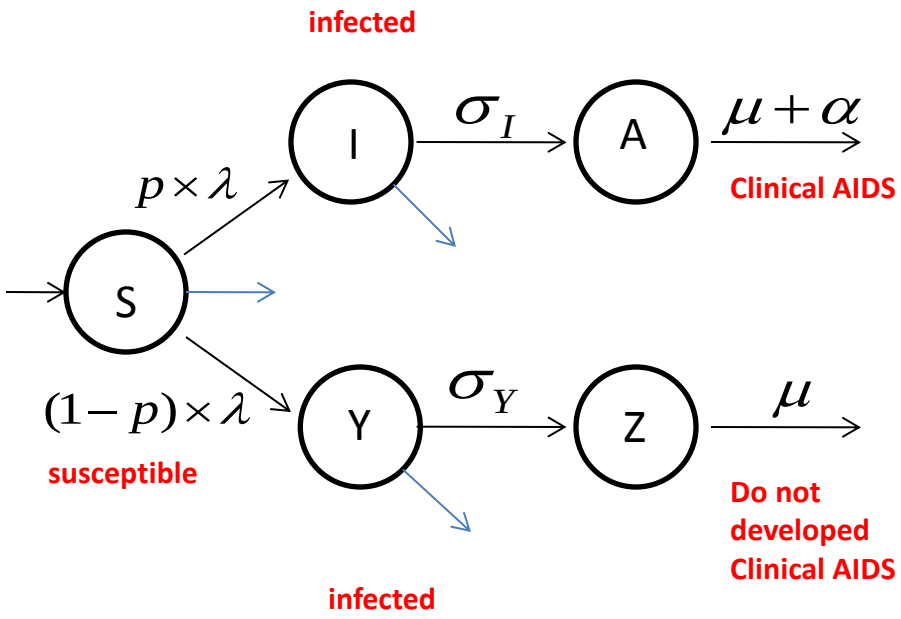
New HIV infections in South Africa



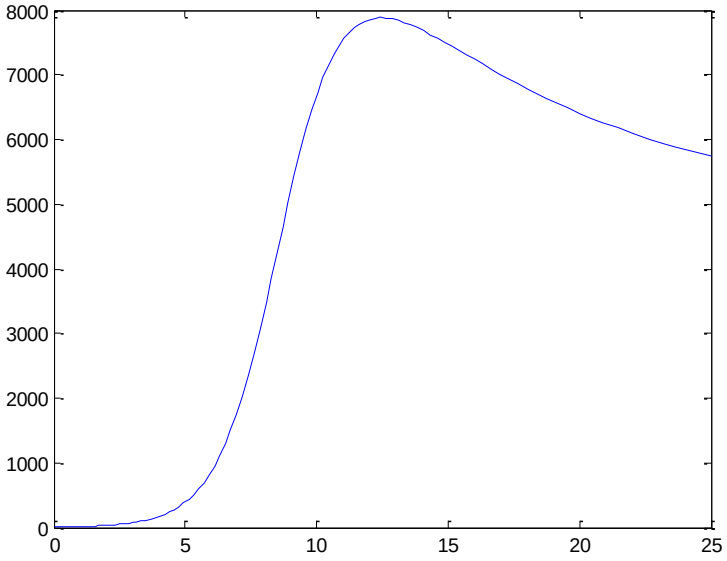
Can we say that the pattern that we observed is a results of intervention policy ?

Example: HIV/AIDS

Transmission model for AIDS



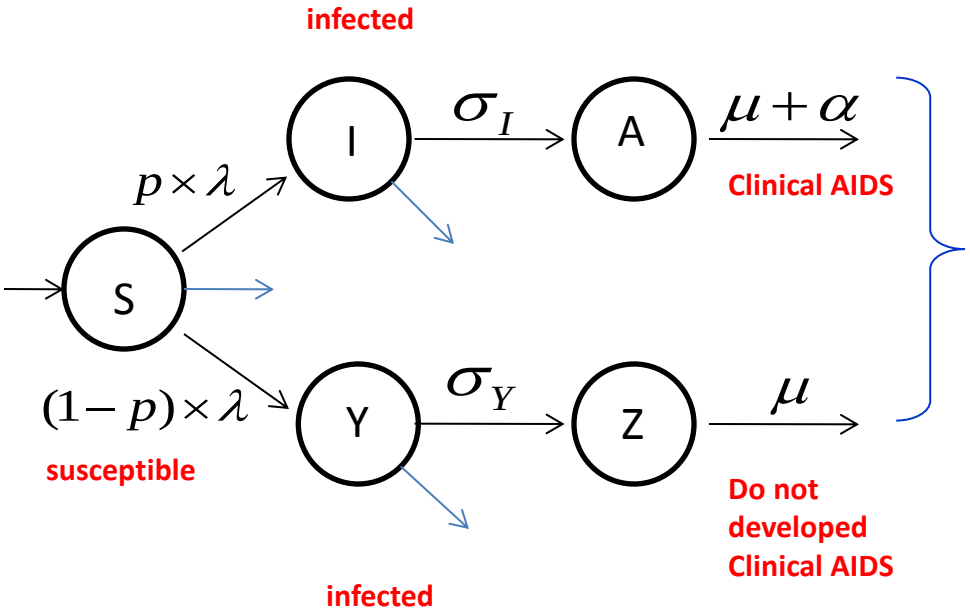
Number of infected individuals



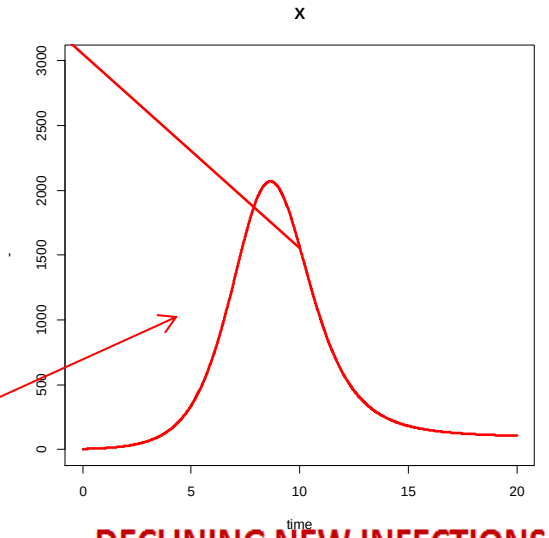
Capasso 2008, Anderson and May 1991, Anderson 1988

Example: HIV/AIDS – new infections

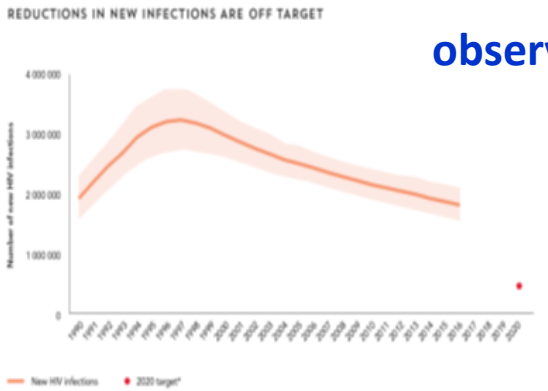
Transmission model for AIDS



Solution of the model



DECLINING NEW INFECTIONS



observed

Capasso 2008, Anderson and May 1991, Anderson 1988

Observed data from the initial outbreak AIDS in UK (Healy and Tillett, 1998)

GLM for count data

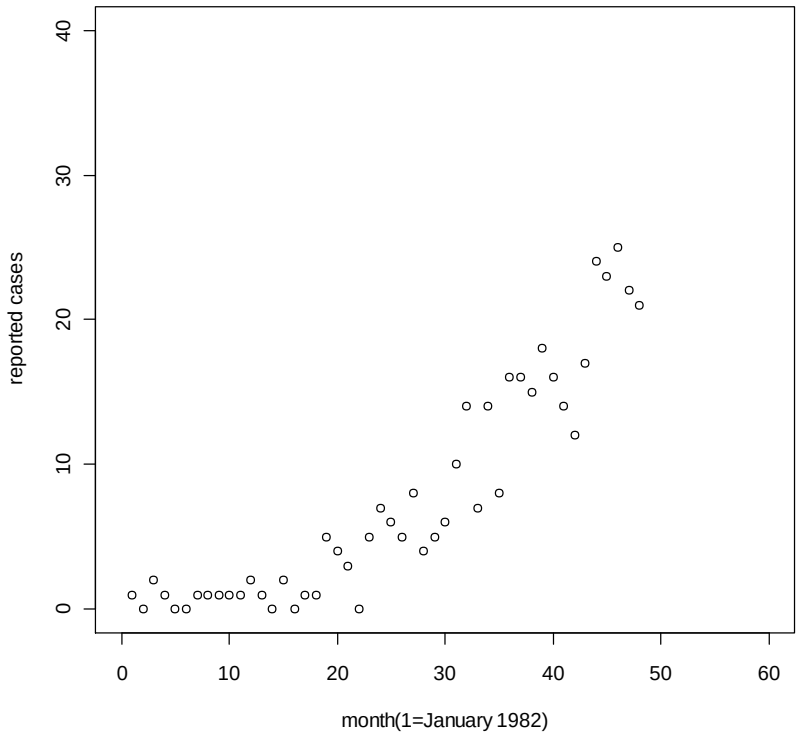
$$I(t) \sim Poisson(\mu(t))$$

$$\mu(t) = I(0)e^{\Lambda t}$$

Initial number of cases at t=0

Exponential growth

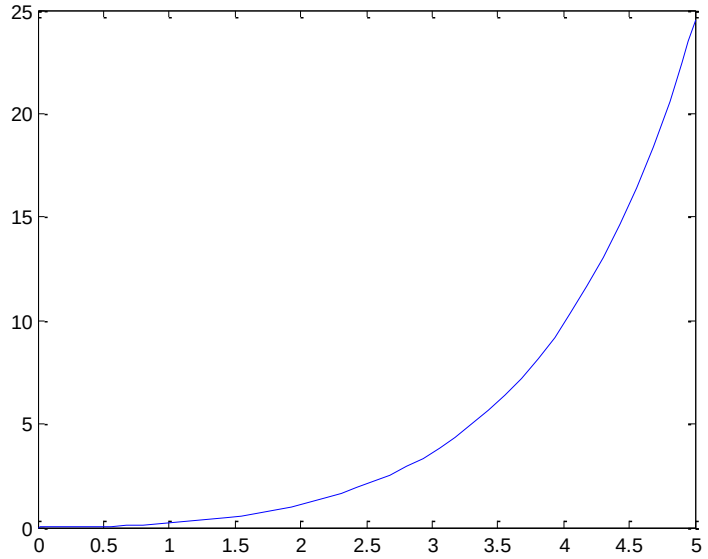
Monthly number of cases (1982-1986)



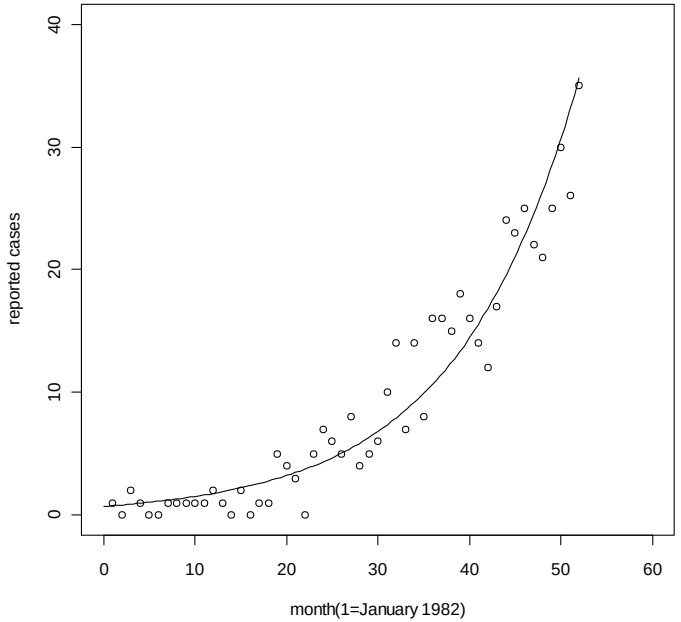
Healy and Tillett (1998)

Initial outbreak AIDS in UK – data and predicted means

Predicted by the transmission model



Predicted by the data

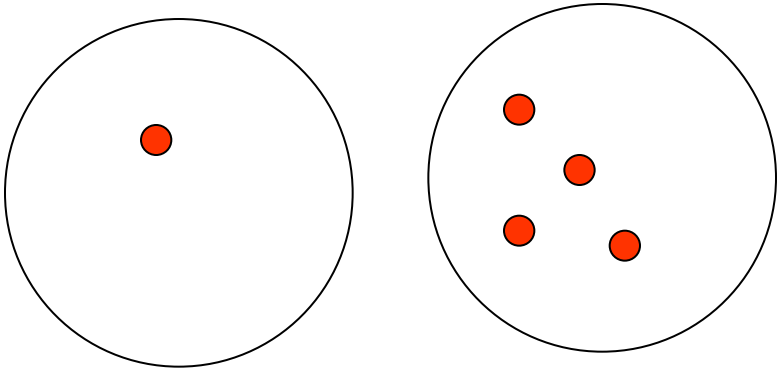


This course: only transmission model, without fitting the models to the data.

Transmission and Transmission models

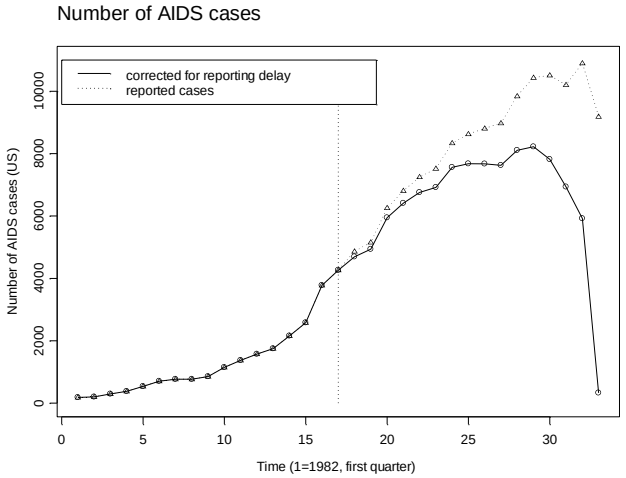
Transmission

- How does a disease spread in the population ?

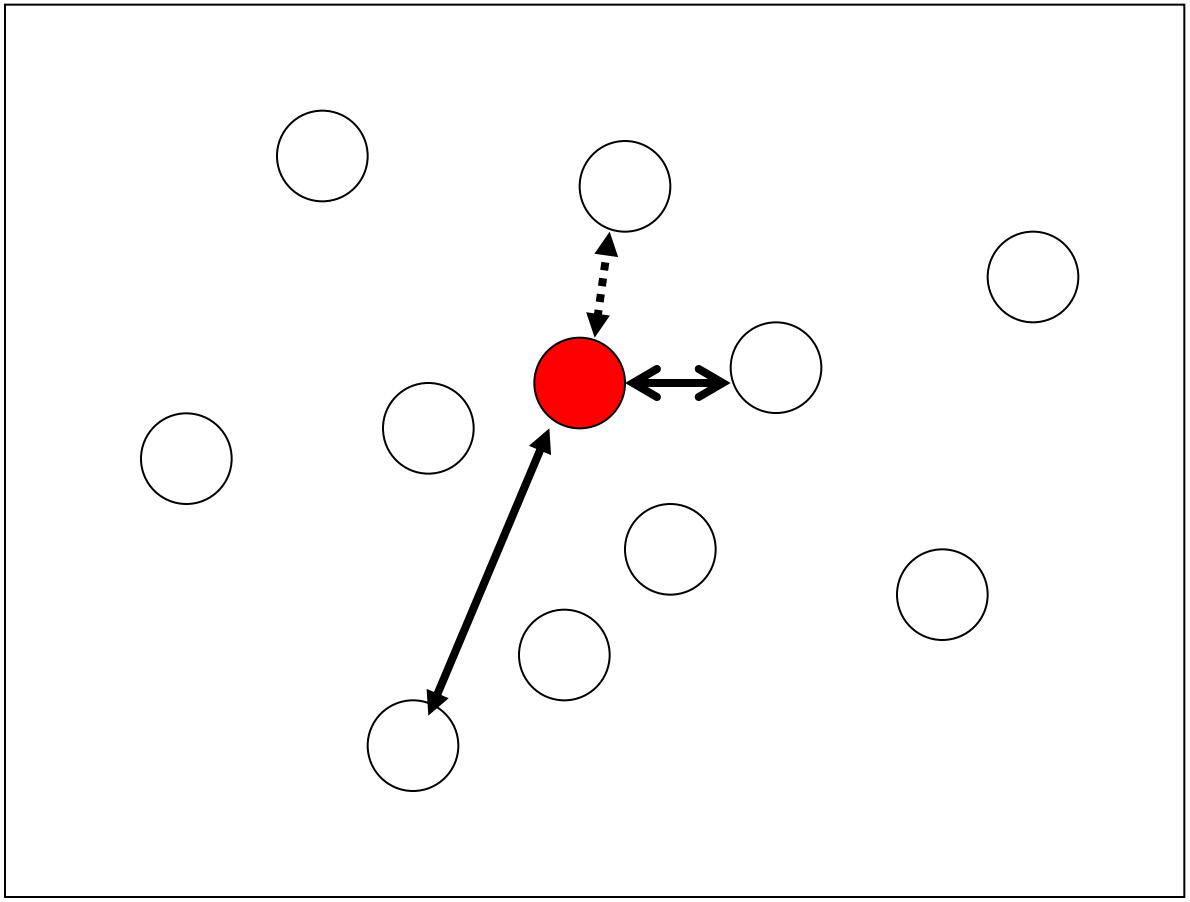


population

population



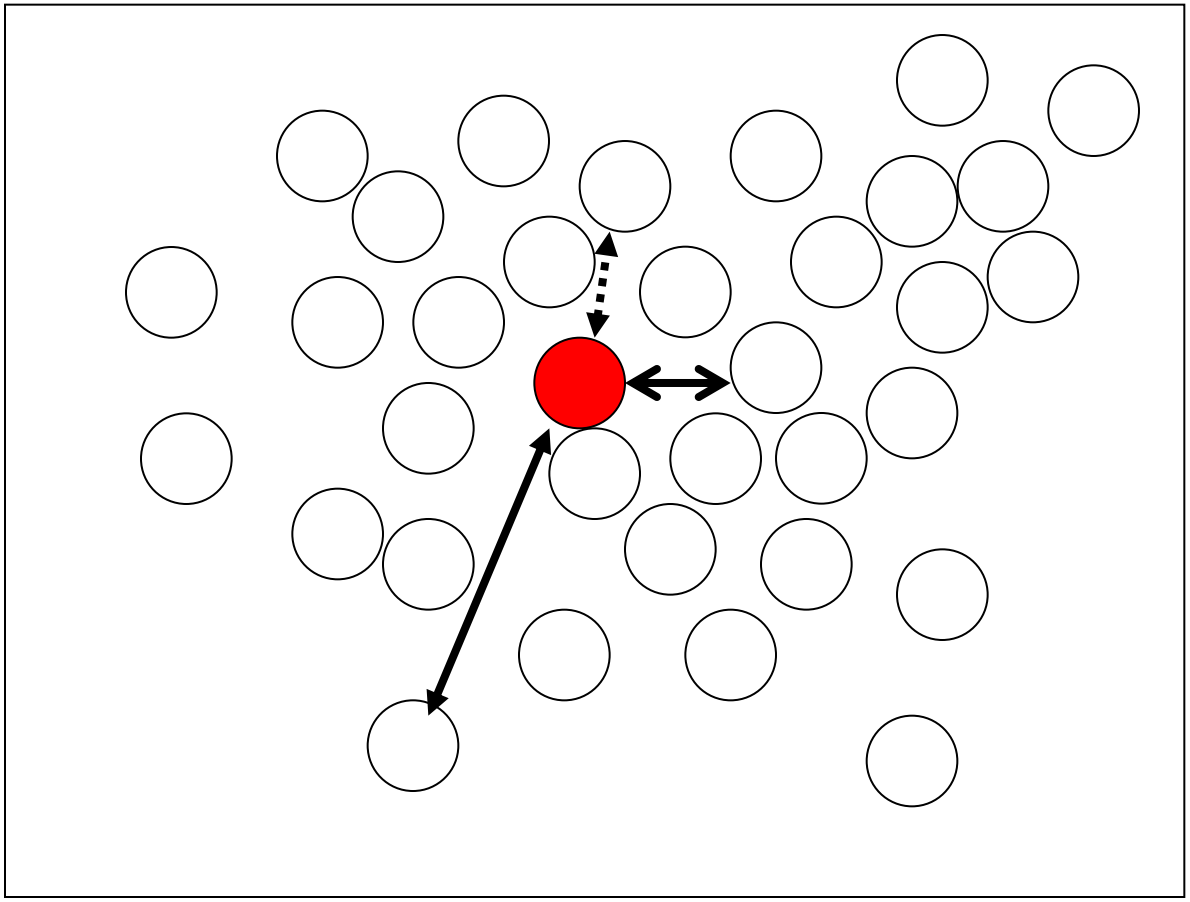
The Mass-Action Principle



Contacts are made in random.

Number of new cases=P(transmission) X # of infectious X # of susceptible

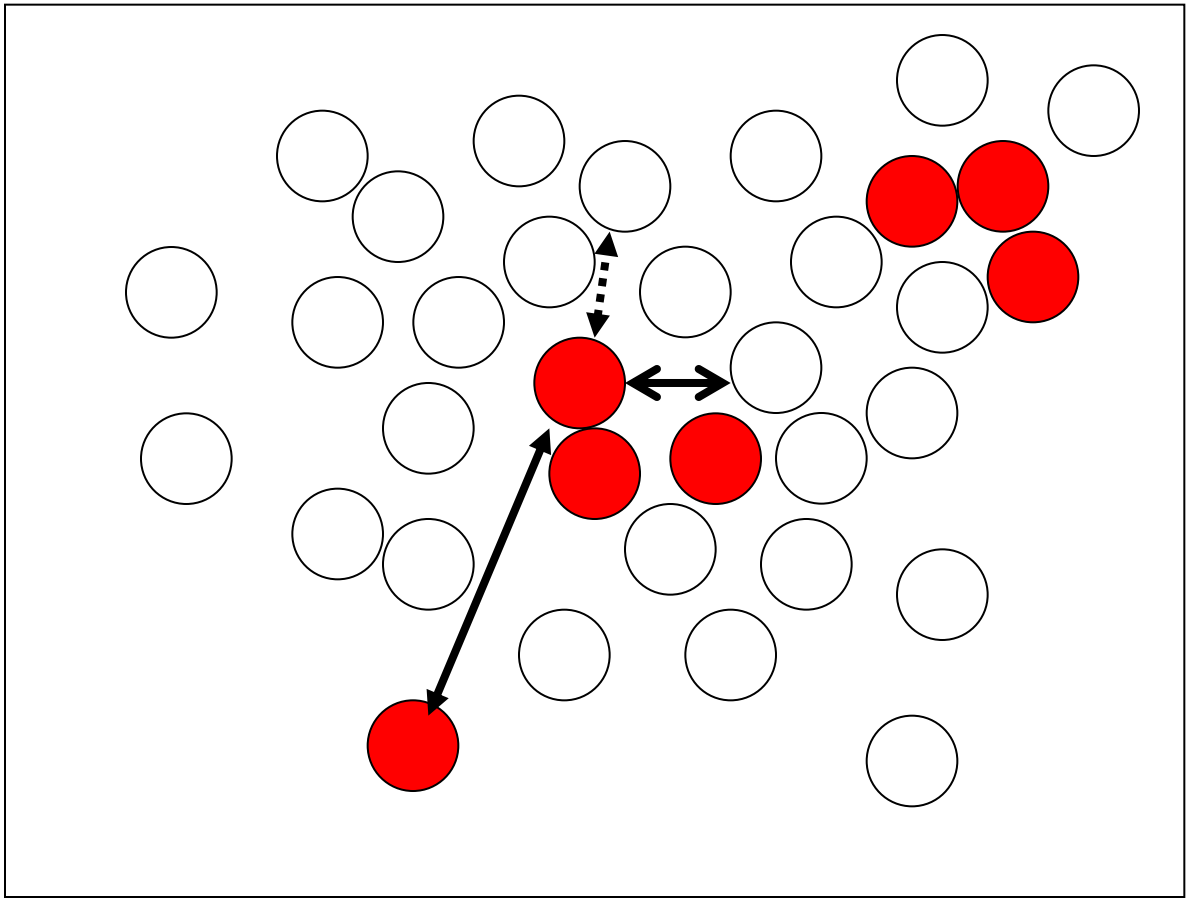
The Mass-Action Principle



Contacts are made in random.

Number of new cases=P(transmission) X # of infectious X # of susceptible

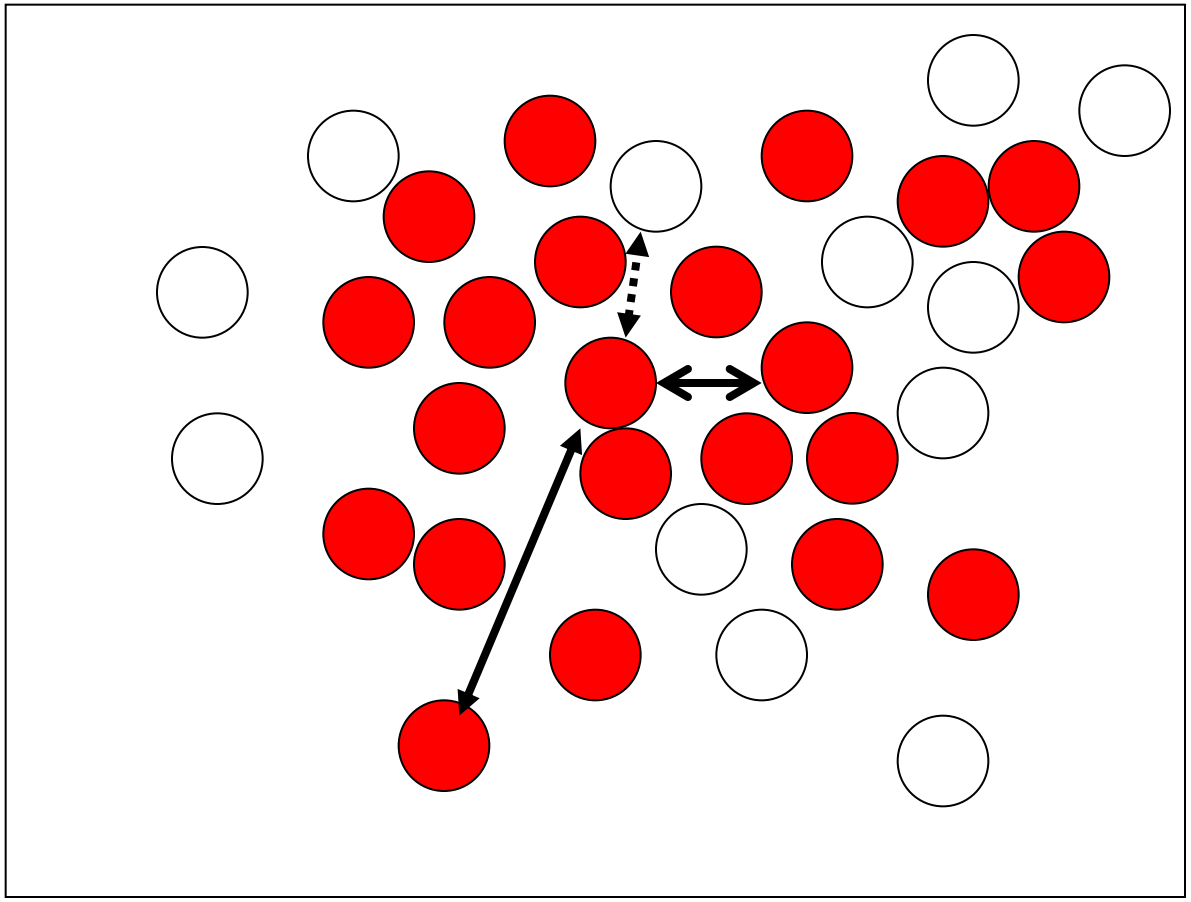
The Mass-Action Principle



Contacts are made in random.

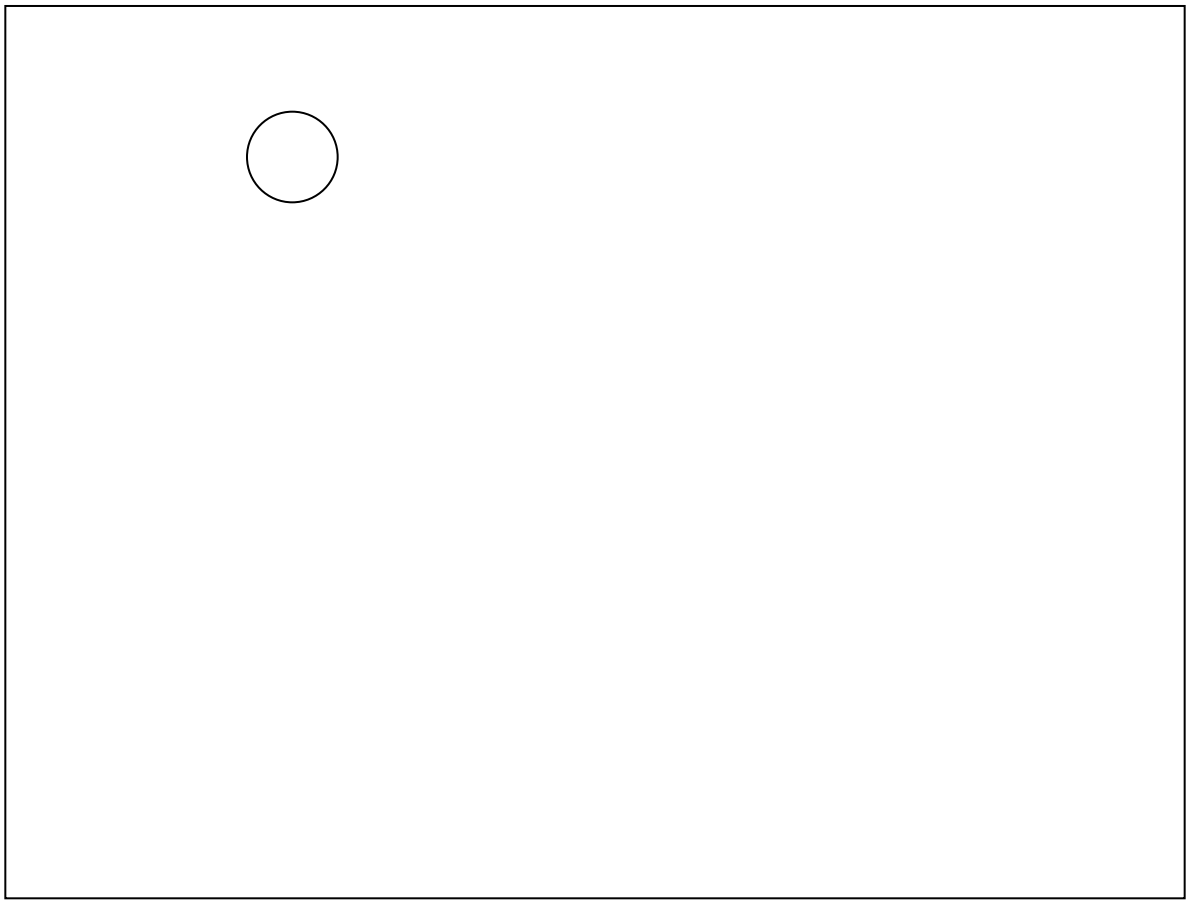
Number of new cases=P(transmission) X # of infectious X # of susceptible

The Mass-Action Principle

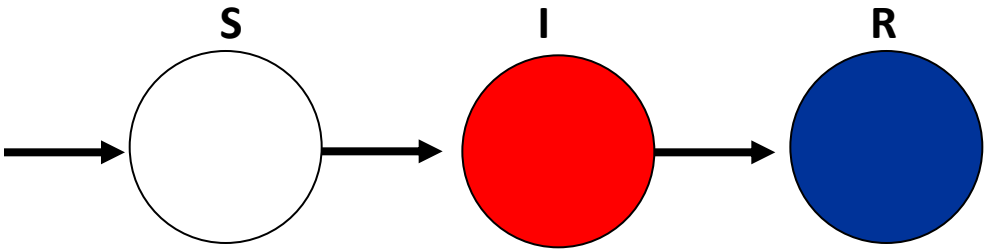


Contacts are made in random.

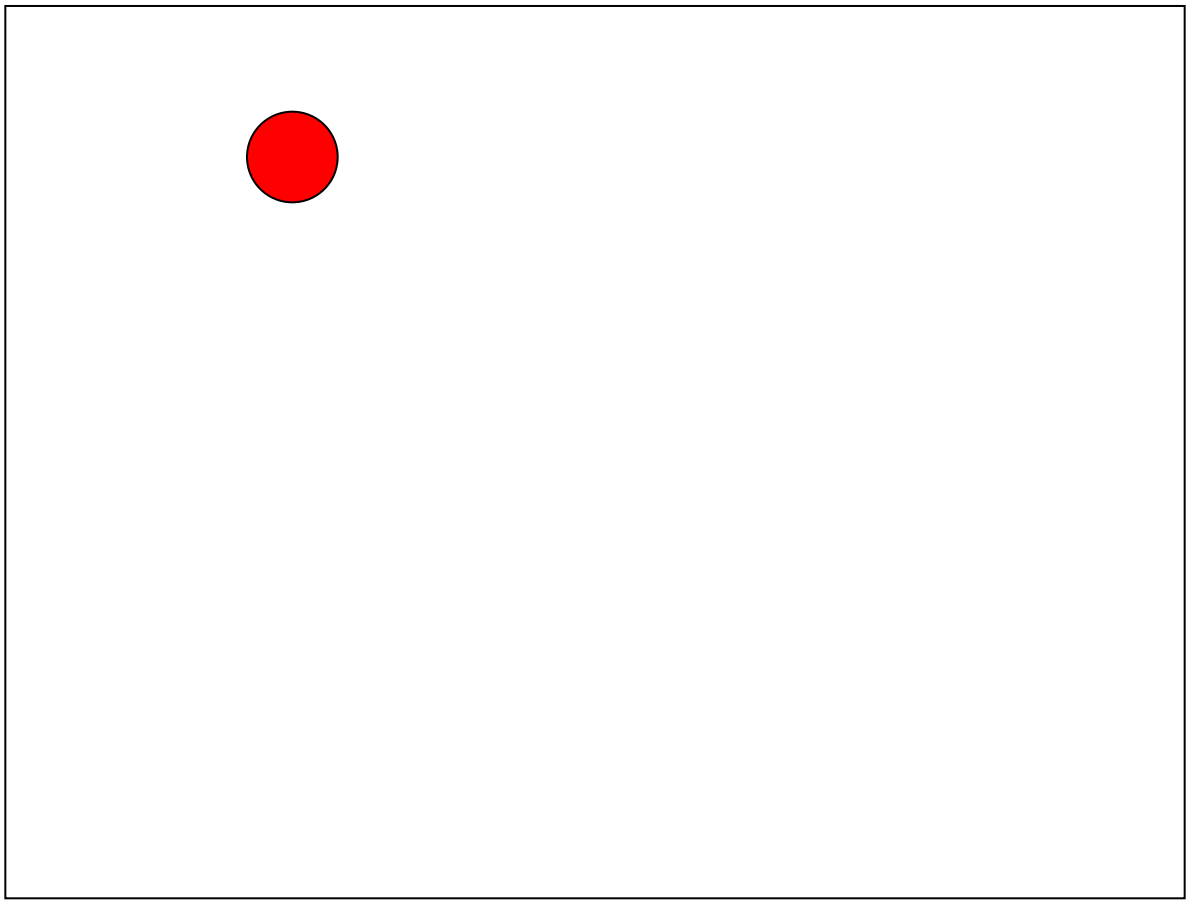
Number of new cases=P(transmission) X # of infectious X # of susceptible



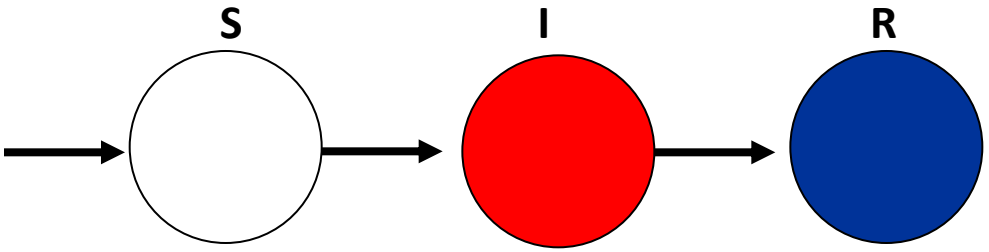
At time t_0, the individual is not infected, i.e susceptible



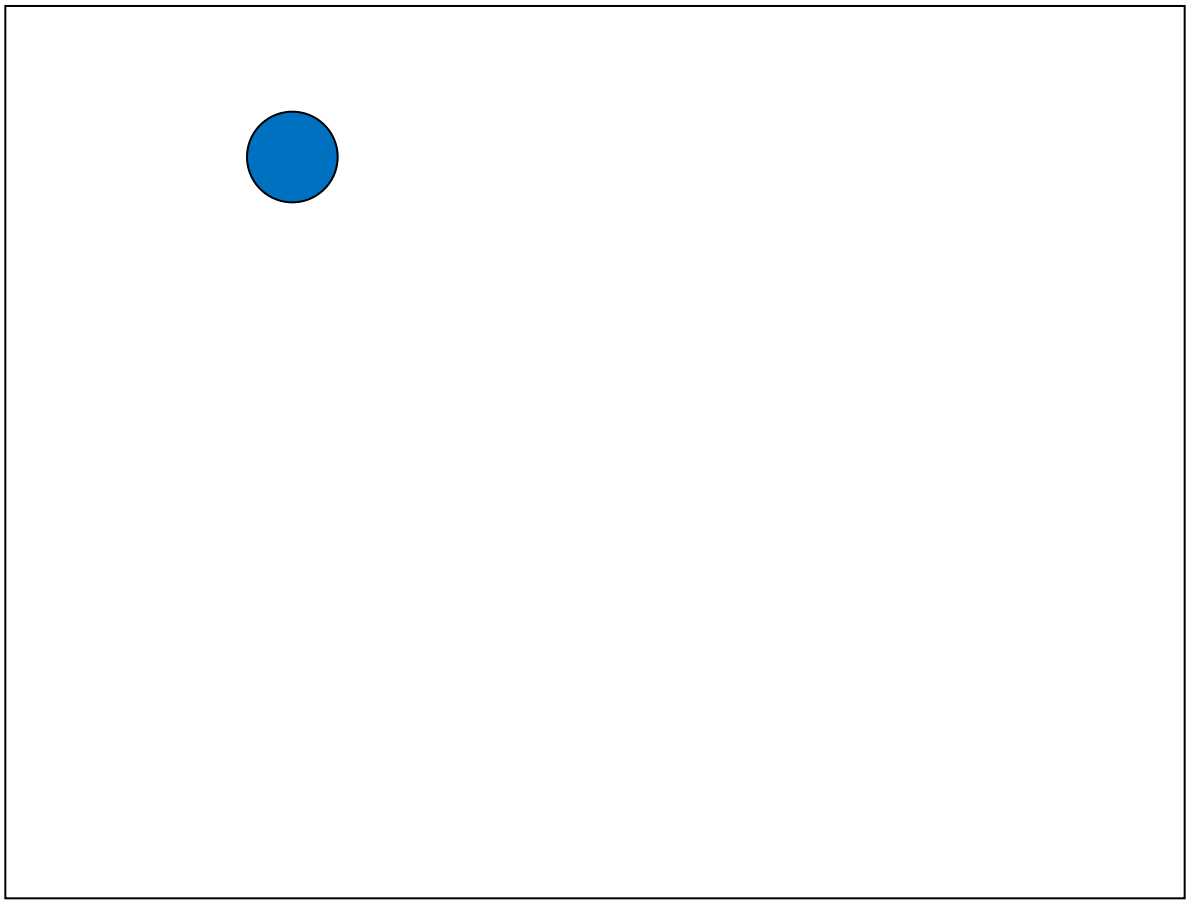
Flow diagram



At time t_1, the individual is infected,

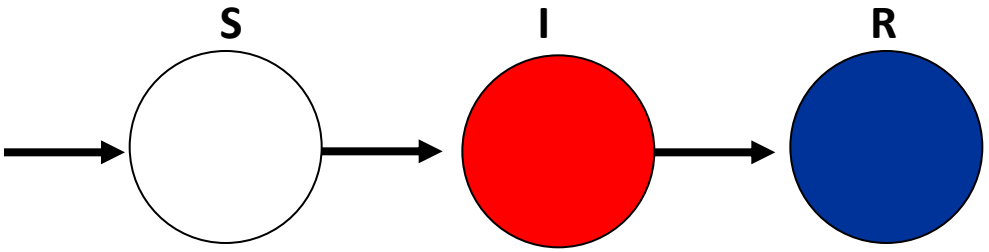


Flow diagram



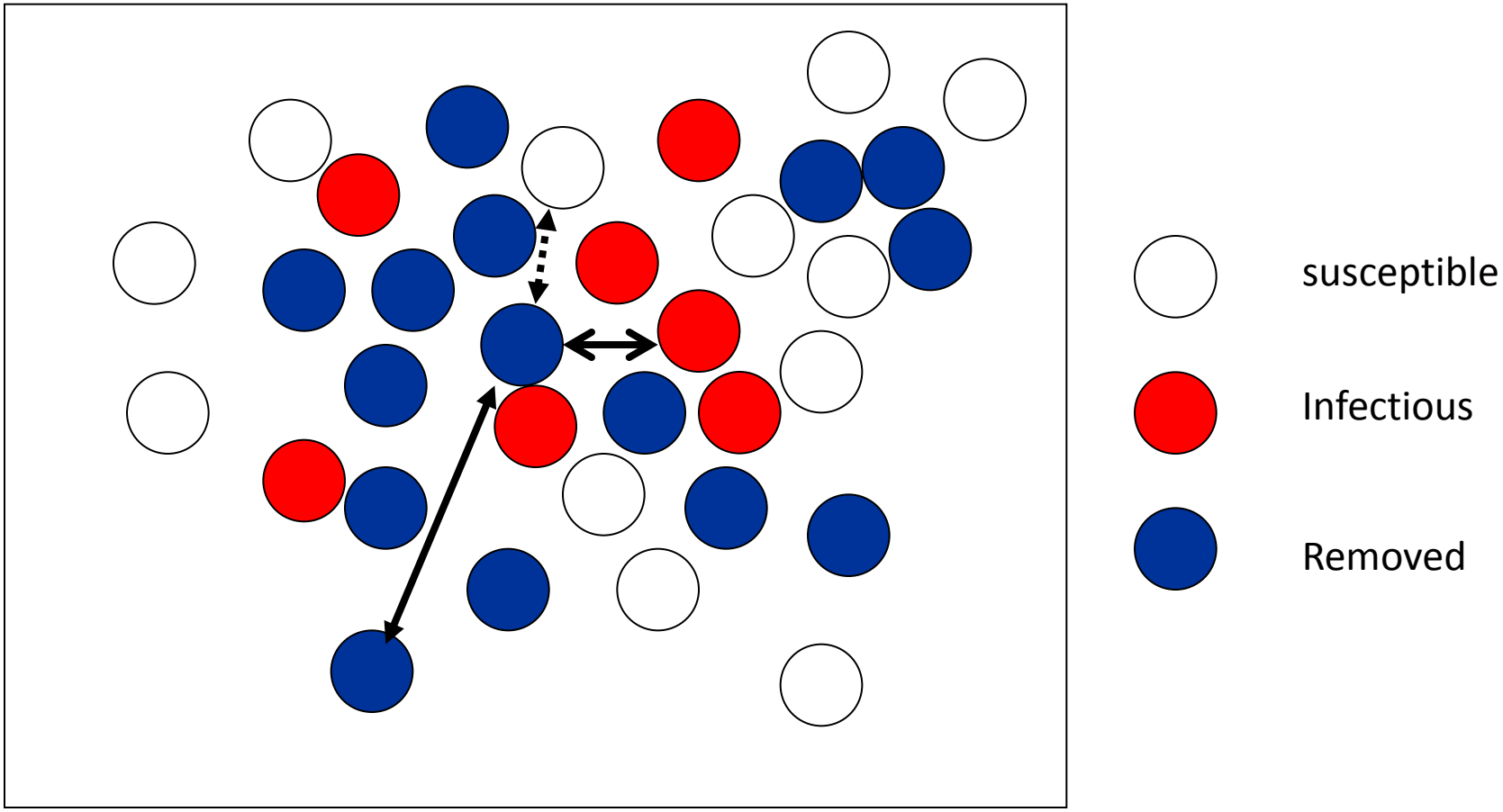
At time t_k, the individual is recovered.

If the immunity if life long, this individual is removed (i.e. cannot be infected again)

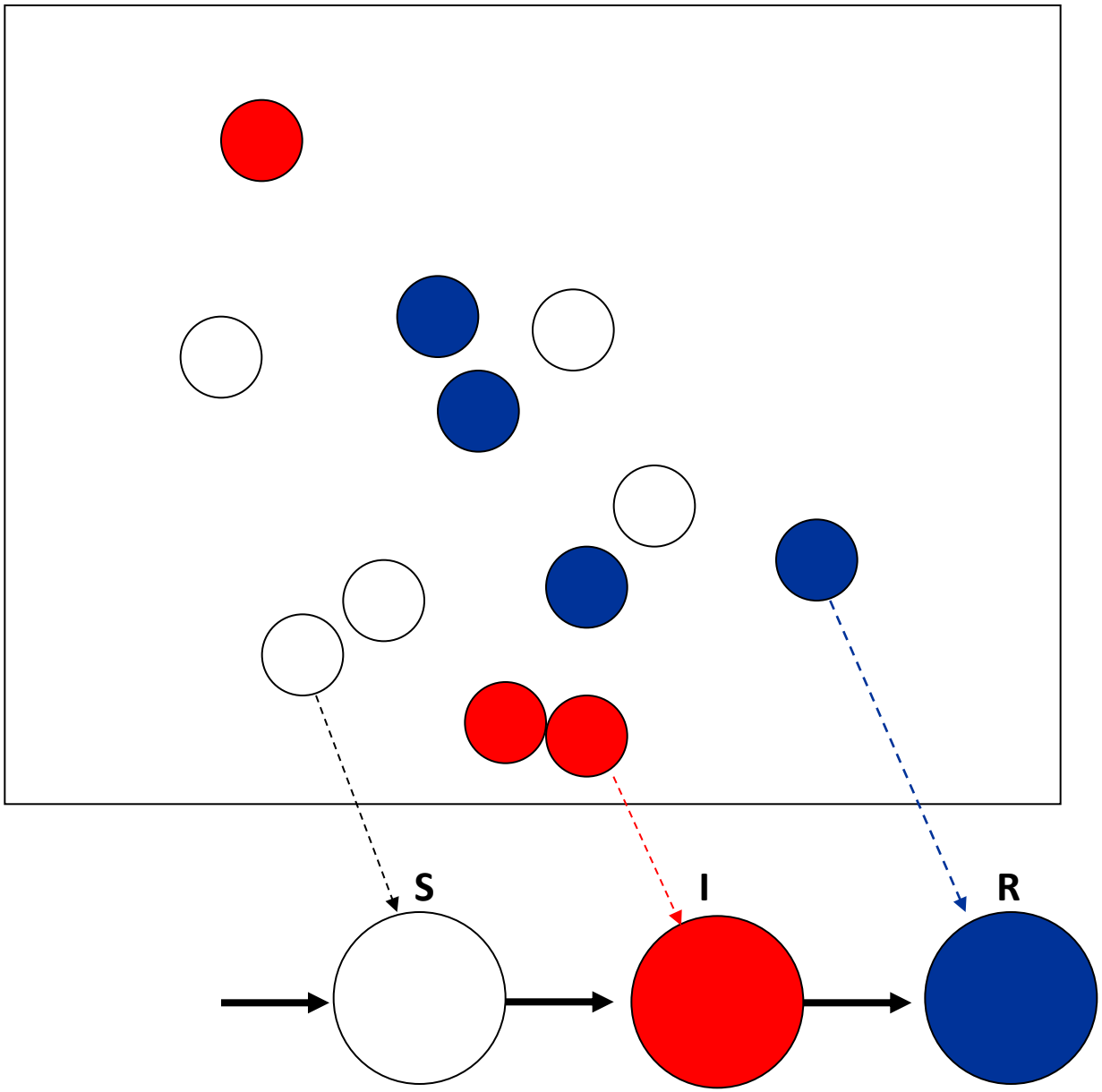


Flow diagram

The Mass-Action Principle



Susceptible Infectious Removed



The population is divided into three classes or compartments

Flow diagram

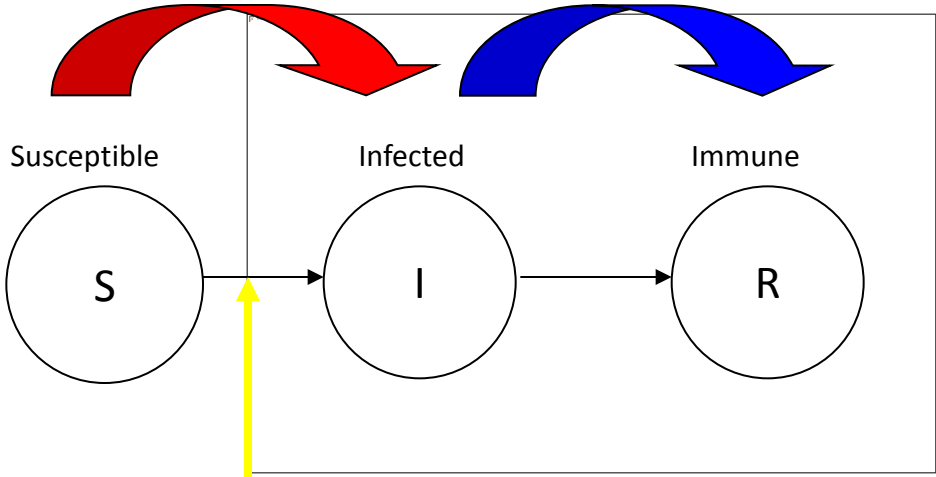
Transmission model

The change in the susceptible class:

Individuals are entered to the susceptible class (NS_{in}) and in the same time other are infected (NS_{out})

$$S(t+1)=S(t)+NS_{in}(t)-NS_{out}(t)$$

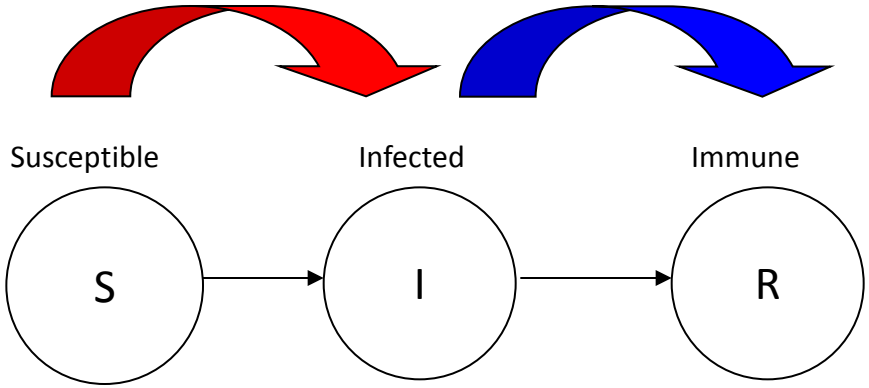
$$S(t+1)-S(t)=NS_{in}(t)-Ns_{out}(t)$$



The SIR model

Transmission model

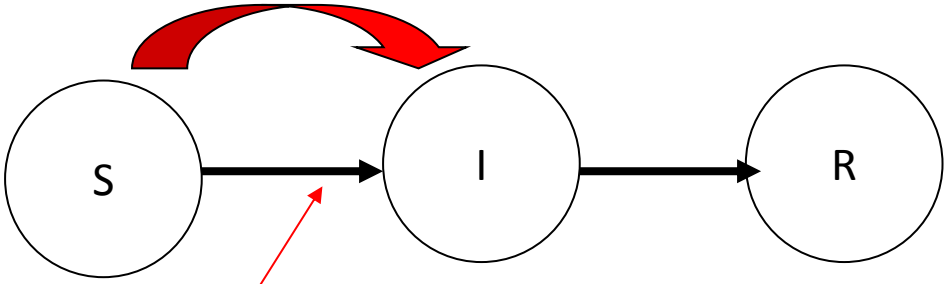
$$\frac{dS(t)}{dt} = -\lambda S(t)$$
$$\frac{dI(t)}{dt} = \lambda S(t) - \sigma I(t)$$
$$\frac{dR(t)}{dt} = \sigma I(t)$$



The SIR model

How do we know the parameters ?
How do the data look like ?

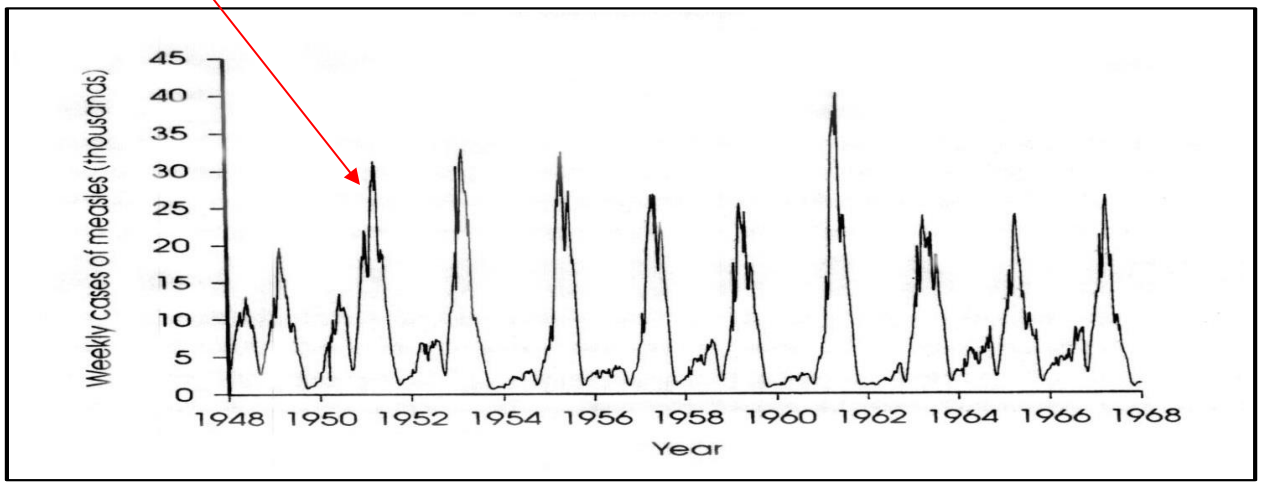
Example Incidence data : Measles in UK



Transmission model

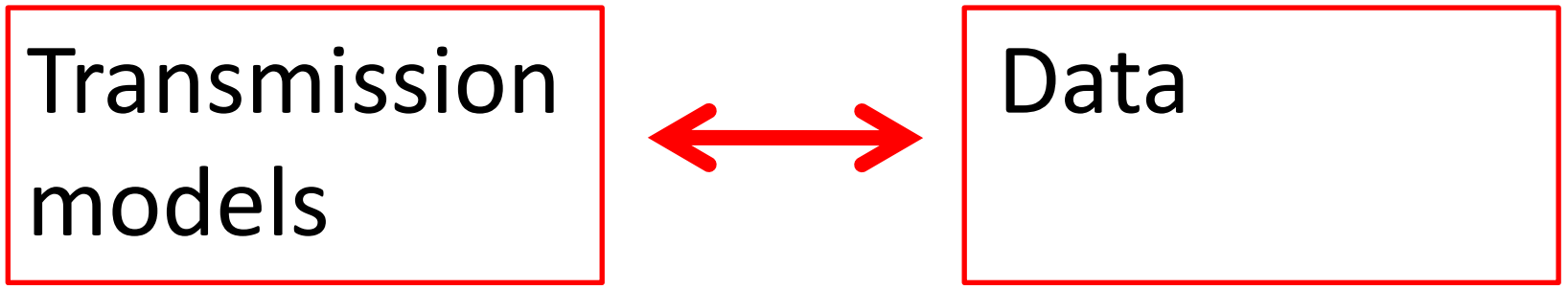
The weekly number of individuals who move from the susceptible to the infected class

Data



Time unit=week

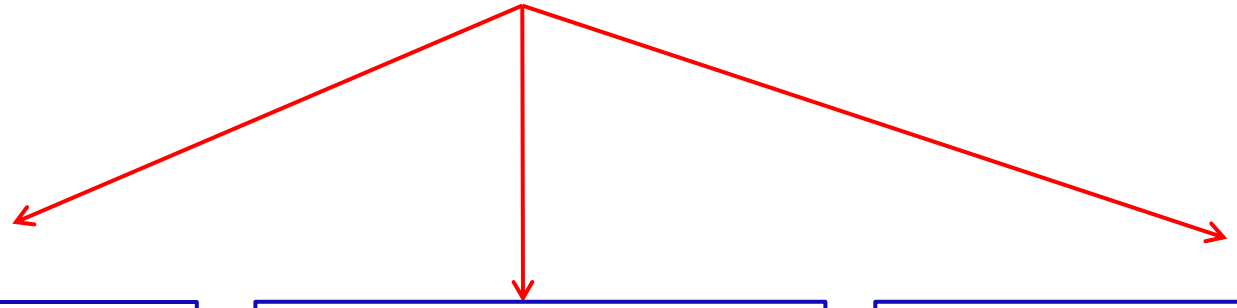
Summary



How can we relate the transmission models to the data ?

Transmission models and data

Three different types of data structures



CASE 1

Incidence data.

CASE 2

Outbreak data.

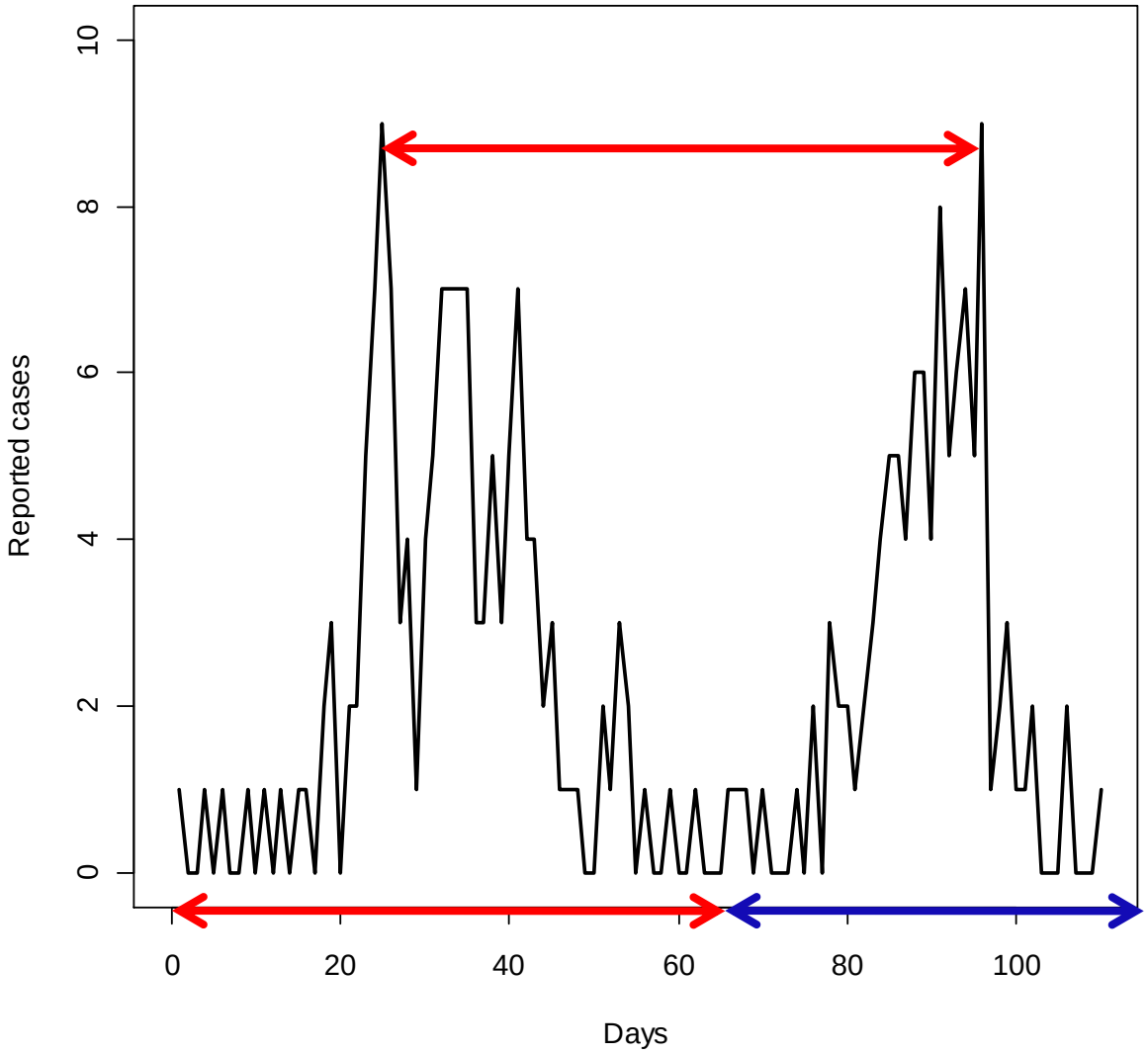
CASE 3

Serology.

Transmission model for the diseases.

Do we see the same pattern in the data ?

Example 1: Outbreak of SARS in Canada

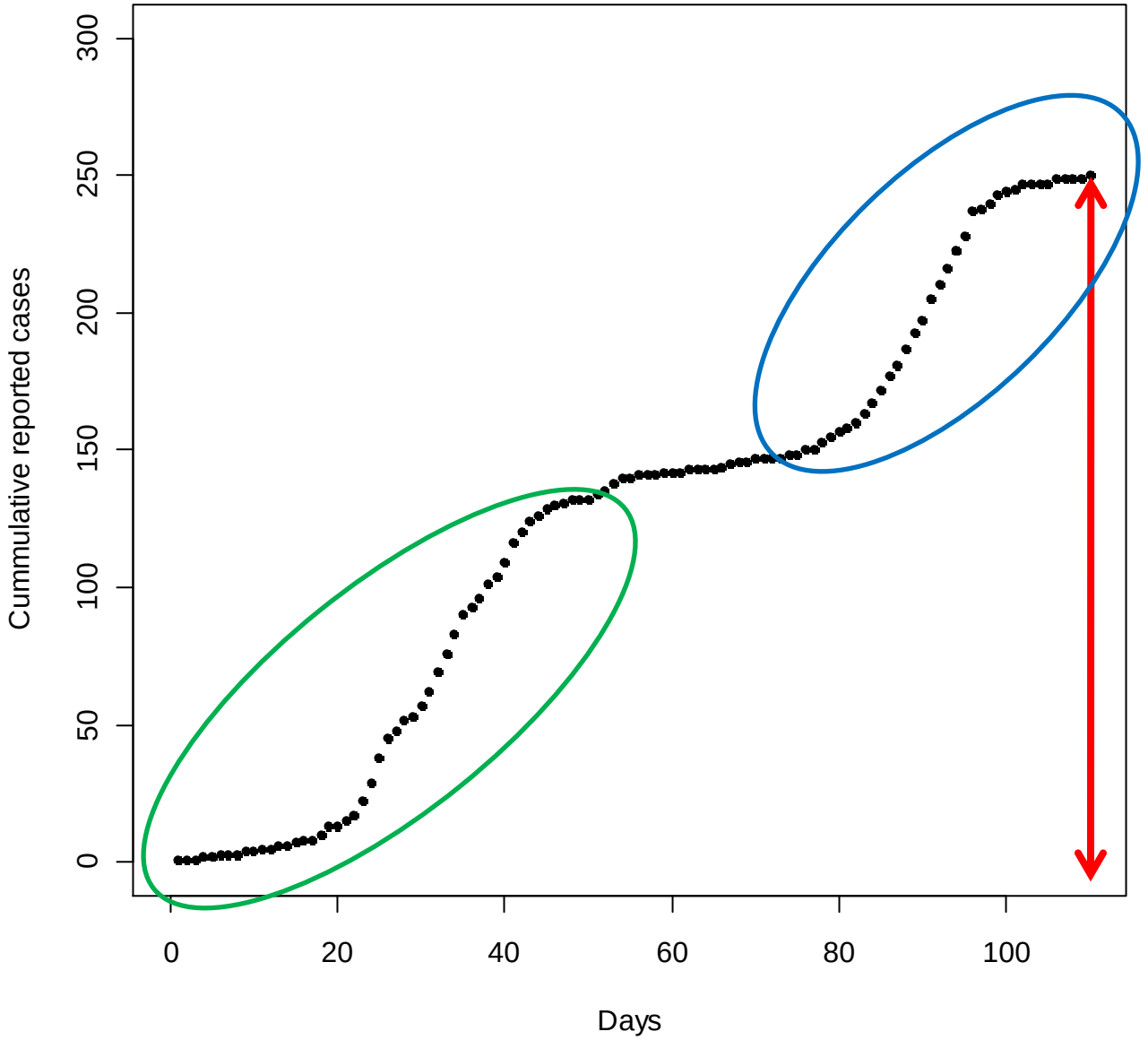


Two outbreaks.

Inter epidemic period of about 60 days.

Number of cases per time unit: count data

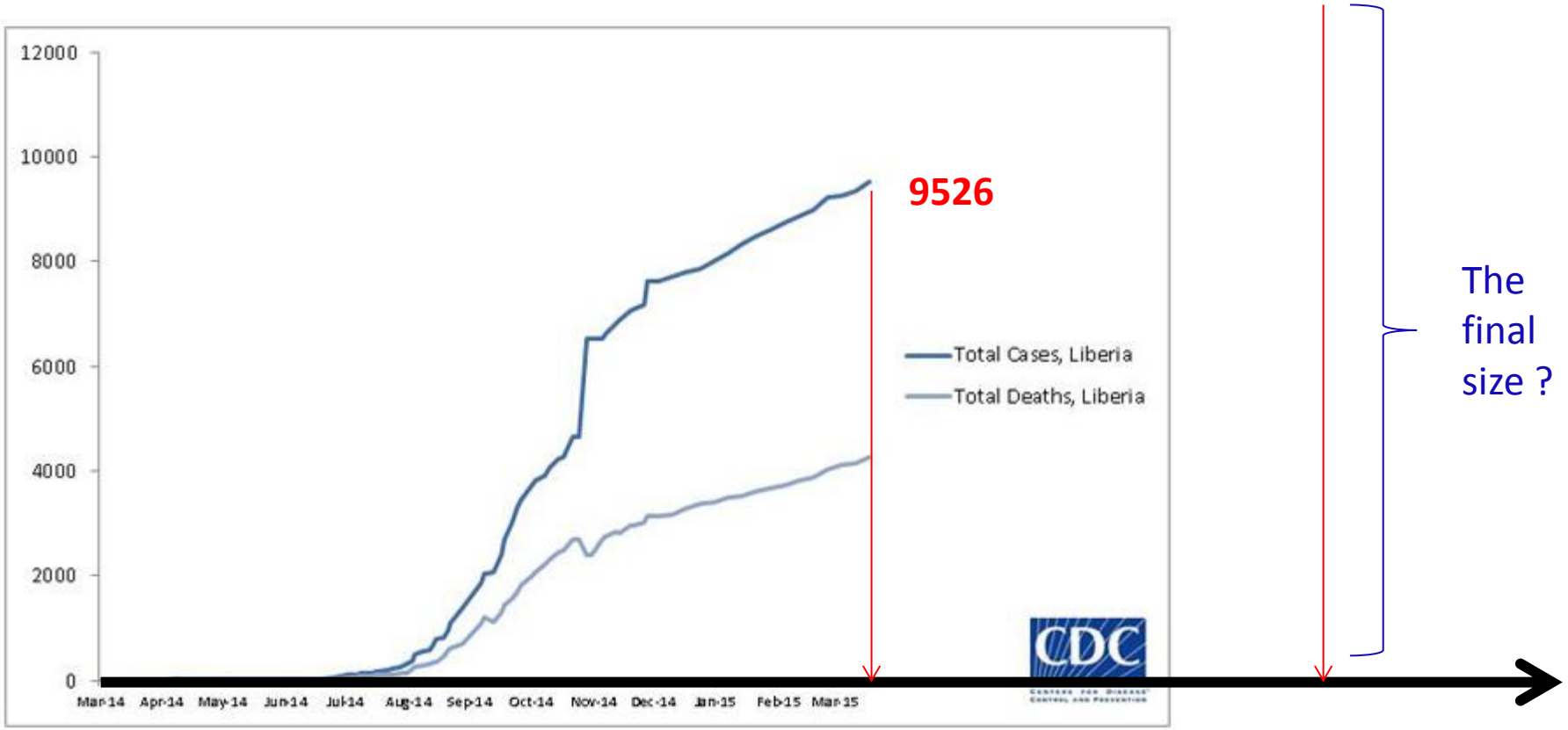
Outbreak of SARS in Canada



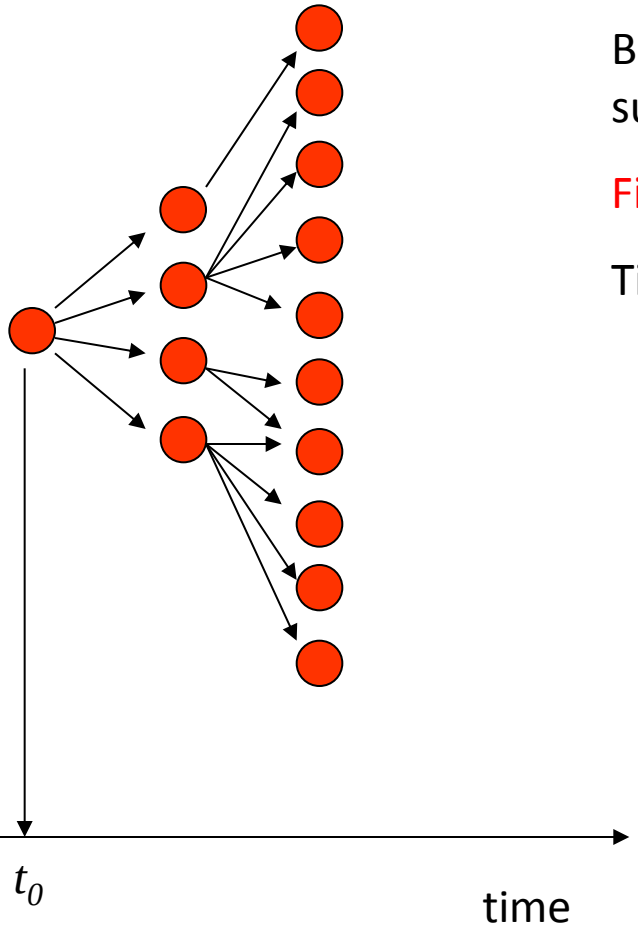
The final size of the epidemic.

We would like to know the final size as soon as possible.

Ebola cases until 18/03/2015 in Liberia



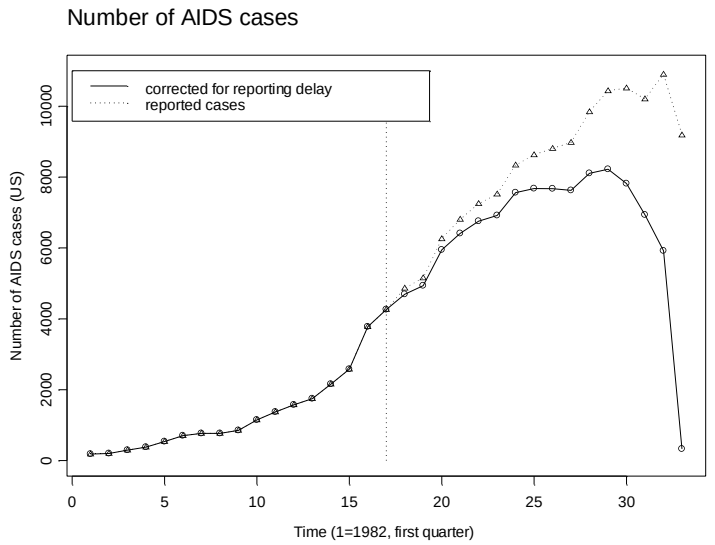
Example 2: Early models for HIV/AIDS
Case zero ?



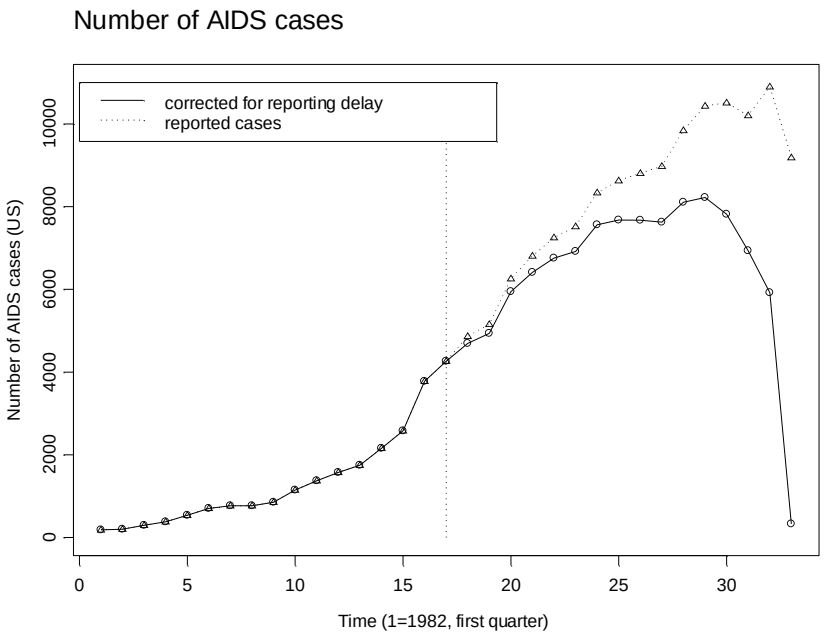
Before t_0, all individual in the population are susceptible.

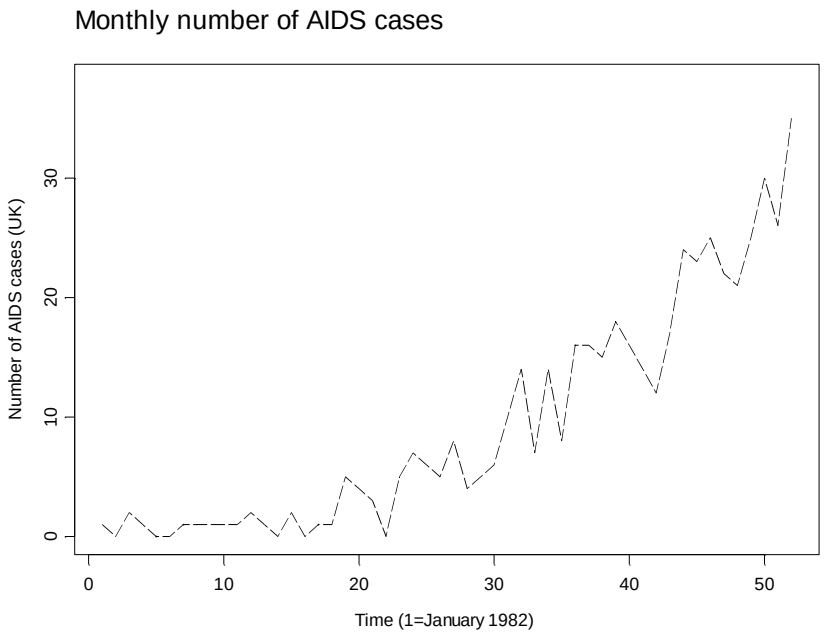
First case is introduced to the population at t_0.

Time and number of contacts per time unit.



Outbreak of AIDS in US/UK





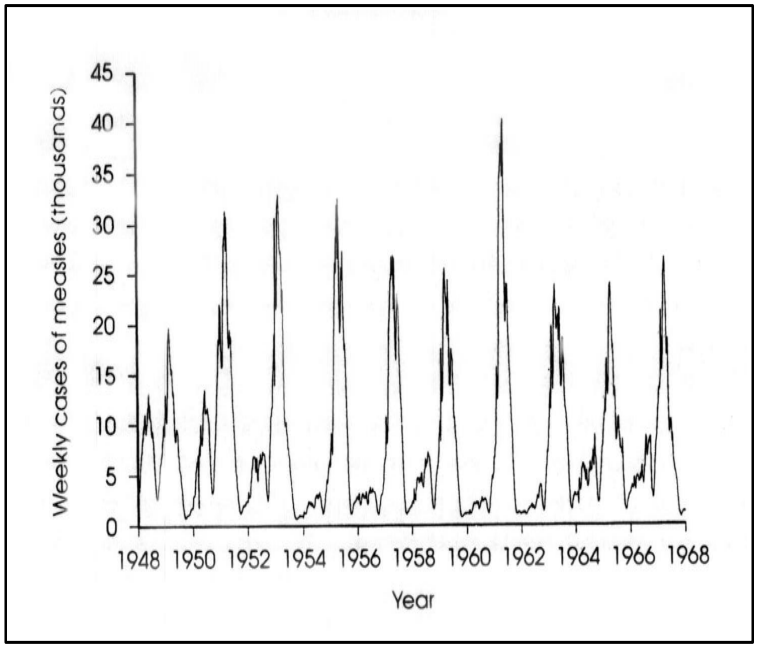
If there is a case zero, how can we take this into account when we model the data ?

Example 3: Incidence data - measles in UK (1948-1968)

New cases per time unit (incidence).

The national immunization program against measles in England and Wales began in 1968.

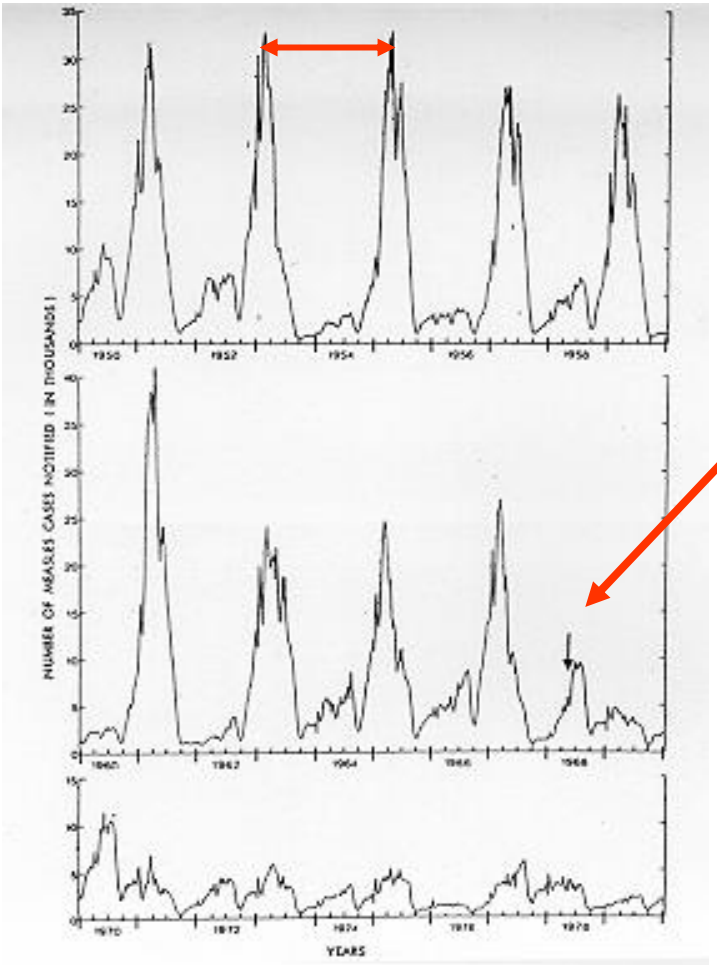
Pre vaccination data.



15

Measles in England and Wales

How can we estimate the length of the inter epidemic period ?



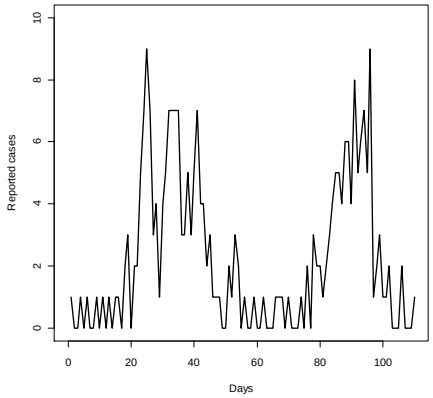
Vaccination

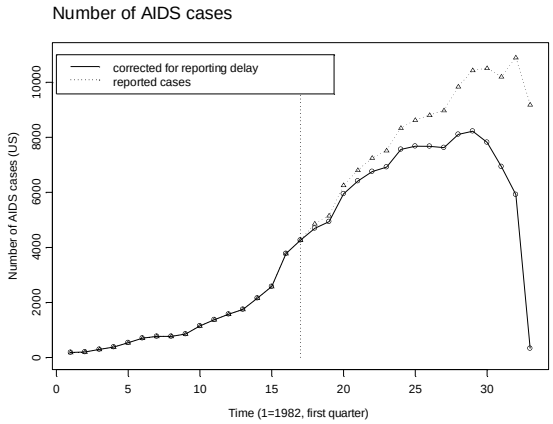
1967

1978-1979

Summary

Data

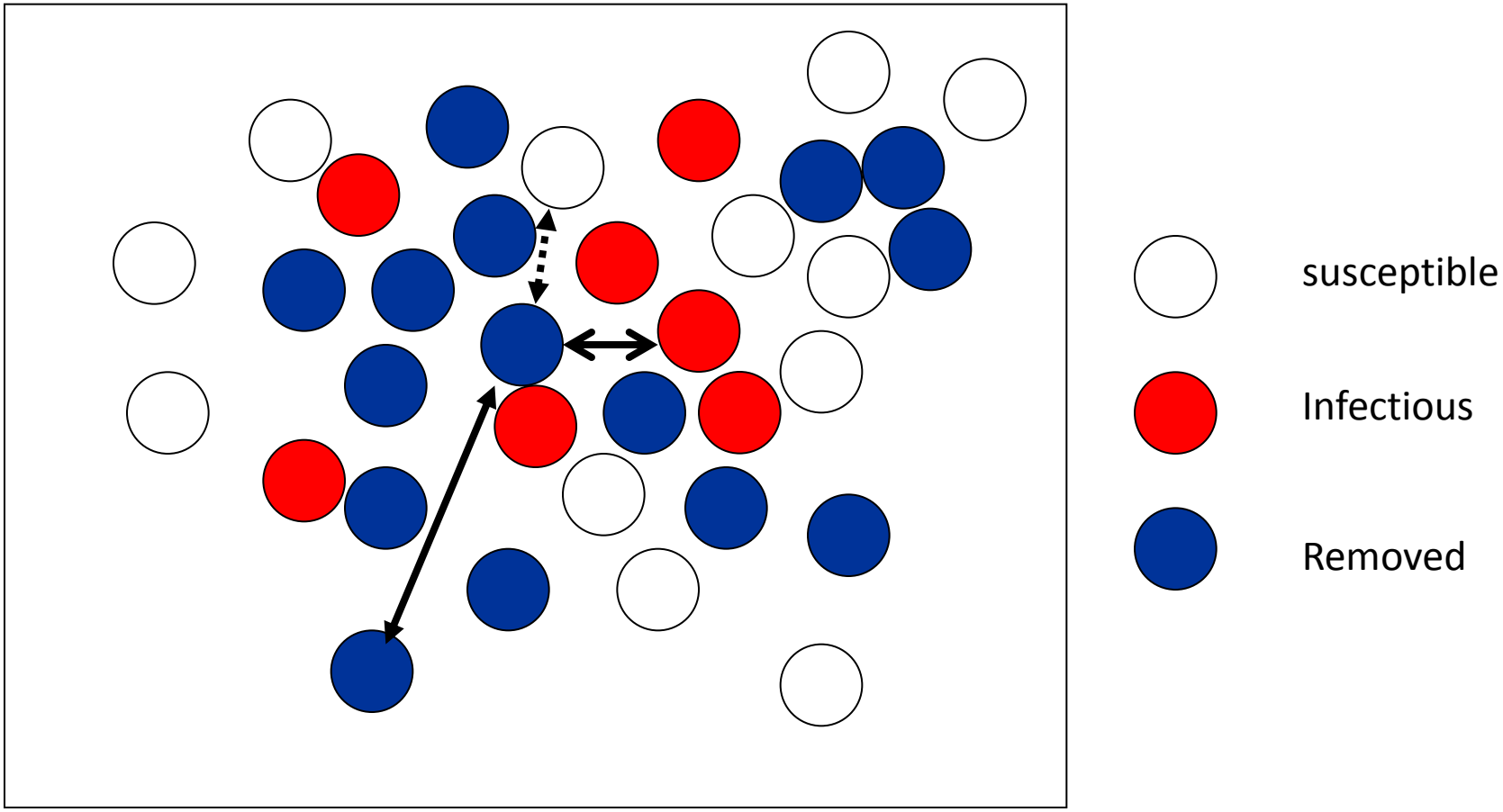




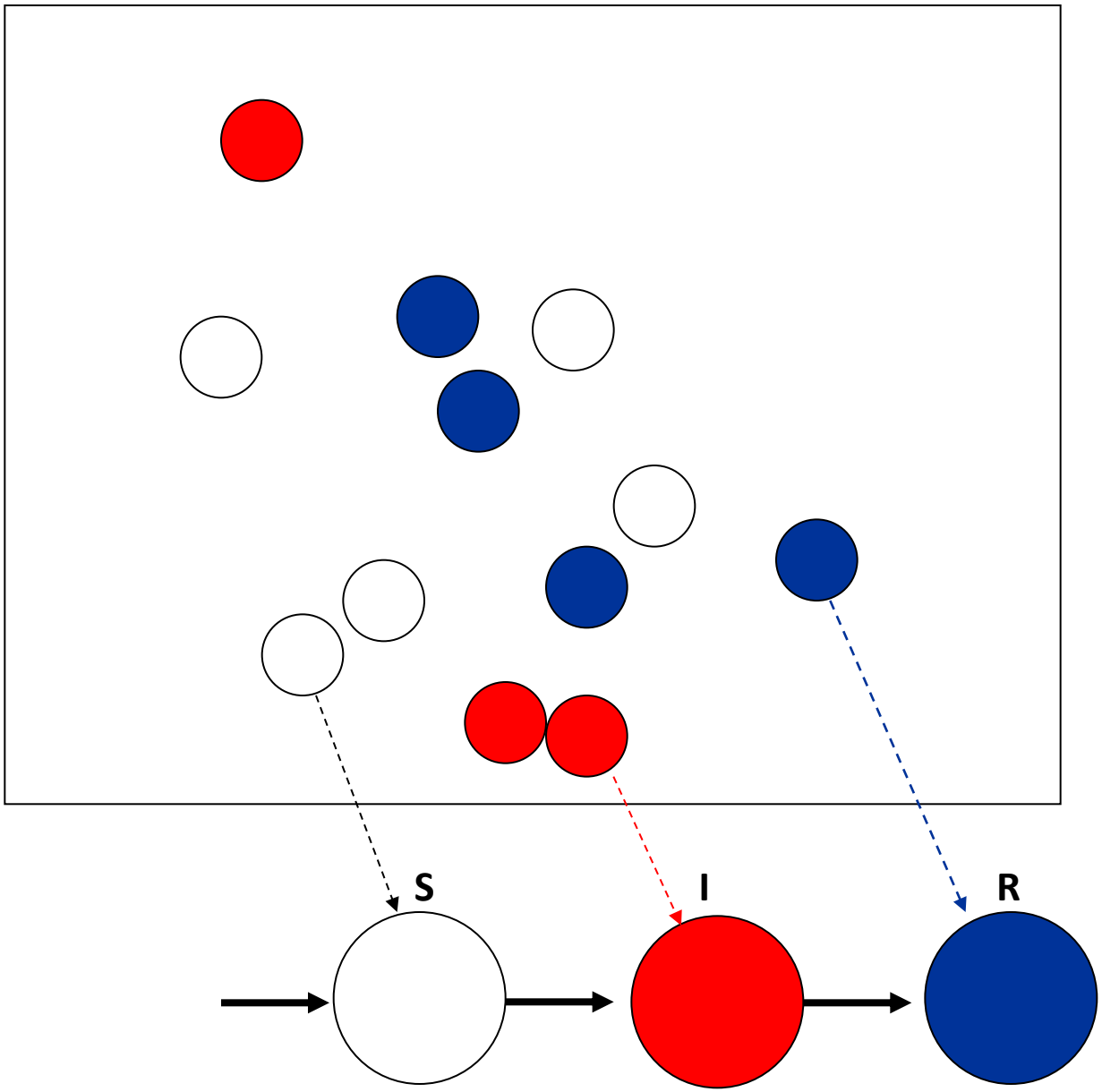
We observed the data, but what is the mechanism that generate the data ?

Transmission and transmission models

The Mass-Action Principle



Susceptible Infectious Removed

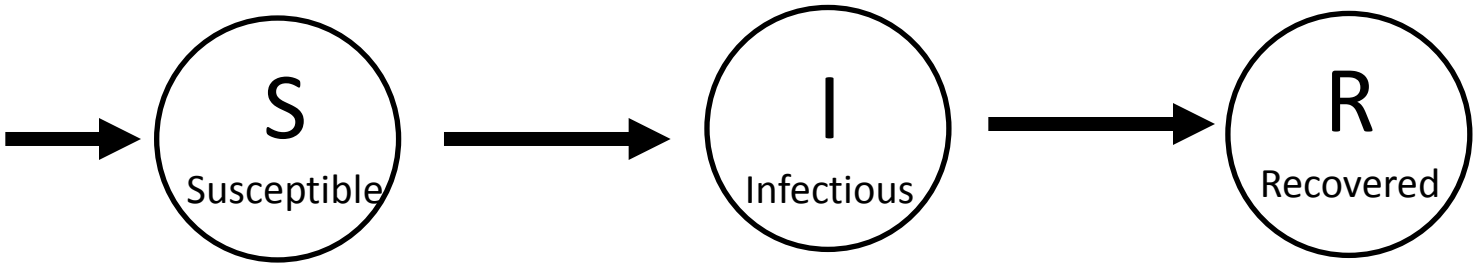


The population is divided into three classes or compartments

Flow diagram

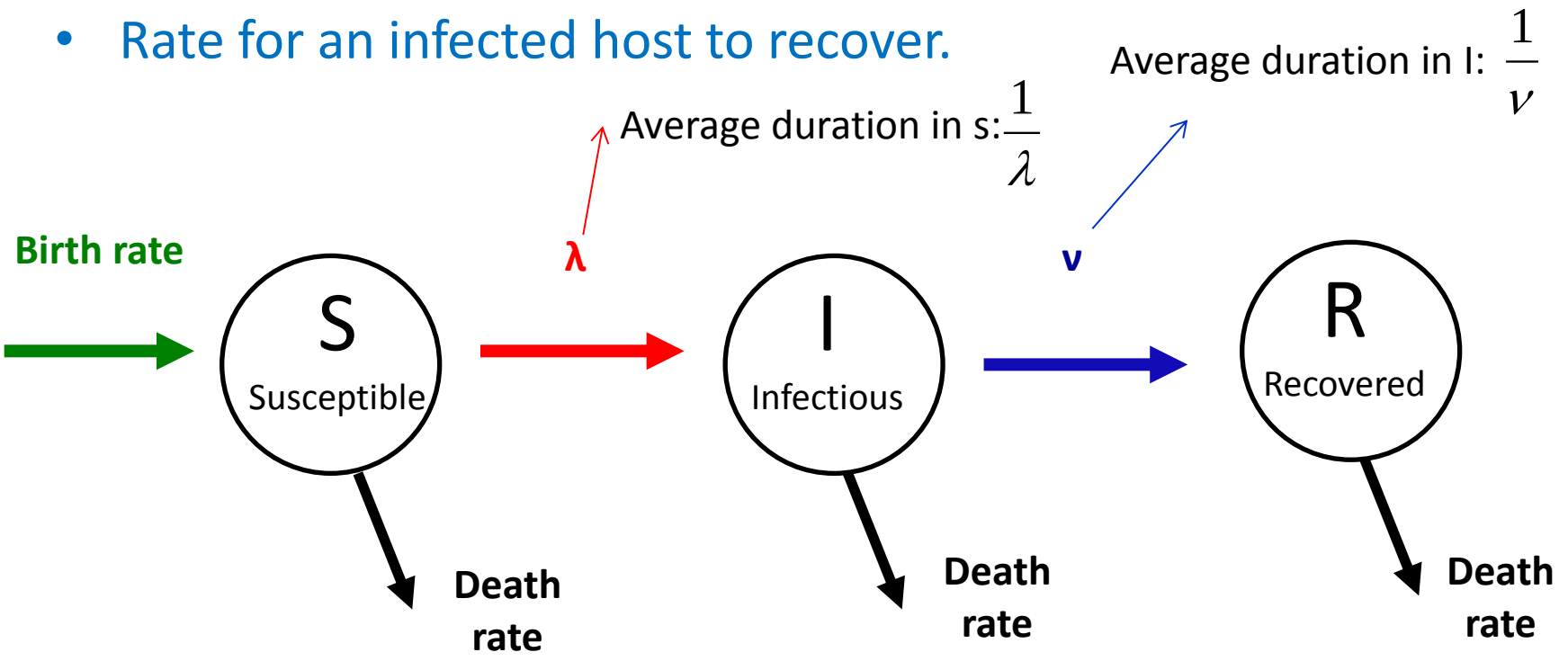
Example 1: infections conferring immunity SIR model

- The natural history of the disease can be represented as "processes": individuals flowing over time between the different states.
  - The disease states are represented by "compartments" (boxes), hence these models are often called **compartmental models.**
  - The flows between states are represented by arrows.

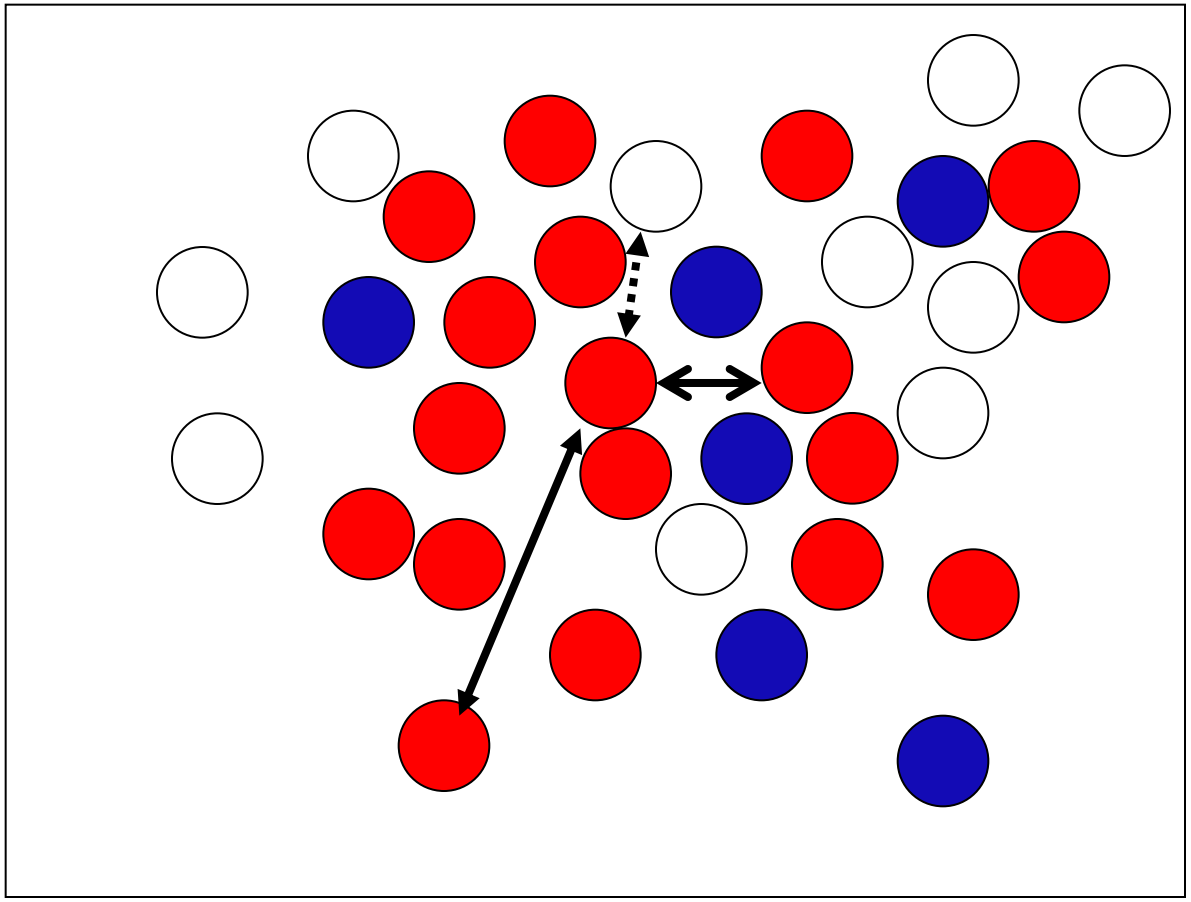


Rates of flow between disease states

- Birth rate = Death rate.
- Rate of acquisition of the infection for a susceptible: the "**Force of Infection**" (FOI).
- Rate for an infected host to recover.



The Mass-Action Principle and the force of infection



Contacts are made in random.

Number of new cases:

$$\beta \times I \times S$$

Transmission probability per contact

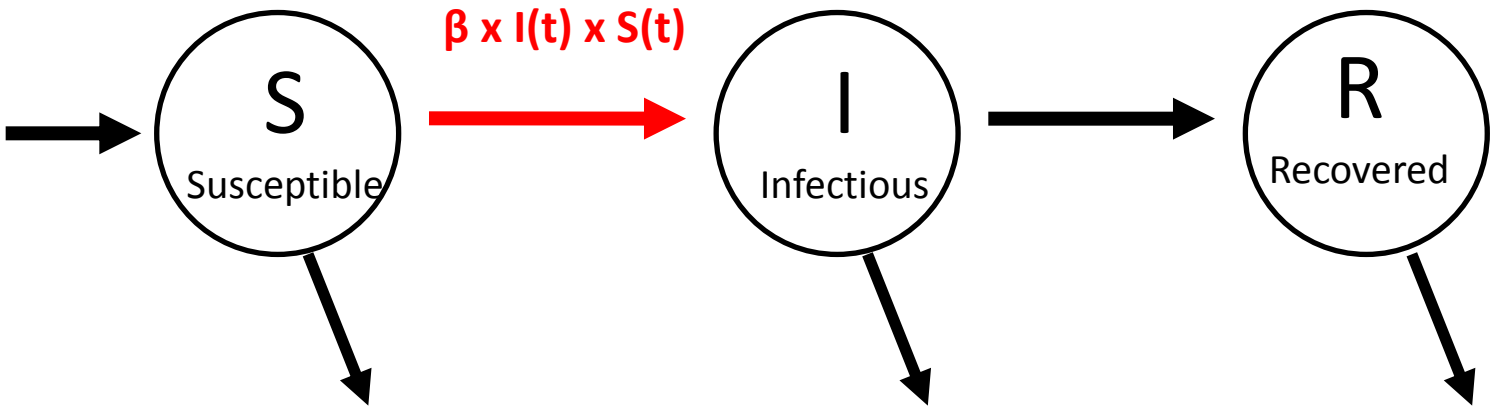
Number of new cases=P(transmission) X # of infectious X # of susceptible

The force of infection

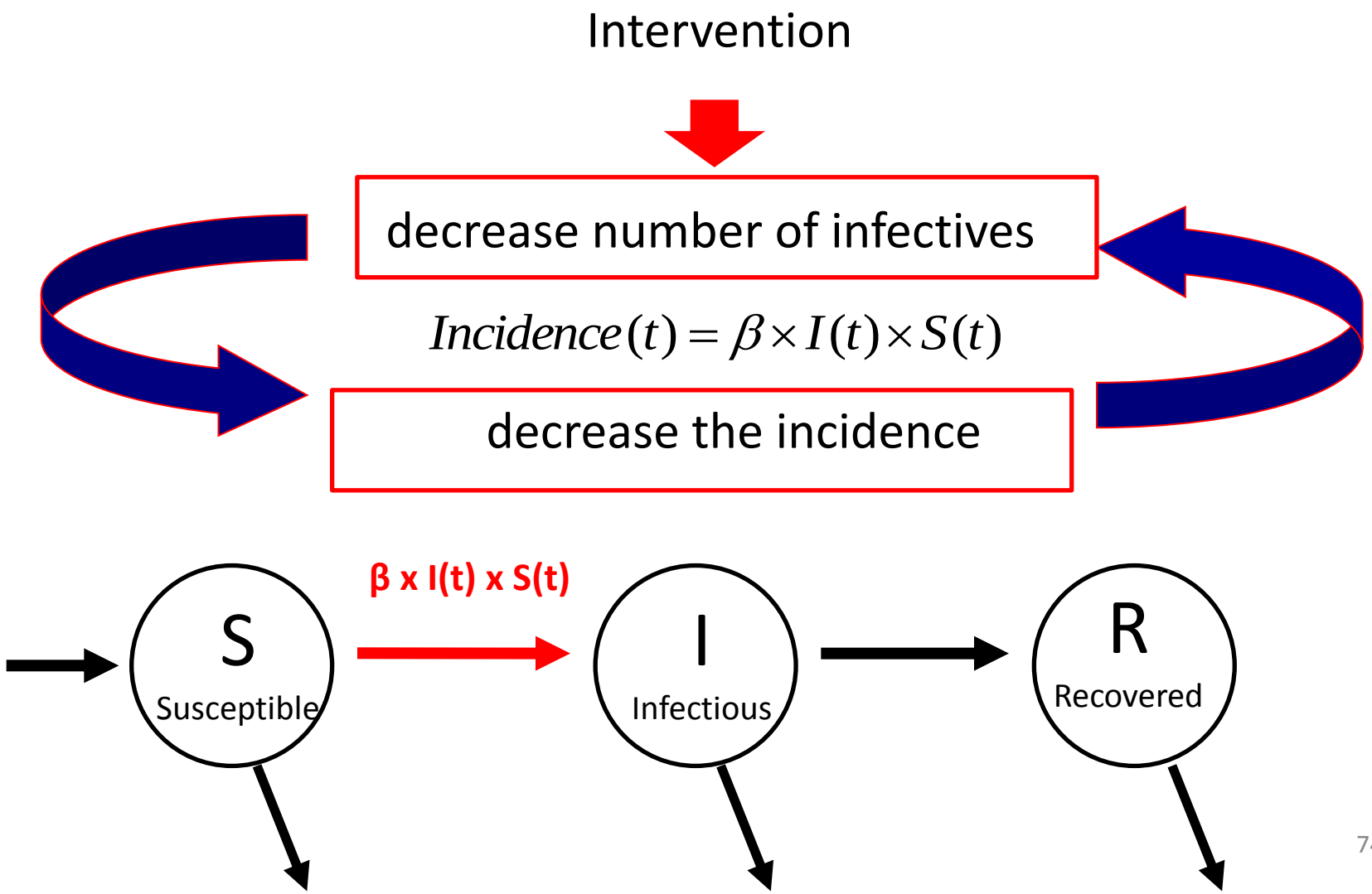
Hence, the number of new infectious cases per unit of time

$$Incidence(t) = \underbrace{\beta \times I(t)}_{\text{The force of infection}} \times S(t)$$

An important underlying assumption is that individuals "mix" homogeneously within the population.

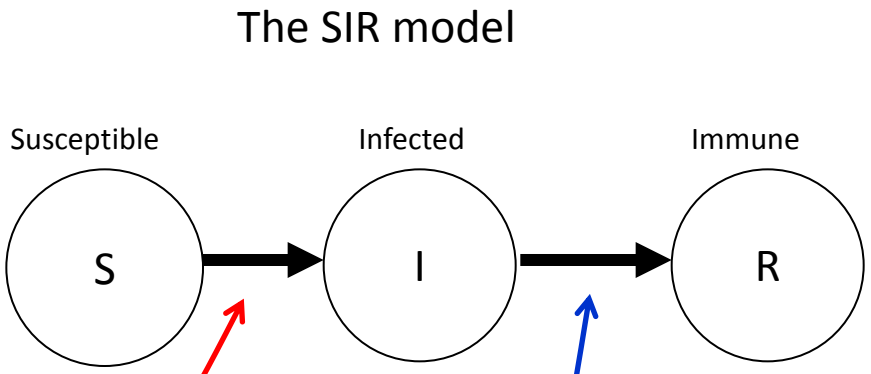


Positive Feedback



First approximation: Discrete time steps

Difference Equations: the change in number of individuals in each compartment



$$S(t+\Delta t) = s(t) - \lambda S(t)\Delta t$$

$$I(t+\Delta t) = I(t) + \lambda S(t)\Delta t - \sigma I(t)\Delta t$$

$$R(t+\Delta t) = R(t) + \sigma I(t)\Delta t$$

Continuous-time model

$$S(t+\Delta t) = s(t) - \lambda S(t)\Delta t$$

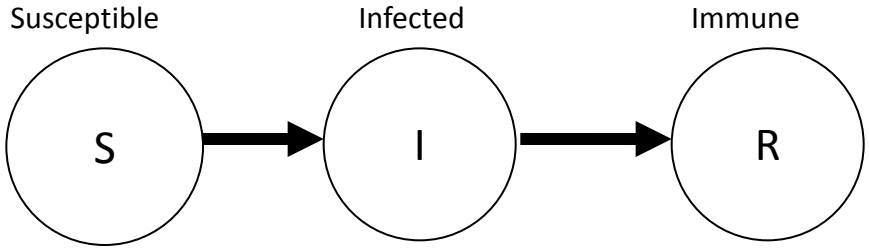
As Δt → 0 we have

$$\frac{S(t+\Delta t) - s(t)}{\Delta t} = -\lambda S(t)$$

The change in the susceptible class

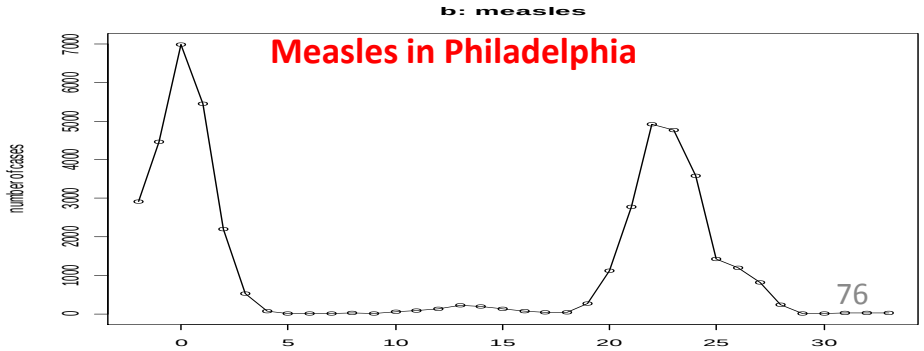
$$\frac{dS(t)}{dt} = -\lambda S(t)$$

The SIR model



How realistic is the model ?

Can we use this type of model to describe a disease ?

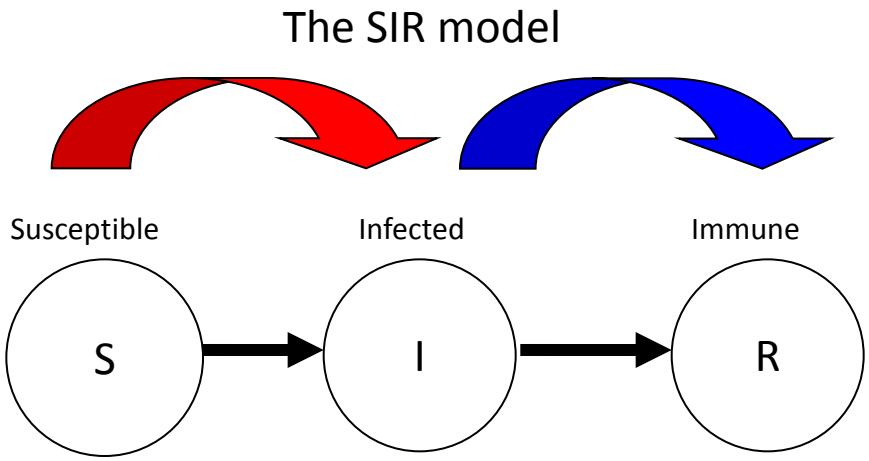


The SIR Model

$$\frac{dS(t)}{dt} = -\lambda S(t)$$

$$\frac{dI(t)}{dt} = \lambda S(t) - \sigma I(t)$$

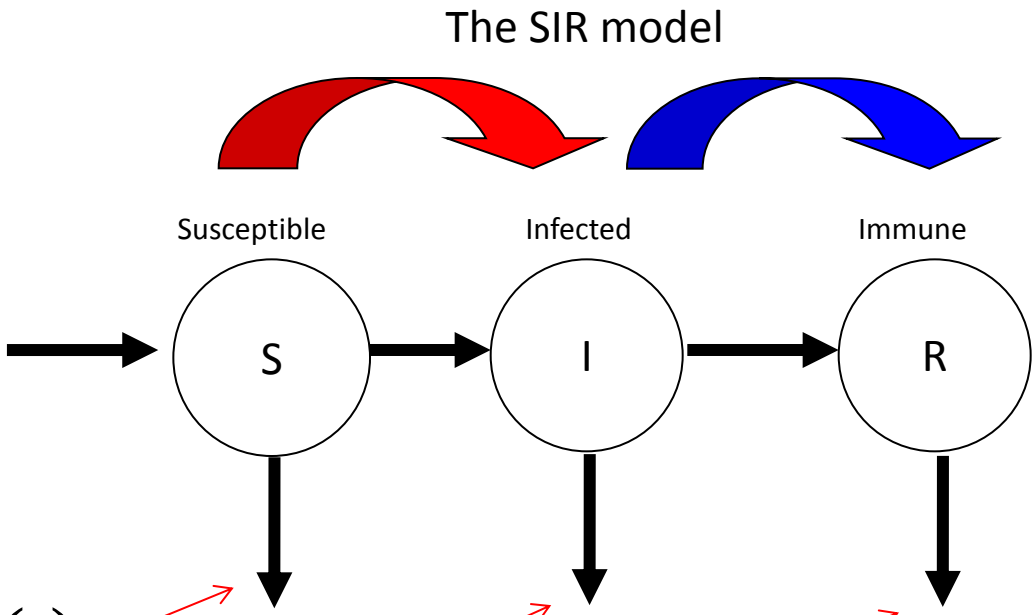
$$\frac{dR(t)}{dt} = \sigma I(t)$$



Closed population

The SIR model: open population

The flow of individuals in and outside the population.

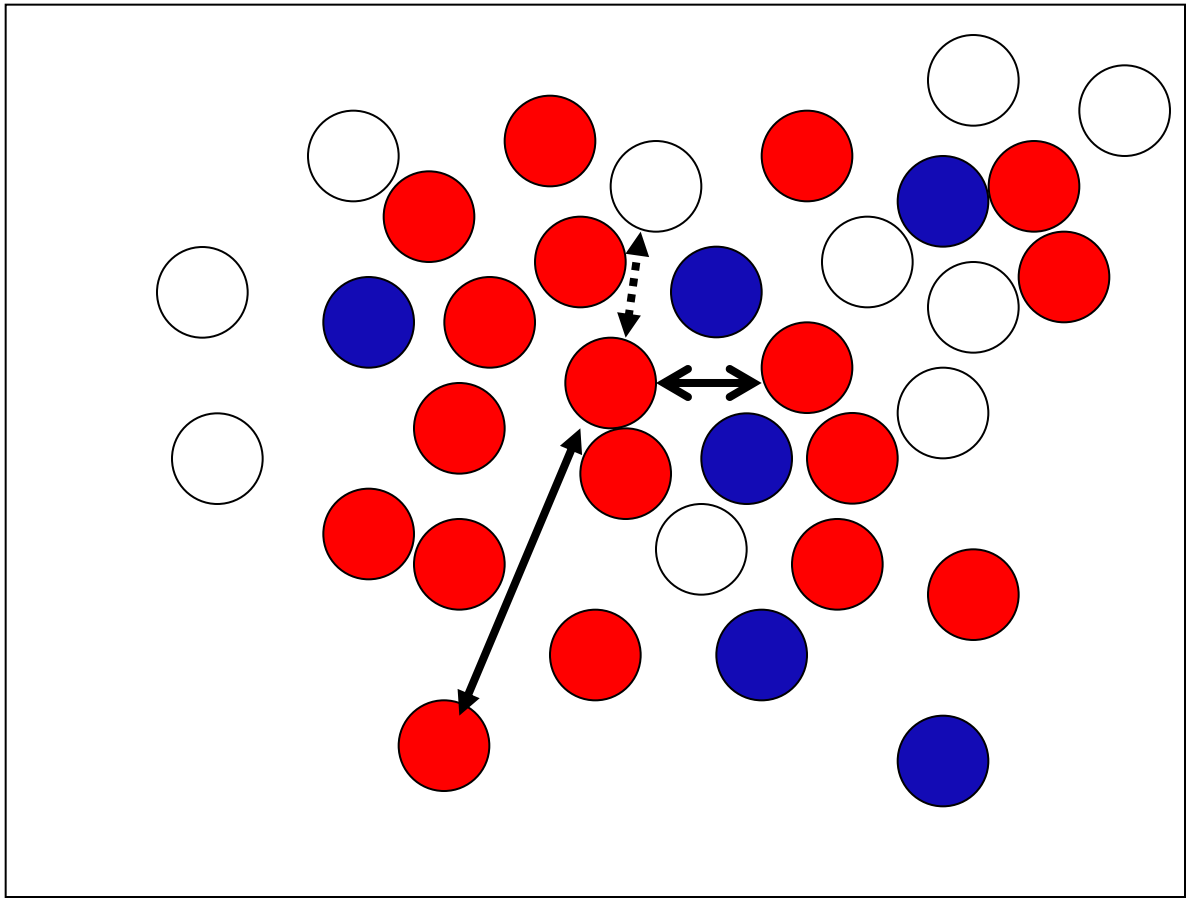


$$\frac{dS(t)}{dt} = N\mu - \lambda S(t) - \mu S(t)$$

$$\frac{dI(t)}{dt} = \lambda S(t) - \sigma I(t) - \mu I(t)$$

$$\frac{dR(t)}{dt} = \sigma I(t) - \mu R(t)$$

The Mass-Action Principle



Contacts are made in random.

Number of new cases:

$$\beta \times I \times S$$

Transmission probability per contact

Number of new cases=P(transmission) X # of infectious X # of susceptible

SIR model in open population: Dynamic aspects

- In order to understand the dynamic of the SIR model we need to allow for time dependent force of infection.
- Open population.
- Mass action principle:

Number of new cases=P(transmission) X # of infectious X # of susceptible

$$\lambda(t) = \beta \times I(t)$$

Time dependent force of infection

$$\frac{dS(t)}{dt} = -\lambda(t)S(t)$$

$$\frac{dI(t)}{dt} = \lambda(t)S(t) - \sigma I(t)$$

$$\frac{dR(t)}{dt} = \sigma I(t)$$

$$\frac{dS(t)}{dt} = -\beta \times I(t) \times S(t)$$

$$\frac{dI(t)}{dt} = \beta \times I(t) \times S(t) - \sigma I(t)$$

$$\frac{dR(t)}{dt} = \sigma I(t)$$

$$\lambda(t) = \beta \times I(t)$$

time dependent

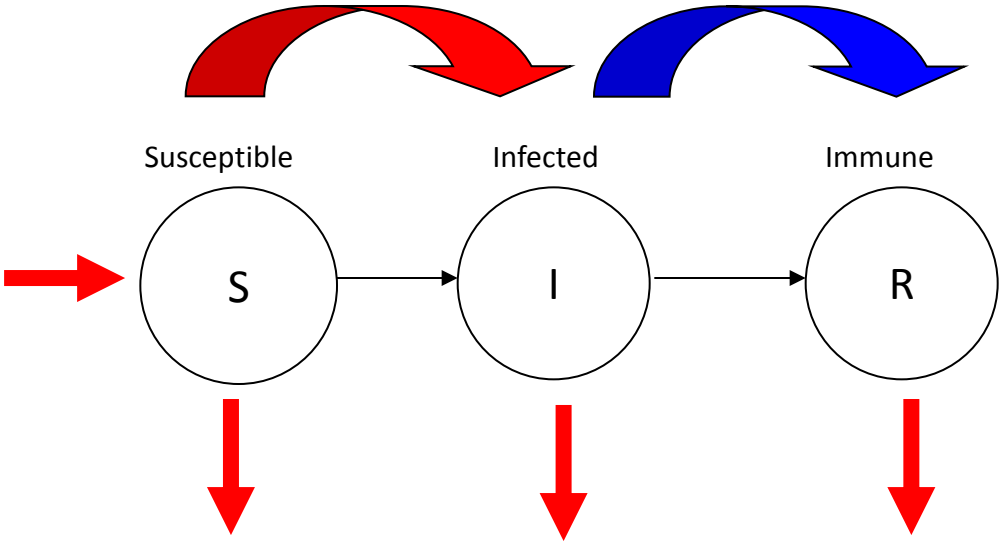
constant

SIR transmission model in open population

$$\frac{dS(t)}{dt} = N\mu - \beta I(t)S(t) - \mu S(t)$$

$$\frac{dI(t)}{dt} = \beta I(t)S(t) - (\sigma + \mu)I(t)$$

$$\frac{dR(t)}{dt} = \sigma I(t) - \mu R(t)$$



Birth rate=death rate=μ.

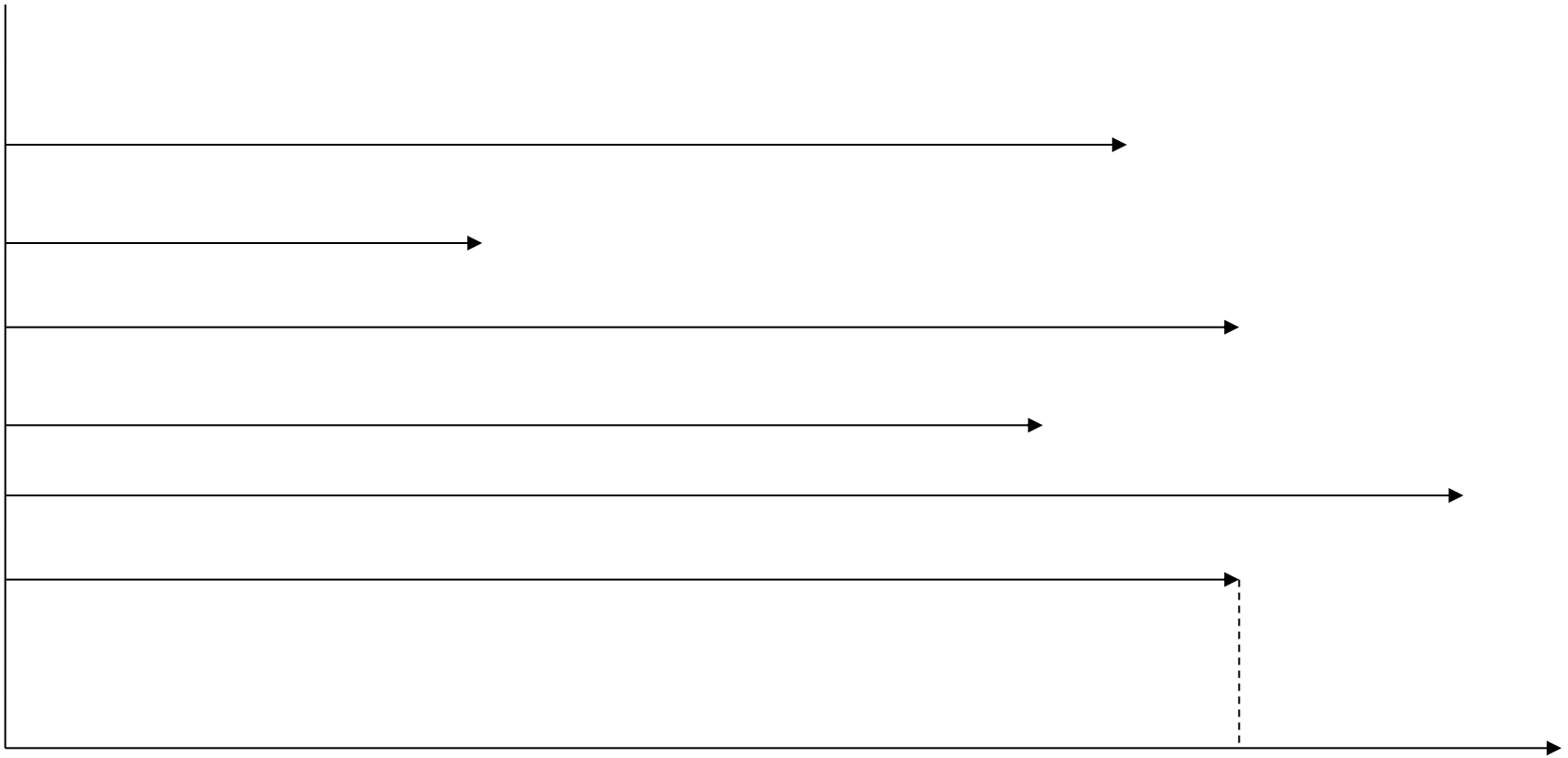
$$N = S + I + R$$

- Constant population size over time.
- Flow of individuals into the population is equal to the flow out.

Transmission parameters

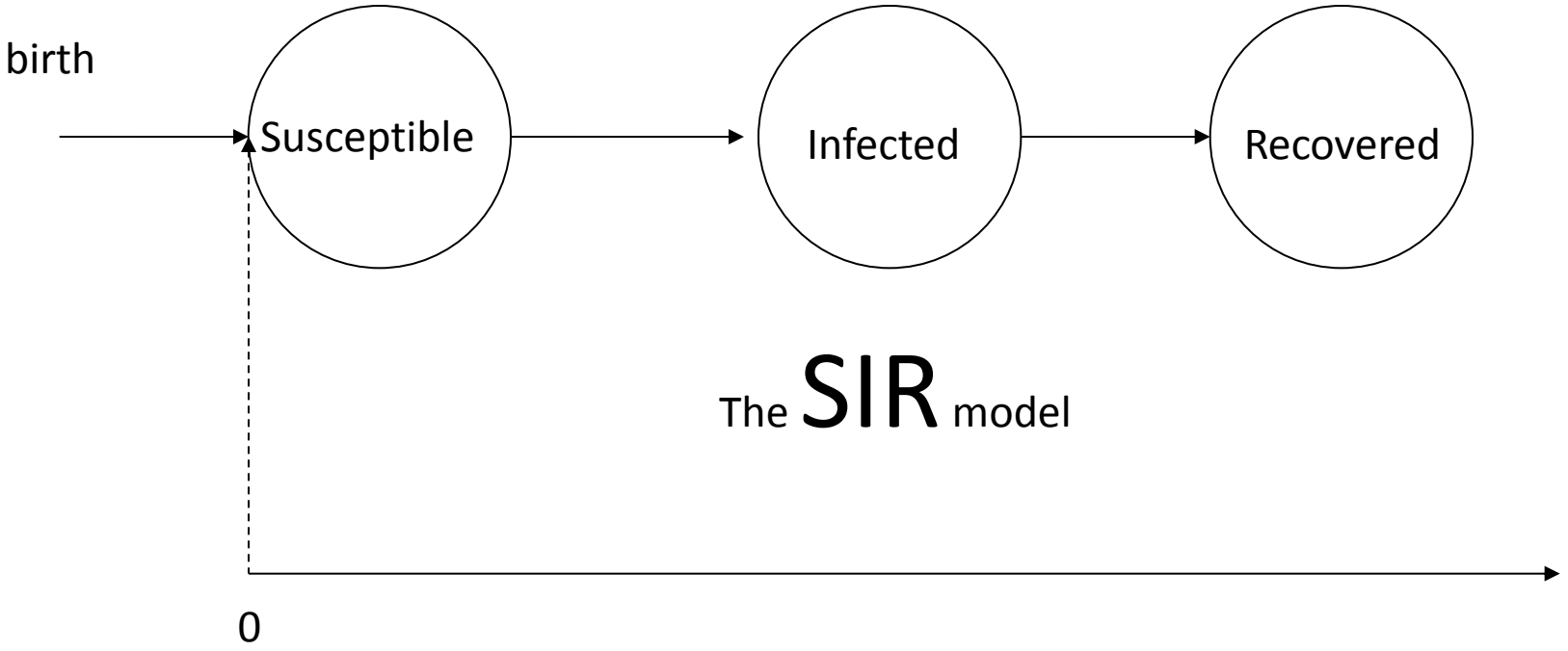
Average age at infection

Follow up on individuals in the population



Average age at infection

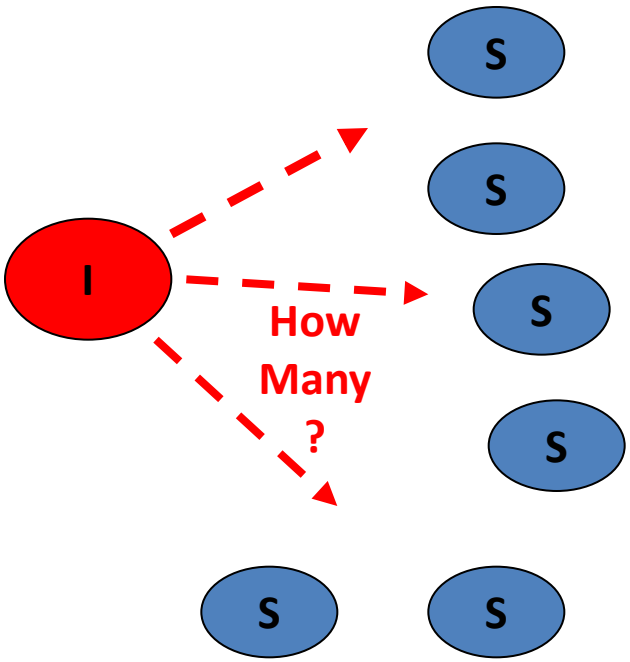
- On average, how long individuals stay in the susceptible class ?
- Average duration in the susceptible class.



A : The average at infection.

The basic reproductive number

Average number of new infectious cases generated by one primary case during her(his) entire period of infectiousness in a totally susceptible population.



- ***R_0* below 1** $\rightarrow$ No invasion of the infection within the population; only small epidemics.
- ***R_0* above 1** $\rightarrow$ Endemic infection; the bigger the value of R_0 the bigger the potential of spread of the infection within the population.

The Basic Reproduction Number "R_0"

- In the (very simple) case of homogeneous contacts:

$$R_0 = b \times N \times D$$

Transmission rate

Population size

Mean duration of infectiousness

- In more realistic models the "computation" of R_0 is more complex but the concept of "R_0" remains the same.

$$R_0 = \beta \times N \times D = \beta \times N \times \frac{1}{\sigma}$$

$$\begin{cases} \dfrac{dS(t)}{dt} = -\beta \times I(t) \times S(t) \\ \dfrac{dI(t)}{dt} = \beta \times I(t) \times S(t) - \sigma I(t) \\ \dfrac{dR(t)}{dt} = \sigma I(t) \end{cases}$$

The Basic Reproduction Number R_0

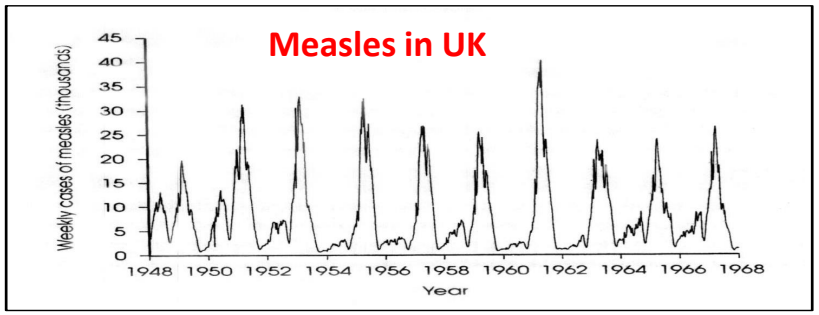
- R_0 is
  - disease specific: transmissibility of the pathogen, duration of infectiousness
  - Population-specific: population density, “contact pattern”

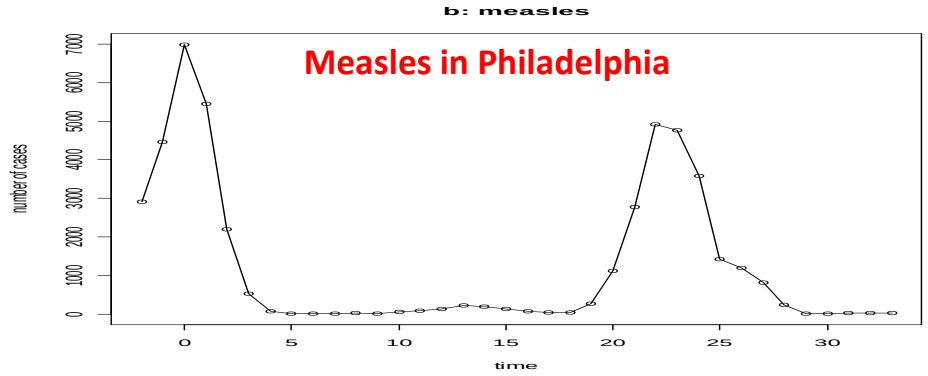
- R_0 is estimated from field data or, more often, derived from **data and a transmission model**.

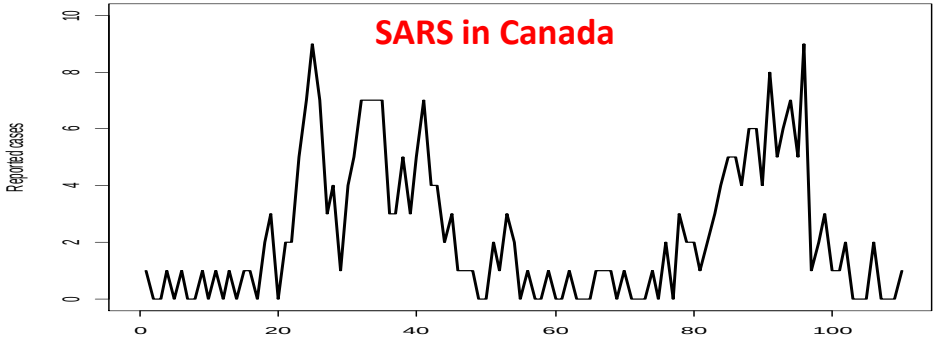
SIR transmission model in R: the deSolve R package

R program: ModelingIDinR1_V1_Stat&Dynam_Sep2019.R

Number of cases over time







Same patterns for different diseases.

Can we model this pattern ?

15

Can we **estimate** the parameters of the model ?

Transmission models in R

- We need to integrate the system of the ordinary differential equation.

$$\frac{dS(t)}{dt} = -\lambda S(t)$$
$$\frac{dI(t)}{dt} = \lambda S(t) - \sigma I(t)$$
$$\frac{dR(t)}{dt} = \sigma I(t)$$

Closed population

- deSolve package in R.
- Numerical integration using of ODE system.

Transmission models in R

SIR model
(open population)

$$\frac{dS(t)}{dt} = N\mu - \beta IS - \mu S$$
$$\frac{dI(t)}{dt} = \beta IS - (\sigma + \mu)I$$
$$\frac{dR(t)}{dt} = \sigma I - \mu R$$

Specification in R

- Model parameters.
- State variables (the value of the parameters at age (time) zero.
- Time range (=age range) for integration.

Transmission models in R

R program

Model parameters → μ, β, σ

State variables → $S(0), I(0), R(0)$

Time range for integration → For example: integrate from age zero to age 50.

Specification of the model →

$$\frac{dS(t)}{dt} = N\mu - \beta IS - \mu S$$

$$\frac{dI(t)}{dt} = \beta IS - (\sigma + \mu)I$$

$$\frac{dR(t)}{dt} = \sigma I - \mu R$$

Specification of the model parameters in R

```
> parameters <- c(mu=1/75,beta=0.001,v=1)
> print(parameters)
        mu       beta          v
0.01333333 0.00100000 1.00000000
```

Life expectancy:
75 years

Recovery rate 1
days.

$$\frac{dS(t)}{dt} = N\mu - \beta IS - \mu S$$
$$\frac{dI(t)}{dt} = \beta IS - (\sigma + \mu)I$$
$$\frac{dR(t)}{dt} = \sigma I - \mu R$$

The state variables (initial values at time 0)

- Let us assume that the population size is 5000.
- At time=0:

$$S(0) = 4999$$

$$I(0) = 1$$

$$R(0) = 0$$

- Specification in R:

```
> state <- c(X=4999,Y=1,Z=0)
> state
   X    Y    Z
4999    1    0
```

SIR transmission model in open population

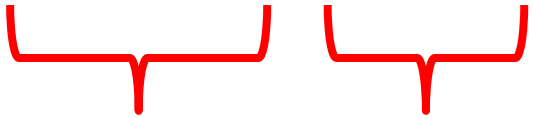
$$\frac{dS(t)}{dt} = N\mu - \beta IS - \mu S$$
$$\frac{dI(t)}{dt} = \beta IS - (\sigma + \mu)I$$
$$\frac{dR(t)}{dt} = \sigma I - \mu R$$

```
SIR<-function(t,state,parameters)
{
with(as.list(c(state,
parameters)),
{
dX <- 5000*mu-beta*Y*X - mu*X
dY <- beta*Y*X - v*Y - mu*Y
dZ <- v*Y -mu*Z
list(c(dX, dY, dZ))
})
}
```

```
> parameters <- c(mu=,beta=,v=)
```

Running the model

```
require(deSolve)
out<-as.data.frame(ode(y=state,times=times,func=SIR,parms=parameters))
```

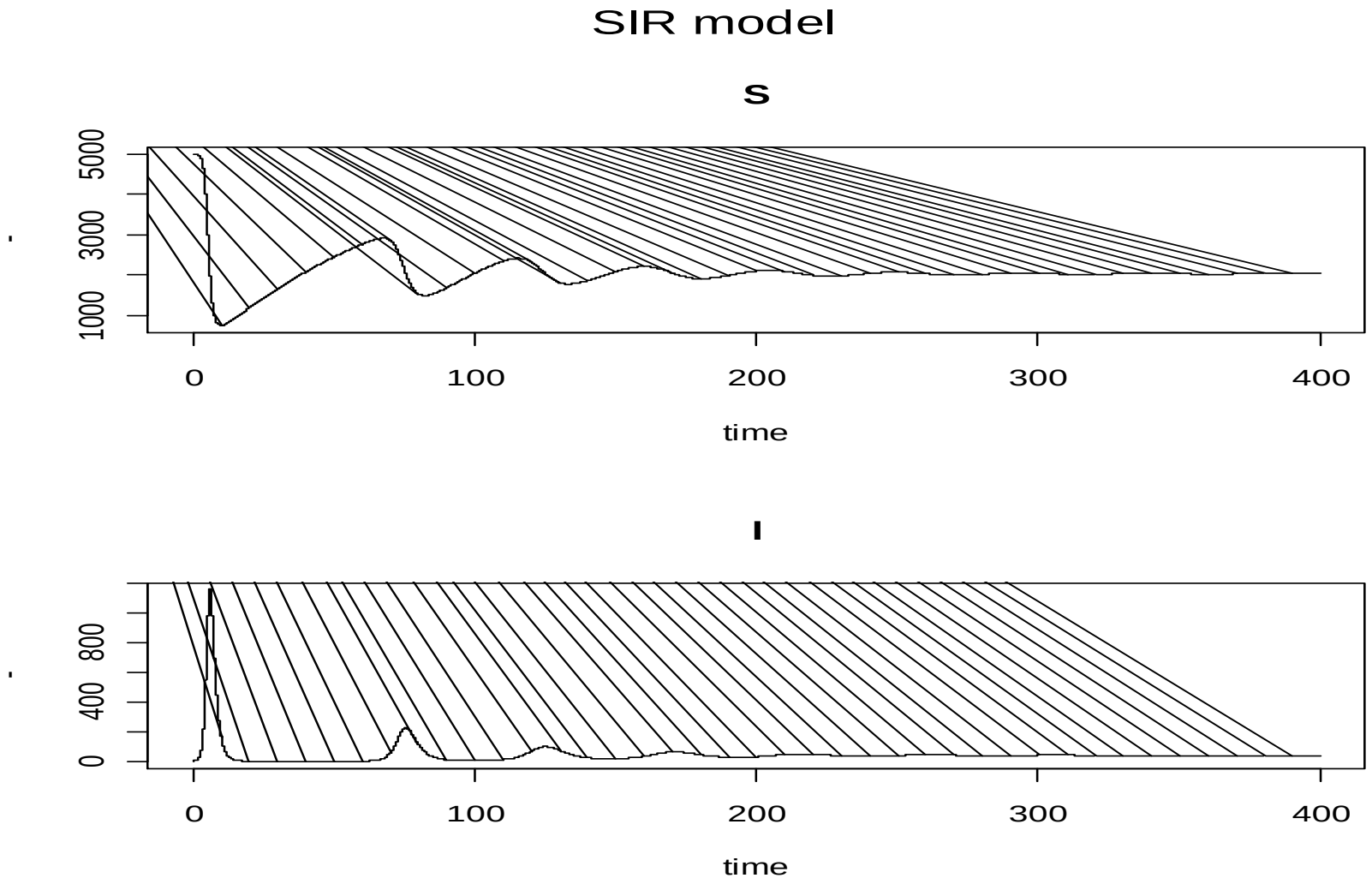


Time range for integration.

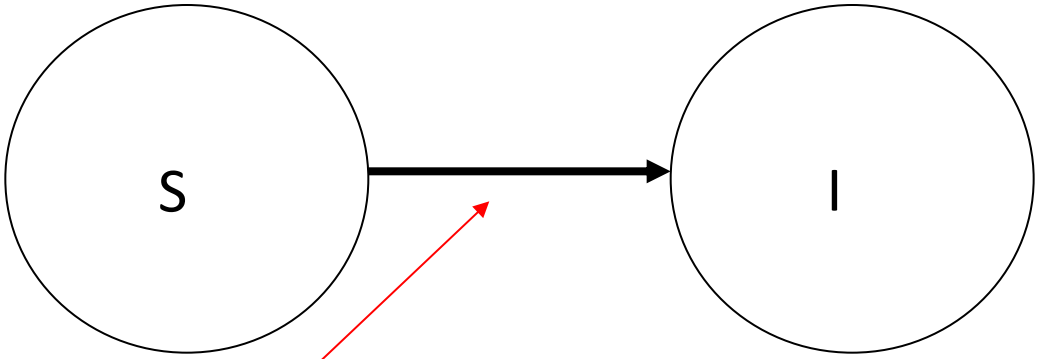
The model

Numerical integration using ordinary differential equation

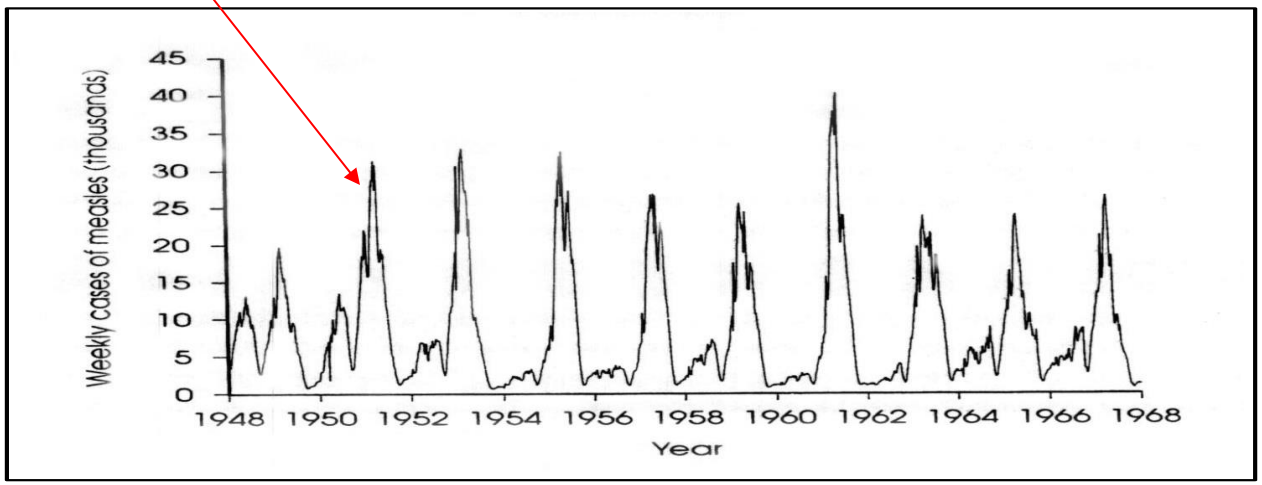
Solution for the model



Incidence data : Measles in UK

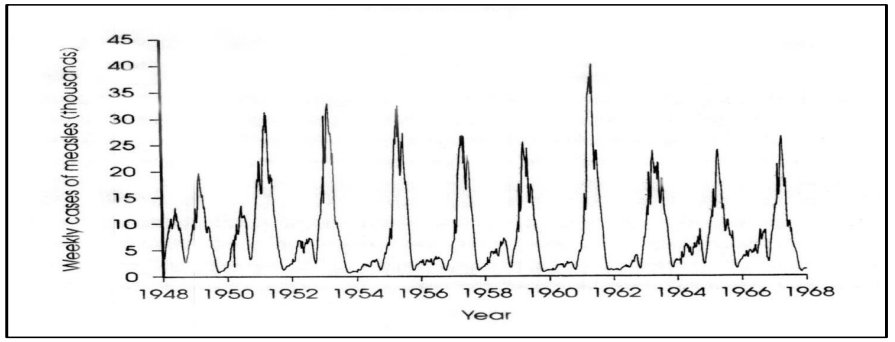


The weekly number of individuals who move from the susceptible to the infected class

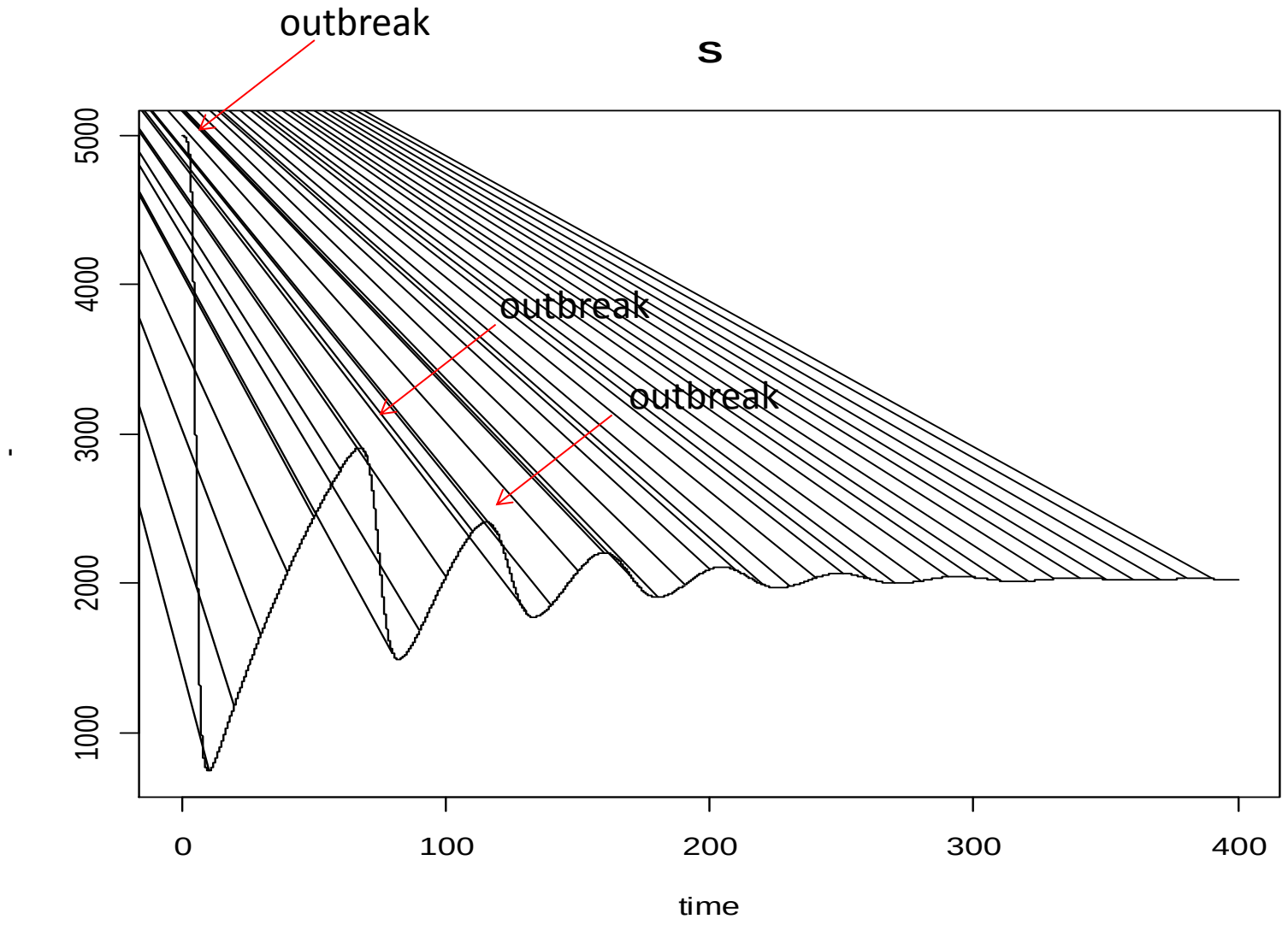


Time unit=week

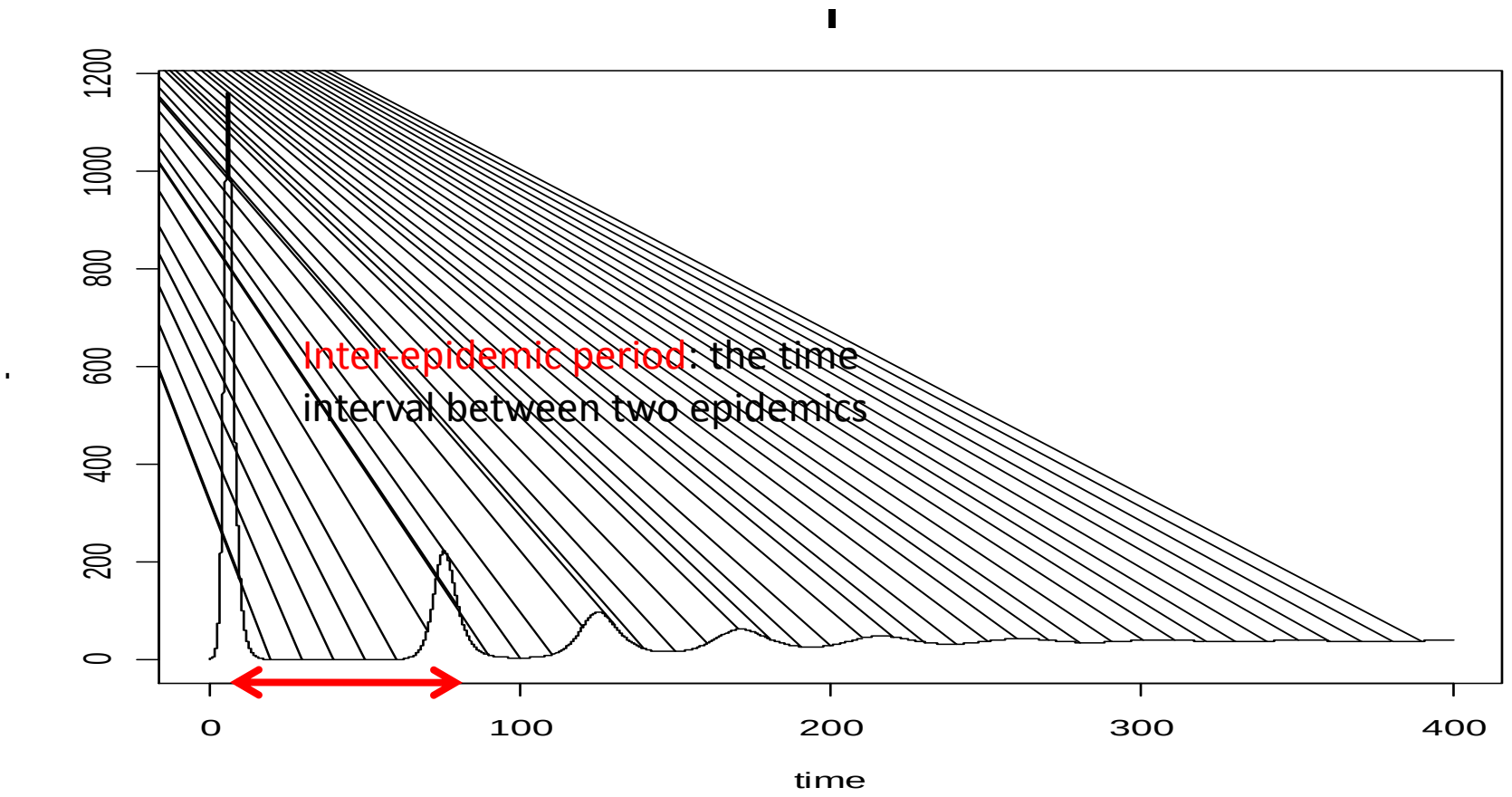
Observed outbreak and predicted outbreak



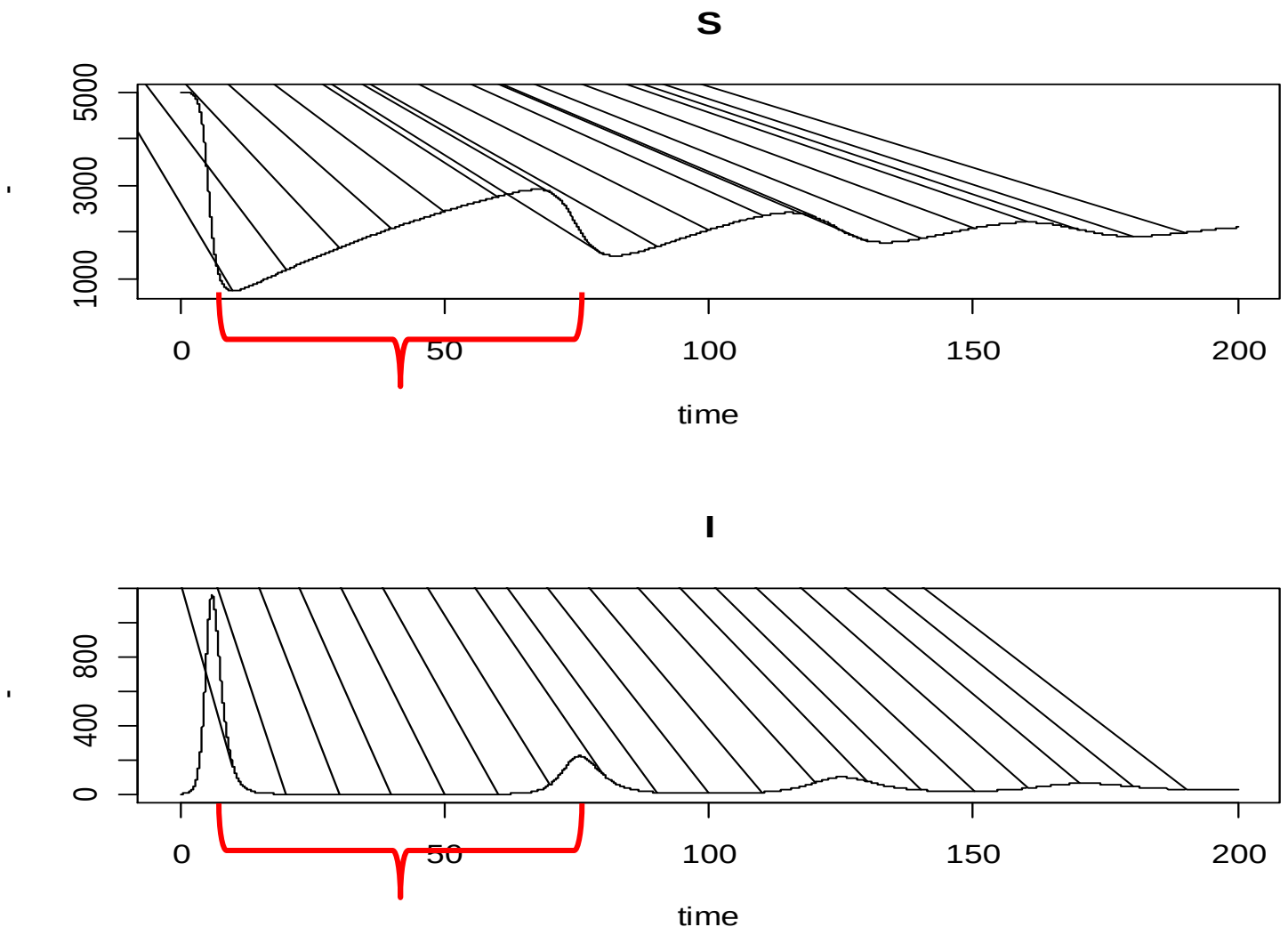
The susceptible class



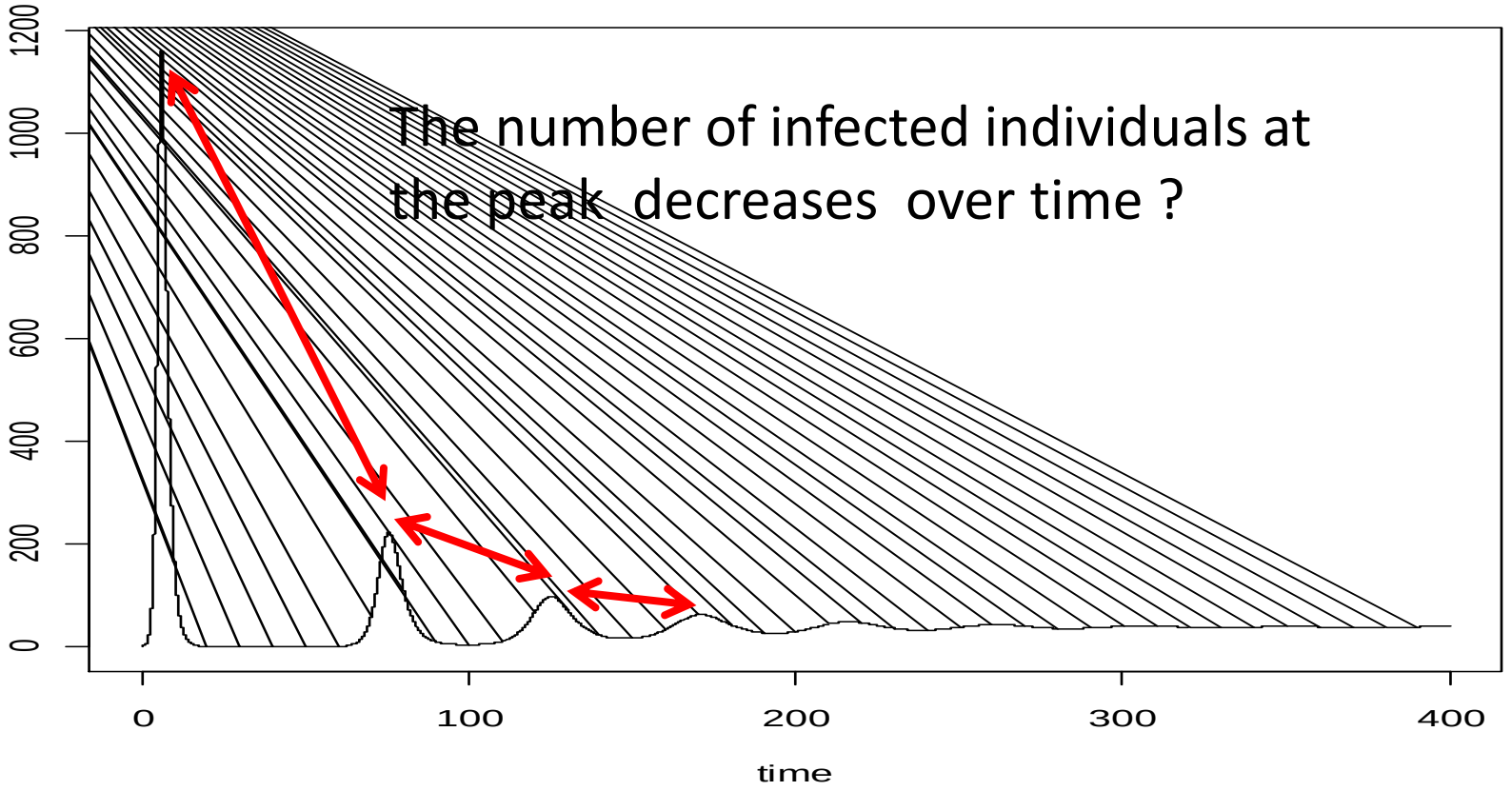
The infected class



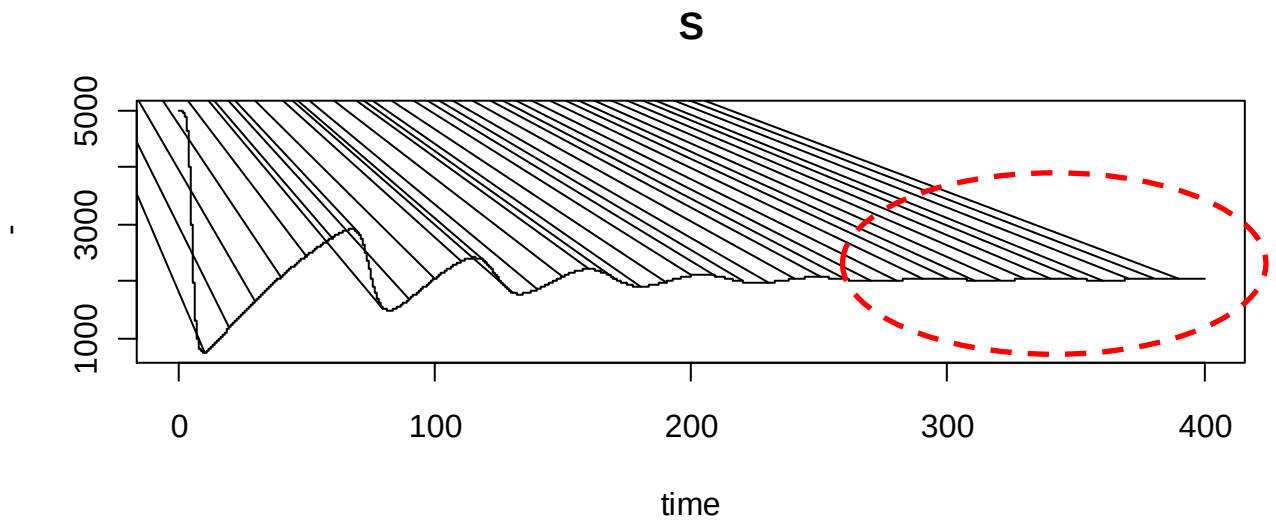
The Inter epidemic period

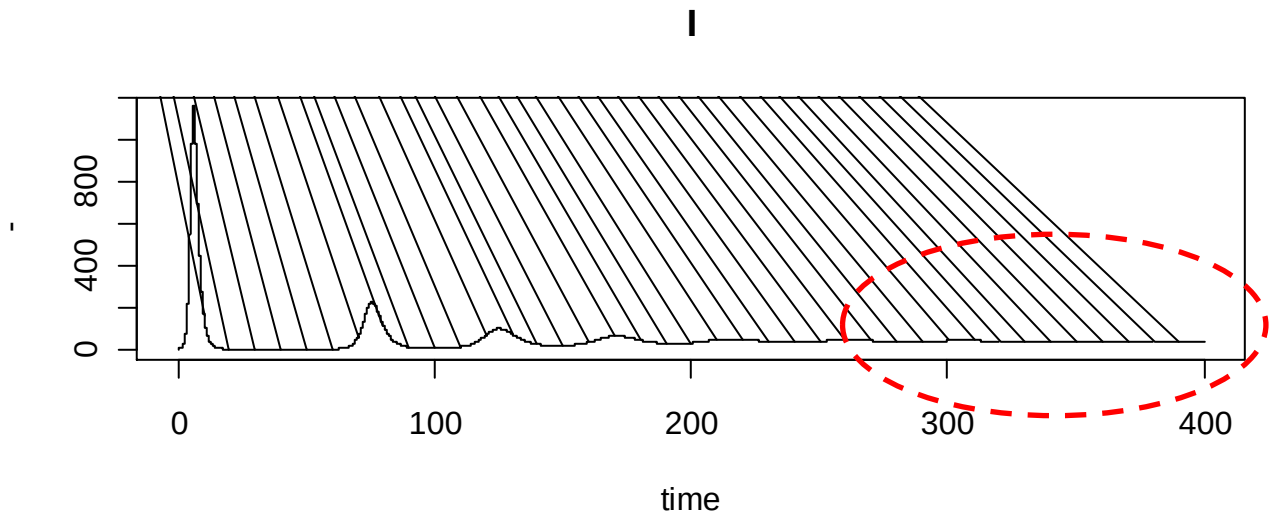


Damping effect ?

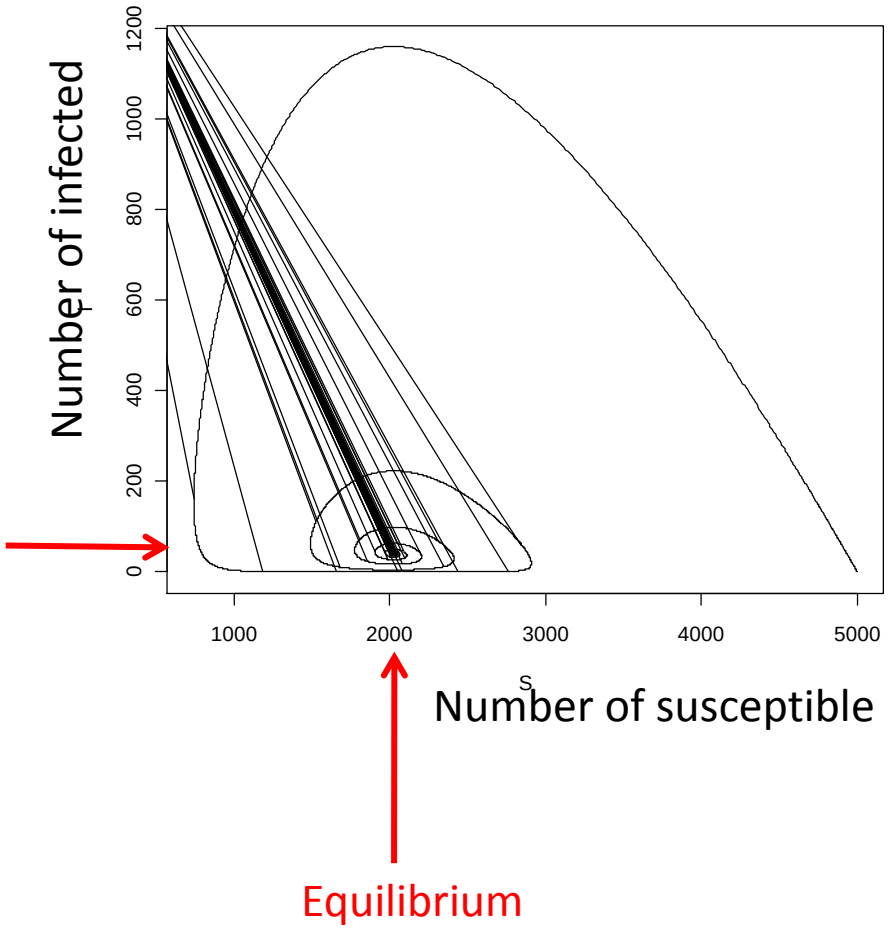


Equilibrium





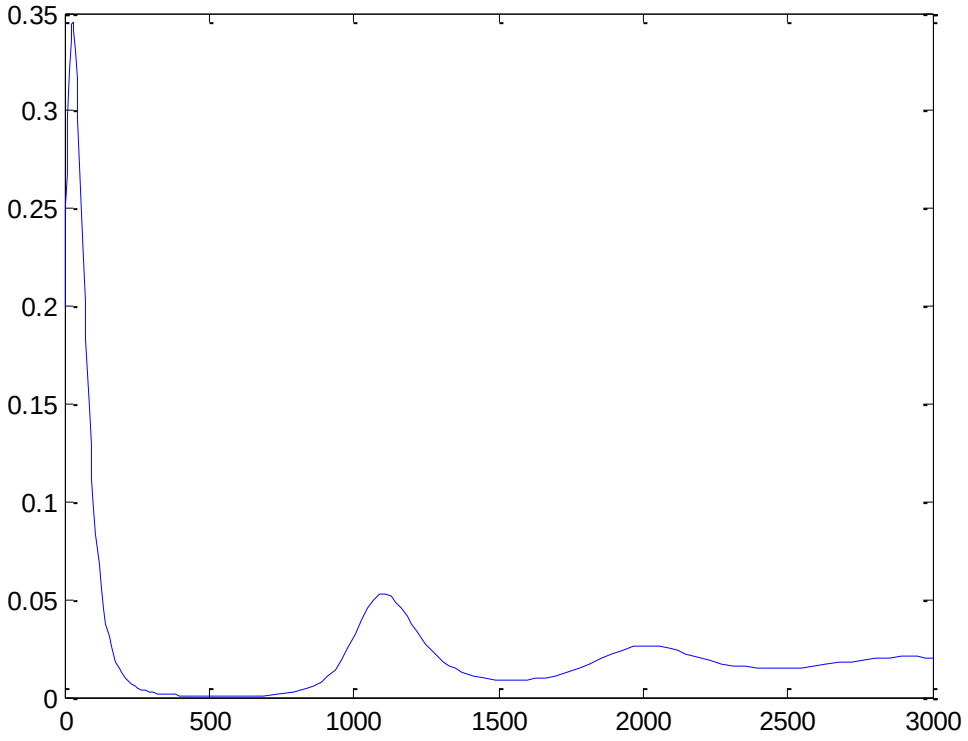
Equilibrium



- At the long run, the infection reach the endemic equilibrium state.
- At each time unit there are the same number of susceptible and infected individuals in the population.

From transmission models to the data: SIR model (dynamic model)

$$\frac{dS(t)}{dt} = N\mu - \beta IS - \mu S$$
$$\frac{dI(t)}{dt} = \beta IS - (\sigma + \mu)I$$
$$\frac{dR(t)}{dt} = \sigma I - \mu R$$

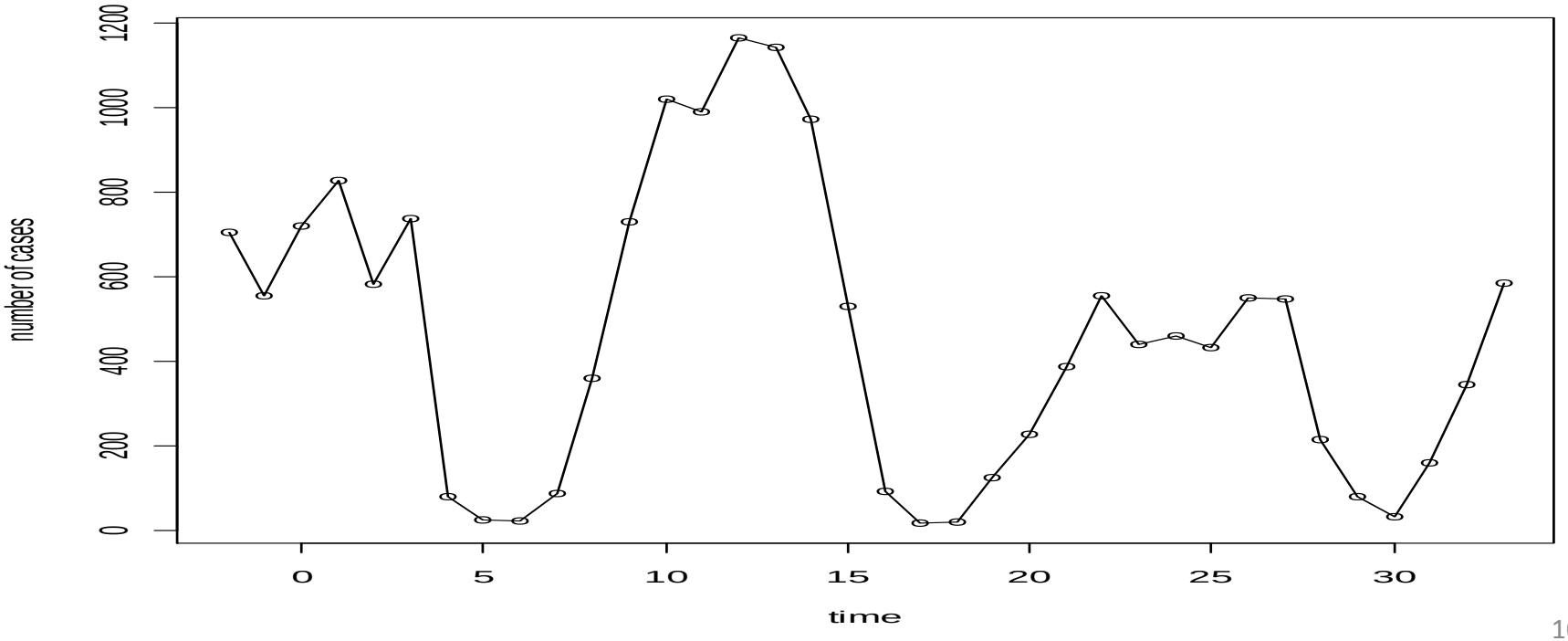


Patterns:

1. Oscillations.
2. Damping effect.
3. Equilibrium value.
4. Inter epidemic period.

Incidence Data
varicella in Philadelphia 1941-1943

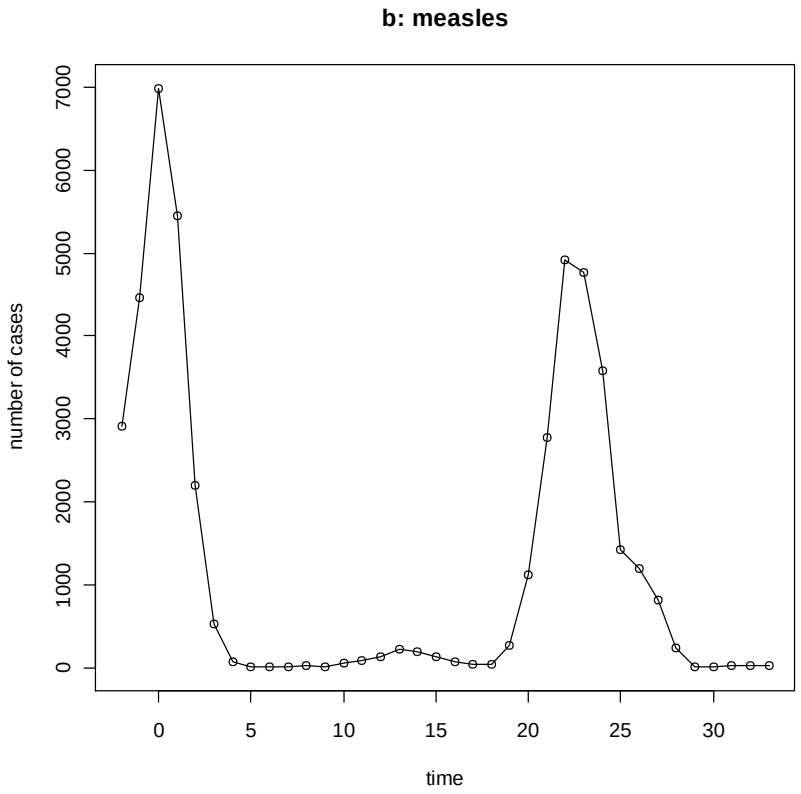
Oscillations seems to be symmetric around the equilibrium value.



Incidence Data
Measles in Philadelphia 1941-1943

- Number of measles cases over a period of 36 months.
- Inter epidemic period ~ 24 months.

- Dumping effect ?



Understanding transmission

SIR model

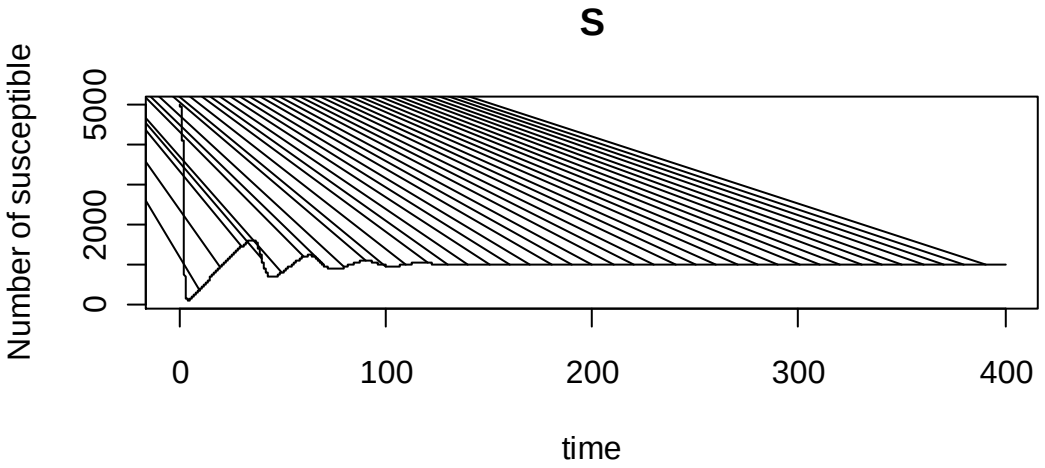
Basic setting:

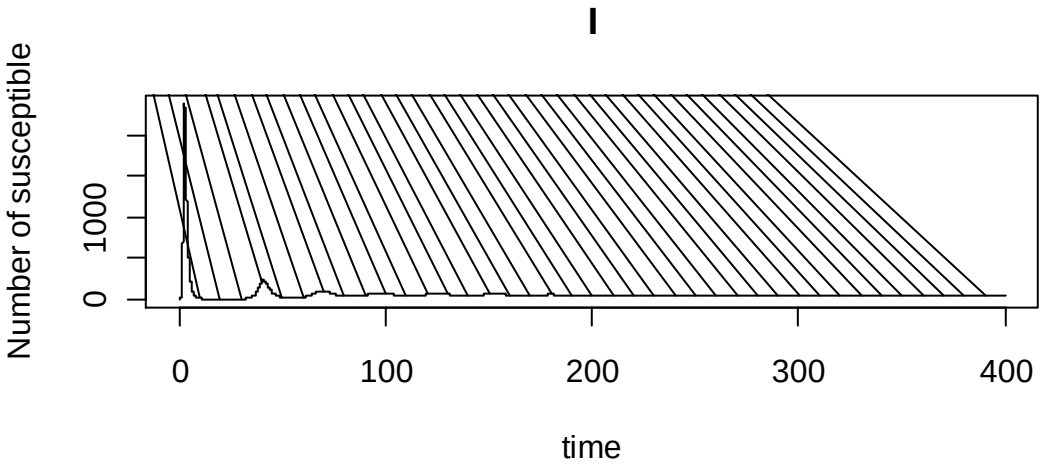
$$N = 5000, \beta = 0.001, \sigma = 1, L = 75$$

$$\frac{dS(t)}{dt} = N\mu - \beta IS - \mu S$$
$$\frac{dI(t)}{dt} = \beta IS - (\sigma + \mu) I$$
$$\frac{dR(t)}{dt} = \sigma I - \mu R$$

$$L = 75 \Rightarrow \mu = \frac{1}{L} = \frac{1}{75}$$

Birth rate=death rate=μ





Effect of β

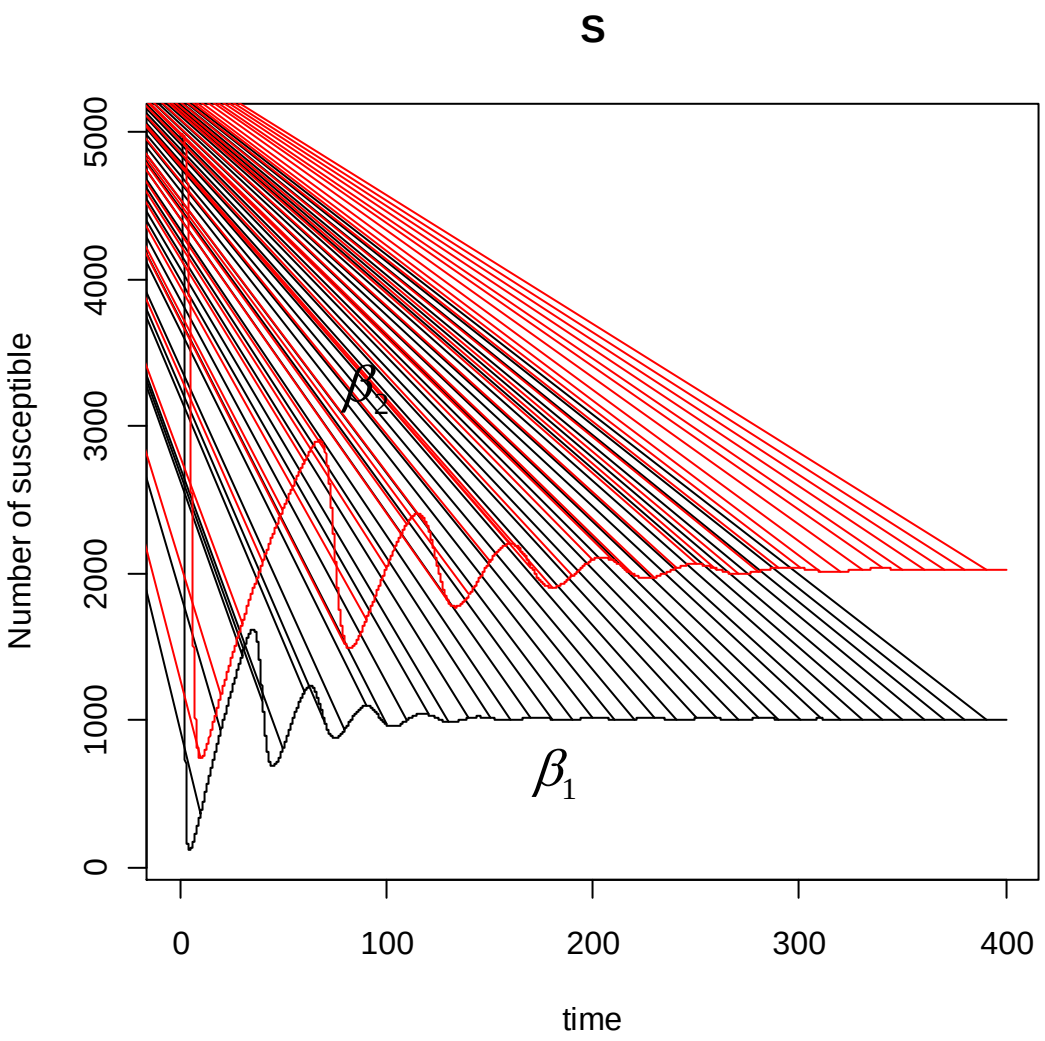
$$N = 5000, \beta = 0.001, \nu = 1, L = 75$$

$$N = 5000, \beta = 0.0005, \nu = 1, L = 75$$

$$\beta_2 < \beta_1$$

$$\beta_2 = \frac{1}{2} \times \beta_1$$

Individuals are infected in a lower rate, i.e, time in the susceptible class is longer.

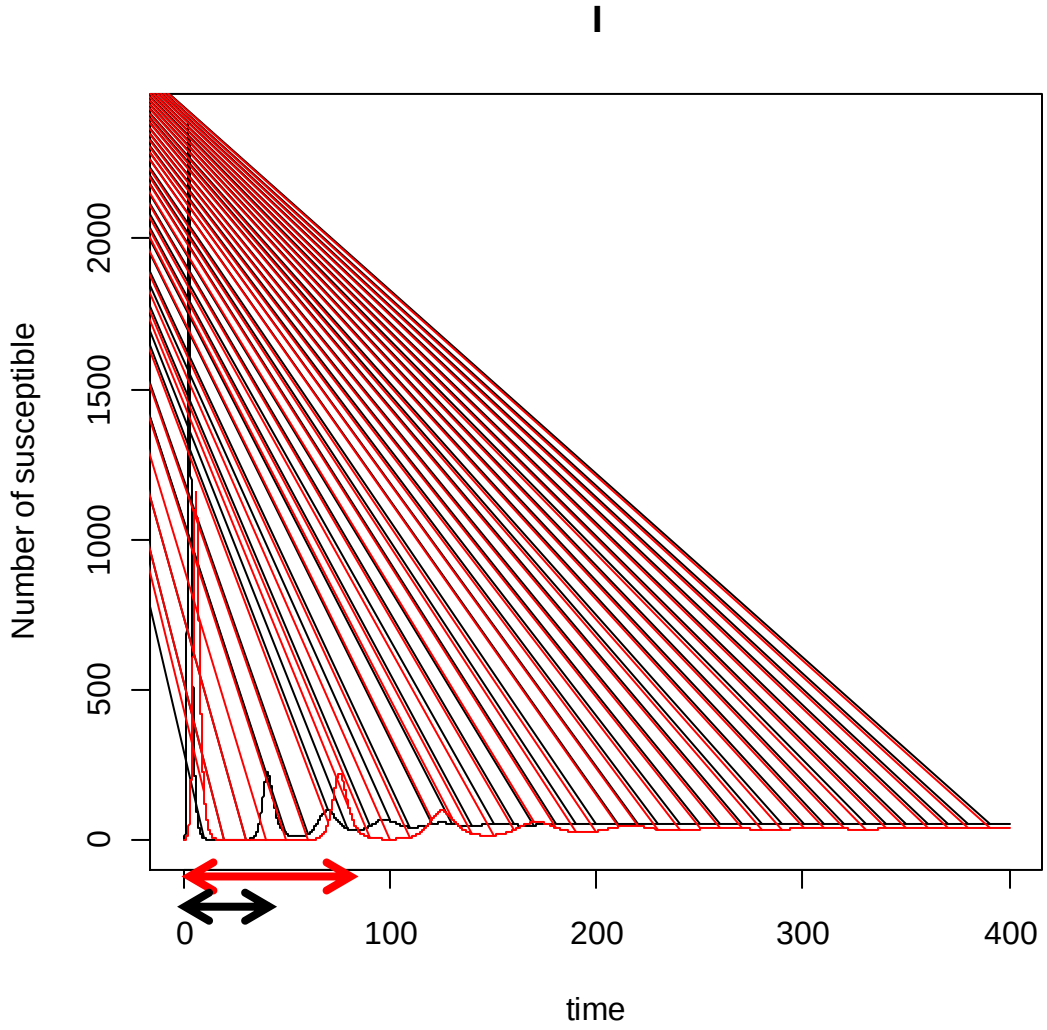


Effect of β

$\beta_2 < \beta_1$

Inter epidemic period.

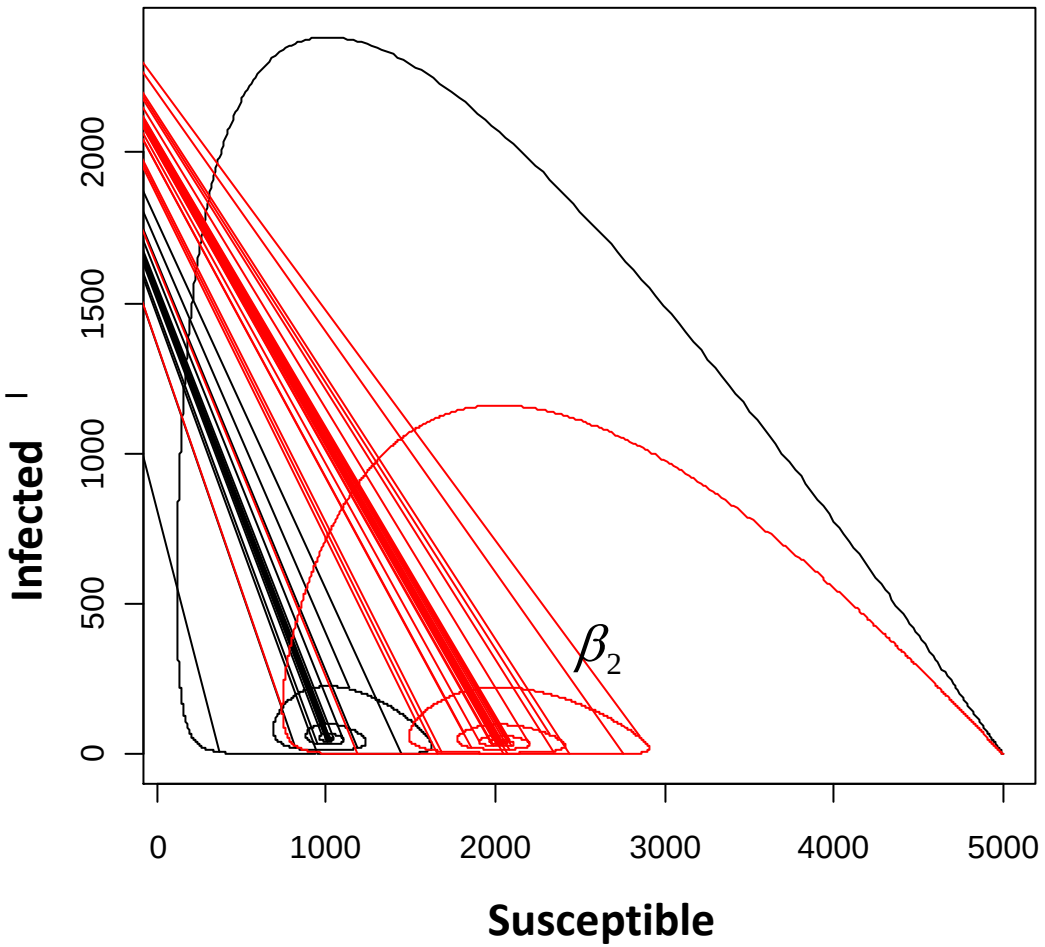
Equilibrium values.



Effect of β

$\beta_2 < \beta_1$

Equilibrium values: more susceptible but the very small difference in number of infected individuals.



Effect of N

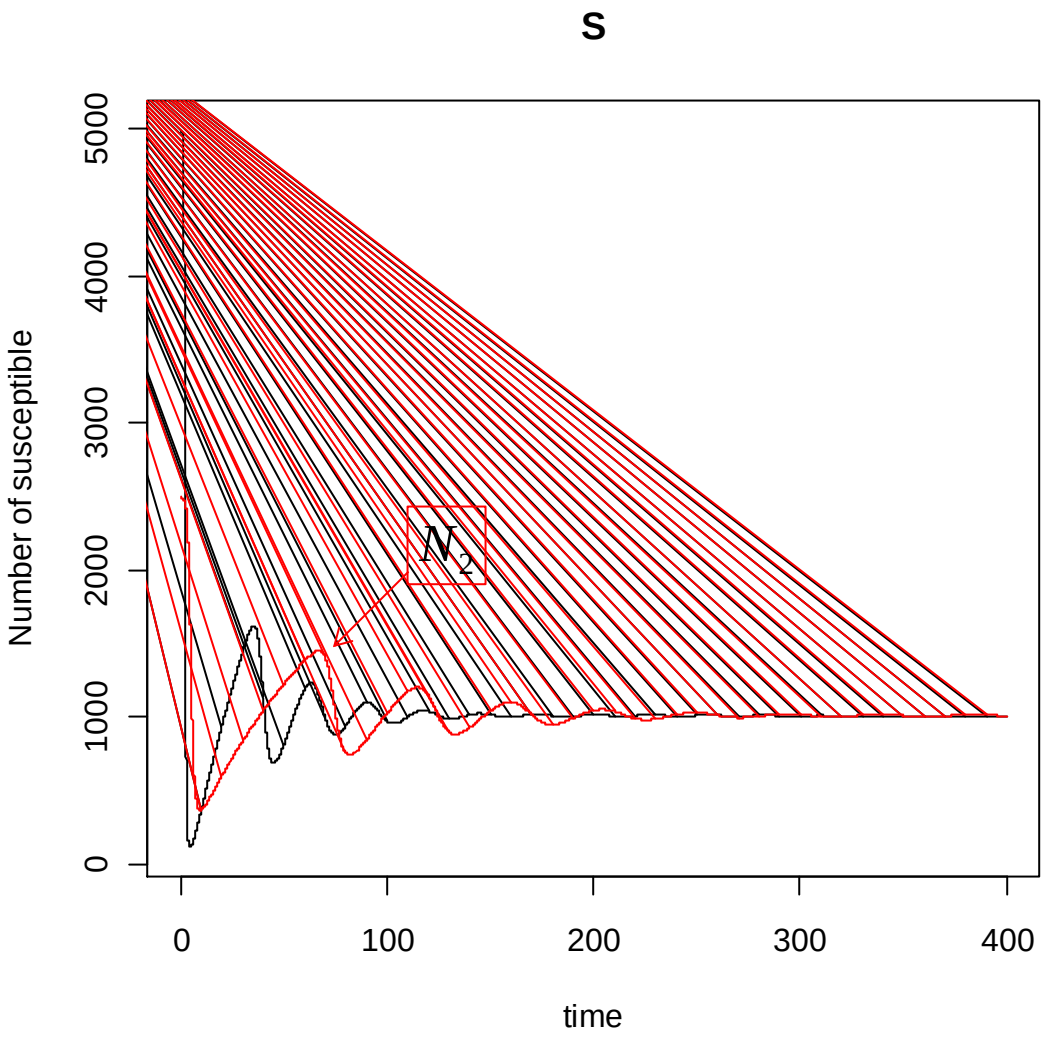
$N = 5000, \beta = 0.001, \nu = 1, L = 75$

$N = 2500, \beta = 0.001, \nu = 1, L = 75$

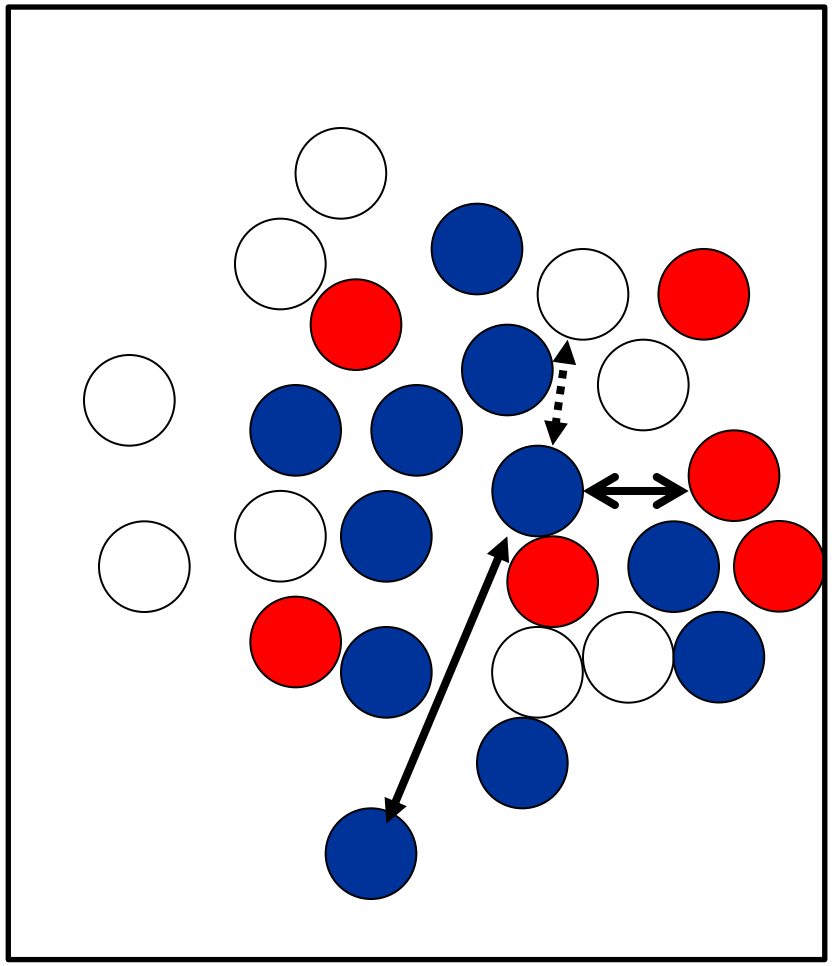
$N_2 < N_1$

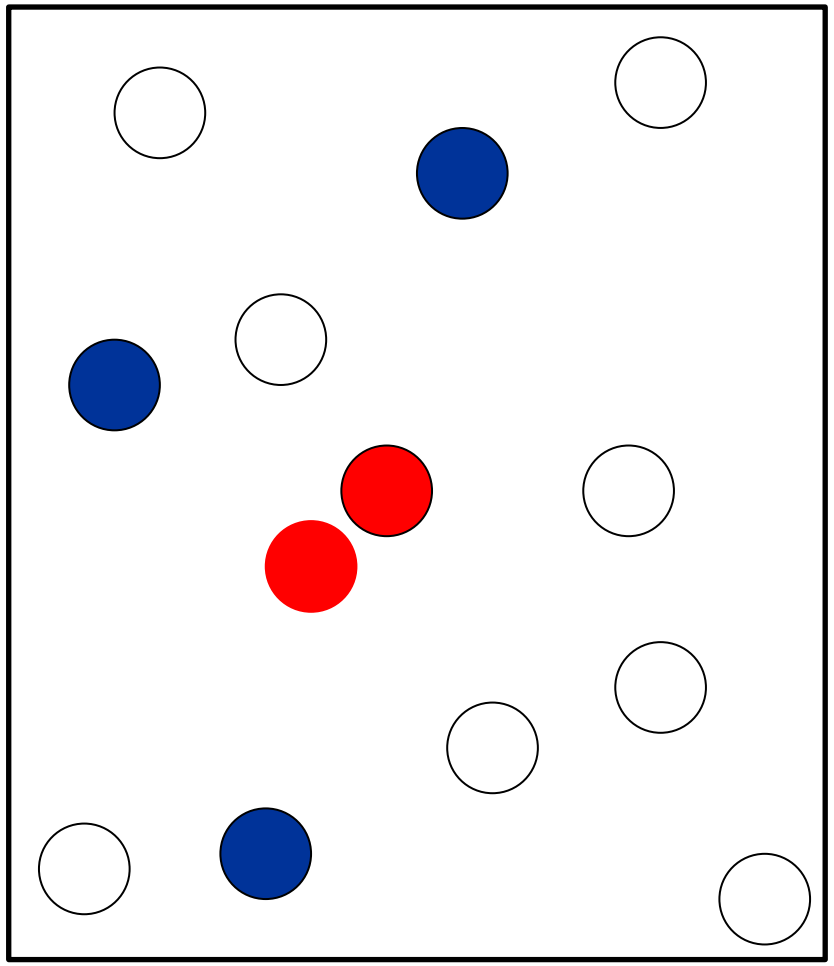
Inter epidemic period.

Equilibrium values.



The effect of N



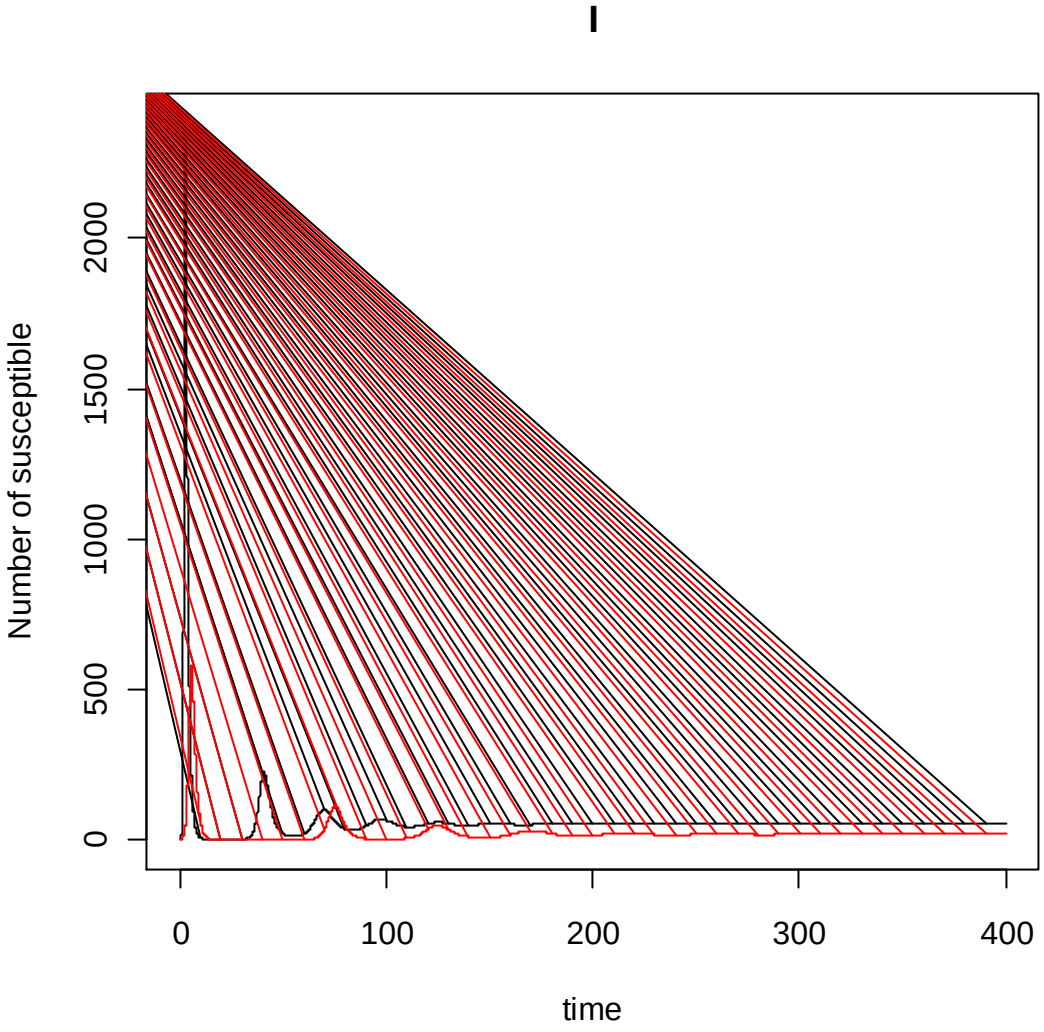


Effect of N

$N_2 < N_1$

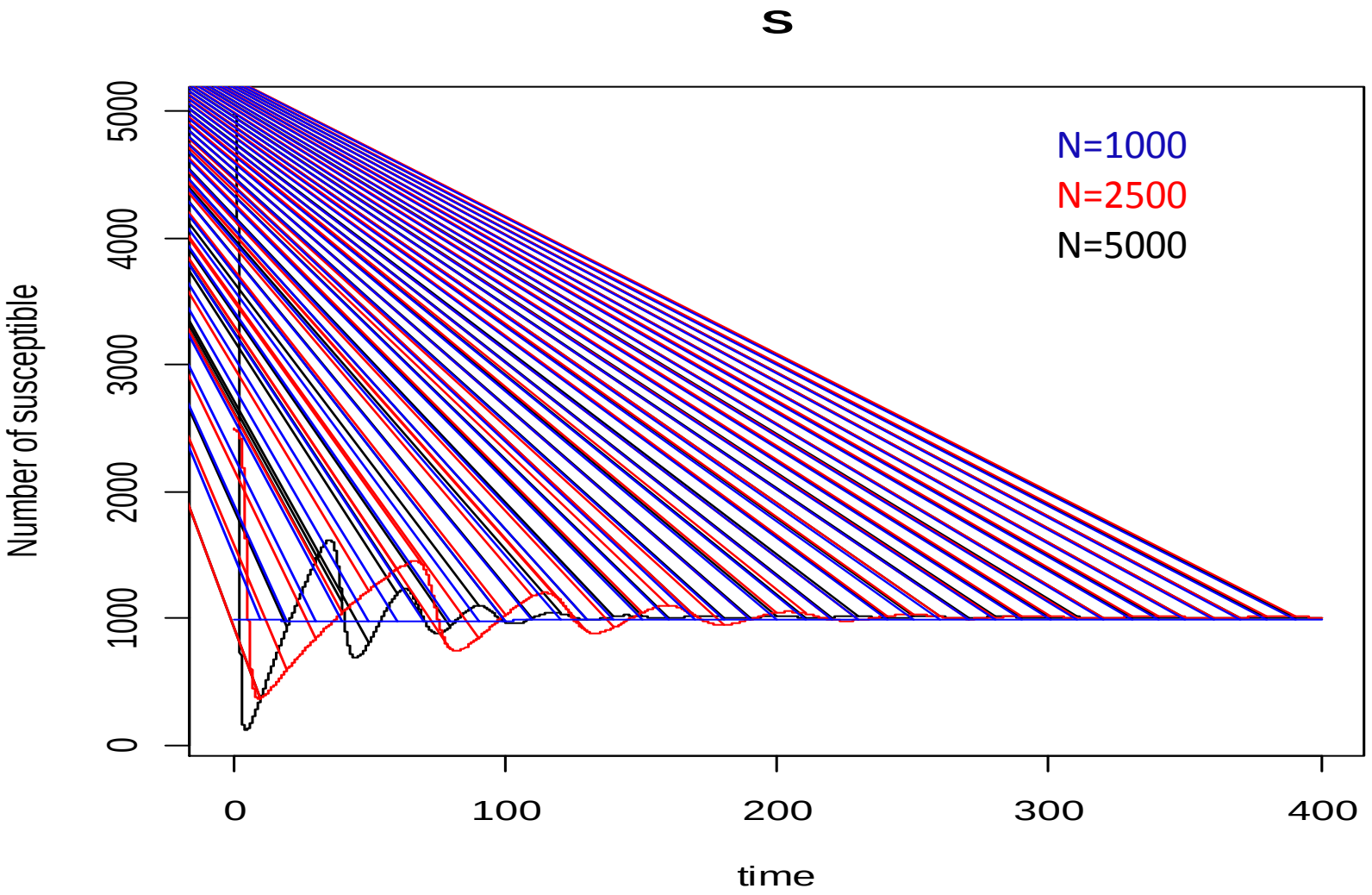
Inter epidemic period is longer.

Susceptible class is built slowly.



Effect of N

- N=1000: the population is too small to start an epidemic.



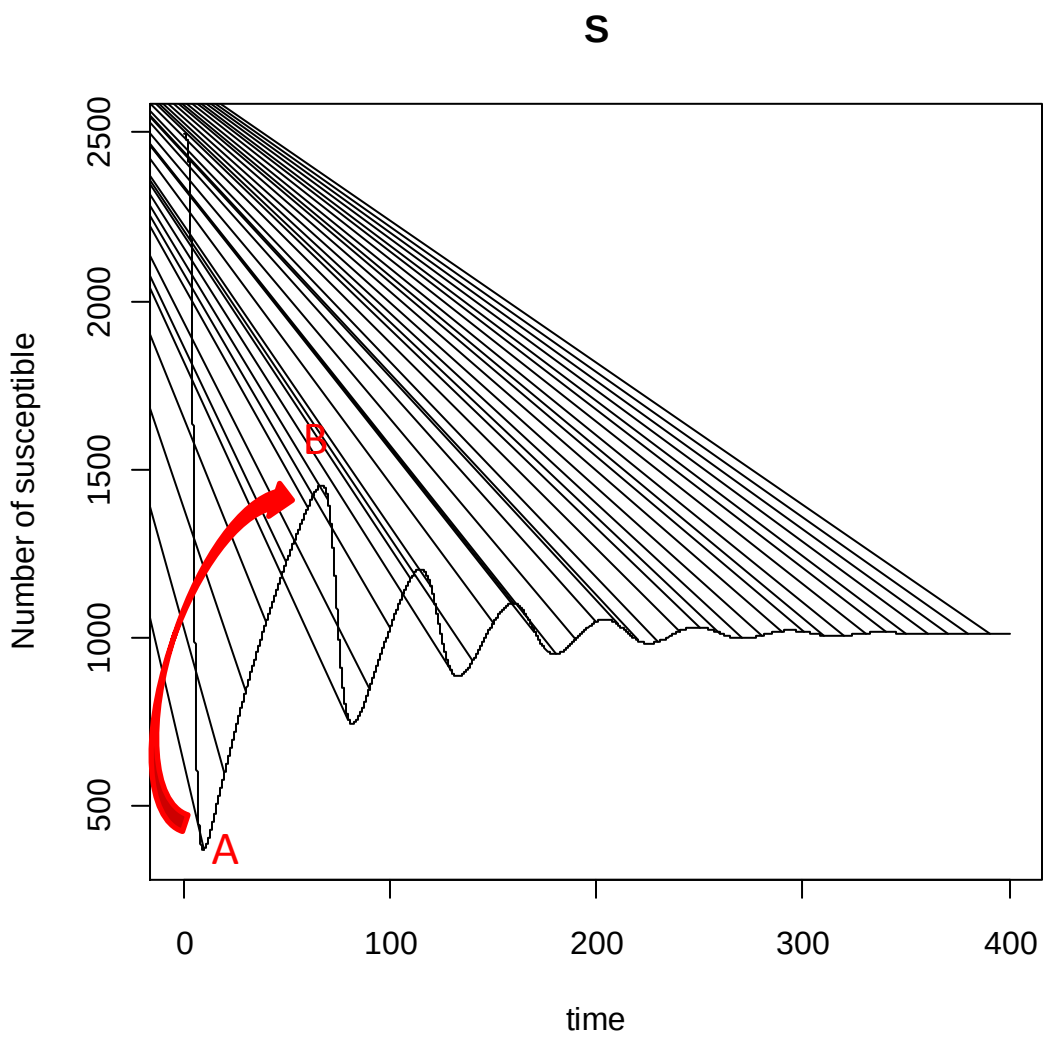
The build up of the susceptible class

Susceptible=the “fuel” for an epidemic.

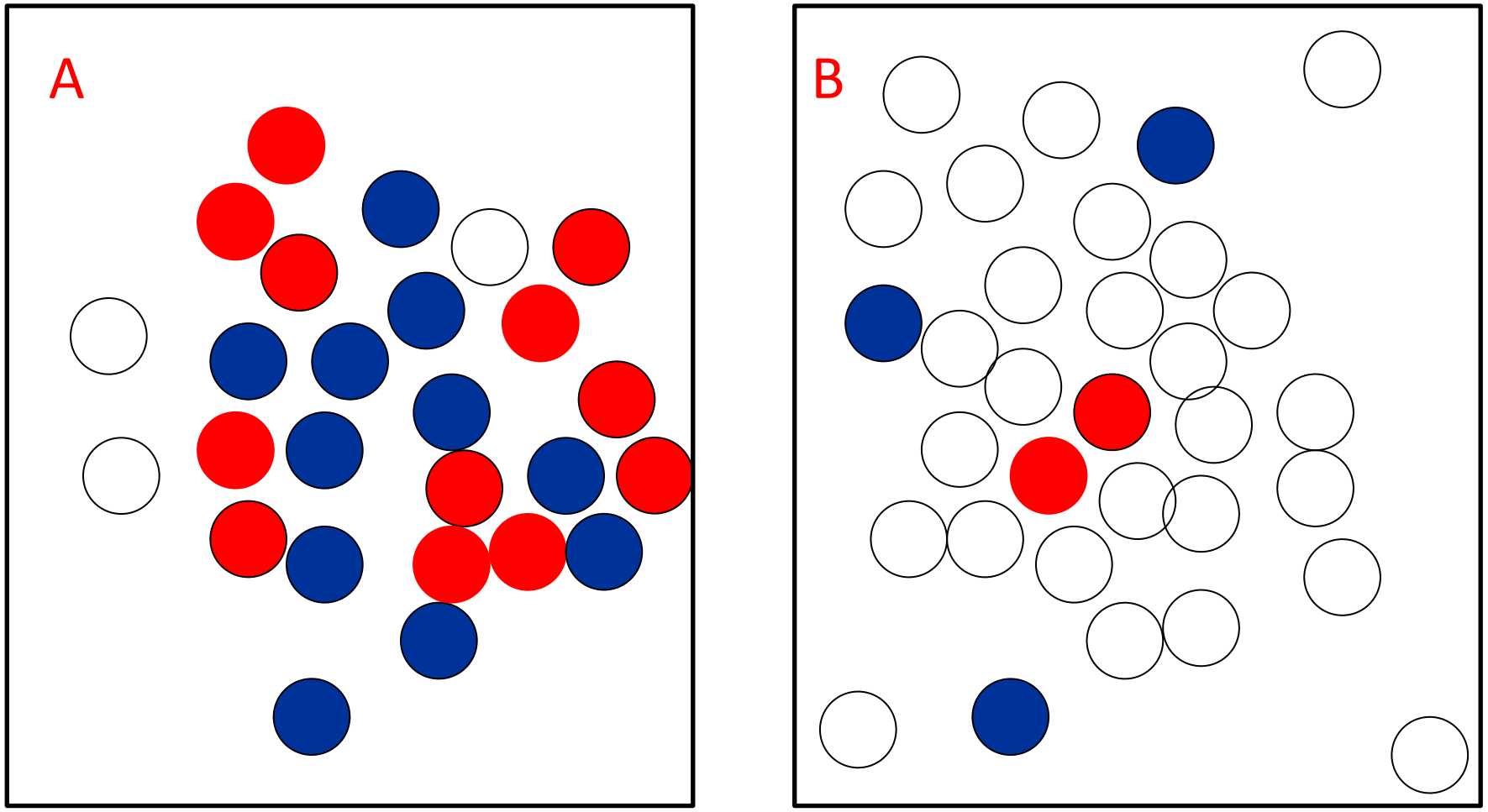
A : Just after an outbreak: low number of susceptible.

B: number of susceptible is large enough for an outbreak.

A to B: the build up of the susceptible class.

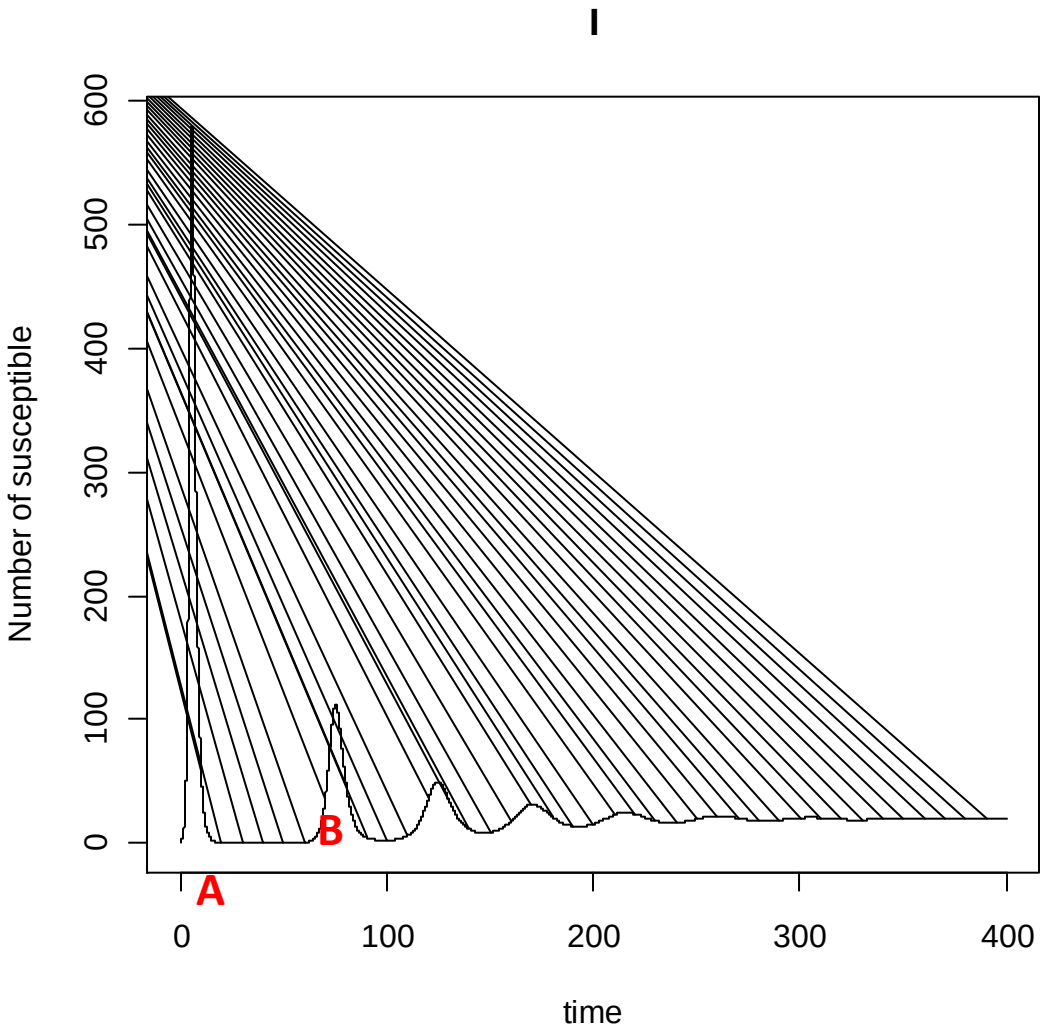


The build up of the susceptible class



Low number of cases

The build up of the susceptible class



Transmission parameters

The basic reproductive number

The fractions of S, I and R

$$s(t)=\frac{S(t)}{N(t)}, i(t)=\frac{i(t)}{N(t)}, r(t)=\frac{R(t)}{N(t)}$$

$$\frac{ds(t)}{dt}=\mu-\tilde{\beta}is-\mu s$$
$$\frac{di(t)}{dt}=\beta is-(\nu+\mu)i$$
$$\frac{dr(t)}{dt}=\nu I-\mu r$$

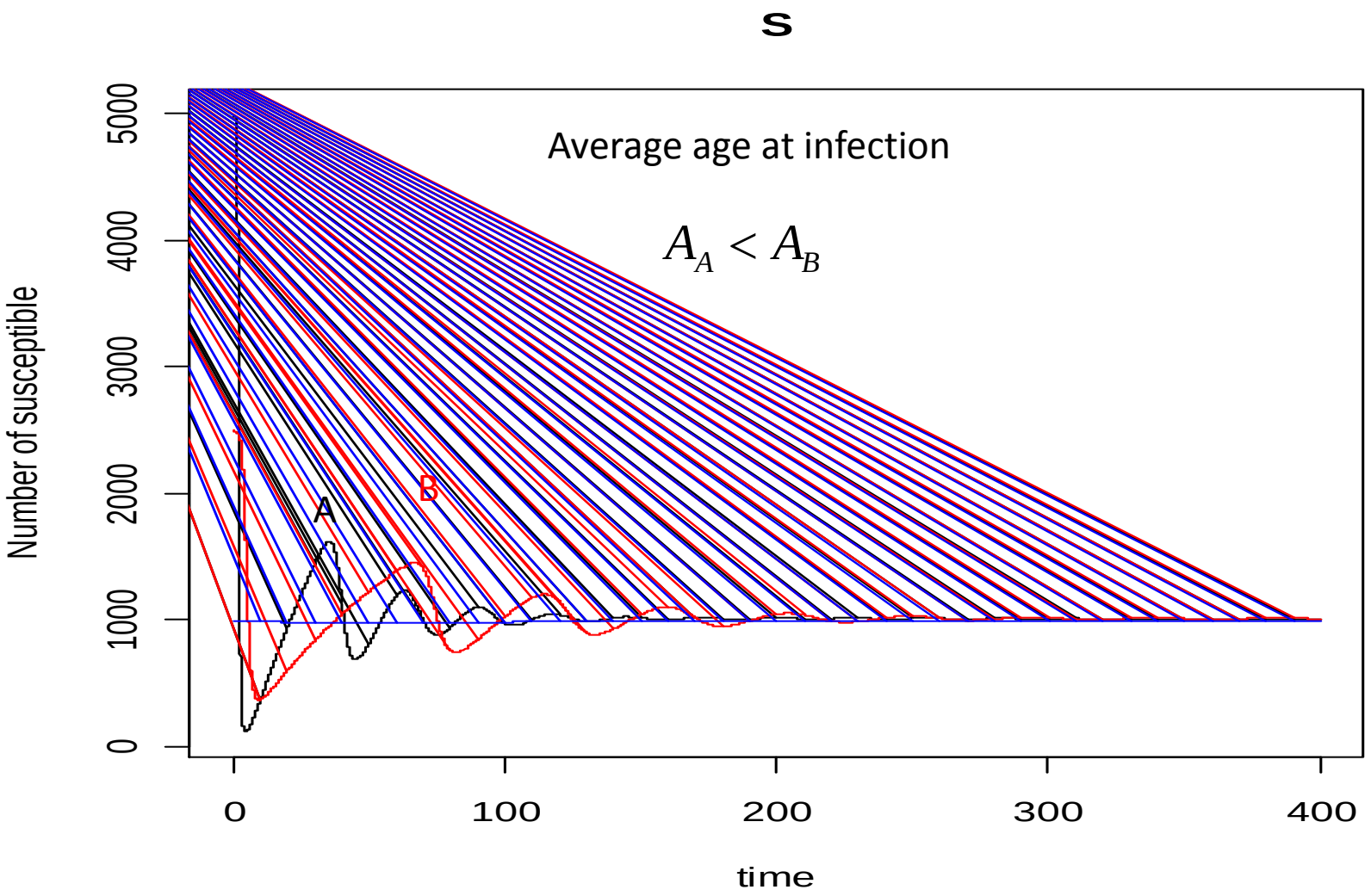
Equilibrium

$$\frac{di(t)}{dt}=0\Rightarrow s(\infty)=\frac{\nu+\mu}{\tilde{\beta}}=\frac{1}{R_0}$$

Condition for transmission

$$\frac{di(t)}{dt}>0\Rightarrow 0>\frac{1}{R_0}\Rightarrow R_0>1$$

The average age at infection

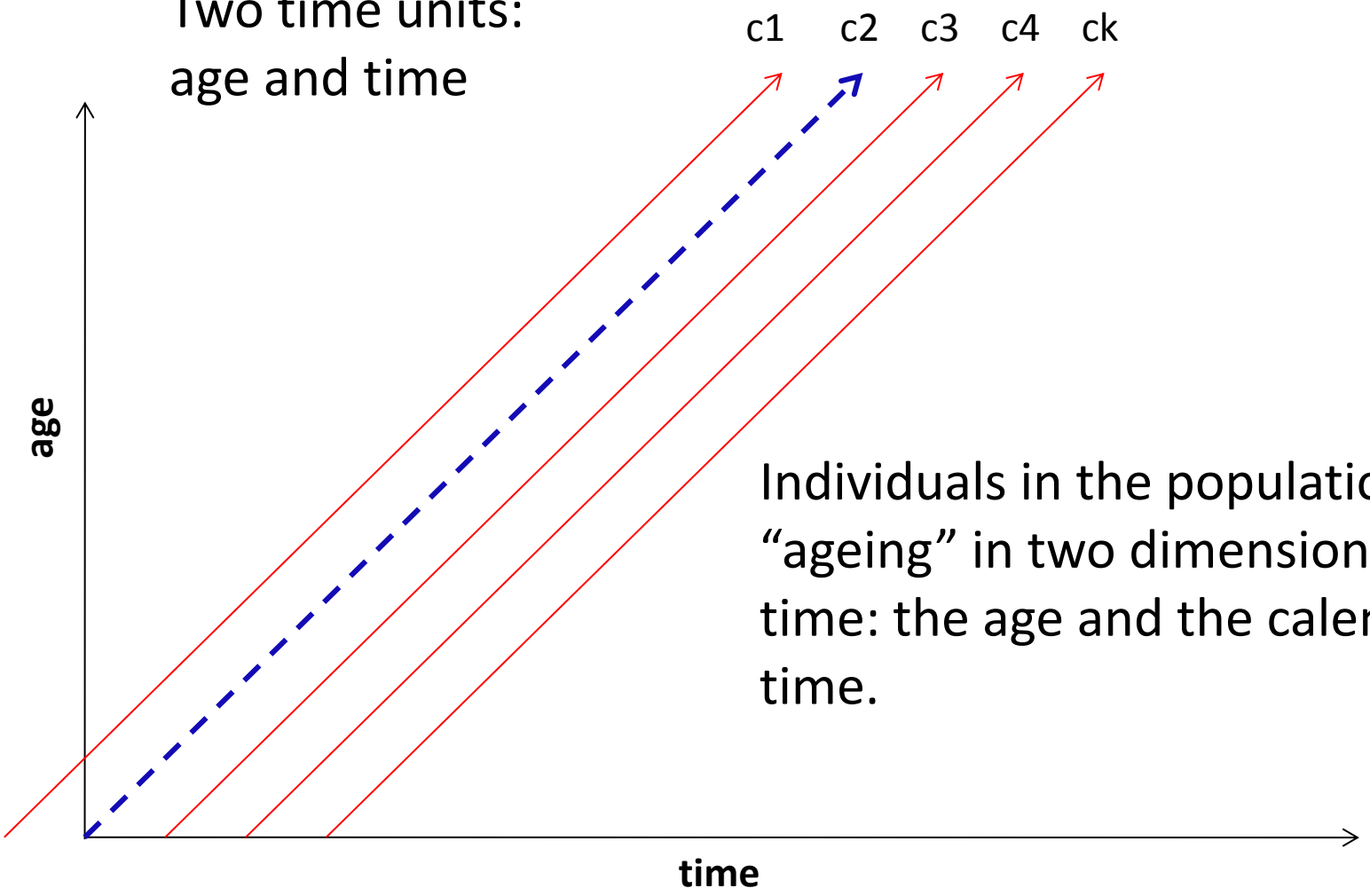


The SIR model in time homogeneity setting

R program: ModelingIDinR1_V1_Stat&Dynam_Sep2019.R

Transmission over age and time

Two time units:
age and time



Individuals in the population "ageing" in two dimensions of time: the age and the calendar time.

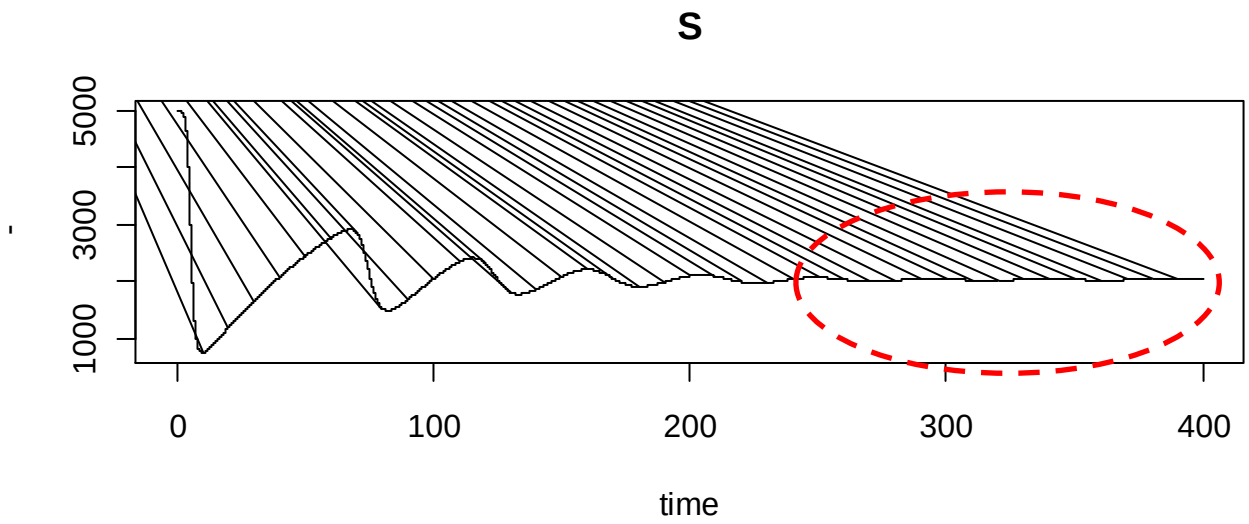
SIR model: transmission over age and time

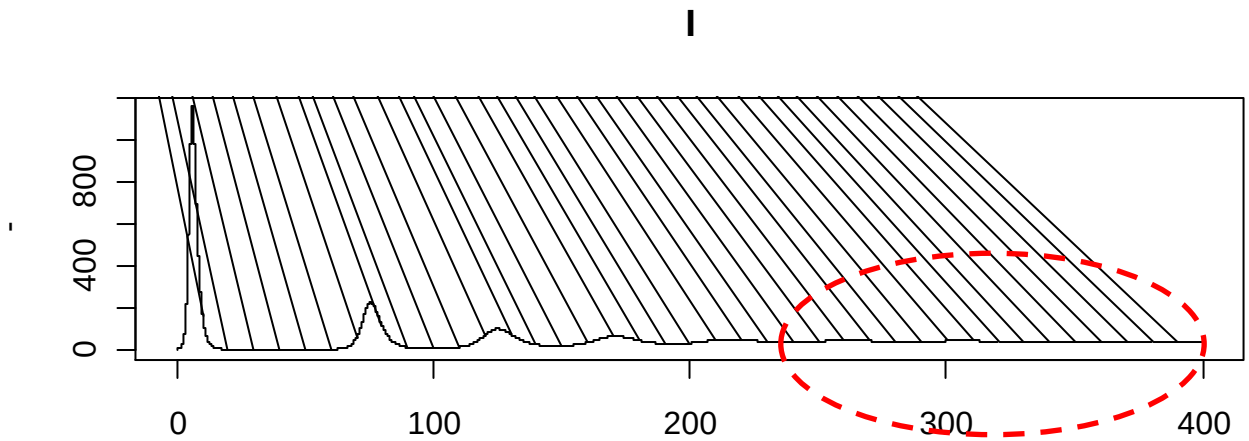
The change in each compartment with respect of age and time.

Age and time dependent force of infection.

$$\frac{dS(a)}{da}+\frac{dS(t)}{dt}=-\lambda(a,t)S(a,t)$$
$$\frac{dI(a)}{da}+\frac{dI(t)}{dt}=\lambda(a,t)S(a,t)-\sigma I(a,t)$$
$$\frac{dR(a)}{da}+\frac{dR(t)}{dt}=\sigma I(a,t)$$

Endemic equilibrium – time homogeneity





$$\frac{dS(t)}{dt} = 0$$

$$\frac{dI(t)}{dt} = 0$$

$$\frac{dR(t)}{dt} = 0$$

SIR model: transmission over age and time

Age and time dependent model (and force of infection).

Time homogeneity

$$\frac{dS(a)}{da}+\frac{dS(t)}{dt}=-\lambda(a,t)S(a,t) \qquad \frac{dS(t)}{dt}=0$$

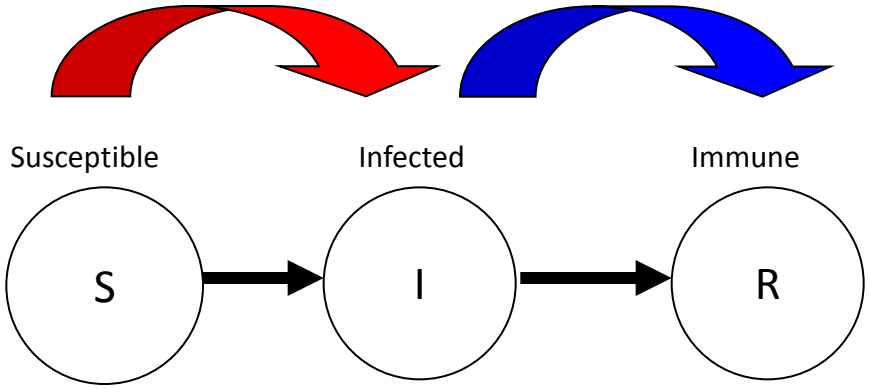
$$\frac{dI(a)}{da}+\frac{dI(t)}{dt}=\lambda(a,t)S(a,t)-\sigma I(a,t) \qquad \frac{dI(t)}{dt}=0$$

$$\frac{dR(a)}{da}+\frac{dR(t)}{dt}=\sigma I(a,t) \qquad \frac{dR(t)}{dt}=0$$

$$\lambda(a,t)\Rightarrow\lambda(a)$$

Transmission (the priori) Model: SIR model for closed population

Time homogeneity: all parameters are constant with respect to time.



The SIR model

$$\frac{dS(a)}{da} = -\lambda S(a)$$

$$\frac{dI(a)}{da} = \lambda S(a) - \sigma I(a)$$

$$\frac{dR(a)}{da} = \sigma I(a)$$

The Static model and serology

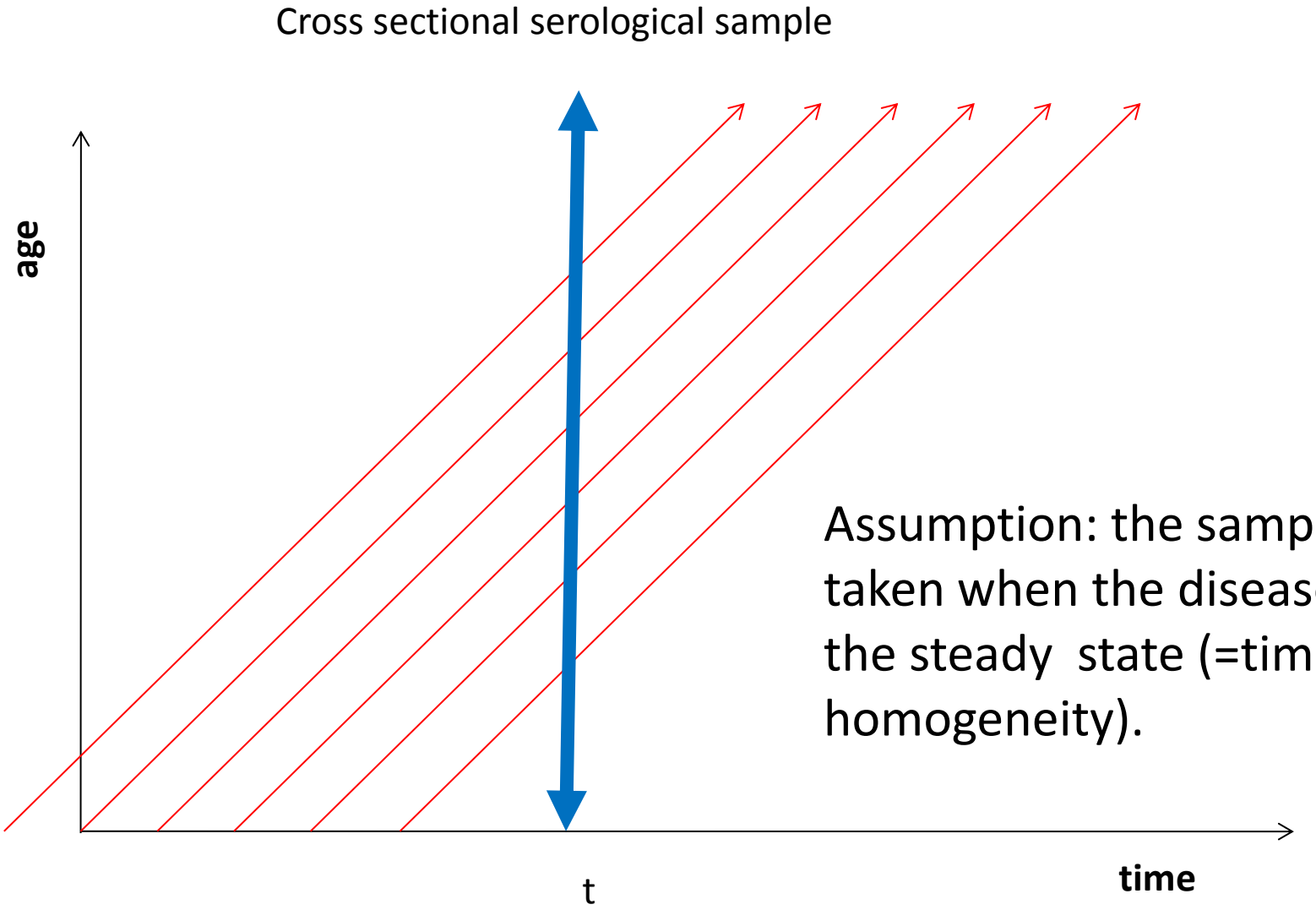
$$\frac{dS(a)}{da} = -\lambda S(a)$$
$$\frac{dI(a)}{da} = \lambda S(a) - \sigma I(a)$$
$$\frac{dR(a)}{da} = \sigma I(a)$$

The time scale of primary interest is age.

How can we estimate the unknown parameters ?

Which type of data we need ?

Cross-sectional sample

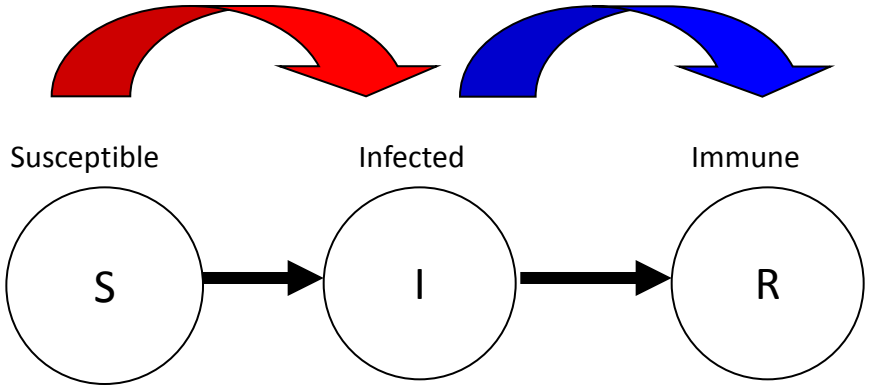


Assumption: the sample was taken when the diseases is in the steady state (=time homogeneity).

Models for closed population and SIR model in time homogeneity setting

The static model

The SIR model for closed population



The SIR model

$$\frac{dS(a)}{da} = -\lambda S(a)$$

$$\frac{dI(a)}{da} = \lambda S(a) - \sigma I(a)$$

$$\frac{dR(a)}{da} = \sigma I(a)$$

SIR model (time homogeneity)

$$\frac{dS(a)}{da} = -\lambda S(a)$$

$$\frac{dI(a)}{da} = \lambda S(a) - \sigma I(a)$$

$$\frac{dR(a)}{da} = \sigma I(a)$$

The force of infection: the rate in which individuals are infected

The recovery rate: the rate in which individuals recovered and move to the immune class.
Assumption: life long immunity.

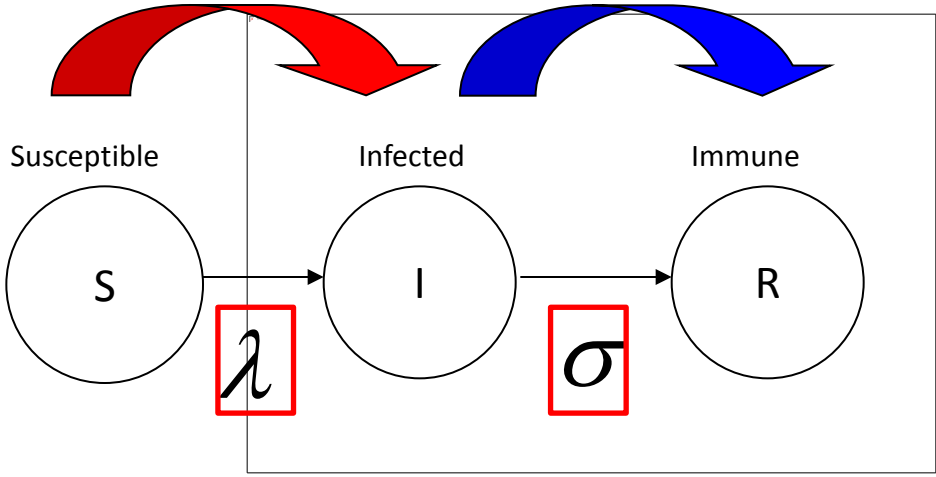
A simple Transmission Model
SIR (time homogeneity)

The change in the susceptible class:

Individuals are leave in rate λ

The change in the infected class:

Individuals are entered in rate λ and leave in rate σ



The SIR model

Example 1: A priori model
SIR model (time homogeneity)

$$\frac{dS(a)}{da} = -\lambda S(a)$$
$$\frac{dI(a)}{da} = \lambda S(a) - \sigma I(a)$$
$$\frac{dR(a)}{da} = \sigma I(a)$$

The force of infection = 0.2.
On average: 5 years in the susceptible class.

$$A = \frac{1}{\lambda}$$

The average age at infection.

The recovery rate: 1/(10 days).

$$D = 10 \Rightarrow \sigma = \frac{1}{D}$$

The unit of the parameters are in years

See slide 141.

Transmission models in R

- We need to integrate the system of the ordinary differential equation.

$$\frac{dS(a)}{da} = -\lambda S(a)$$
$$\frac{dI(a)}{da} = \lambda S(a) - \sigma I(a)$$
$$\frac{dR(a)}{da} = \sigma I(a)$$

- deSolve package in R.
- Numerical integration using of ODE system.

Transmission models in R

SIR model

$$\frac{dS(a)}{da} = -\lambda S(a)$$
$$\frac{dI(a)}{da} = \lambda S(a) - \sigma I(a)$$
$$\frac{dR(a)}{da} = \sigma I(a)$$

Specification in R

- Model parameters.
- State variables (the value of the parameters at age (time) zero.
- Time range (=age range) for integration.

Transmission models in R

R program

Model parameters → λ, σ

State variables → $S(0), I(0), R(0)$

Time range for integration → Integrate from age zero to age 50

Specification of the model →

$$\frac{dS(a)}{da} = -\lambda S(a)$$

$$\frac{dI(a)}{da} = \lambda S(a) - \sigma I(a)$$

$$\frac{dR(a)}{da} = \sigma I(a)$$

Specification of the model parameters in R

```
> parameters <- c(lambda = 0.2, v=36.5)
> parameters
lambda      v
   0.2   36.5
```

The force of infection = 0.2 years^{-1}.

$$5^{-1} = 0.2 = \lambda$$

Recovery rate 10 days.

$$\left(\frac{10}{365}\right)^{-1} = 36.5 = \sigma$$

The unit of the parameters are in years^{-1}

The state variables (initial values at age 0)

- Let us assume that the cohort size is 5000.
- At age=0:

$$S(0) = 4999$$

$$I(0) = 1$$

$$R(0) = 0$$

- Specification in R:

```
> state <- c(X=4999,Y=1,Z=0)
> state
   X   Y   Z
4999   1   0
```

Specification of the model in R

$$\frac{dS(a)}{da} = -\lambda S(a)$$
$$\frac{dI(a)}{da} = \lambda S(a) - \sigma I(a)$$
$$\frac{dR(a)}{da} = \sigma I(a)$$

```
SIR<-
function(t,state,parameters)
{
with(as.list(c(state,
parameters)),
{
dX <- -lambda*X
dY <- lambda*X - v*Y
dZ <- v*Y
list(c(dX, dY, dZ))
})
}
```

We ask from the function to return the values of S, I and R

Specification of the time units for the integration

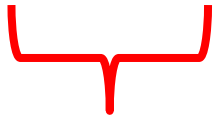
$$\frac{dS(a)}{da} = -\lambda S(a)$$
$$\frac{dI(a)}{da} = \lambda S(a) - \sigma I(a)$$
$$\frac{dR(a)}{da} = \sigma I(a)$$

- The solution of the model: numerical integration.
- Time units: age.
- Integration from age 0 to age 40 by unit of 0.01 years

```
> times<-seq(0,40,by=0.01)
> times
   [1]  0.00  0.01  0.02  0.03  0.04  0.05  0.06  0.07  0.08  0.09  0.10  0.11
  [13]  0.12  0.13  0.14  0.15  0.16  0.17  0.18  0.19  0.20  0.21  0.22  0.23
  [25]  0.24  0.25  0.26  0.27  0.28  0.29  0.30  0.31  0.32  0.33  0.34  0.35
  [37]  0.36  0.37
```

Running the model

```
require(deSolve)
out<-as.data.frame(ode(y=state,times=times,func=SIR,parms=parameters))
```

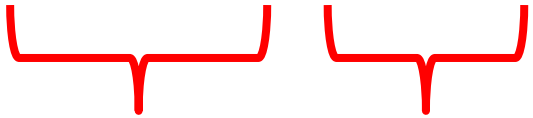


The state variables: the values at age 0.

The model parameters: force of infection (0.2) and recovery rate (10 dats)

Running the model

```
require(deSolve)
out<-as.data.frame(ode(y=state,times=times,func=SIR,parms=parameters))
```



Time range for integration.

The model

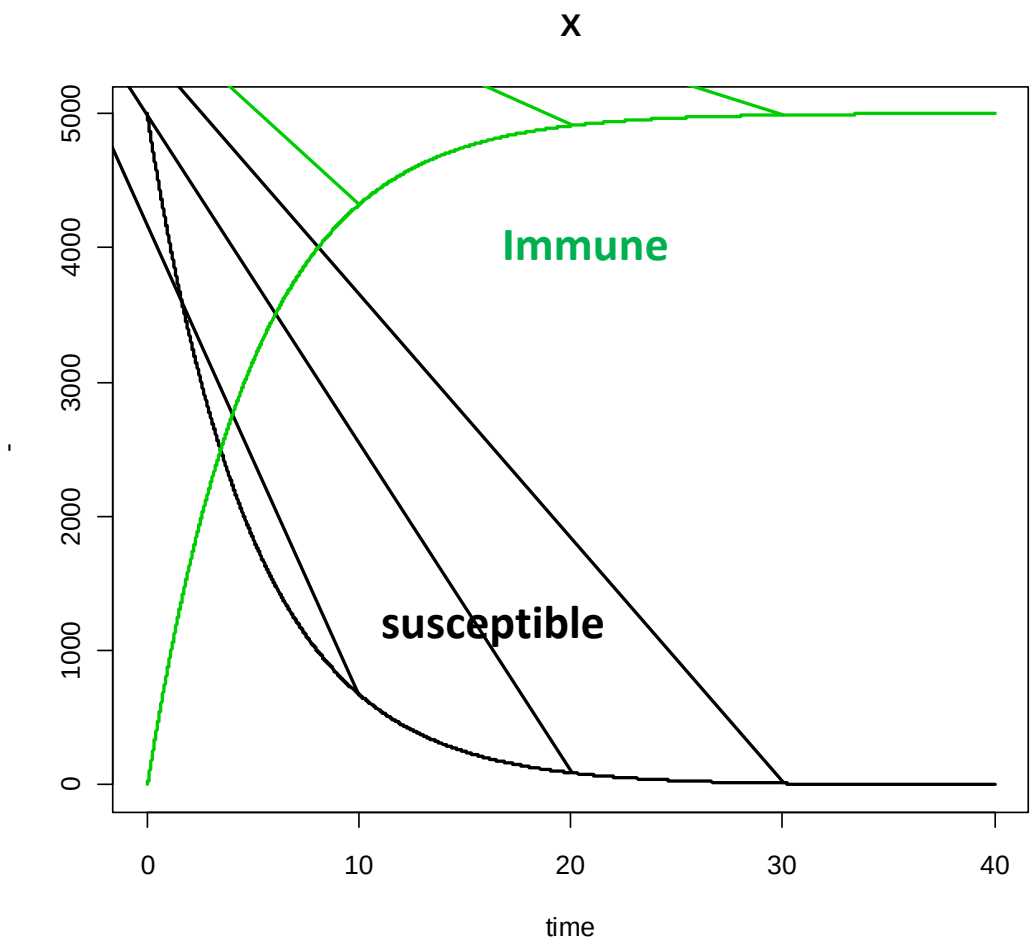
Numerical integration using ordinary differential equation

Solution

```
> require(deSolve)
> out <-
as.data.frame(ode(y=state,times=times,func=SIR,parms=
parameters))
> head(out)
  time         X          Y          Z
1 0.00 4999.000   1.000000   0.000000
2 0.01 4989.012   9.061818   1.926190
3 0.02 4979.044  14.641580   6.314481
4 0.03 4969.096  18.498345  12.405853
5 0.04 4959.168  21.159066  19.673391
6 0.05 4949.259  22.989501  27.751380
```

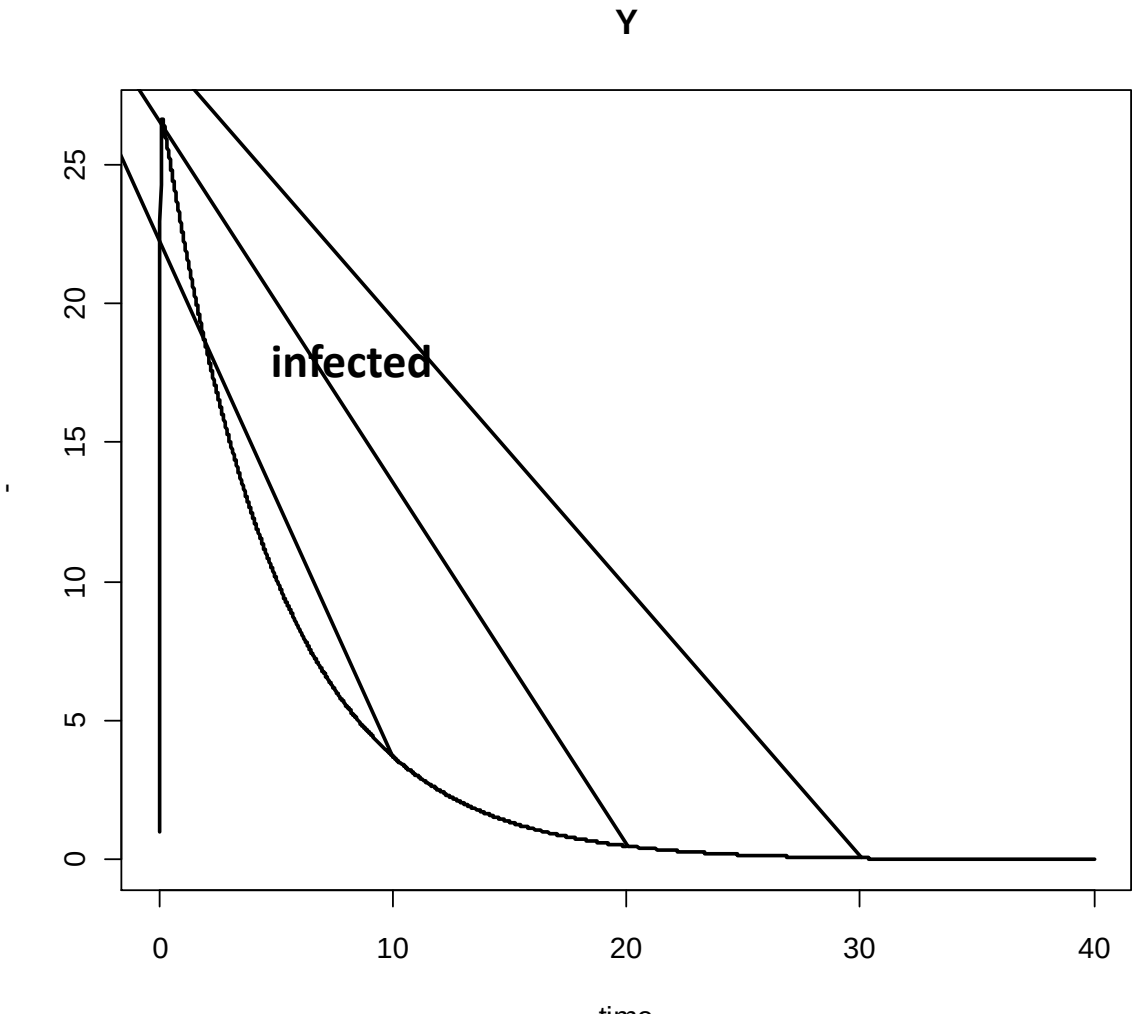
Graphical output

```
> plot (times,out$X ,type="l",main="X", xlab="time", ylab="-",lwd=2)
> lines(times,out$Z,col=3,lwd=2)
```

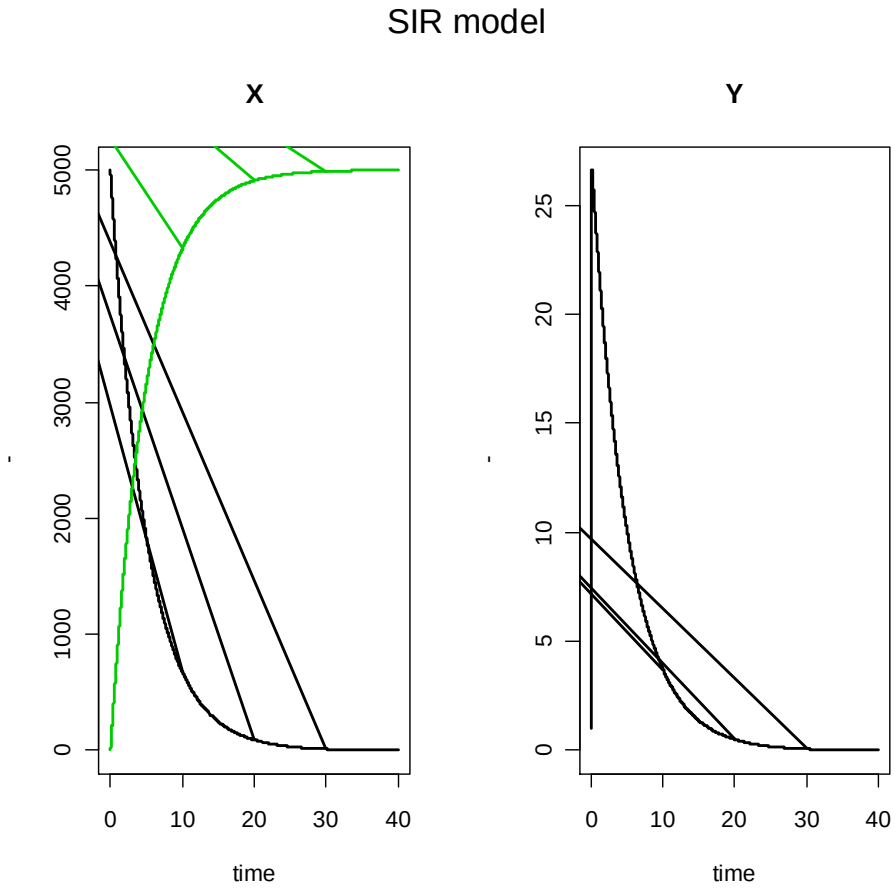


Graphical output

```
> plot (times,out$Y ,type="l",main="Y", xlab="time", ylab="-",lwd=2)
```



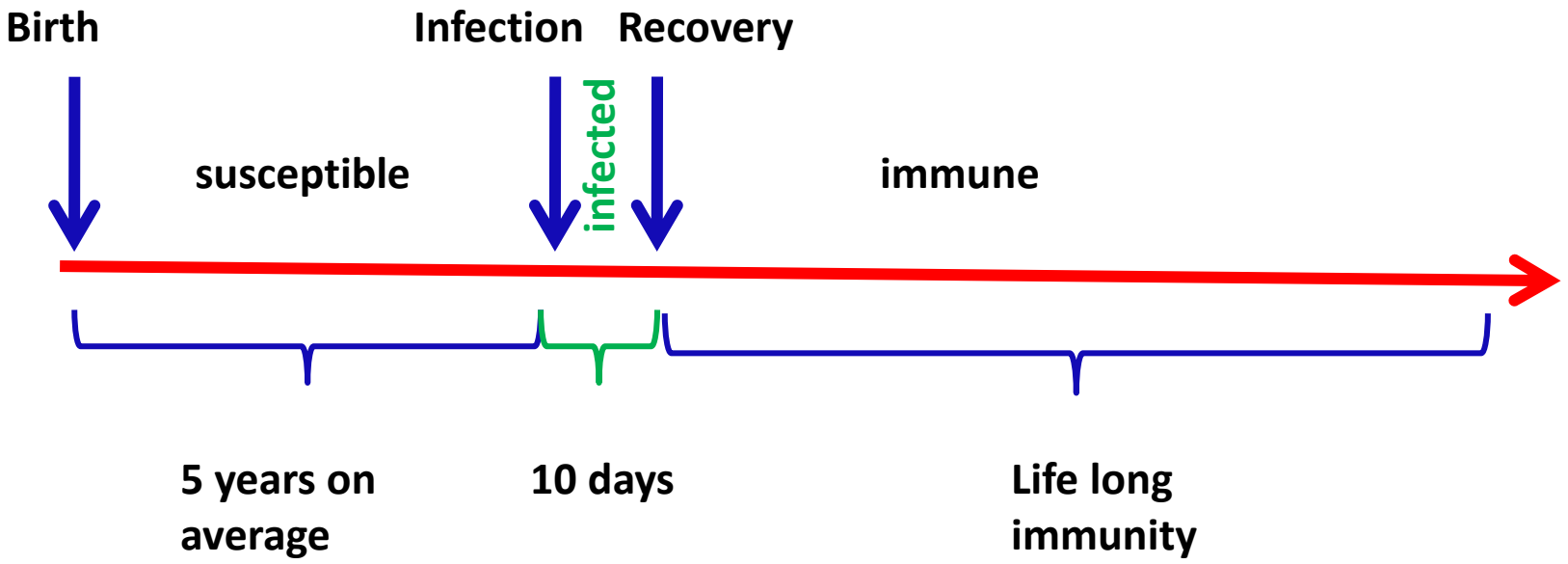
Graphical output



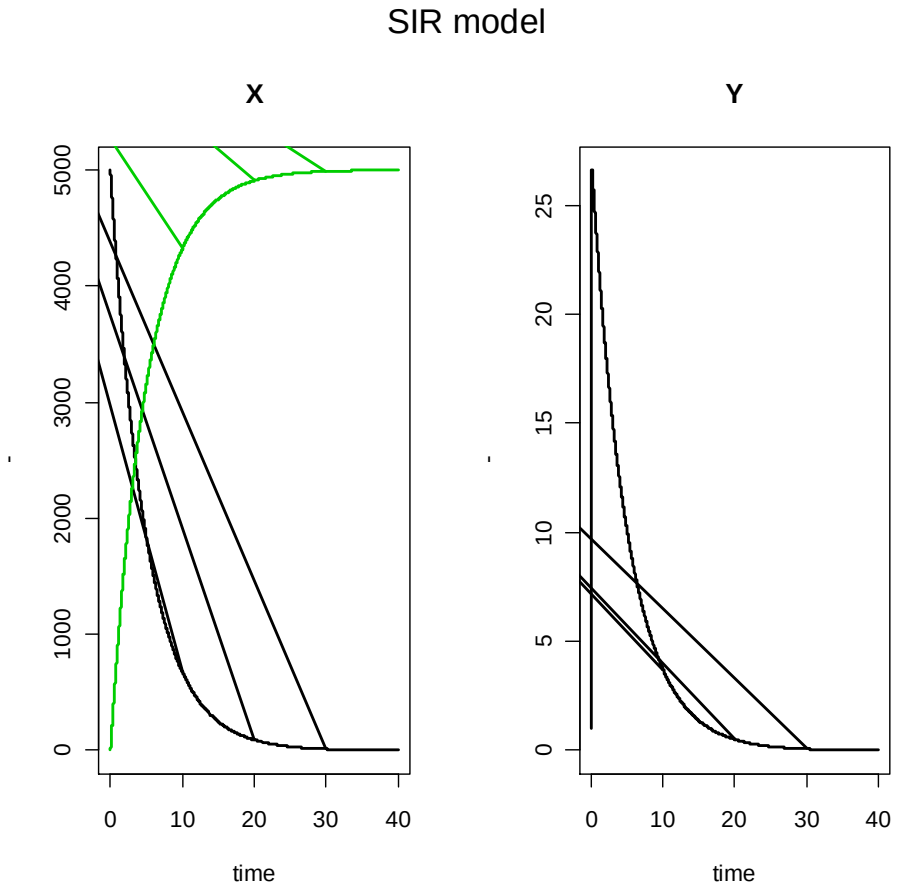
What do we see here ?

Number of infected individuals at each age.

Duration of stay in the different compartments of the models



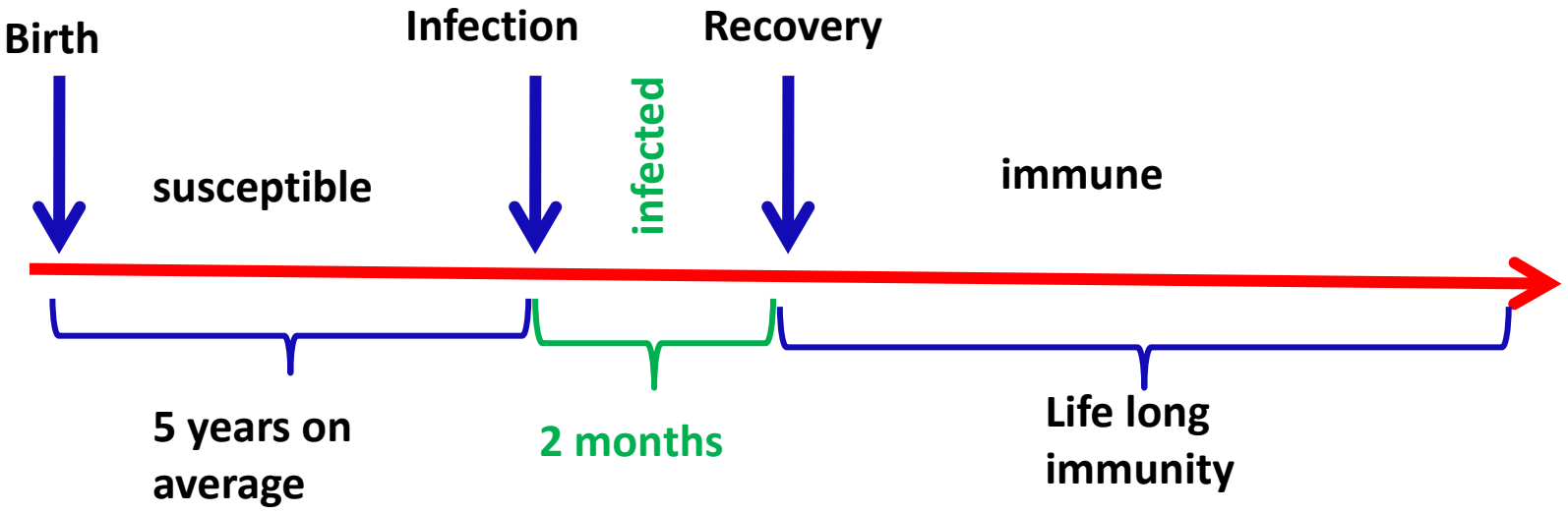
Graphical output



We expect to see only few infected individuals at each age (compared to the number of susceptible and immune).

Duration of stay in the different compartments of the models

Let us assume that the recovery rate is 2 months (i.e. individuals stay in the infected class 2 months)
What do we expect to see ?



The model with recovery rate of 2 months

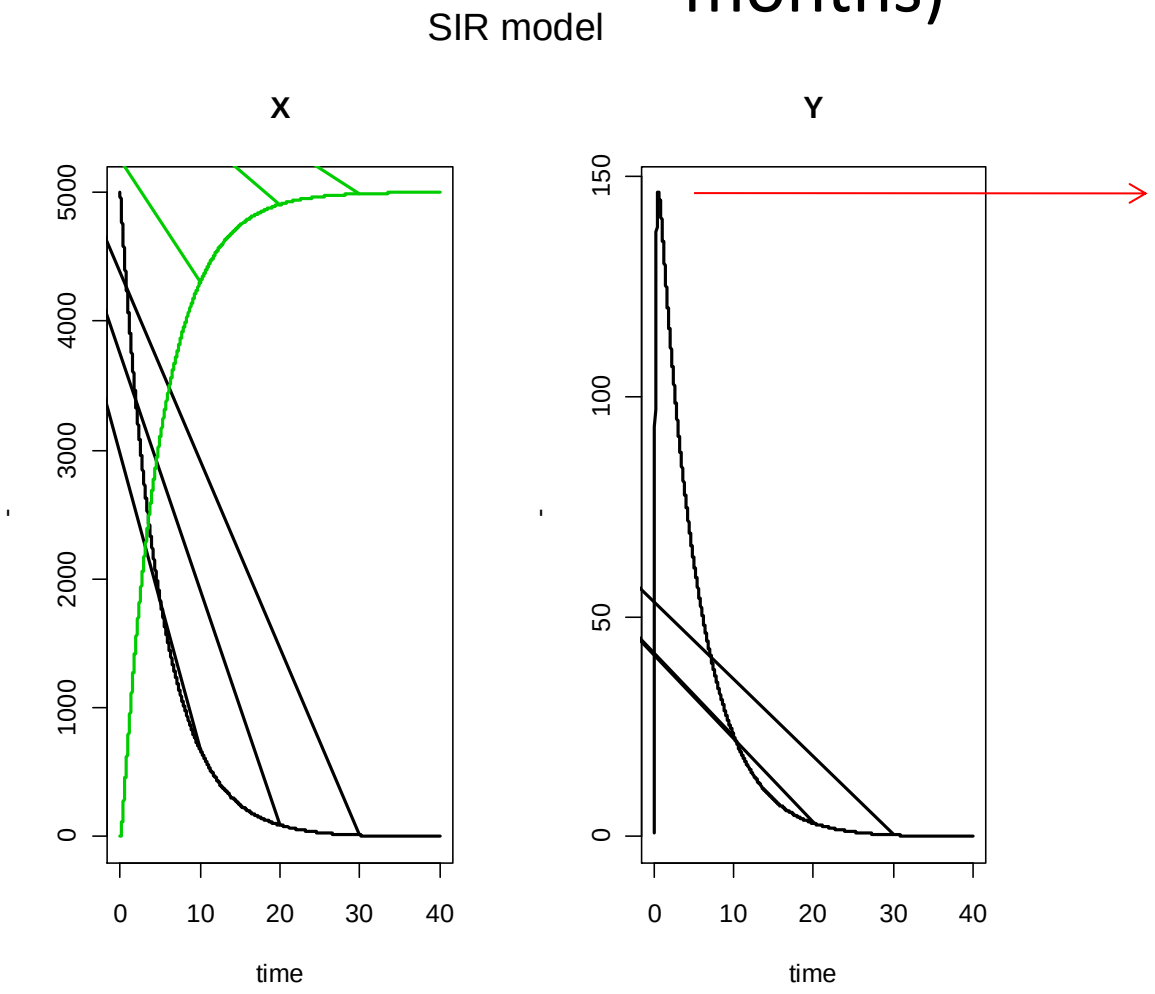
```
1/(60/365)
parameters <- c(lambda = 0.2, v=6.083333)
parameters

state <- c(X=4999,Y=1,Z=0)
state
SIR<-function(t,state,parameters)
{
with(as.list(c(state, parameters)),
{
dX <- -lambda*X
dY <- lambda*X - v*Y
dZ <- v*Y
list(c(dX, dY, dZ))
})
}
times<-seq(0,40,by=0.01)
times
require(deSolve)
out <- as.data.frame(ode(y=state,times=times,func=SIR,parms=parameters))
head(out)
par(mfrow=c(1,2), oma=c(0,0,3,0))
plot (times,out$X ,type="l",main="X", xlab="time", ylab="-",lwd=2)
lines(times,out$Z,col=3,lwd=2)
plot (times,out$Y ,type="l",main="Y", xlab="time", ylab="-",lwd=2)
mtext(outer=TRUE,side=3,"SIR model",cex=1.5)
```

$$\left(\frac{60}{365}\right)^{-1} = 6.08$$

Recover rate of 2 months (60 days)

Graphical output (force of infection of 0.2 and recovery rate of 2 months)

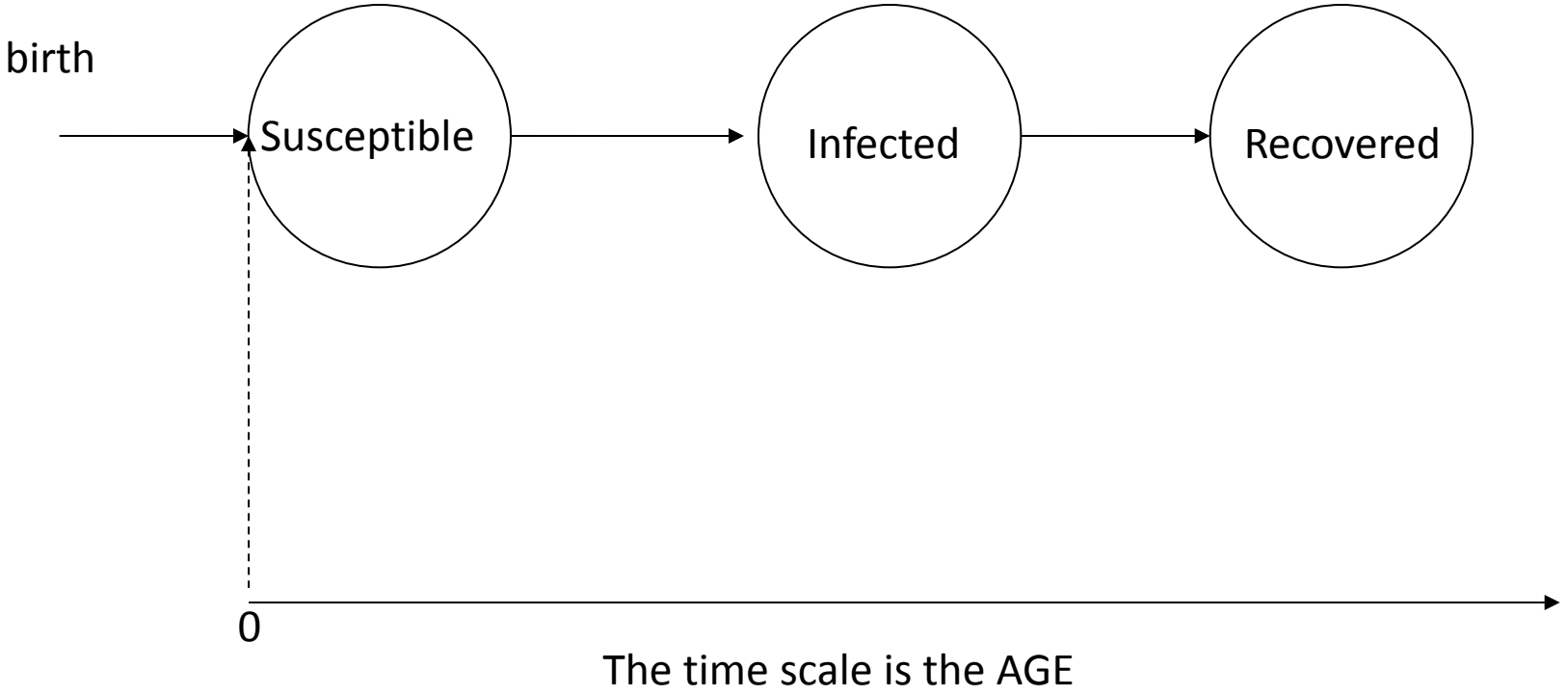


~ 150 infected individuals at the peak (compare with ~25 for recovery rate of 10 days)

Transmission parameters

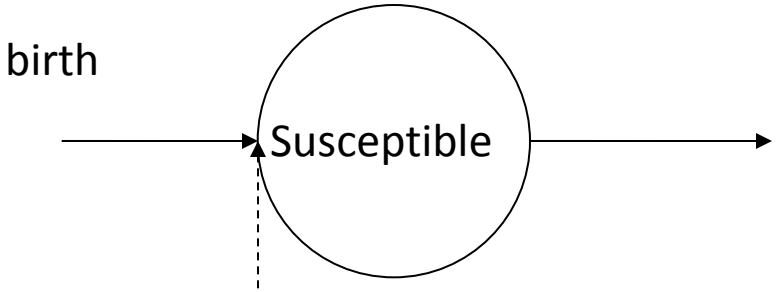
The average age at infection

- On average, how long individuals stay in the susceptible class ?
- Average duration in the susceptible class.



The average age at infection

The change in the susceptible class:

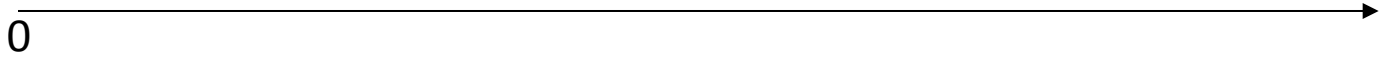


$$\frac{dS(a)}{a} = -\lambda S(a)$$

Average age at infection:

$$A = \frac{1}{\lambda}$$

Duration in the susceptible class.



The time scale is the AGE

Basic reproductive number

$$R_0 \approx \frac{L}{A} = \frac{\text{Life expectancy}}{\text{Average age at infection}}$$

$$L > A \Rightarrow R_0 > 1$$

$$L < A \Rightarrow R_0 < 1$$

- R_0<1: the disease will die out.
- L>A means that , on average, individuals will die before infection.

More about modeling

SIR model with temporary immunity

SIR model with carriers

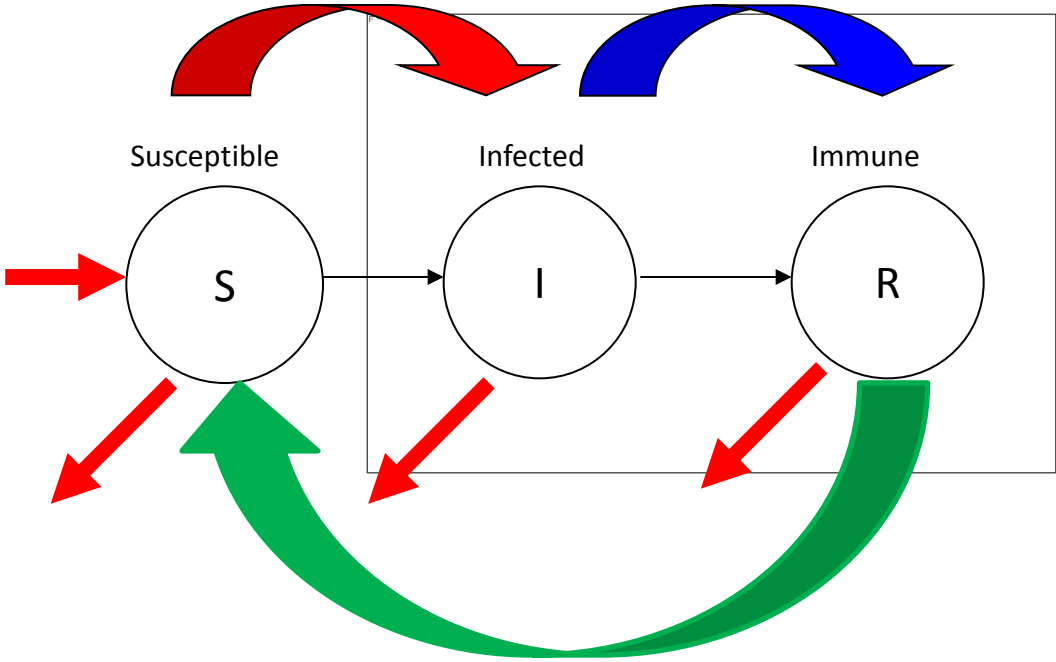
Transmission models for multiple and sub populations.

SIRS model with temporary immunity

$$\frac{dS(t)}{dt} = N\mu - \beta I(t)S(t) - \mu S(t) + \alpha R(t)$$

$$\frac{dI(t)}{dt} = \beta I(t)S(t) - (\sigma + \mu)I(t)$$

$$\frac{dR(t)}{dt} = \sigma I(t) - \mu R(t) - \alpha R(t)$$



$\alpha = 0 \Rightarrow$ SIR with life long immunity

$\alpha > 0 \Rightarrow$ Only temporary immunity after infection and possibility to re infection.

The susceptible class

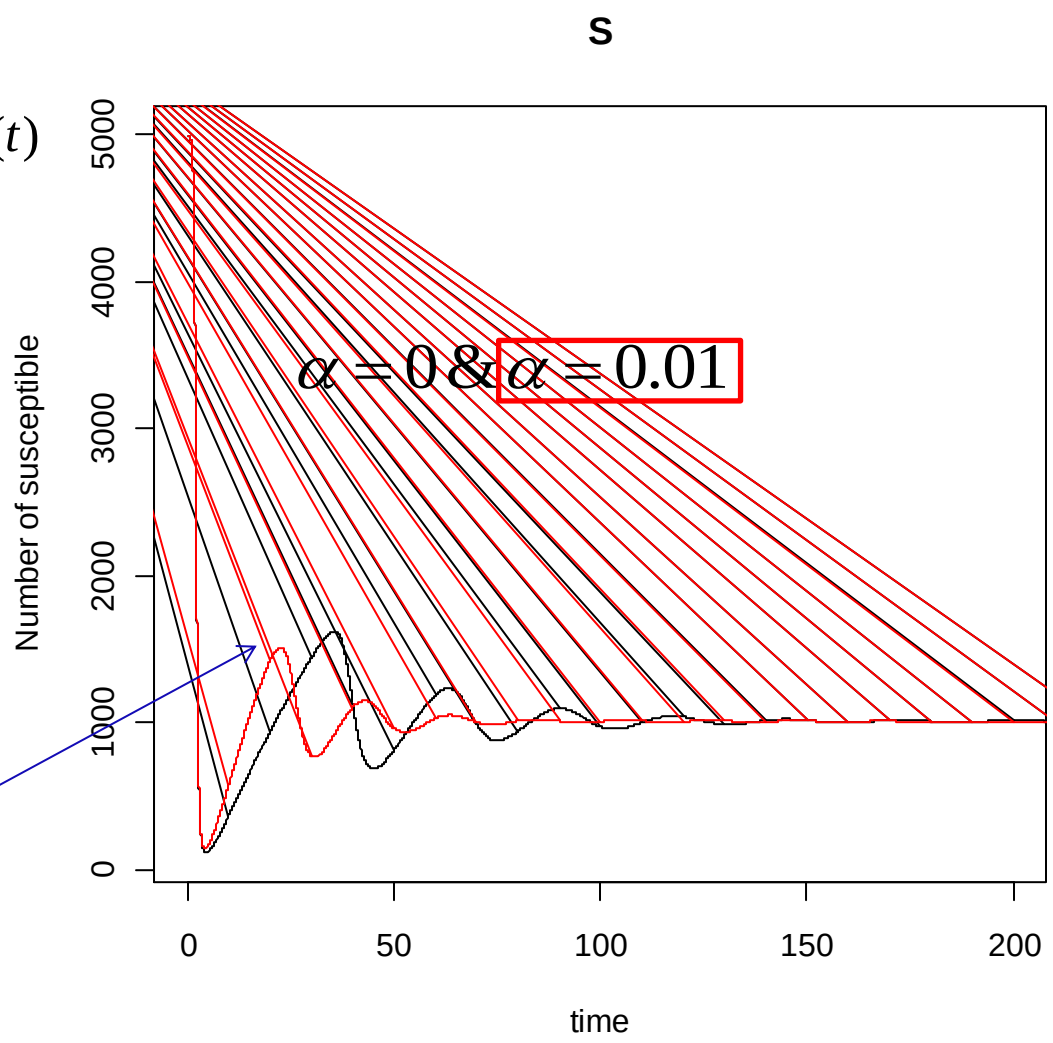
$$\frac{dS(t)}{dt} = N\mu - \beta I(t)S(t) - \mu S(t) + \alpha R(t)$$

$$\frac{dI(t)}{dt} = \beta I(t)S(t) - (\sigma + \mu)I(t)$$

$$\frac{dR(t)}{dt} = \sigma I(t) - \mu R(t) - \alpha R(t)$$

The susceptible class builds up faster.

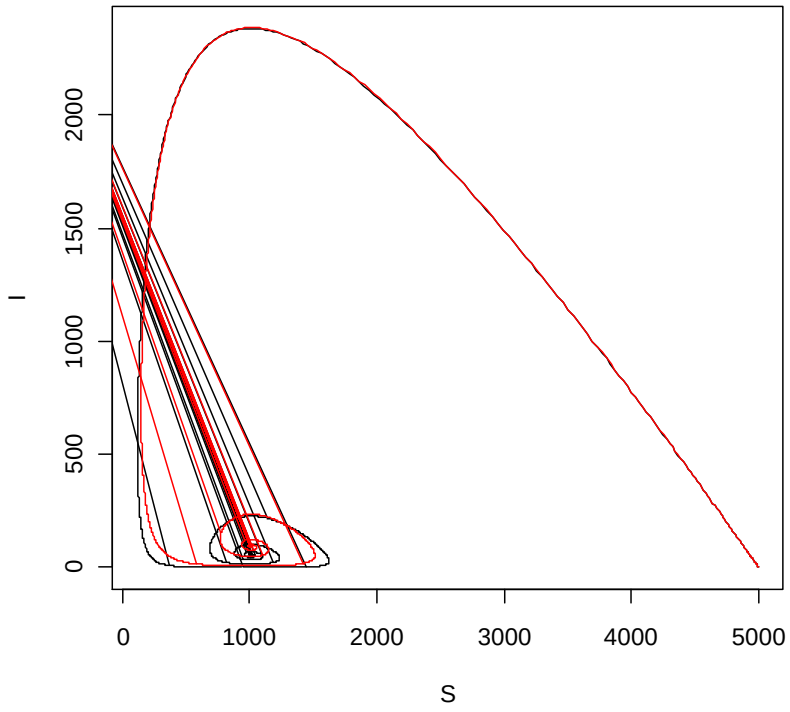
Number of susceptible at the first peak.



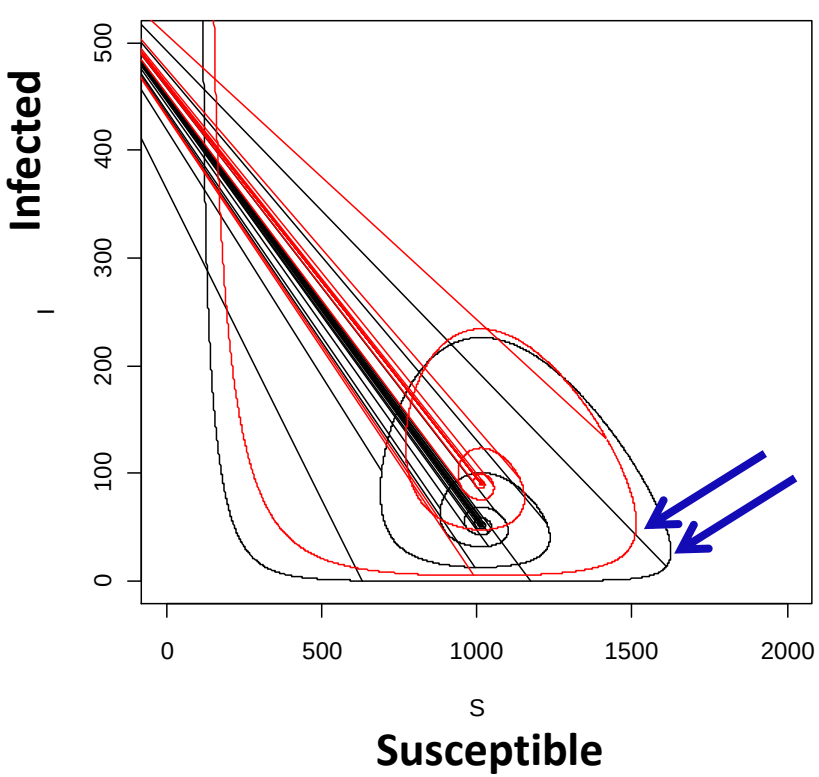
R program: ModelingIDinR5_V1_SIRS_Sep2019.R

Number of susceptible in the first peak

S vs I



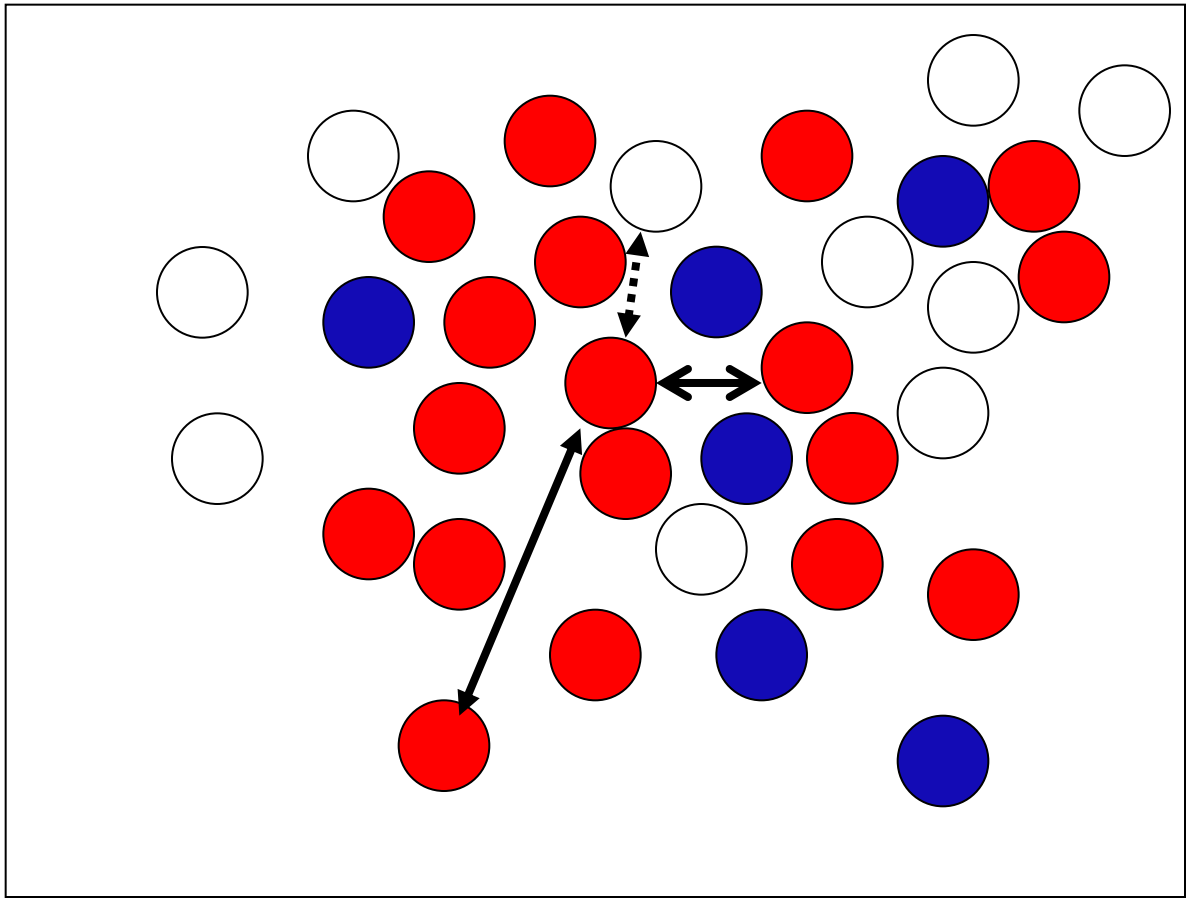
S vs I (zoom in)



Multiple populations

R program: ModelingIDinR1_V1_MultiPop_Sep2019.R

The Mass-Action Principle and the force of infection



Contacts are made in random.

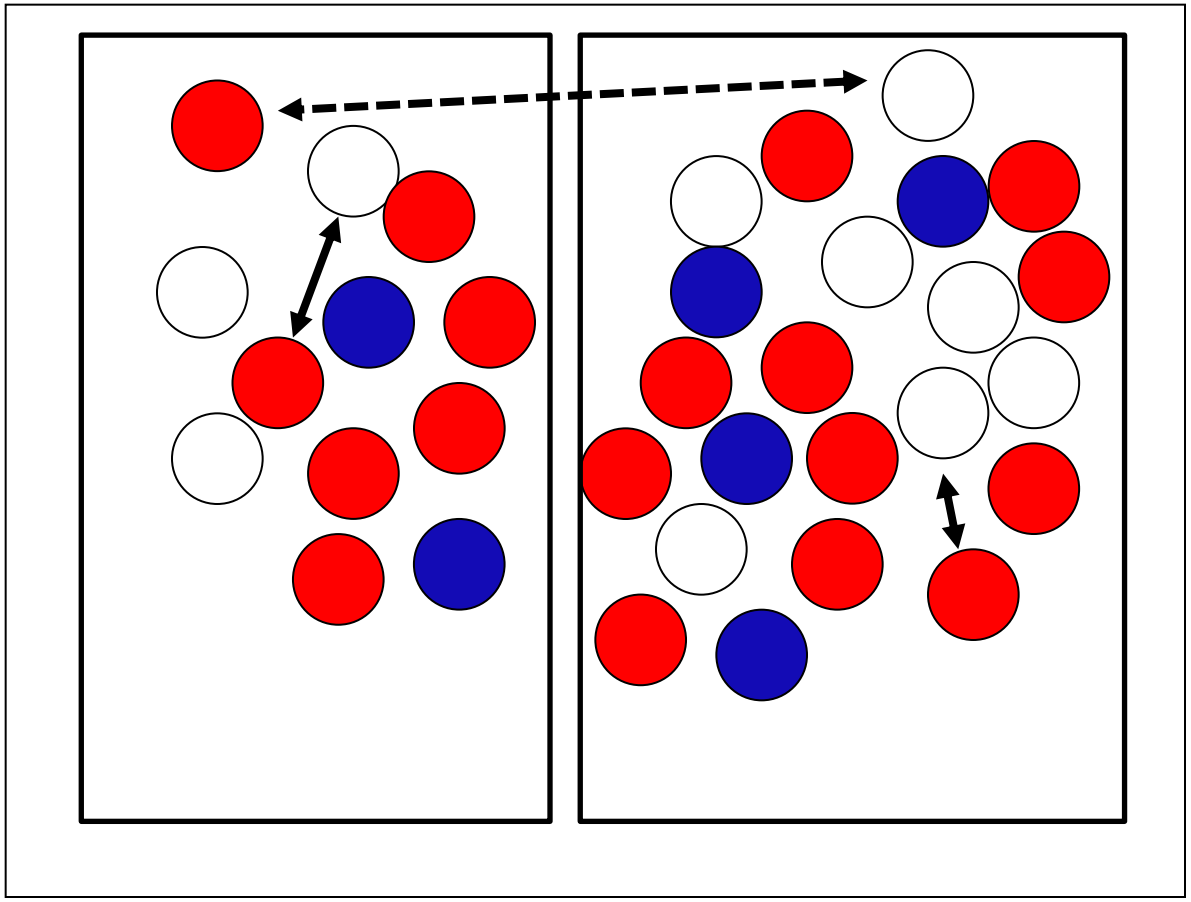
Number of new cases:

$$\beta \times I \times S$$

Transmission probability per contact

Number of new cases=P(transmission) X # of infectious X # of susceptible

Transmission within/between sub populations



Contacts are NOT made in random.

Possible transmission between and within the sub populations.

Transmission revisited

- Until now, we assumed that transmission is **homogeneous** within the population → unique transmission coefficient **β**

$$\textbf{Incidence rate (t)} = \beta \times I(t) \times S(t)$$

- It means that every individual has the same ”chance” to be in contact with every other individual within the population

- In general, this is not very realistic!

Transmission and mixing pattern

- In general, the “mixing pattern” within the population will **NOT be homogeneous**.

- The population is structured with respect to contacts.

- Examples:
  - Childhood infections: measles, mumps, rotavirus, …: greater risk between infants:

    in day care centre, school, ..
  - Sexually transmitted infections: contact only possible within a sexual partnership (not always i.e., transmission among homosexual population).

Transmission and mixing pattern

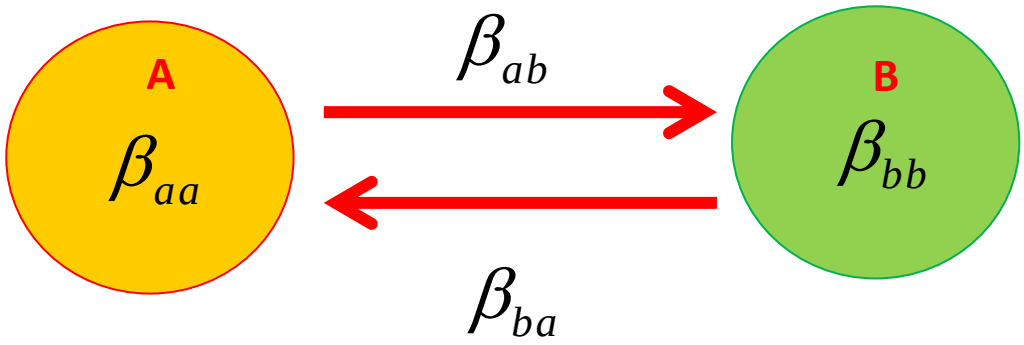
- Even if contacts are not homogeneous, it is often possible to subdivide the total population into sub-populations within which the assumption of homogeneous contacts is acceptable.

- There will be specific transmission coefficients **β**
  - within each sub-population
  - between each pair of sub-populations.

Contact pattern

$$\begin{bmatrix} \beta_{aa} & \beta_{ab} \\ \beta_{ba} & \beta_{bb} \end{bmatrix}$$

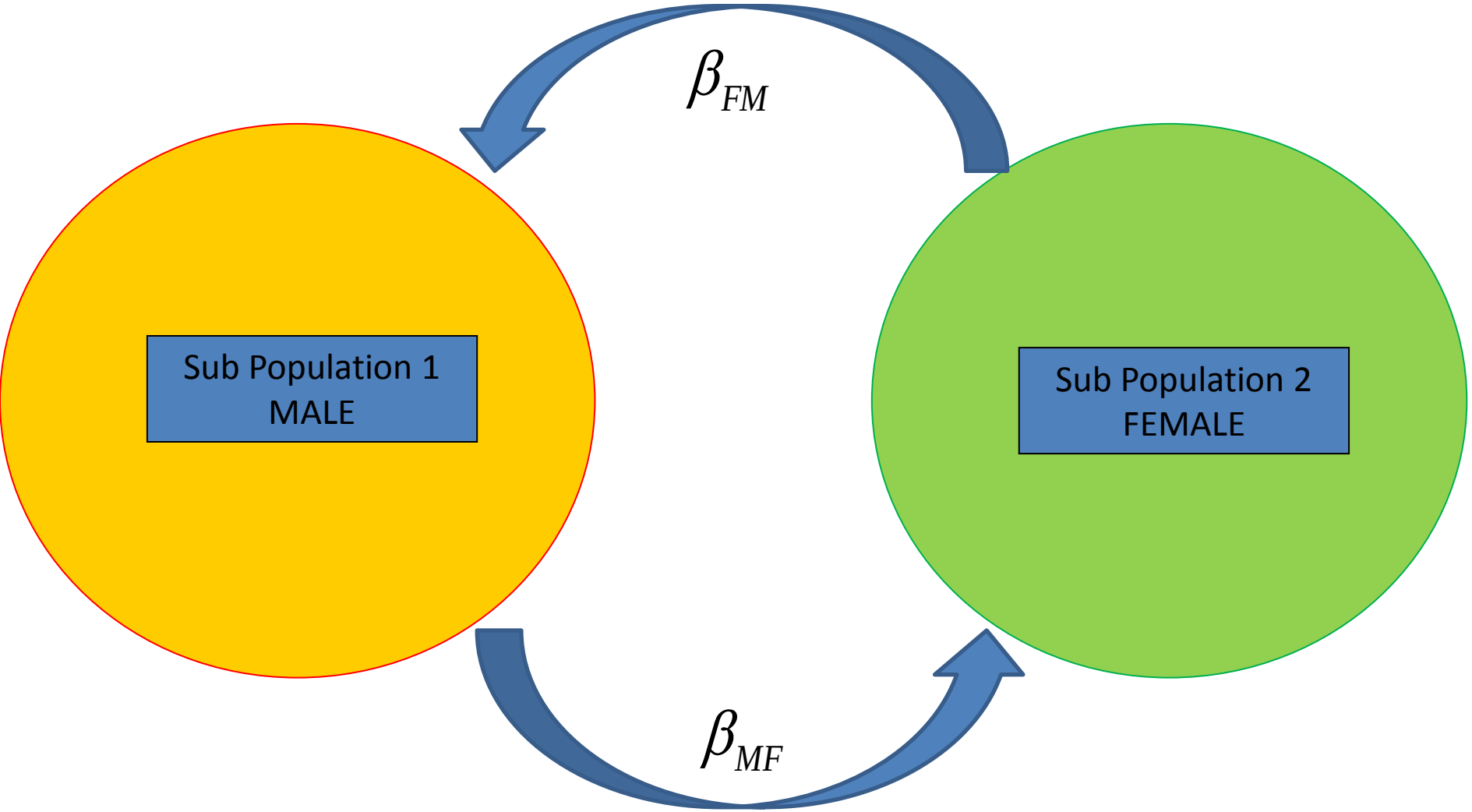
Contact matrix



β_{ab} contact between susceptible from sub population A and infected from subpopulation B

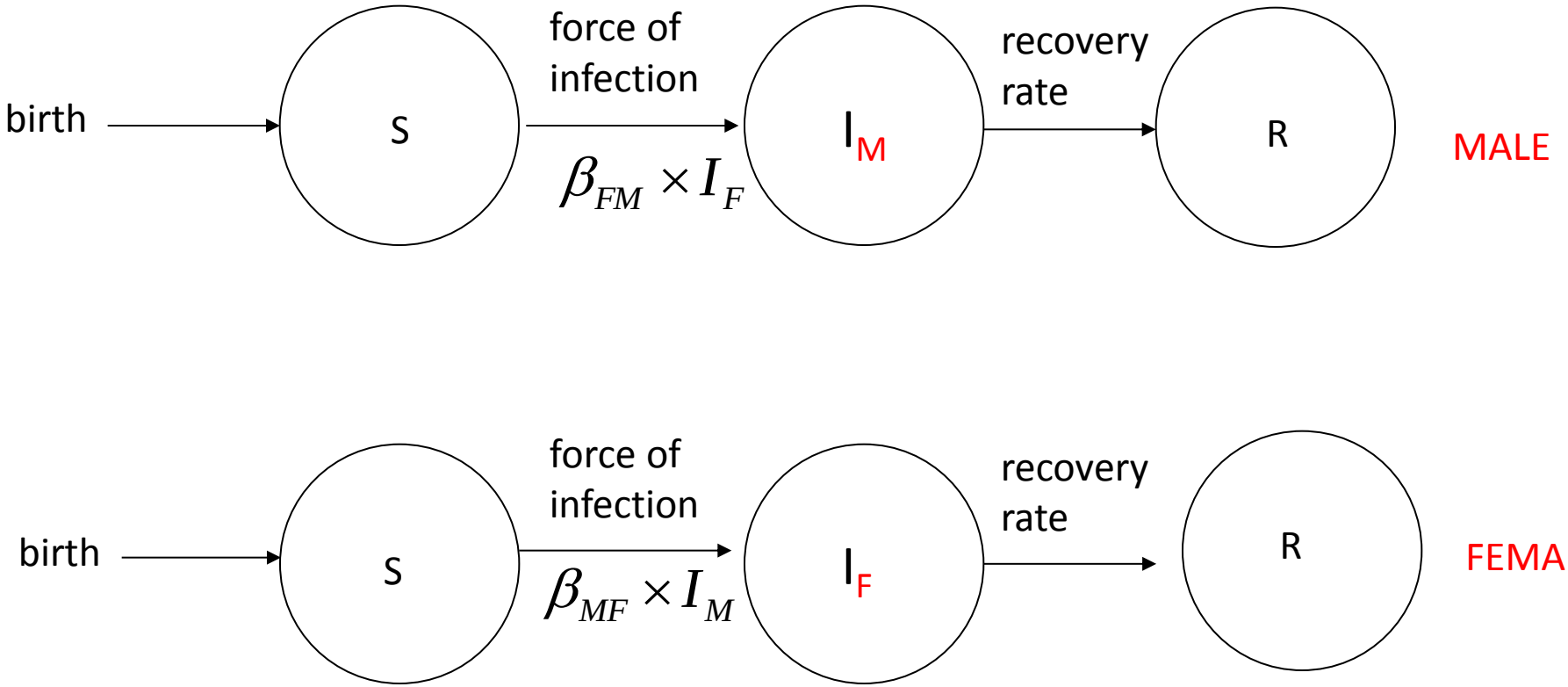
β_{ba} contact between susceptible from sub population B and infected from subpopulation A

Sexually transmission diseases: Gonorrhea



Capasso 2008

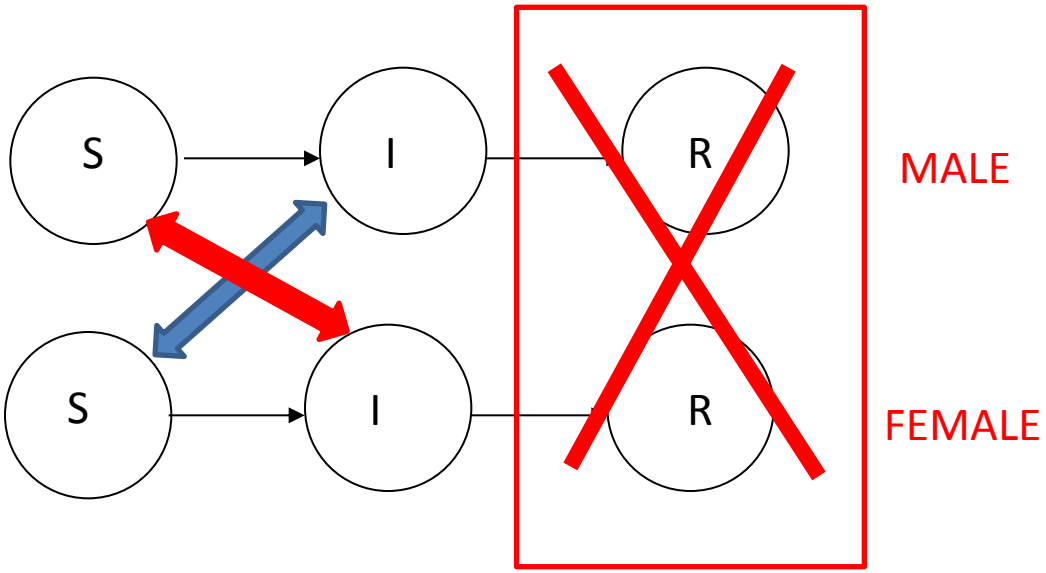
Model structure



$$\begin{bmatrix} & \beta_{FM} \\ \beta_{MF} & \end{bmatrix}$$

Contact patterns

Contact pattern: positive feedback



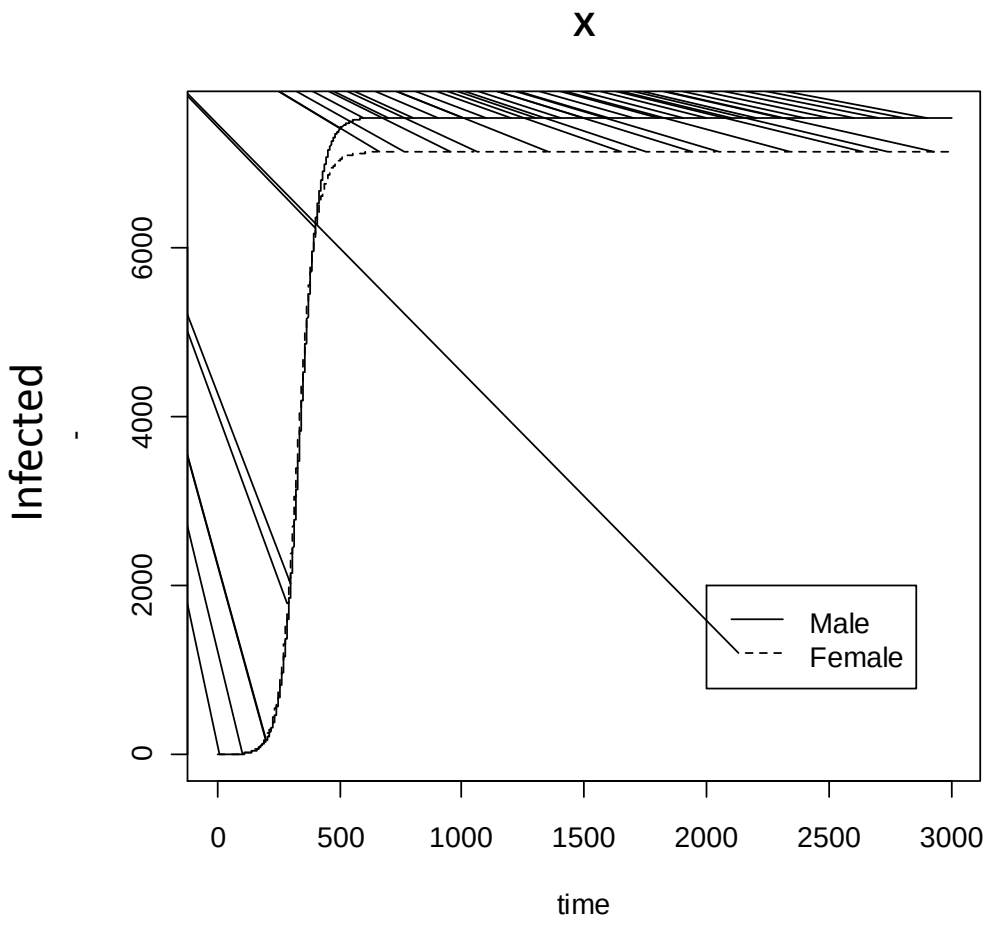
No immune/recovery compartment: all are susceptible or infected.

$$\begin{bmatrix} & \beta_{FM} \\ \beta_{MF} & \end{bmatrix}$$

The contact matrix represents the interaction between the population of MALE and FEMALE.

Positive feedback: one population influences the transmission of the other population.

Example



Parameter setting

$$\beta_{FM} = 0.000003$$

$$\beta_{MF} = 2 \times \beta_{FM}$$

$$N_M = 10000$$

$$N_F = 15000$$

Parameters in R:

```
parameters <- c(beta1=0.000003,beta2=0.000006,v1=0.007,v2=0.05,N1=10000,N2=15000)
```

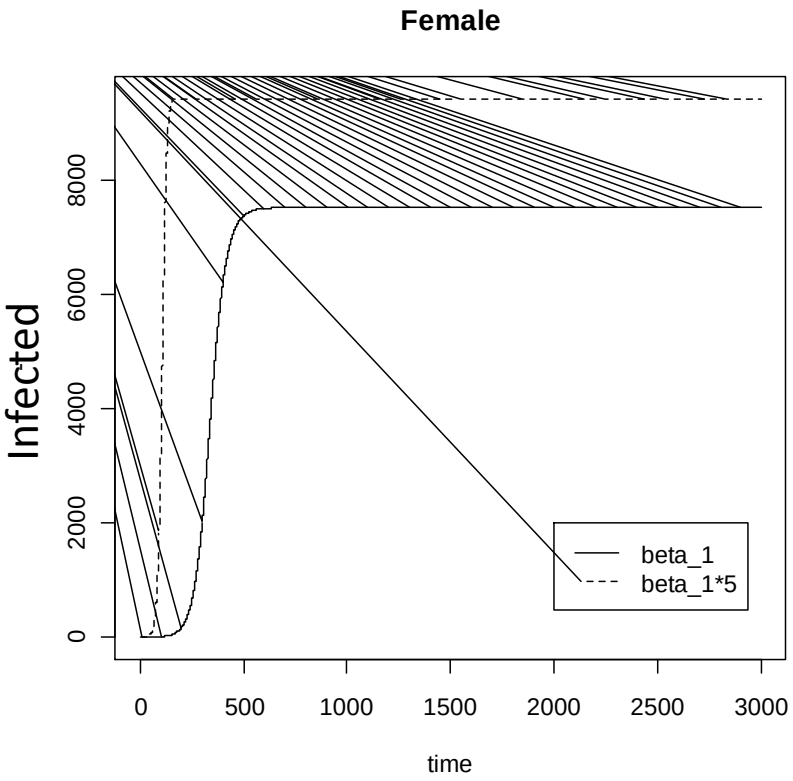
Example

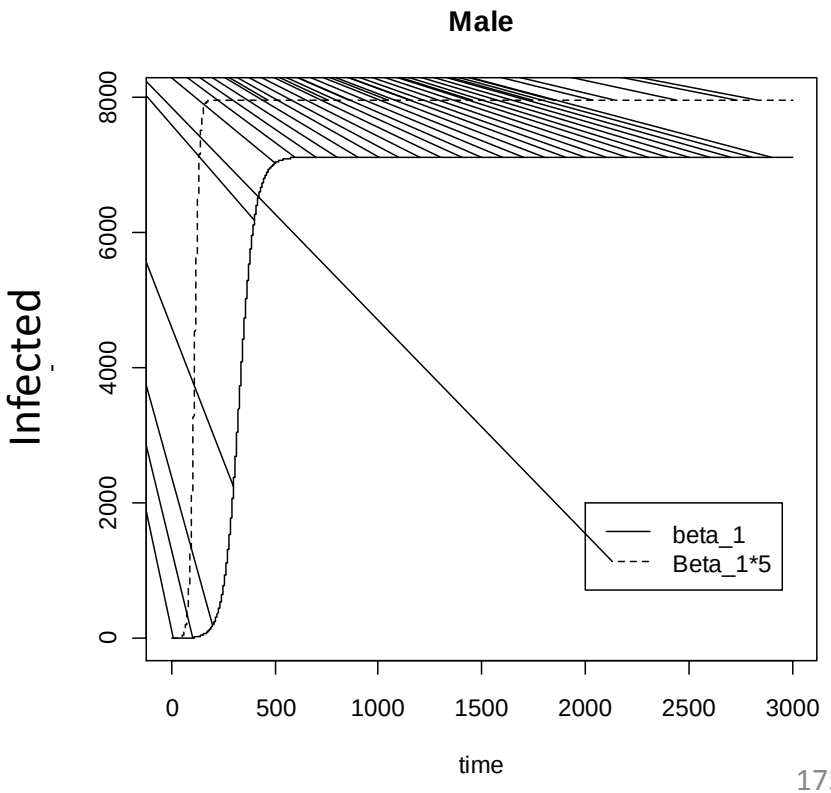
Parameter setting:

$$\beta_{FM} = \beta_{MF} \times 5$$

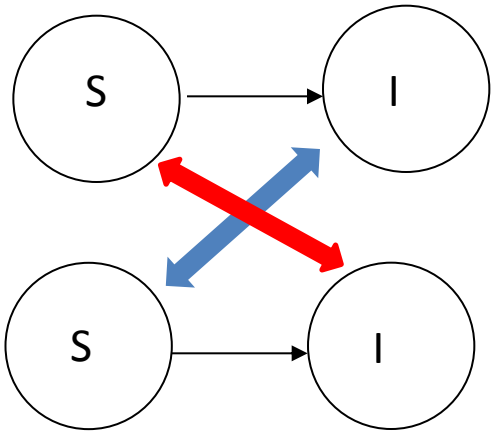
Transmission from female to male is 5 times higher than transmission from male to female.

$$\beta_{MF} = 0.000006$$
$$N_M = 10000$$
$$N_F = 15000$$





Transmission model for gonorrhea in R



MALE

FEMALE

$$(N_F - I_F)I_M$$

Susceptible female

Infected male

THE ODE system

$$\frac{dI_F(t)}{dt} = \beta_{MF}(N_F - I_F)I_M - \nu_1 I_F$$

$$\frac{dI_M(t)}{dt} = \beta_{MF}(N_M - I_M)I_F - \nu_2 I_M$$

$$\begin{bmatrix} & \beta_{FM} \\ \beta_{MF} & \end{bmatrix}$$

Only between population transmission.

Transmission model for gonorrhea in R

```
parameters <- c(beta1=0.000003,beta2=0.000006,v1=0.007,v2=0.05,N1=10000,N2=15000)
state <- c(Y1=1,Y2=0)
times<-seq(0,3000,by=0.1)

Gonorrhea<-function(t,state,parameters)
{
with(as.list(c(state, parameters)),
{
dY1 <- beta1*(N1-Y1)*Y2-v1*Y1
dY2 <- beta2*(N2-Y2)*Y1-v2*Y2
list(c(dY1,dY2))
})
}
```

$$\frac{dI_F(t)}{dt} = \beta_{MF}(N_F - I_F)I_M - \nu_1 I_F$$
$$\frac{dI_M(t)}{dt} = \beta_{MF}(N_M - I_M)I_F - \nu_2 I_M$$

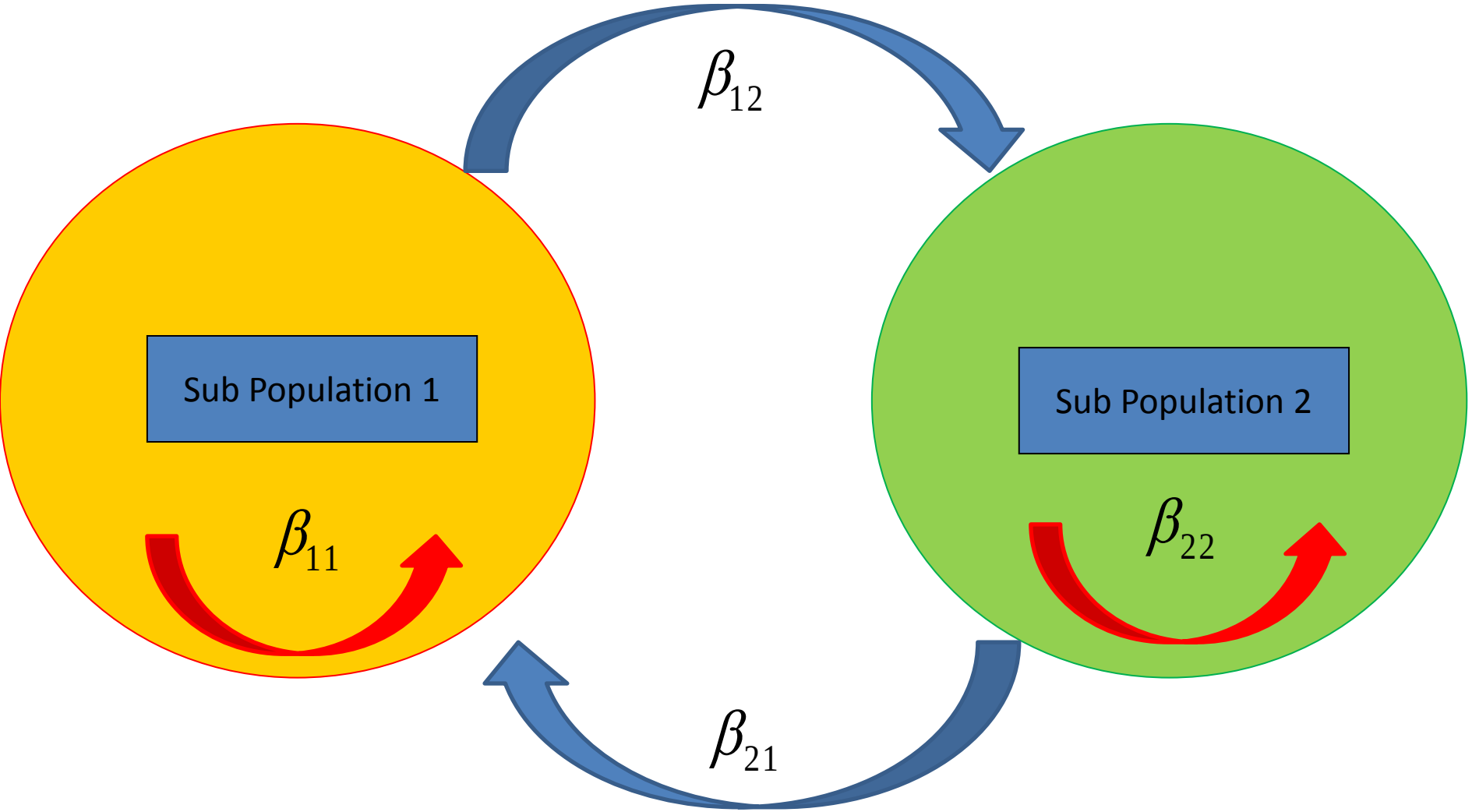
Contact matrix

$$\begin{bmatrix} & \beta_{FM} \\ \beta_{MF} & \end{bmatrix}$$

Running the model in R:

```
require(deSolve)
out <- as.data.frame(ode(y=state,times=times,func=Gonorrhea,parms=parameters))
```

Two interacting sub population



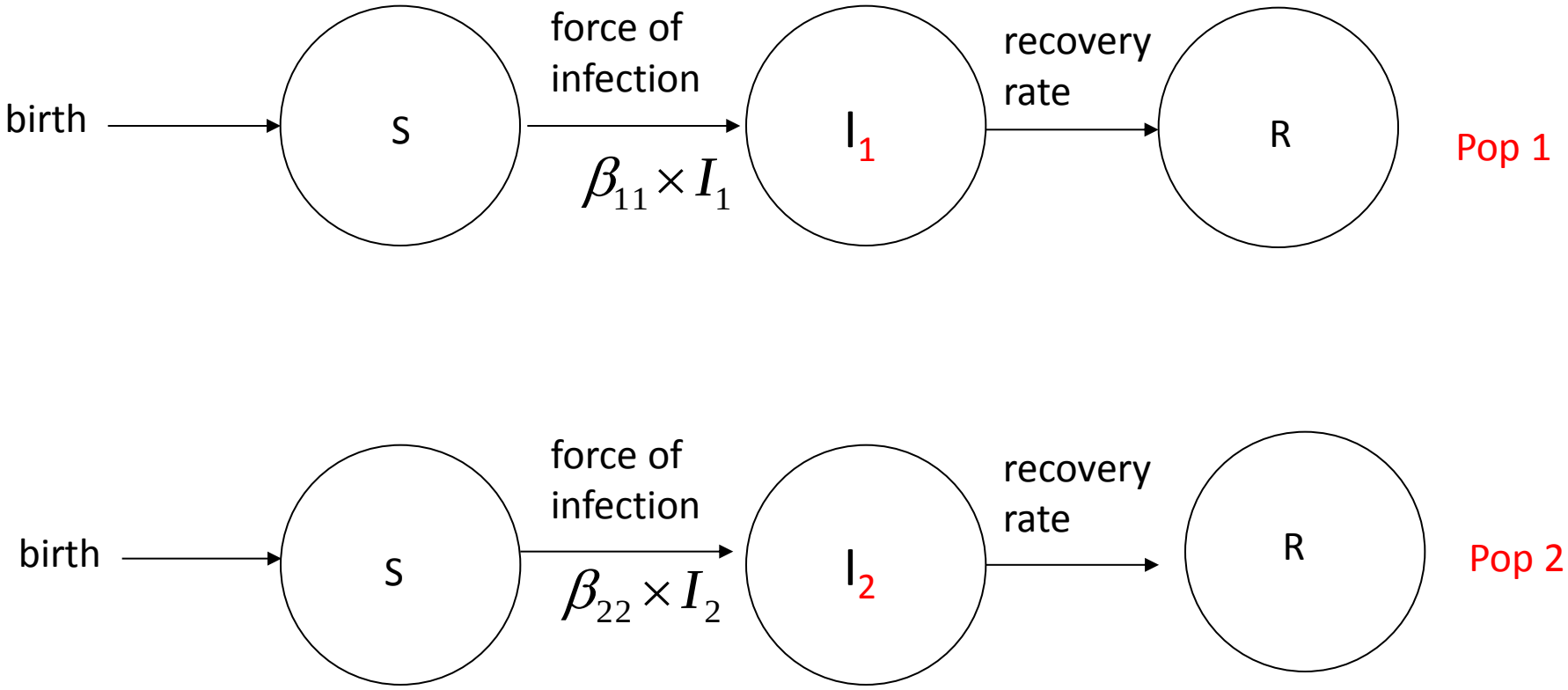
Contact pattern

$$\begin{bmatrix} \beta_{11} & \beta_{12} \\ \beta_{12} & \beta_{22} \end{bmatrix}$$

The contact matrix represent the interaction between the two sub populations.

Transmission occurs within a population and between the populations.

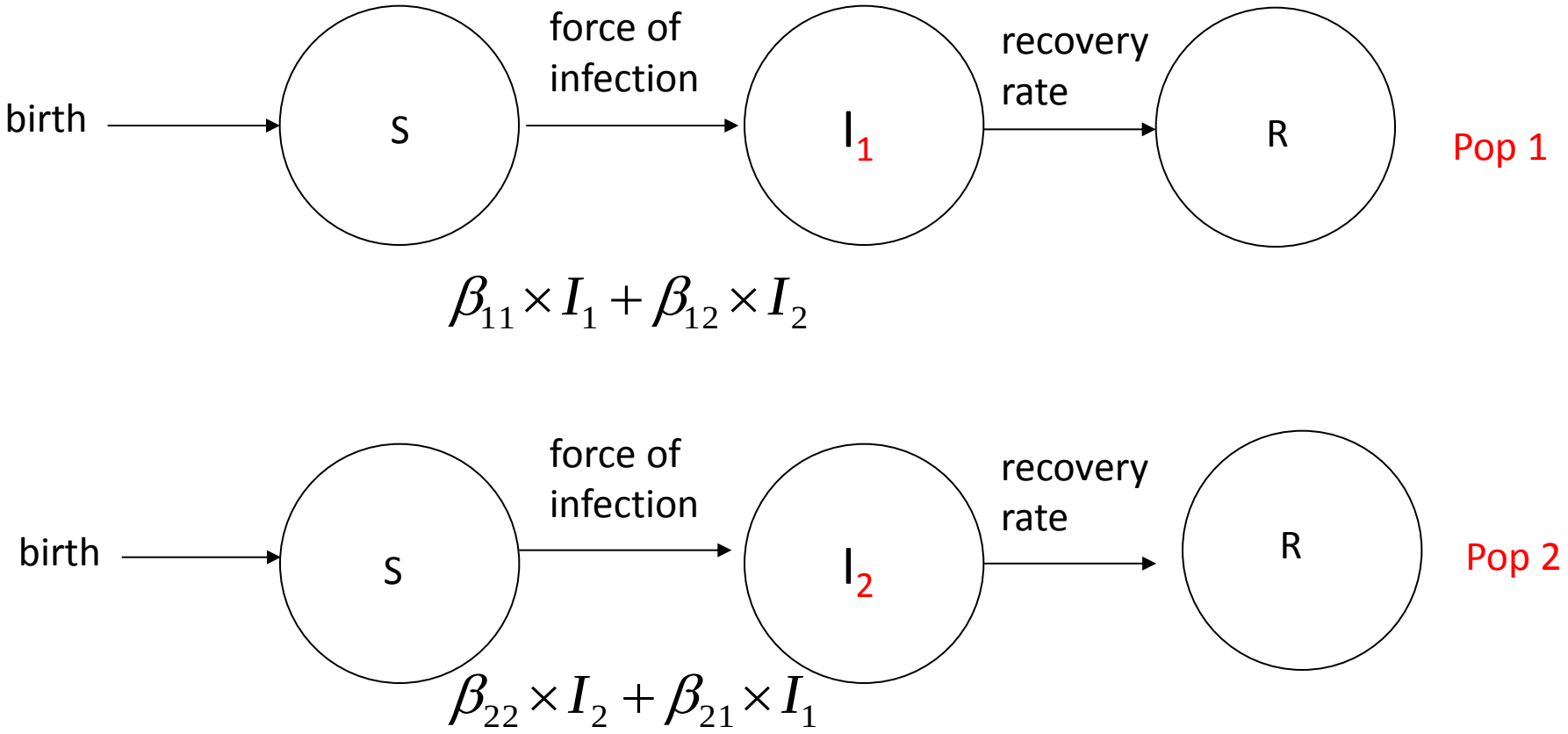
Model structure 1



$$\begin{bmatrix} \beta_{11} & 0 \\ 0 & \beta_{22} \end{bmatrix}$$

Contact patterns: only within group transmission

Model structure 2



$$\begin{bmatrix} \beta_{11} & \beta_{12} \\ \beta_{21} & \beta_{22} \end{bmatrix}$$

Contact patterns: transmission within/between populations

Model Structure

$$\frac{dS_1(t)}{dt} = \mu - (\beta_{11} I_1 + \beta_{12} I_2) S_1 - \mu S_1$$
$$\frac{dI_1(t)}{dt} = (\beta_{11} I_1 + \beta_{12} I_2) S_1 - \nu_1 I_1 - \mu I_1$$
$$\frac{dR_1(t)}{dt} = \nu_1 I_1 - \mu R_1$$

$$\frac{dS_2(t)}{dt} = \mu - (\beta_{21} I_1 + \beta_{22} I_2) S_2 - \mu S_2$$
$$\frac{dI_2(t)}{dt} = (\beta_{21} I_1 + \beta_{22} I_2) S_2 - \nu_2 I_2 - \mu I_2$$
$$\frac{dR_2(t)}{dt} = \nu_2 I_2 - \mu R_2$$

Contact patterns

$$\begin{bmatrix} \beta_{11} & \beta_{12} \\ \beta_{21} & \beta_{22} \end{bmatrix}$$

Example (I)

Parameter setting

$$\begin{bmatrix} \beta_{11}=0.05 & \beta_{12}=0.075 \\ \beta_{21}=0.075 & \beta_{22}=0.05 \end{bmatrix}$$

$$\begin{bmatrix} \beta_{11}=0.05 & \beta_{12}=0.05 \\ \beta_{21}=0.075 & \beta_{22}=0.05 \end{bmatrix}$$

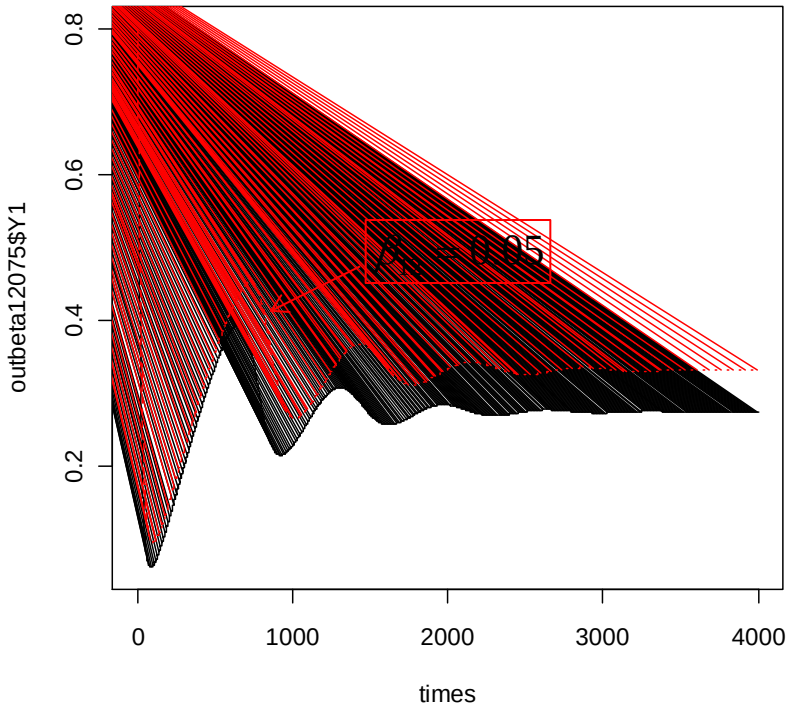
Decreasing the value of transmission parameter between the populations.

Parameters settings in R:

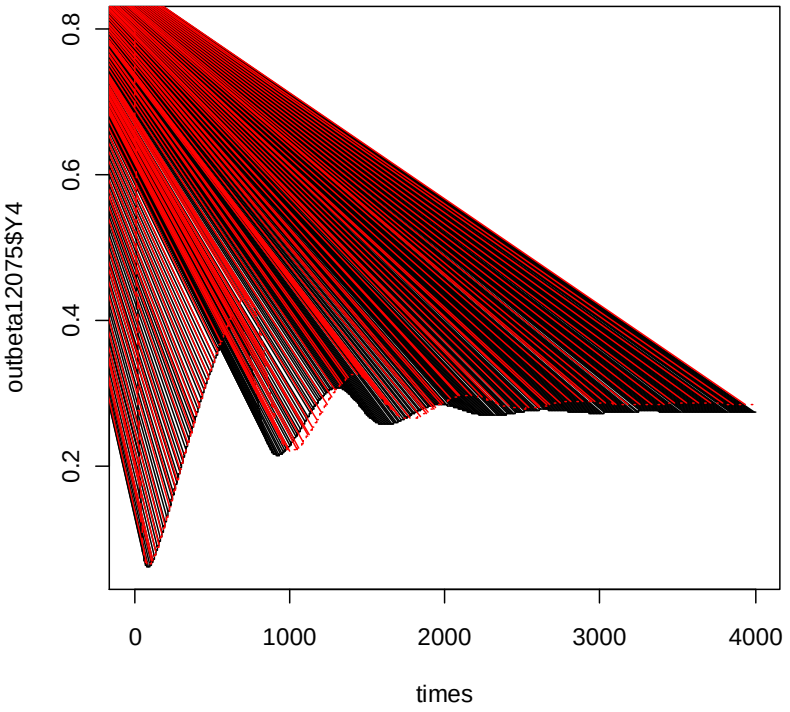
```
parameters <- c(beta11=0.05,beta12=0.075,beta21=0.075,beta22=0.05,v1=1/30,v2=1/30,mu=0.001)
state <- c(Y1=0.8,Y2=0.2,Y3=0,Y4=0.8,Y5=0.2,Y6=0)
```

Susceptible in the two sub populations

Susceptible in population 1



Susceptible in population 2



Example (2)

Parameter setting

$$\begin{bmatrix} \beta_{11} = 0.05 & \beta_{12} = 0.075 \\ \beta_{21} = 0.075 & \beta_{22} = 0.05 \end{bmatrix}$$

$$\begin{bmatrix} \beta_{11} = 0.05 & \beta_{12} = 0.00 \\ \beta_{21} = 0.075 & \beta_{22} = 0.05 \end{bmatrix}$$

In the second setting:

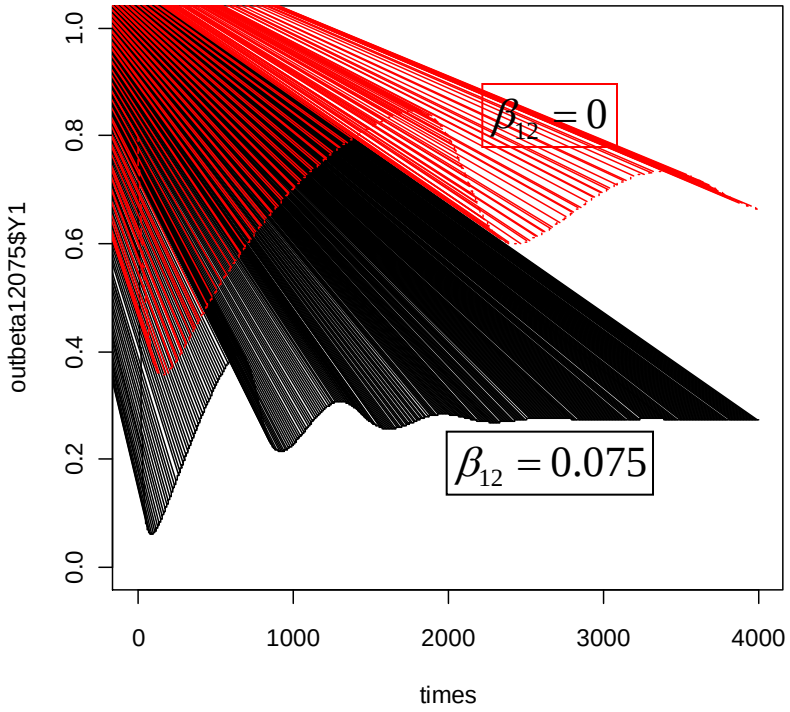
Per contact:

Susceptible from pop. 1 with infected pop. 2: no transmission.

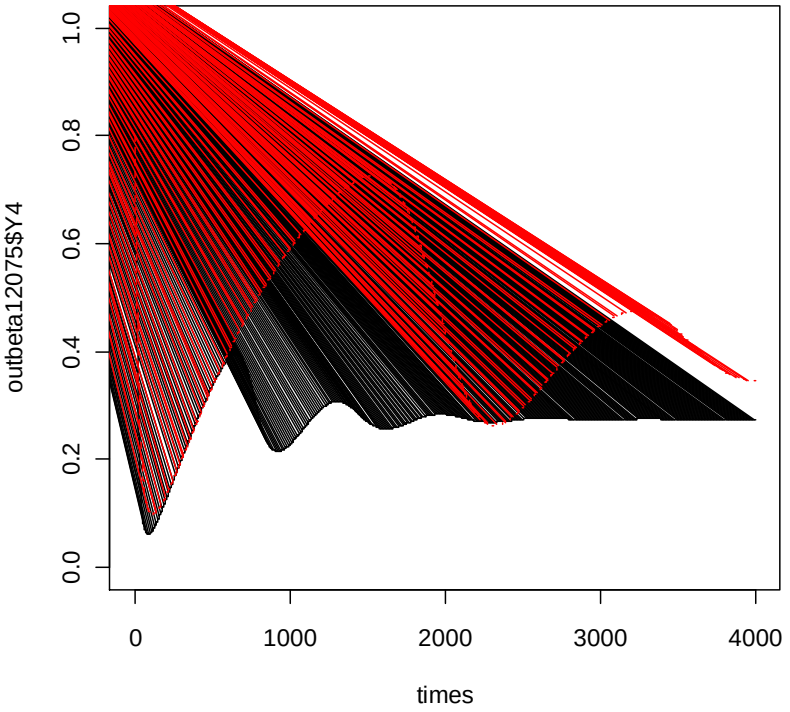
Susceptible from pop. 2 with infected pop. 1: transmission is possible.

Susceptible in the two sub populations

Susceptible in population 1



Susceptible in population 2



Example: positive feedback

Parameter setting

$$\begin{bmatrix} \beta_{11} = 0.05 & \beta_{12} = 0.075 \\ \beta_{21} = 0.075 & \beta_{22} = 0.05 \end{bmatrix}$$

$$\begin{bmatrix} \beta_{11} = 0.0 & \beta_{12} = 0.075 \\ \beta_{21} = 0.075 & \beta_{22} = 0.05 \end{bmatrix}$$

In the second setting:

First population:

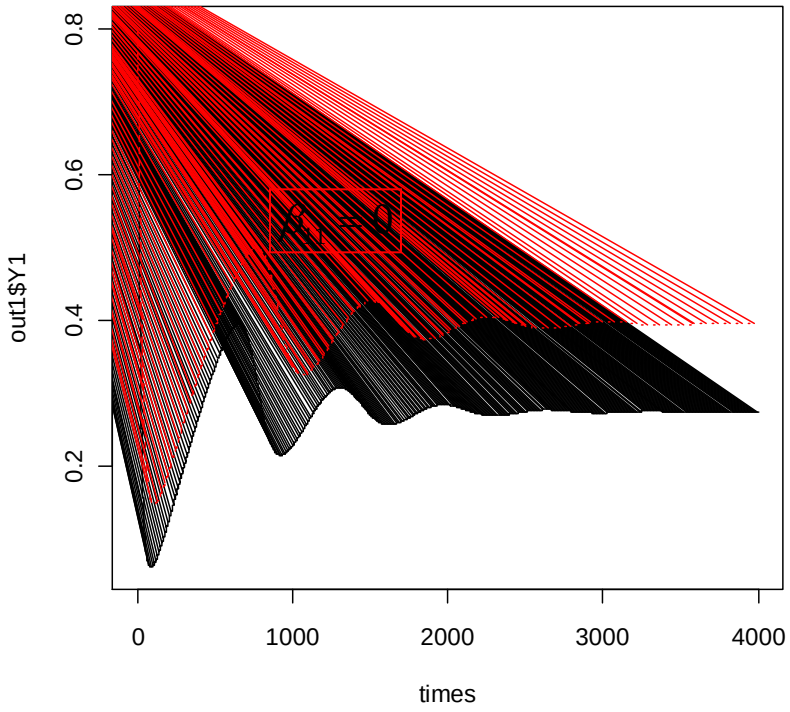
All transmission via contact between the populations.

Second population:

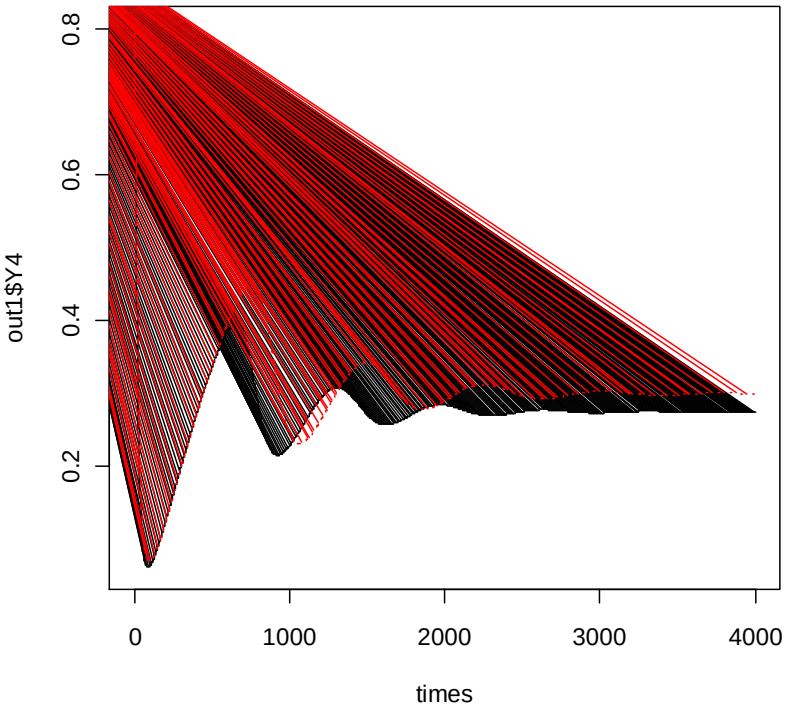
Transmission within / between the populations.

Susceptible in the two sub populations

Susceptible in population 1



Susceptible in population 2



Transmission model for two interacting populations in R

```
parameters <- c(beta11=0.05,beta12=0.075,beta21=0.075,beta22=0.05,v1=1/30,v2=1/30,mu=0.001)
state <- c(Y1=0.8,Y2=0.2,Y3=0,Y4=0.8,Y5=0.2,Y6=0)
times<-seq(0,10000,by=0.01)


SIRtwo<-function(t,state,parameters)
{
with(as.list(c(state, parameters)),
{
dY1 <- -(beta11*Y2+beta12*Y5)*Y1+mu-mu*Y1
dY2 <- (beta11*Y2+beta12*Y5)*Y1-v1*Y2-mu*Y2
dY3 <- v1*Y2 - mu*Y3
dY4 <- -(beta21*Y2+beta22*Y5)*Y4+mu-mu*Y4
dY5 <-  (beta21*Y2+beta22*Y5)*Y4-v2*Y5-mu*Y5
dY6 <- v2*Y5-mu*Y6
list(c(dY1,dY2,dY3,dY4,dY5,dY6))
})
}

times<-seq(0,4000,by=0.01)
require(deSolve)
out <- as.data.frame(ode(y=state,times=times,func=SIRtwo,parms=parameters))
head(out)
```

$$\begin{bmatrix} \beta_{11}=0.05 & \beta_{12}=0.075 \\ \beta_{21}=0.075 & \beta_{22}=0.05 \end{bmatrix}$$

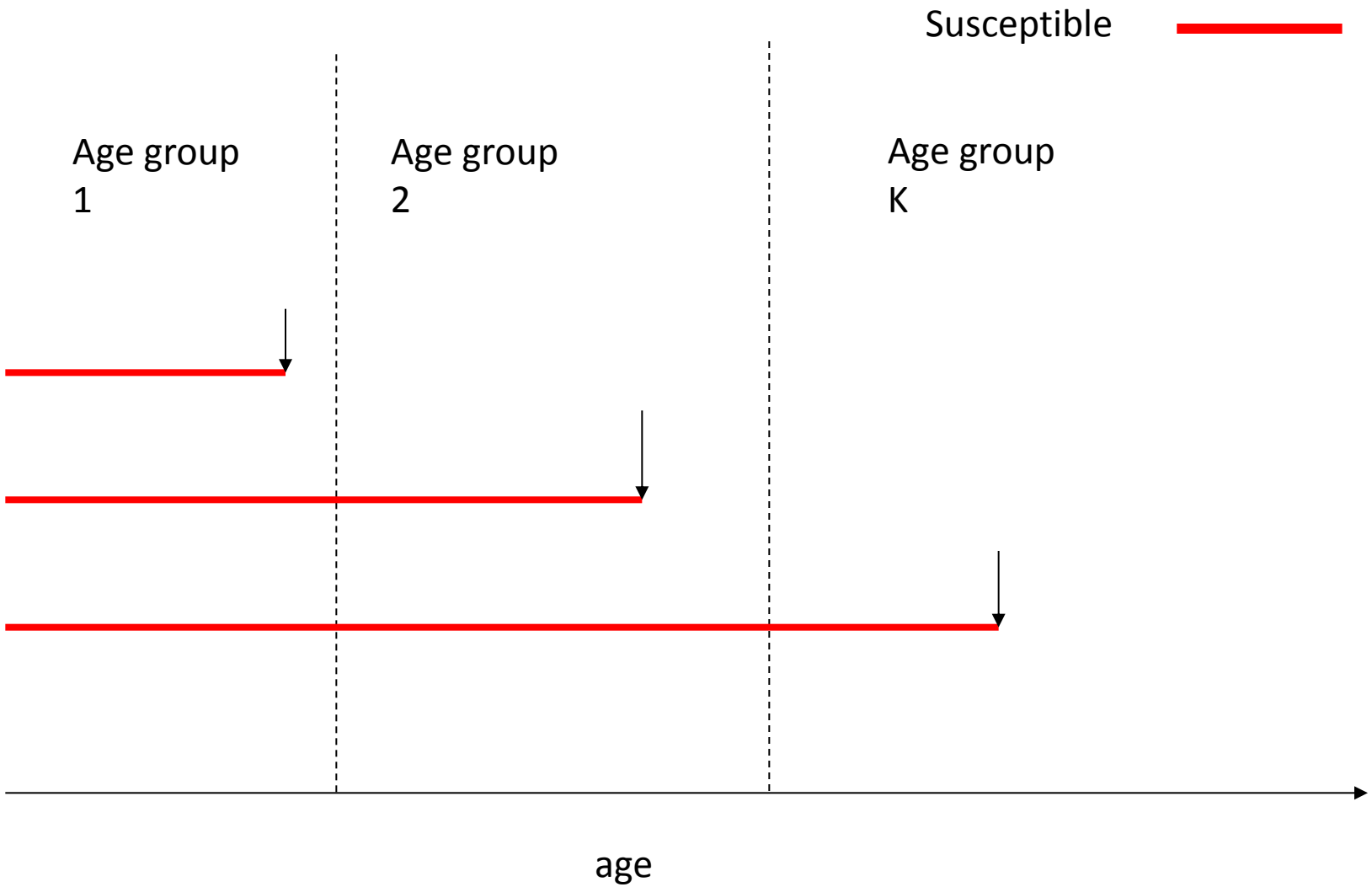
Age Structured population

R program: ModelingIDinR1_V1_MultiPop_Sep2019.R

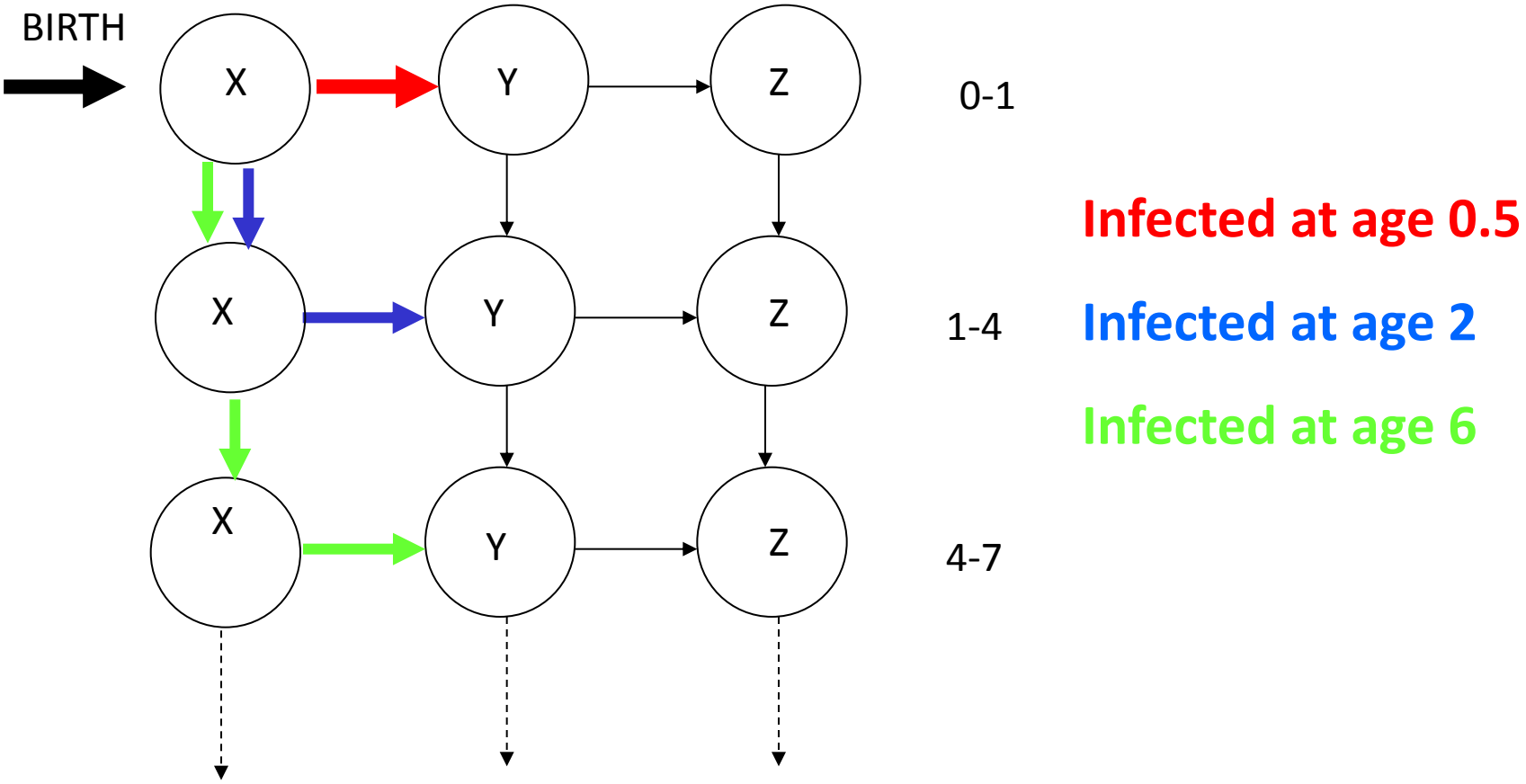
Age Structured population

- The population is divided by age groups.
- Examples:
  - People has a tendency to mix with their own age group (children in the same class at school, students in the university).
  - Children and parents (between groups transmission).

Age Structured population



Age Structured population



Contact patterns

Population with two age groups:

Case 1: transmission only within the age groups:

$$\begin{bmatrix} \beta_{11} & 0 \\ 0 & \beta_{22} \end{bmatrix}$$

Case 2: transmission within and between the age groups:

$$\begin{bmatrix} \beta_{11} & \beta_{12} \\ \beta_{21} & \beta_{22} \end{bmatrix}$$

Model Structure: two age groups

$$\frac{dS_1(t)}{dt} = N\mu - (\beta_{11}I_1 + \beta_{12}I_2)S_1 - \mu S_1 - \eta S_1$$
$$\frac{dI_1(t)}{dt} = (\beta_{11}I_1 + \beta_{12}I_2)S_1 - \nu_1 I_1 - \mu I_1 - \eta I_1$$
$$\frac{dR_1(t)}{dt} = \nu_1 I_1 - \mu R_1 - \eta R_1$$

First age group

$$\frac{dS_2(t)}{dt} = \eta S_1 - (\beta_{21}I_1 + \beta_{22}I_2)S_{21} - \mu S_2$$
$$\frac{dI_2(t)}{dt} = \eta I_1 + (\beta_{21}I_1 + \beta_{22}I_2)S_2 - \nu_2 I_2 - \mu I_2$$
$$\frac{dR_2(t)}{dt} = \eta R_1 + \nu_2 I_2 - \mu R_2$$

Second age group

Contact patterns

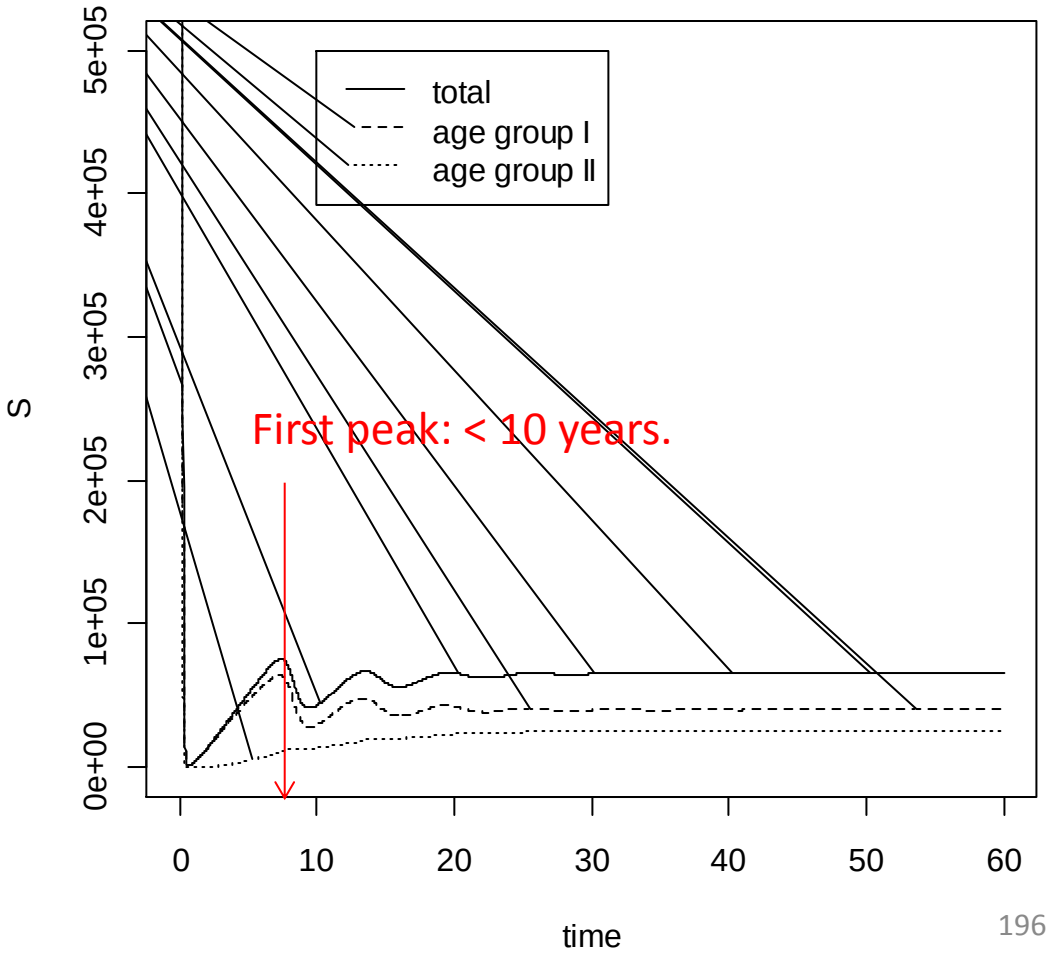
$$\begin{bmatrix} \beta_{11} & \beta_{12} \\ \beta_{21} & \beta_{22} \end{bmatrix}$$

Example (1)

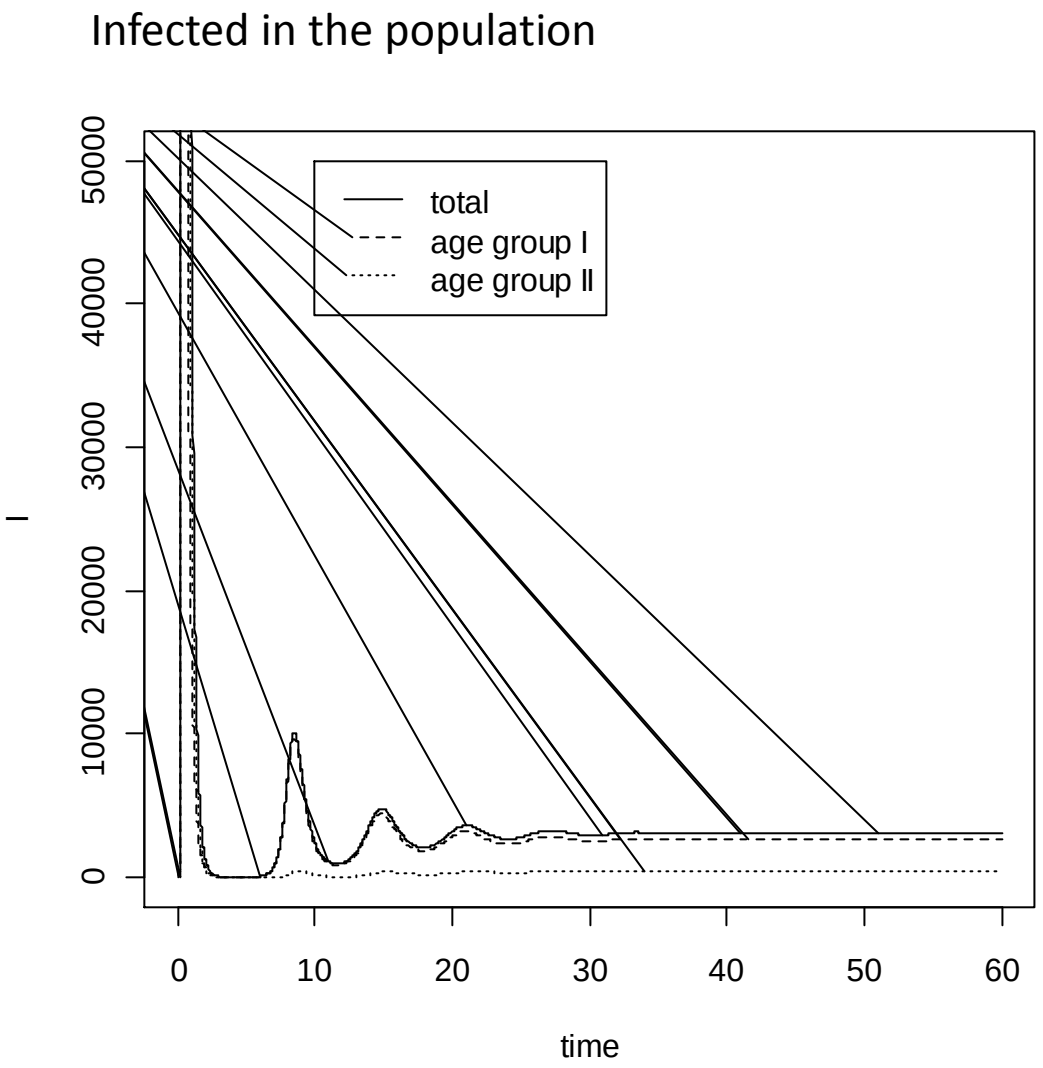
Parameter setting

$$\begin{bmatrix} \beta_{11} = 0.0001 & \beta_{12} = 0.000075 \\ \beta_{12} = 0.000075 & \beta_{22} = 0.0001 \end{bmatrix}$$

Susceptible in the population



Example


Infected in the population
total
age group I
age group II
I
0
10000
20000
30000
40000
50000
0
10
20
30
40
50
60
time

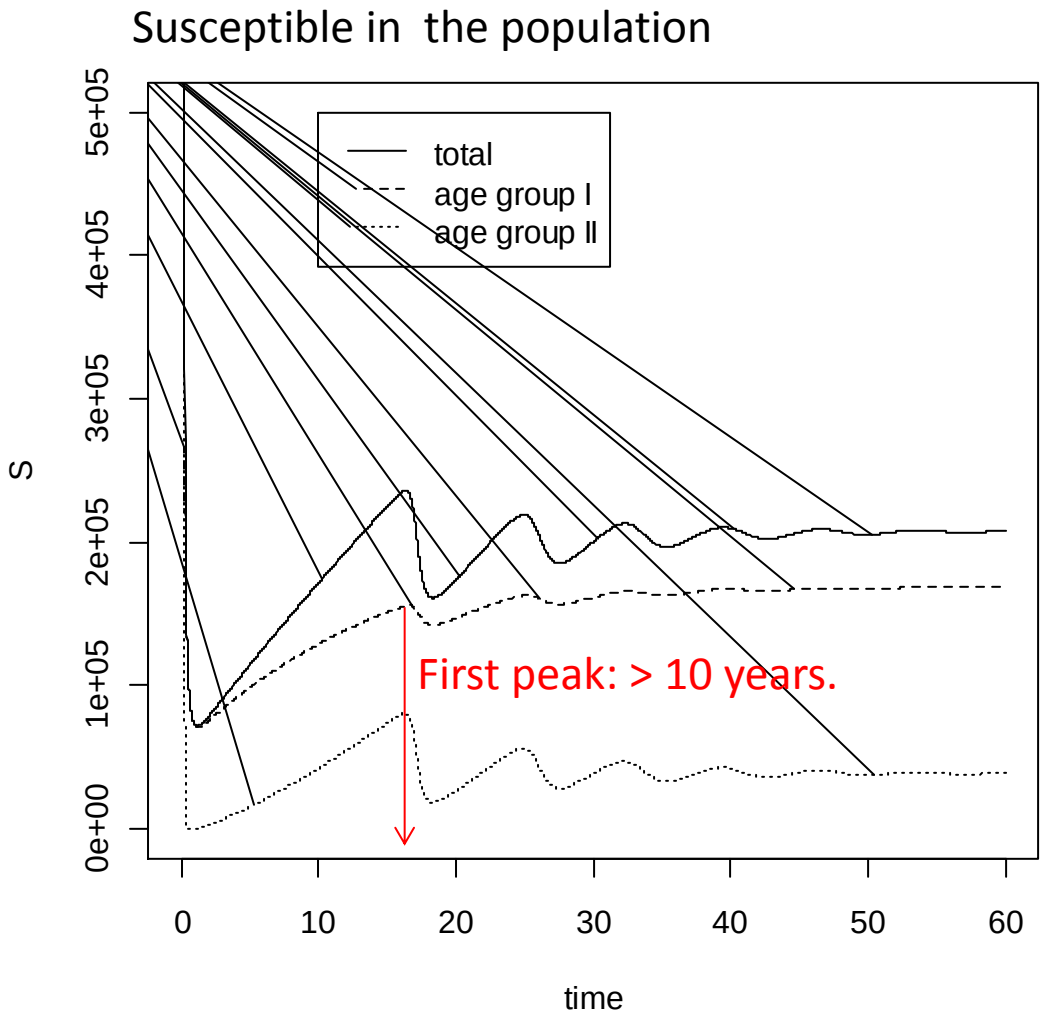
Example (2)

New parameter setting

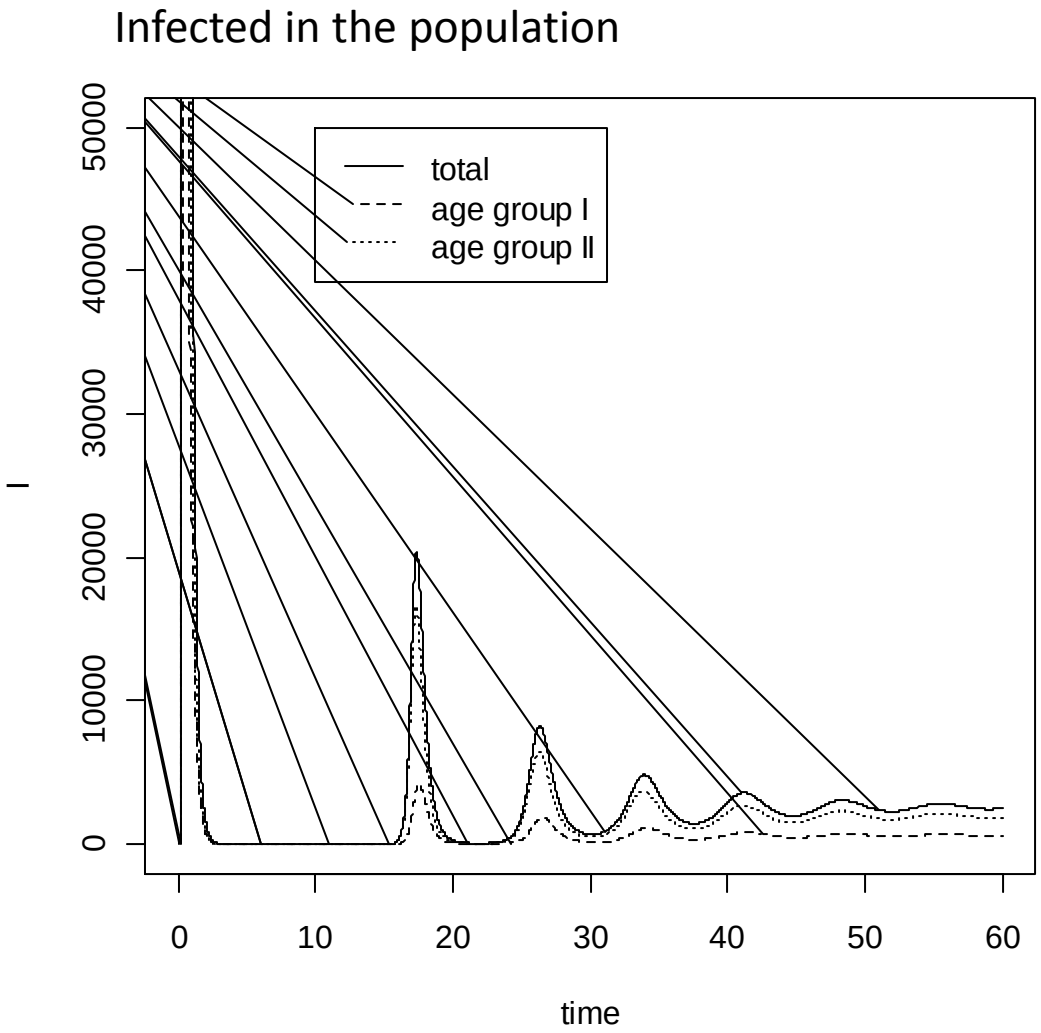
$$\begin{bmatrix} \beta_{11} = 0.000001 & \beta_{12} = 0.000075 \\ \beta_{12} = 0.000075 & \beta_{22} = 0.0001 \end{bmatrix}$$

Transmission within the first age group is lower.

$$\beta_{11} = 0.000001 < \beta_{22} = 0.0001$$



Example


Infected in the population
I
0
10000
20000
30000
40000
50000
0
10
20
30
40
50
60
time
total
age group I
age group II

Transmission model for age structured populations in R

```
parameters <- c(beta11=0.0001,beta12=0.0000075,beta21=0.0000075,beta22=0.0001,
                v1=4,v2=4,mu=1/75,mu2=1/20,N=1000000)
state <- c(Y1=266665,Y2=1,Y3=0,Y4=733334,Y5=0.0,Y6=0)

SIRtwo<-function(t,state,parameters)
{
with(as.list(c(state, parameters)),
{
dY1 <- -(beta11*Y2+beta12*Y5)*Y1+N*mu-mu*Y1-mu2*Y1
dY2 <- (beta11*Y2+beta12*Y5)*Y1-v1*Y2-mu*Y2-mu2*Y2
dY3 <- v1*Y2 - mu*Y3-mu2*Y3
dY4 <- -(beta21*Y2+beta22*Y5)*Y4-mu*Y4+mu2*Y1
dY5 <-  (beta21*Y2+beta22*Y5)*Y4-v2*Y5-mu*Y5+mu2*Y2
dY6 <- v2*Y5-mu*Y6+mu2*Y3
list(c(dY1,dY2,dY3,dY4,dY5,dY6))
})
}

times<-seq(0,60,by=0.01)
require(deSolve)
out <- as.data.frame(ode(y=state,times=times,func=SIRtwo,parms=parameters))
```

$$\begin{bmatrix} \beta_{11}=0.0001 & \beta_{12}=0.000075 \\ \beta_{12}=0.000075 & \beta_{22}=0.0001 \end{bmatrix}$$

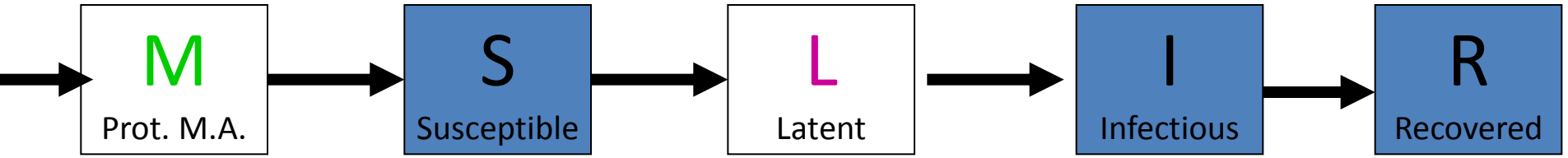
More about transmission models

MSLIR & SIS models

MSLIR (MSEIR) model

Sometimes, one might need to refine a S I R model in order to account for additional "states":

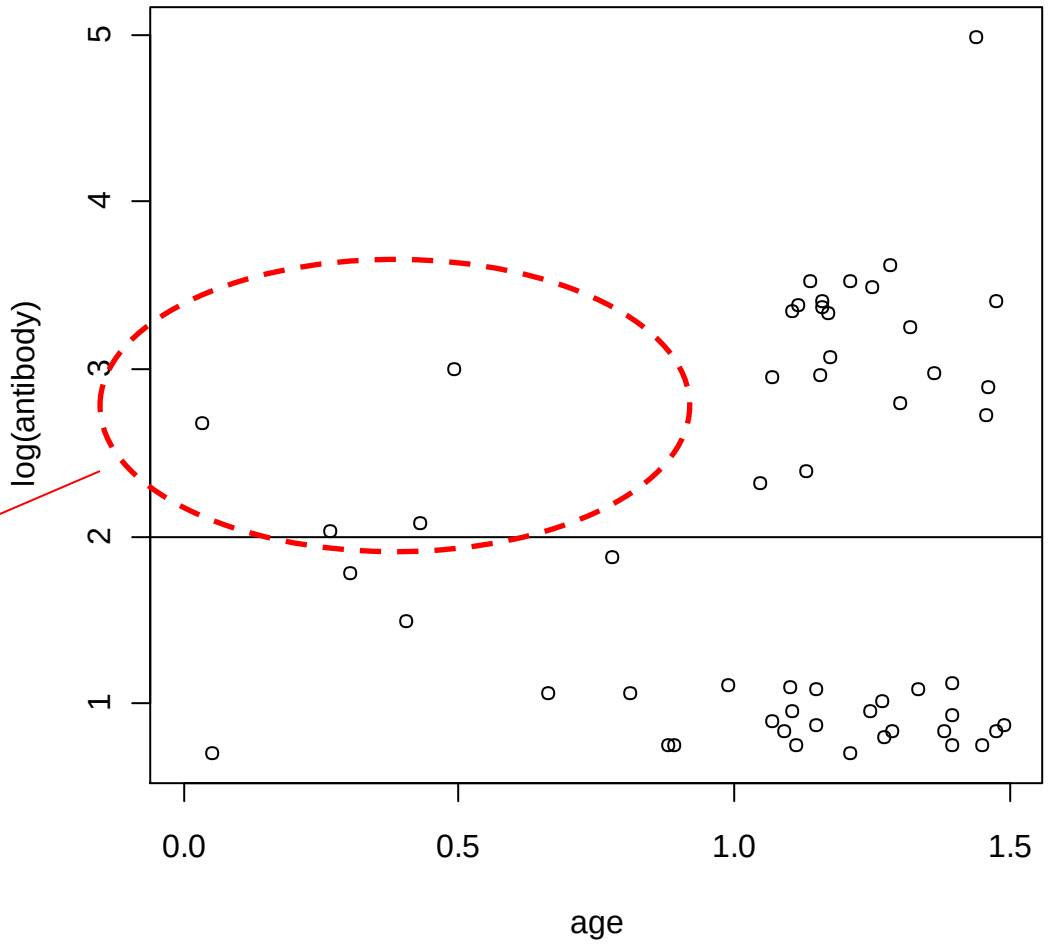
- Temporary protection against infection conferred by maternal antibodies (during first few months of life) → State **M**
- Period during which the individual is infected but
- not yet infectious → state **L** (Latent)



Maternal antibody for VZV in Belgium

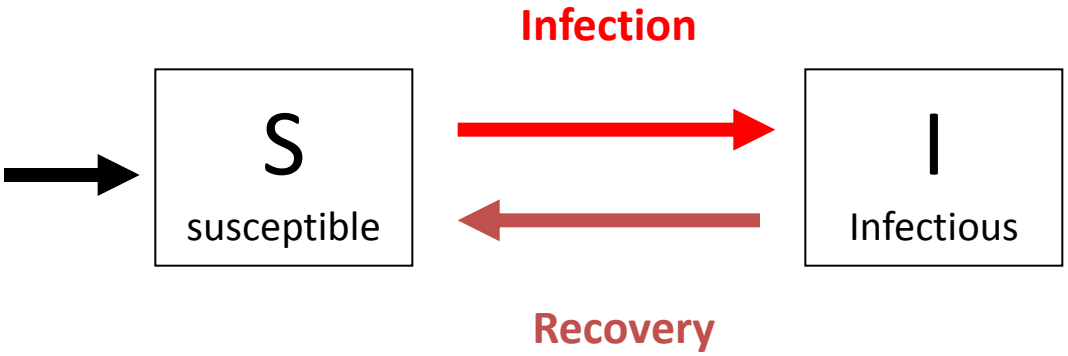
New born are protected for few months (i.e not yet susceptible)

Not infected yet due to maternal antibody.



SIS model

- For some infections, individuals can be re-infected after recovery.
- Example: gonorrhoea



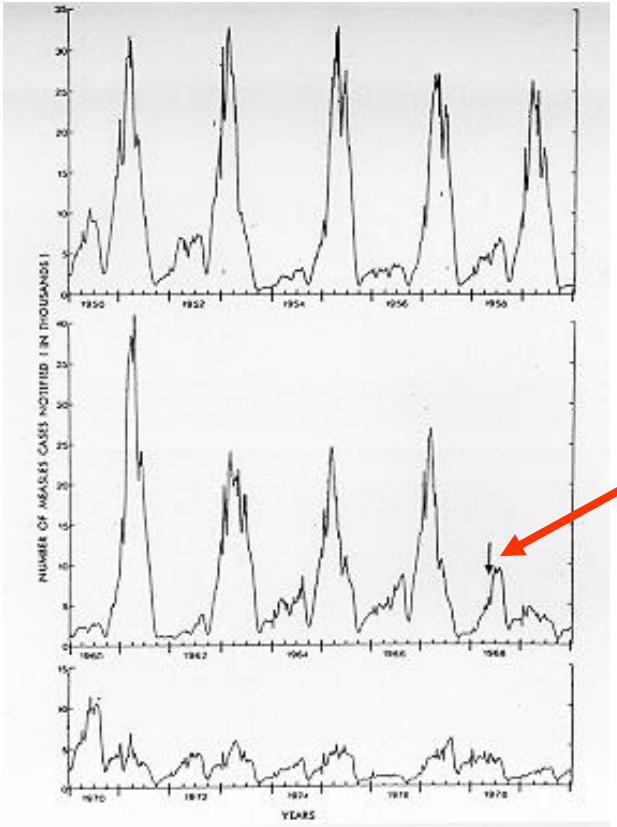
Such a model is called a S I S model

Vaccination: Intervention and Control

R program: ModelingIDinR1_V1_Vaccination_Sep2019.R

Measles in England and Wales

Measles in England and Wales

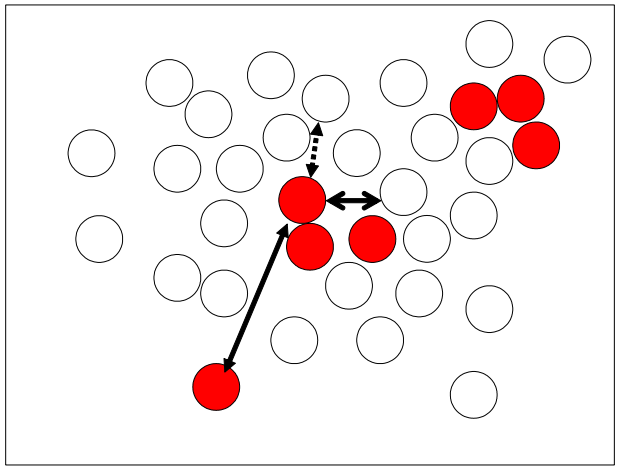


- Vaccination in 1967:
  - Reduction in number of cases.

Intervention and control

What we can do in order to control an infectious disease ?

The Mass-Action Principle



Contacts are made in random.

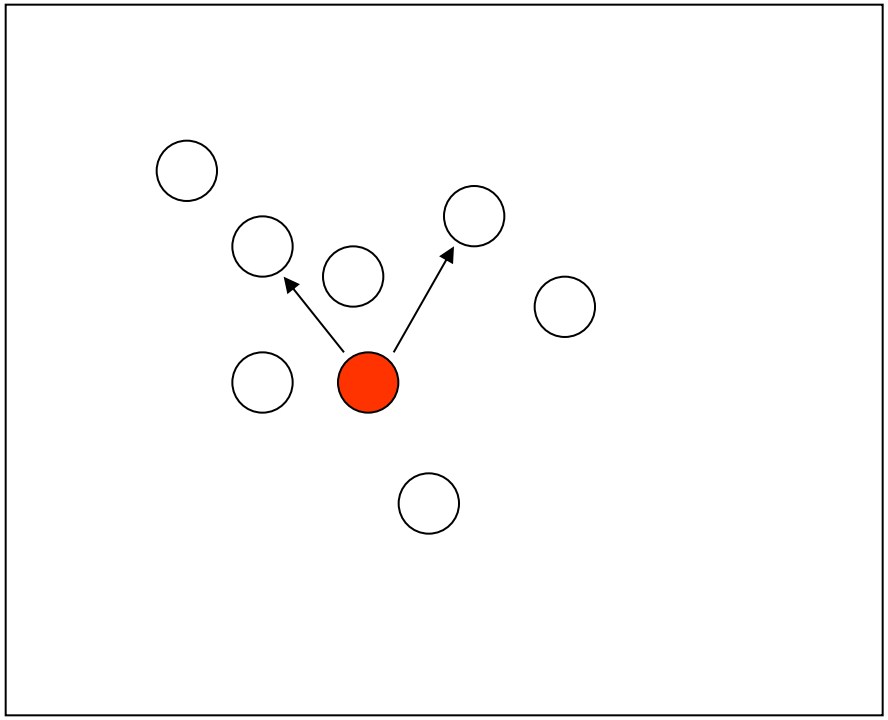
Stop the contacts between infectious and susceptible individuals.

It is not so easy to do!!!

Number of new cases=P(transmission) X # of infectious X # of susceptible

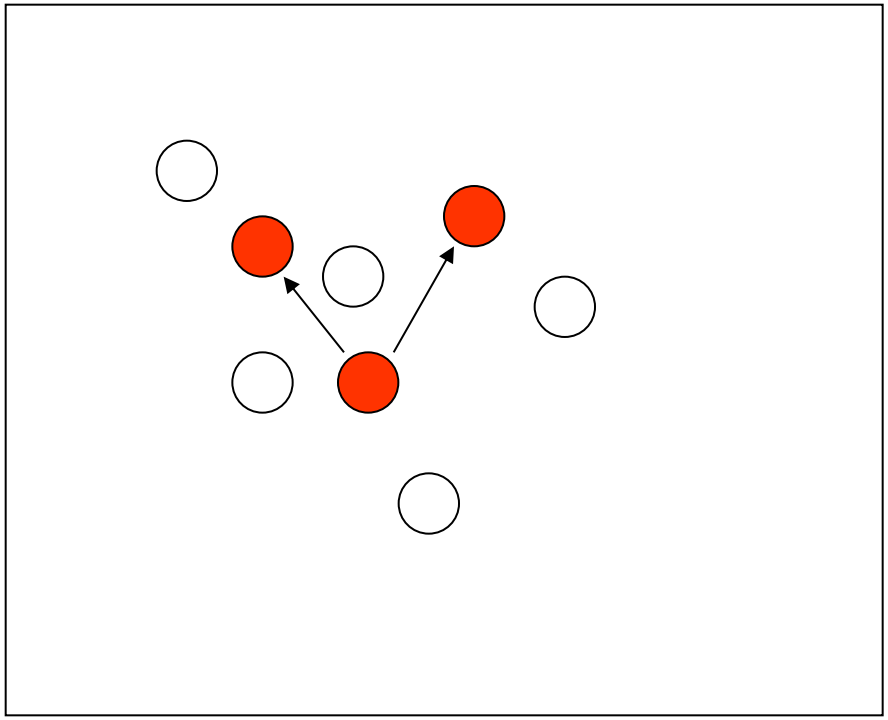
Intervention and control

First case

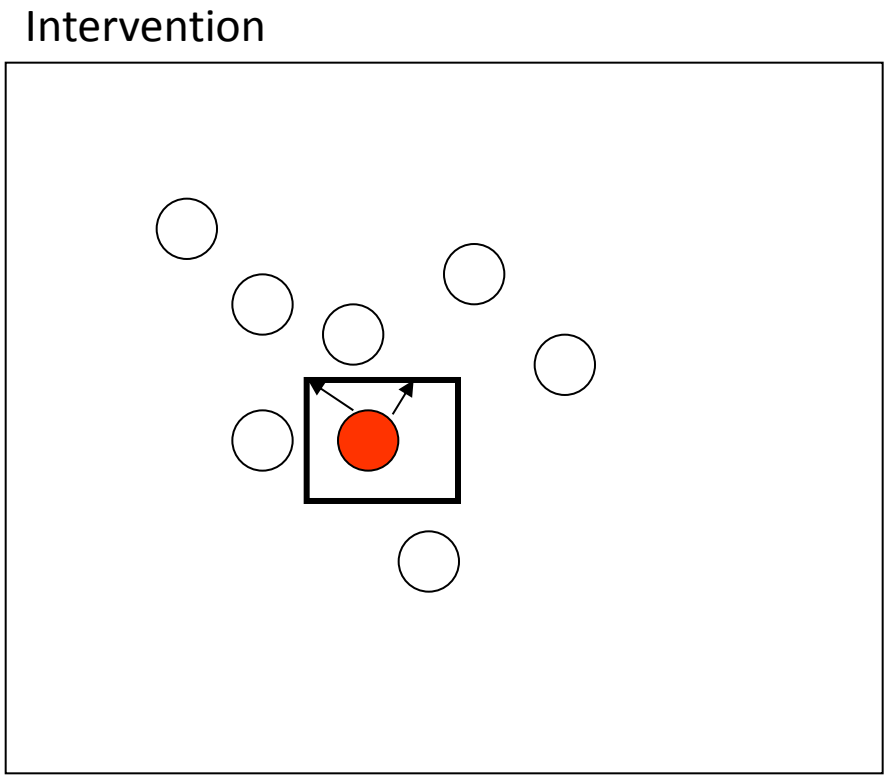


Intervention and control

Without intervention

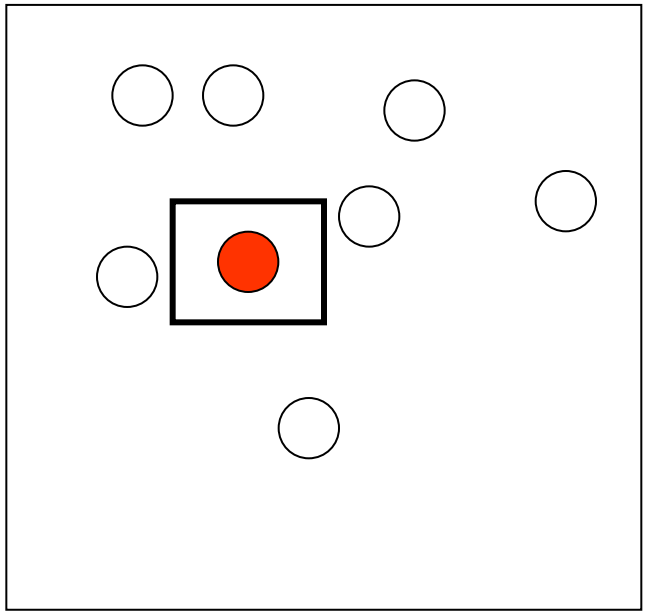


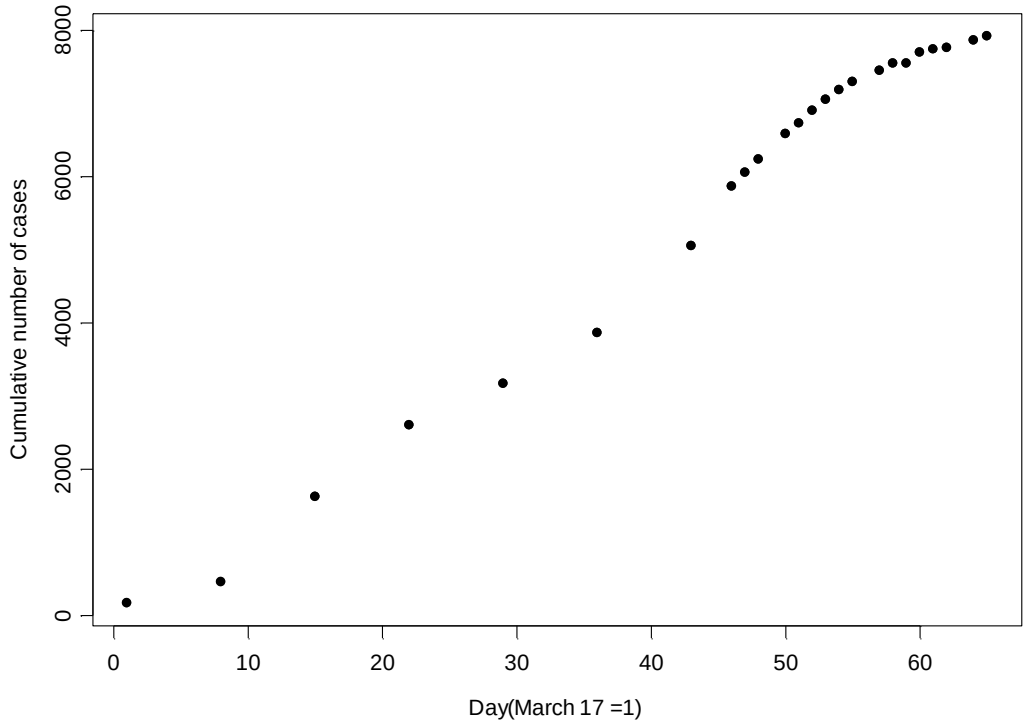
Intervention and control



Intervention and control

Intervention policy: reduce the number of contacts between infected and susceptible (for example SARS).

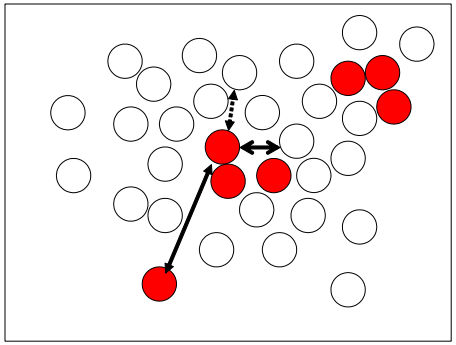




Intervention and control

What we can do in order to control an infectious disease ?

The Mass-Action Principle



Contacts are made in random.

Number of new cases=P(transmission) X # of infectious X # of susceptible

Stop the contacts between the infectious and susceptible individuals.

⇩

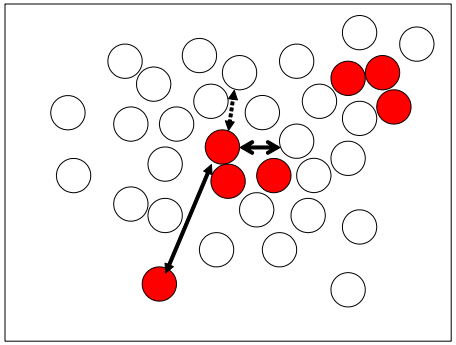
Stop the contacts between the virus and the susceptible individuals.

The massive campaign for condom use in the 80's as a control measure against HIV/AIDS.

Intervention and control

What we can do in order to control an infectious disease ?

The Mass-Action Principle



Contacts are made in random.

Number of new cases=P(transmission) X # of infectious X # of susceptible

In order to control the number of contacts we need to understand how the disease spread….

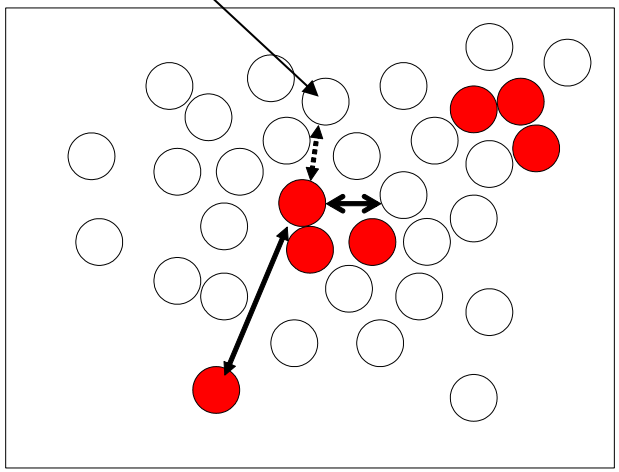
….or what is the transmission process.

Intervention and control

- What we can do in order to control an infectious disease ?

Focus of susceptible and protected them

The Mass-Action Principle

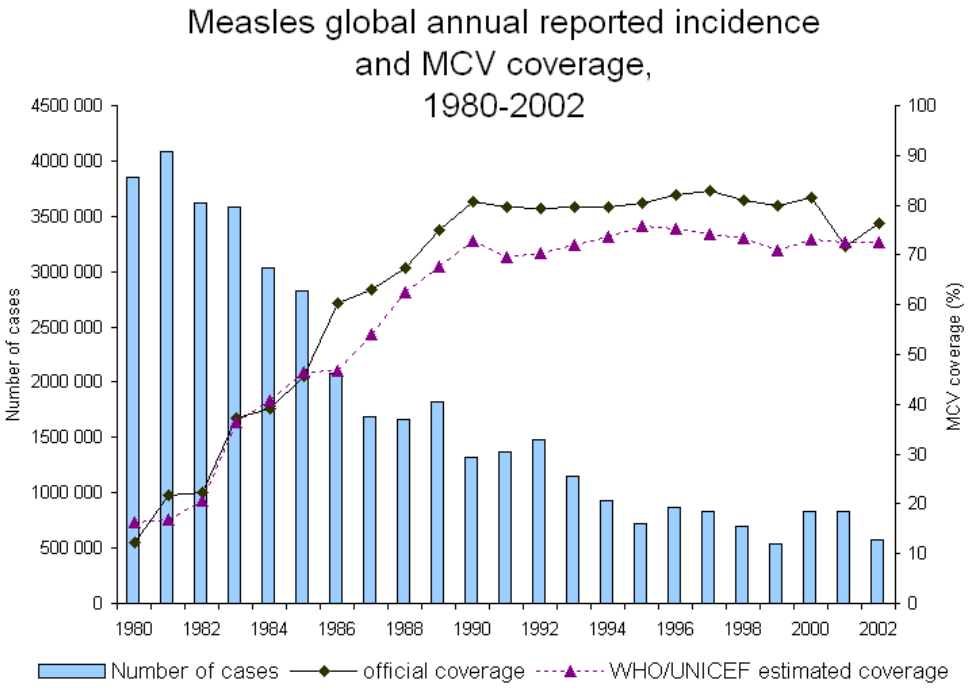


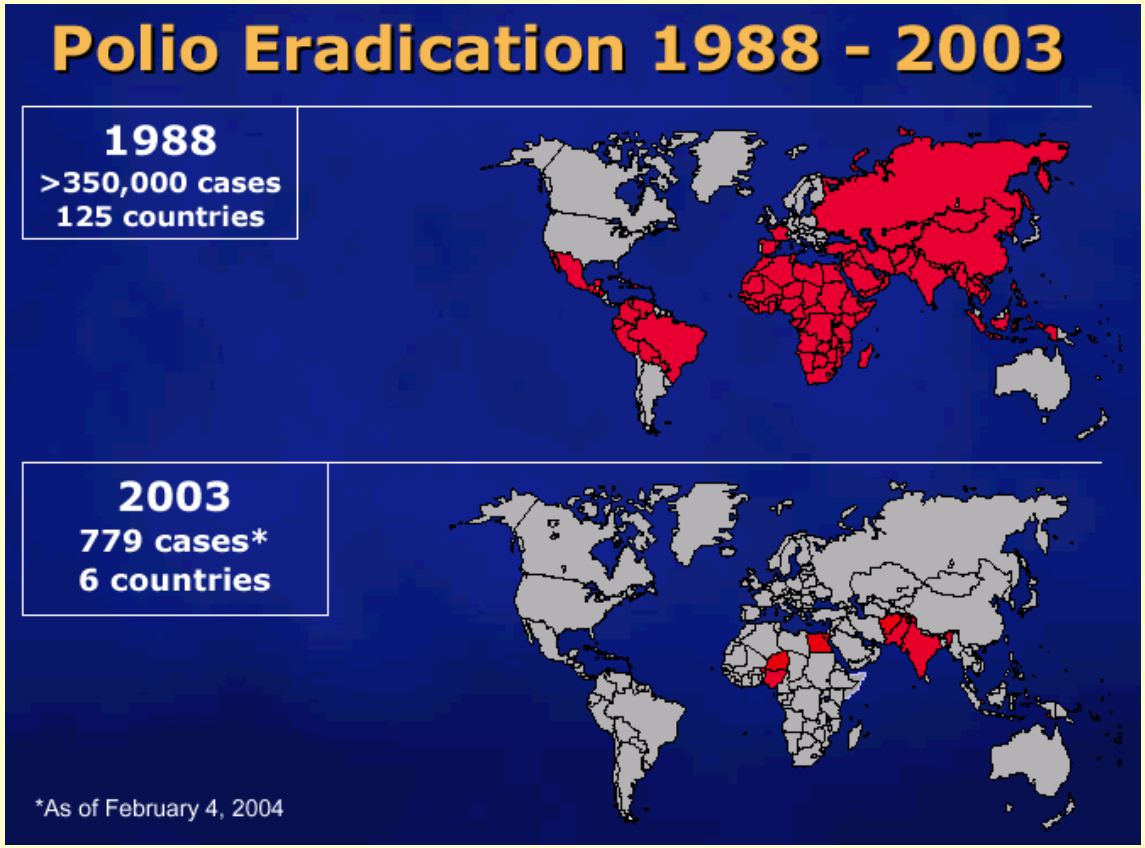
Contacts are made in random.

Vaccinate the susceptible.

Number of new cases=P(transmission) X # of infectious X # of susceptible

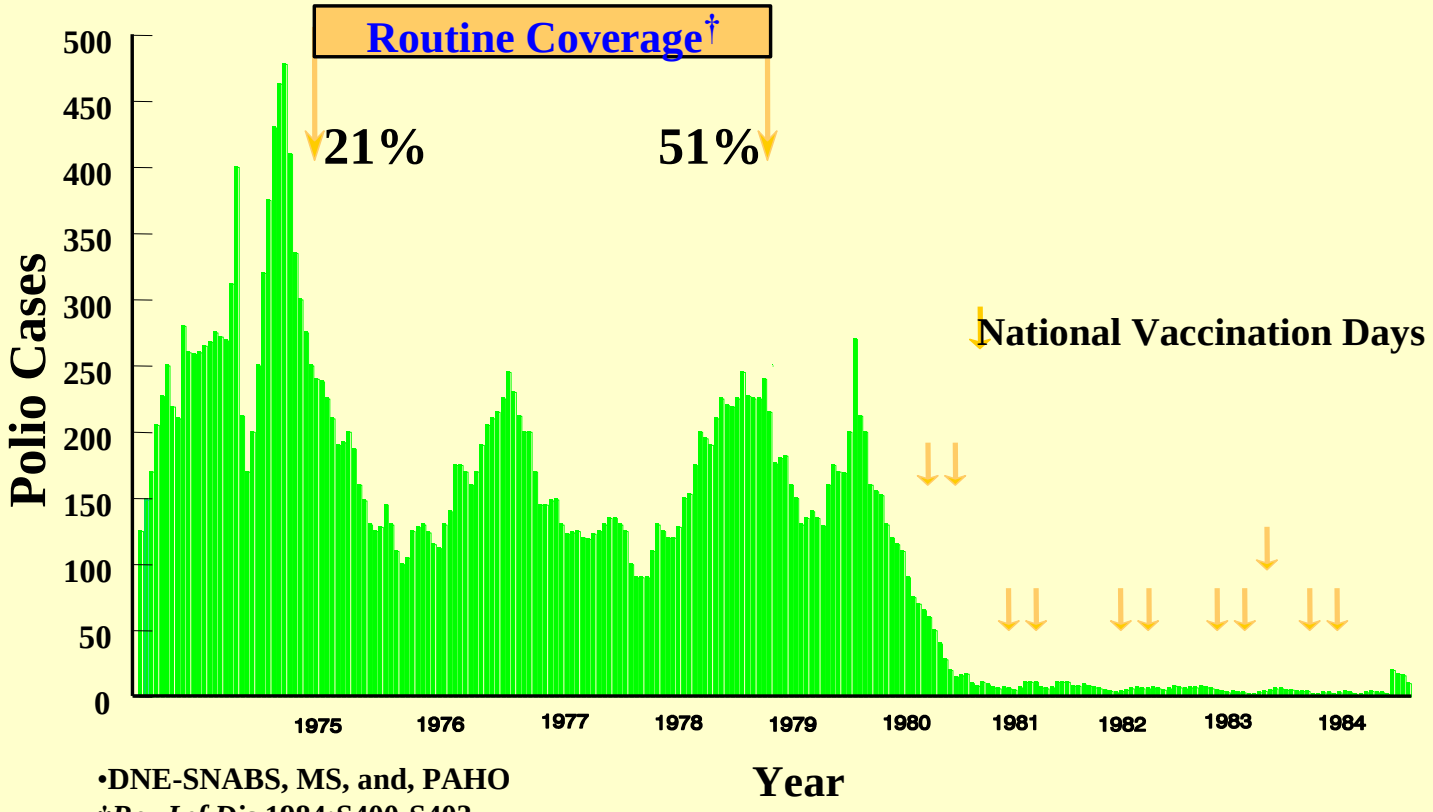
Vaccination against measles




Polio Eradication 1988 - 2003
1988
>350,000 cases
125 countries
2003
779 cases*
6 countries
*As of February 4, 2004

1

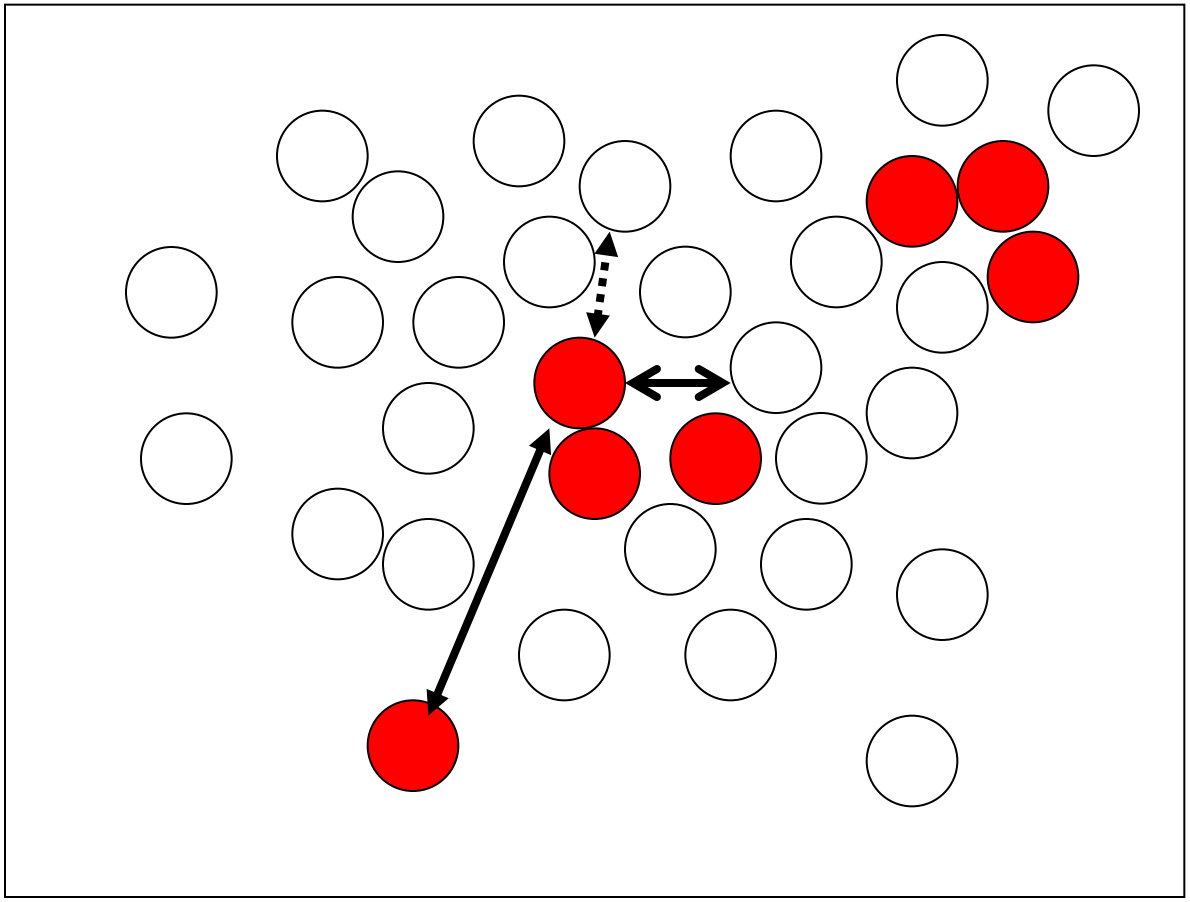
Polio Cases by Four-Week Period Brazil, 1975-1984*

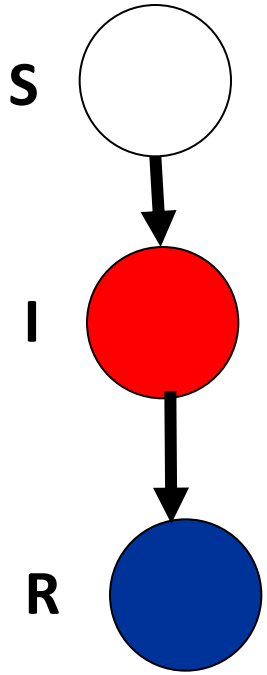


•DNE-SNABS, MS, and, PAHO

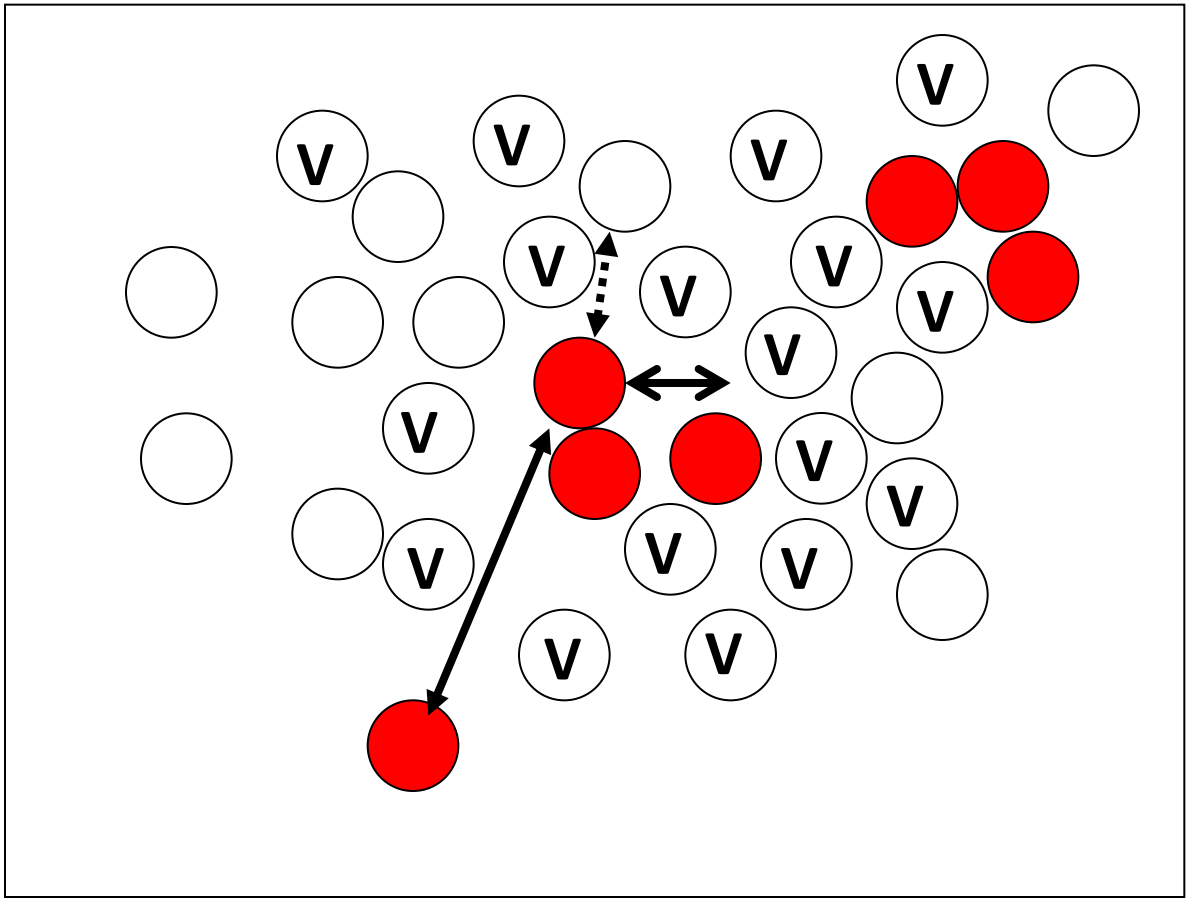
†*Rev Inf Dis* 1984;S400-S403

Vaccination

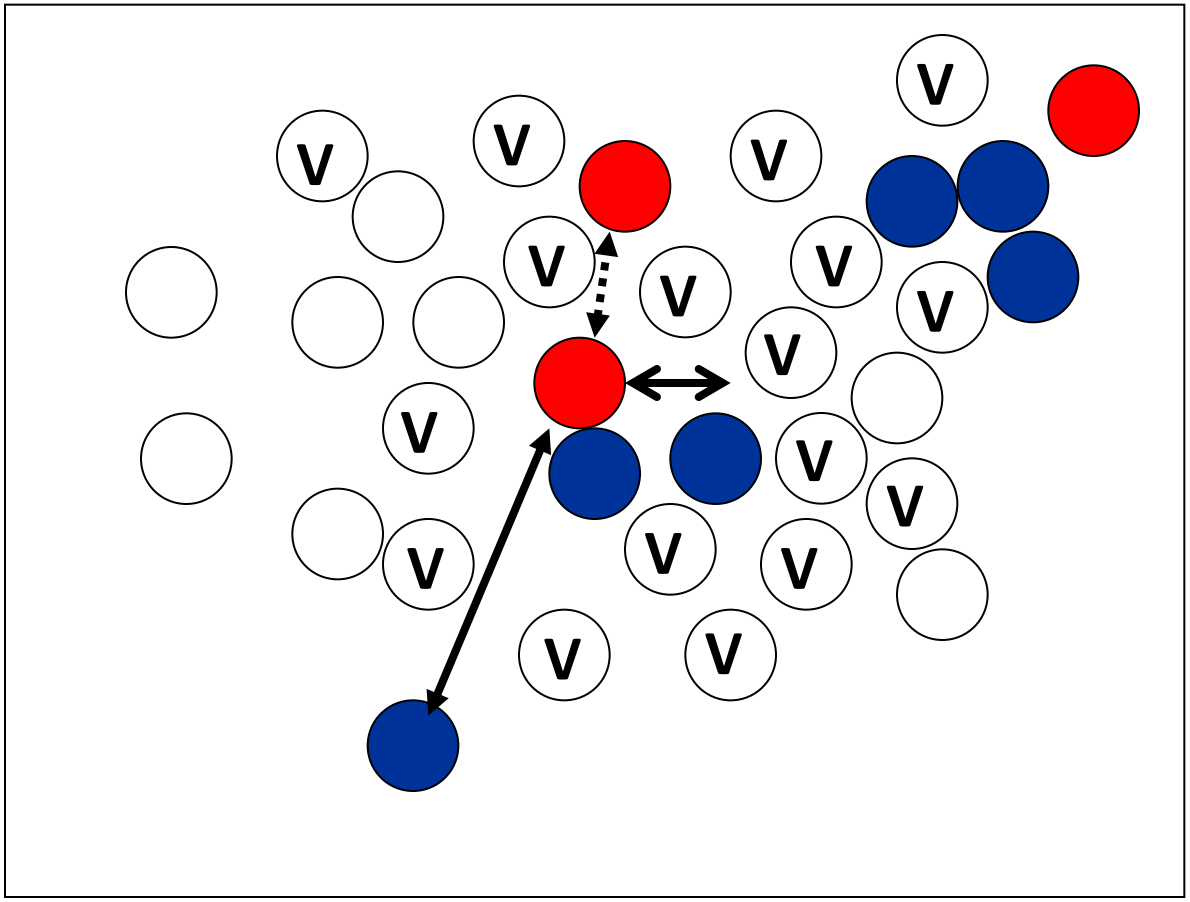


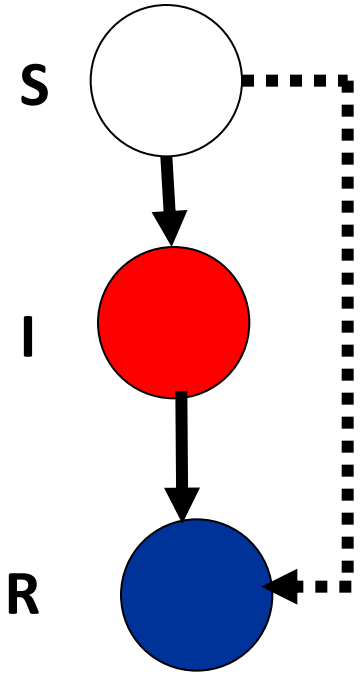


Vaccination



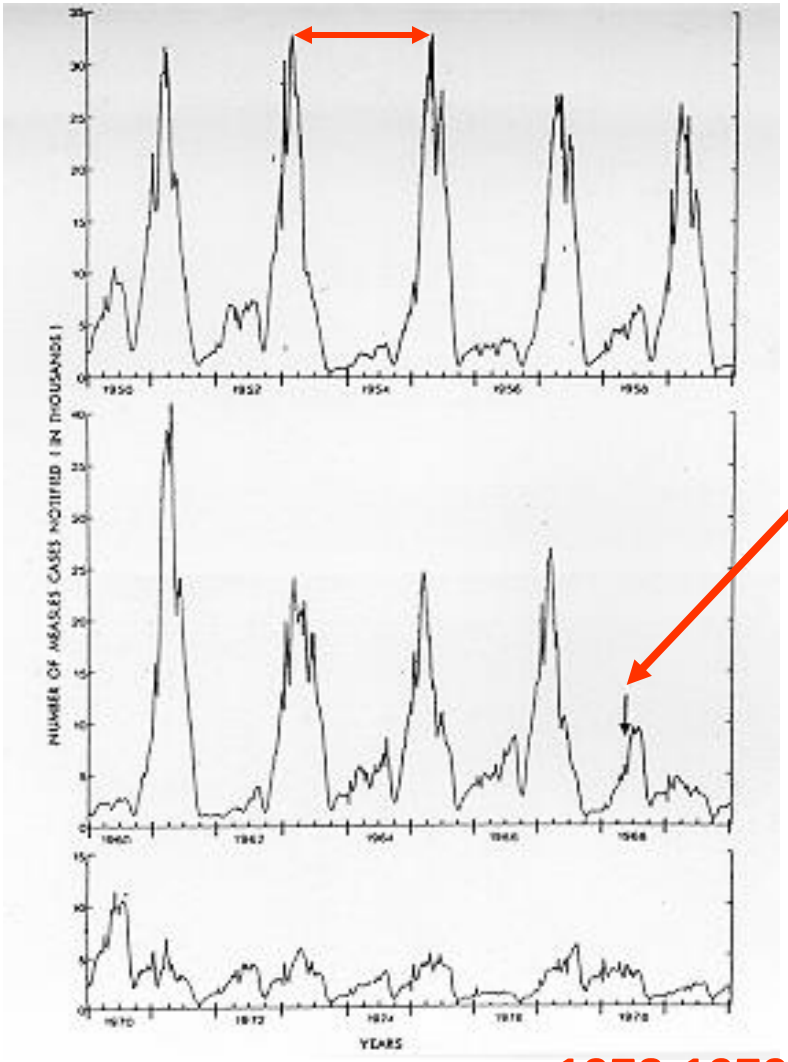
Vaccination





Example: vaccination of measles in UK

Measles in England and Wales



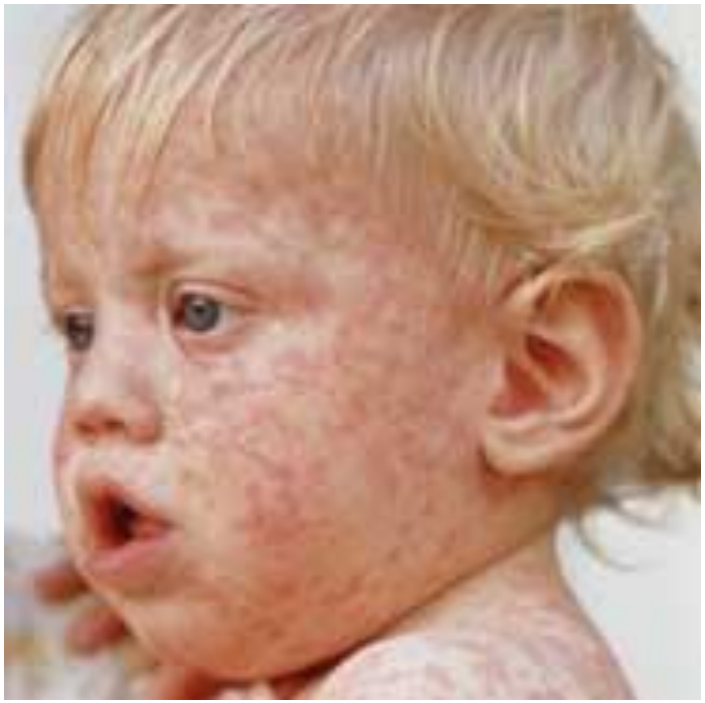
Vaccination

1967

1978-1979

TIMESONLINE August 31, 2007

- By June 10 only 136 cases of measles had been confirmed.
- But just over 11 weeks later this number has risen to 480, with new cases being detected every day.
- This compares with 756 cases recorded during the whole of 2006 – the highest year on record.



http://www.timesonline.co.uk/tol/life_and_style/health/child_health/article2358240.ece

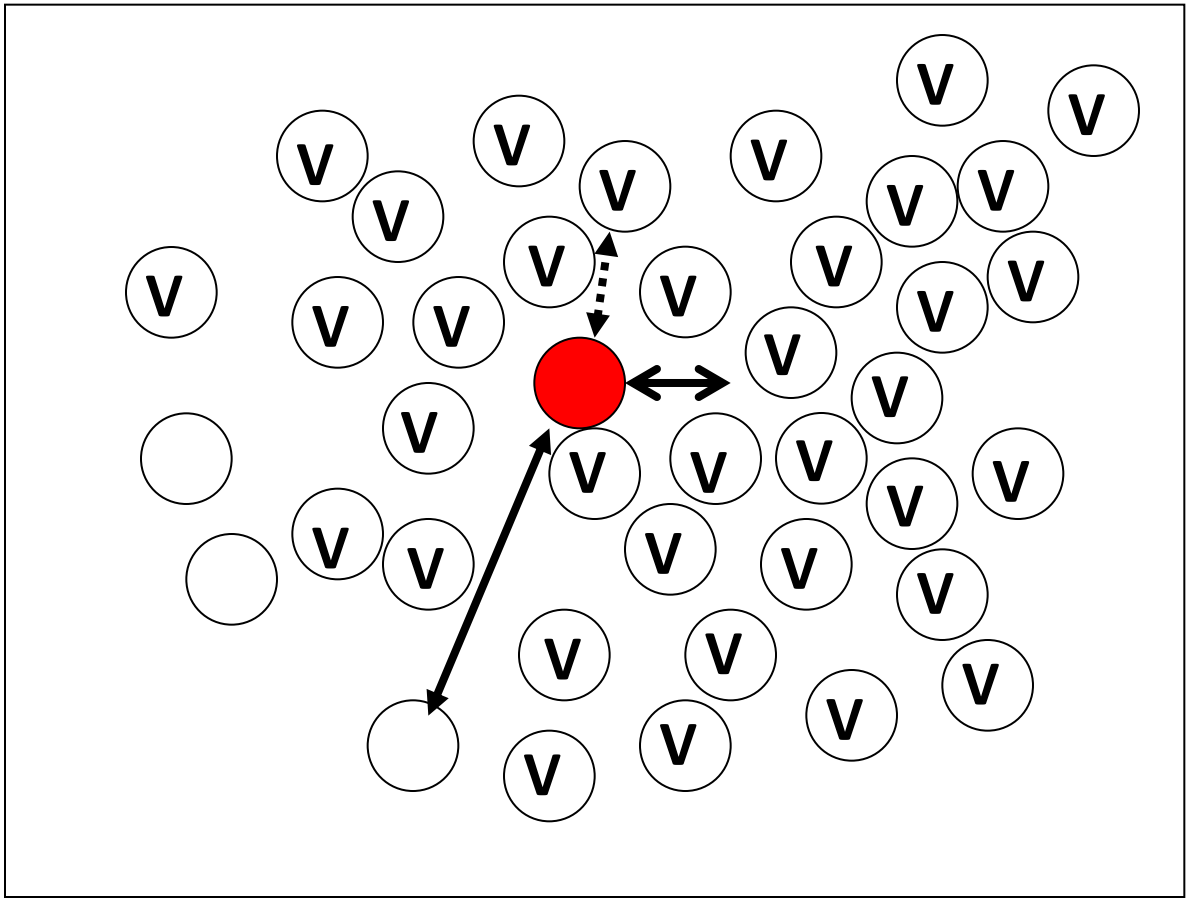
THE INDEPENDENT ON SUNDAY

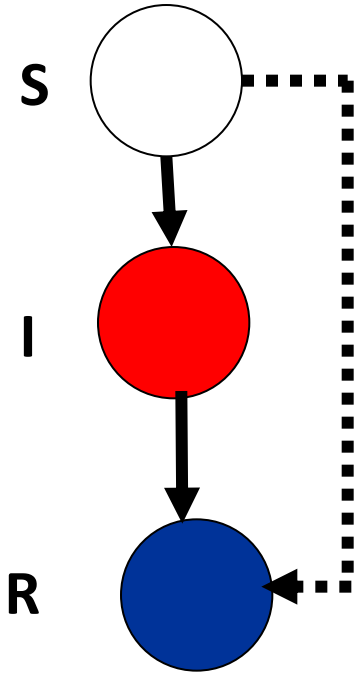
Saturday, 21 June 2008

- It was difficult to explain the large increase this year, the HPA said, but parents not vaccinating their children and a lower uptake of a second MMR "booster" dose are thought to be key factors.
- In UK, vaccination rates against MMR fell from 92 per cent a decade ago to 79 per cent in 2004.
- Vaccination rates against MMR vary widely across the UK and are especially low in London.
- In the last quarter of 2007, the rate stood at 71 per cent for children at age two (first dose) and 50 per cent at age five (second dose) compared with the 95 per cent coverage needed to maintain herd immunity and prevent endemic spread.

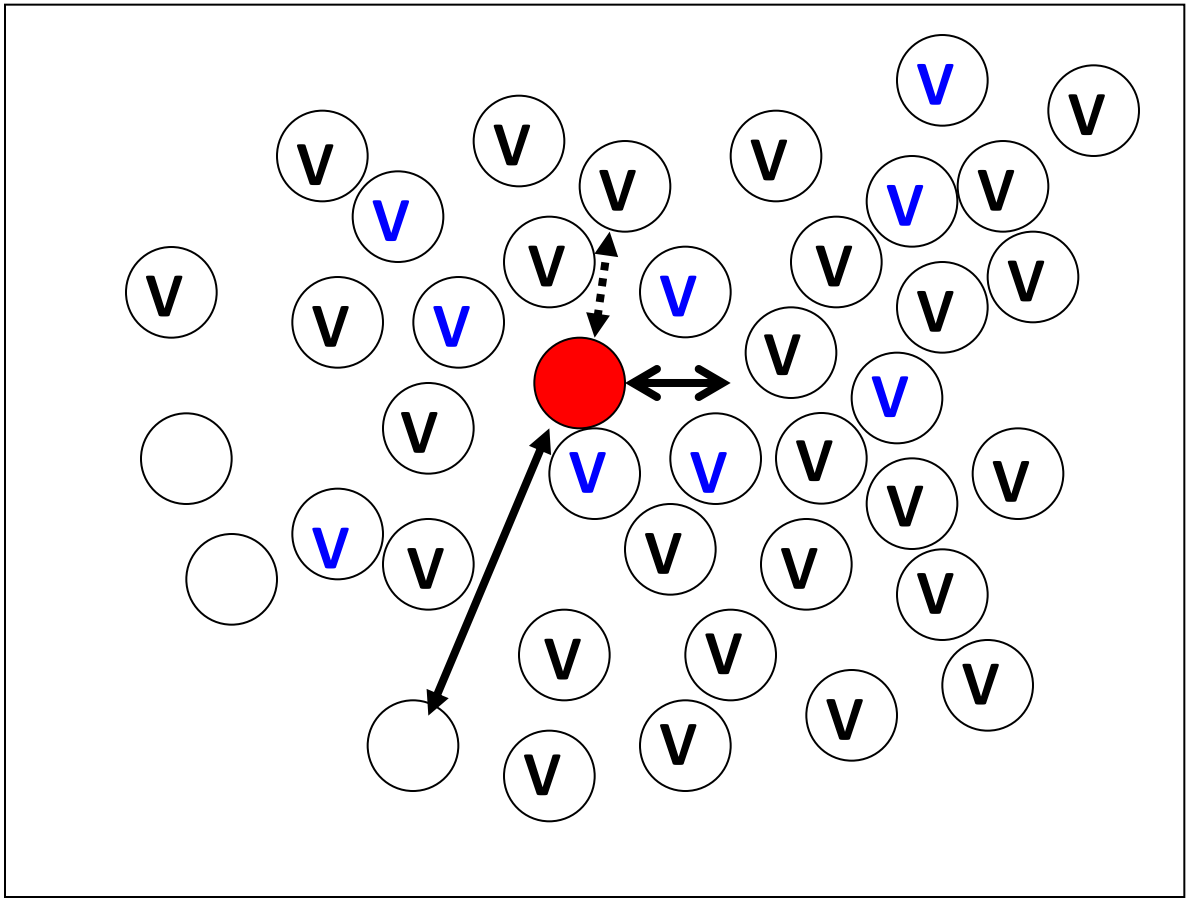
http://www.independent.co.uk/life-style/health-and-wellbeing/health-news/official-warning-measles-endemic-in-britain-851584.html

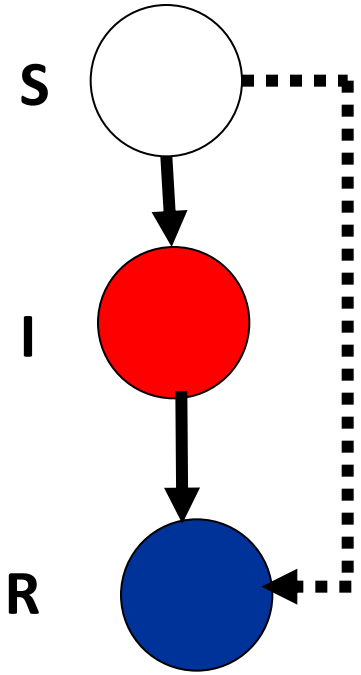
Vaccination rates ~92%





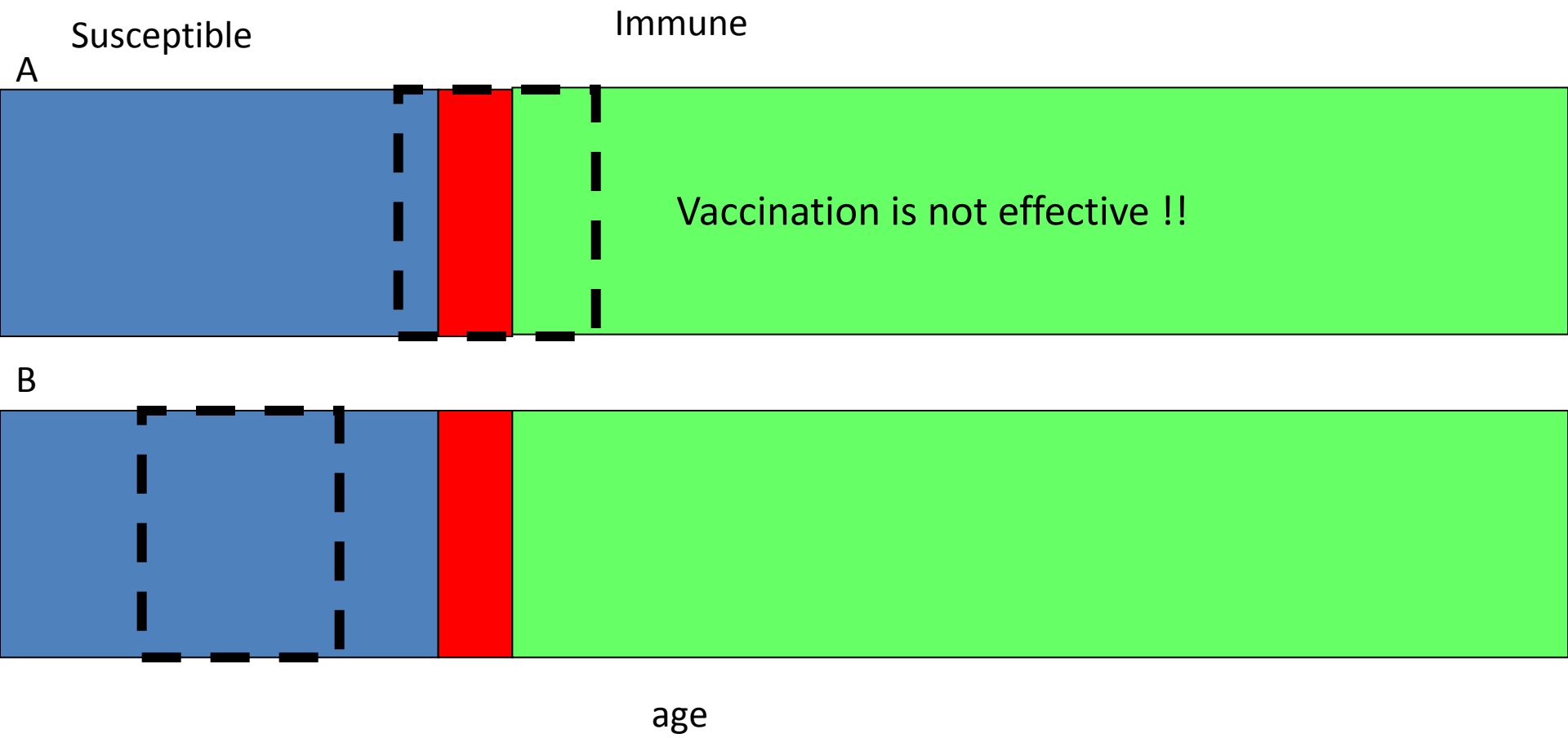
Vaccination rates ~70%





The time window for vaccination

When do we need to vaccinate ?

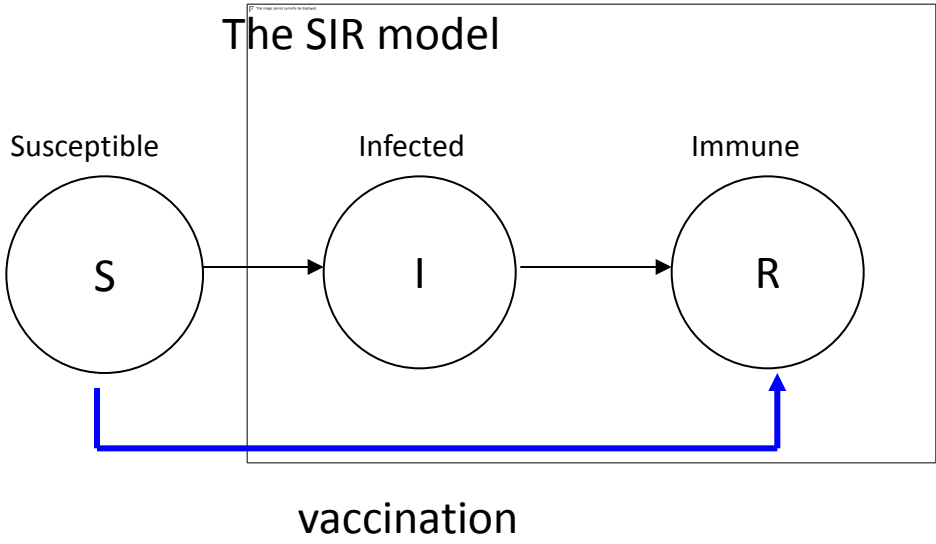


Vaccination rate

If the vaccination rate decreases more individuals stay in the susceptible class.

The probability for a contact between infected individual and susceptible increases.

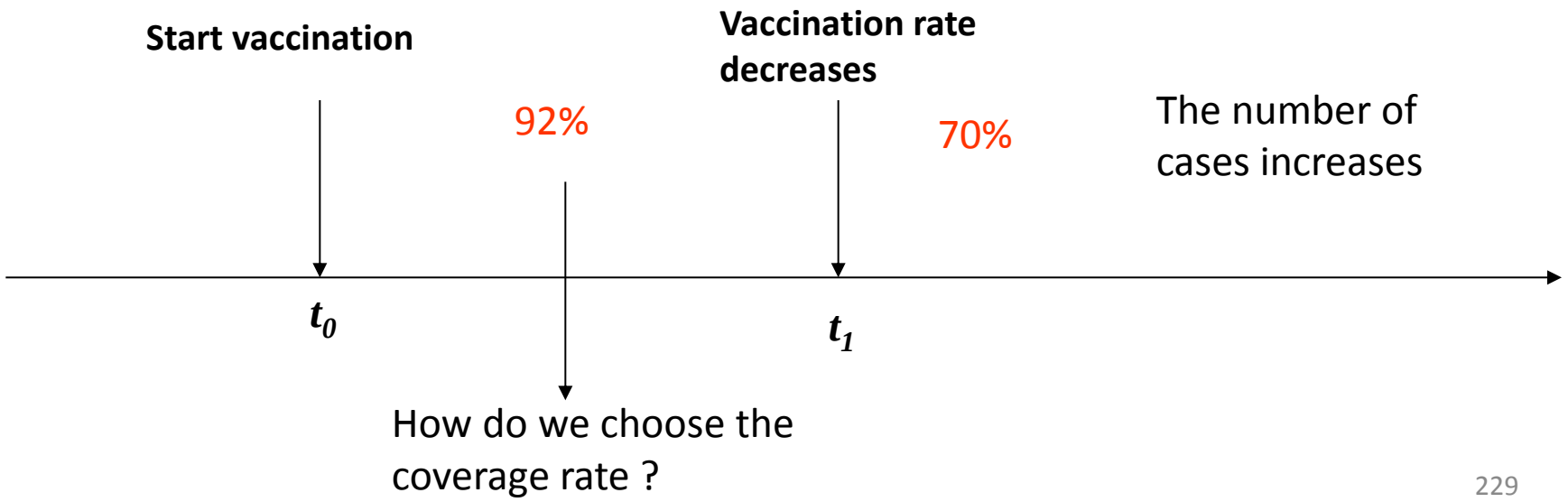
The “fuel” for an infection is not the number of infectious individuals but the number of susceptible.



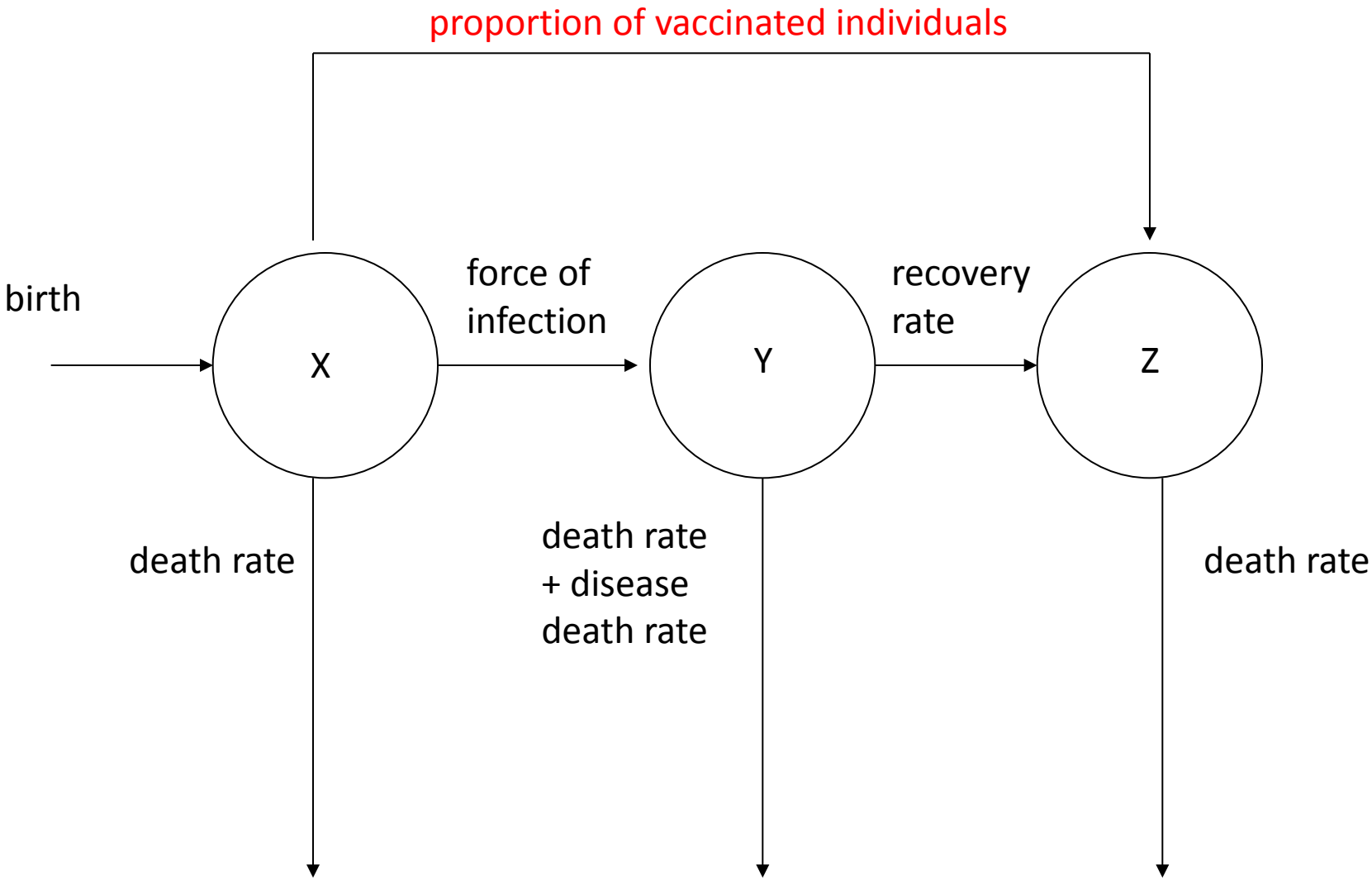
The “fuel” for an epidemic

THE INDEPENDENT ON SUNDAY Saturday, 21 June 2008

- It was difficult to explain the large increase this year, the HPA said, but parents not vaccinating their children and a lower uptake of a second MMR “booster” dose are thought to be key factors.



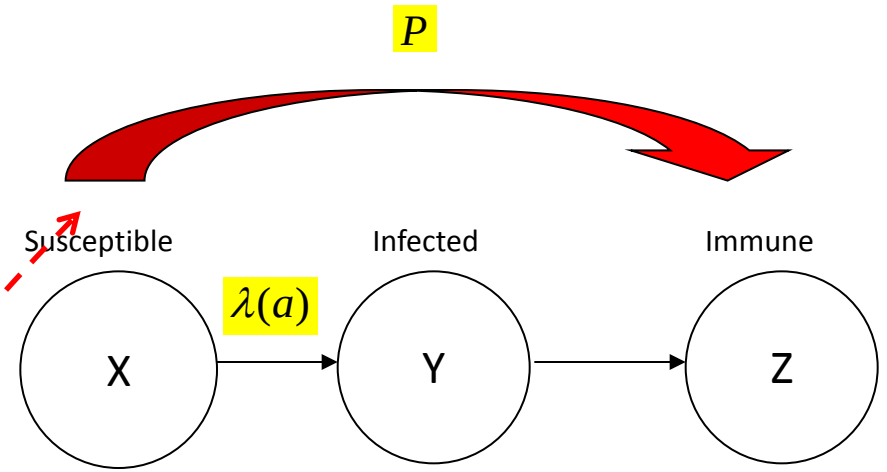
Model Structure: Vaccination in SIR model



Model Structure: Vaccination in SIR model

- Open population:

$$\frac{dS(a)}{da} = (1-P)\times B\mu - \lambda S(a)$$
$$\frac{dI(a)}{da} = \lambda S(a) - \sigma I(a)$$
$$\frac{dR(a)}{da} = P\times B\mu + \sigma I(a)$$



The SIR model

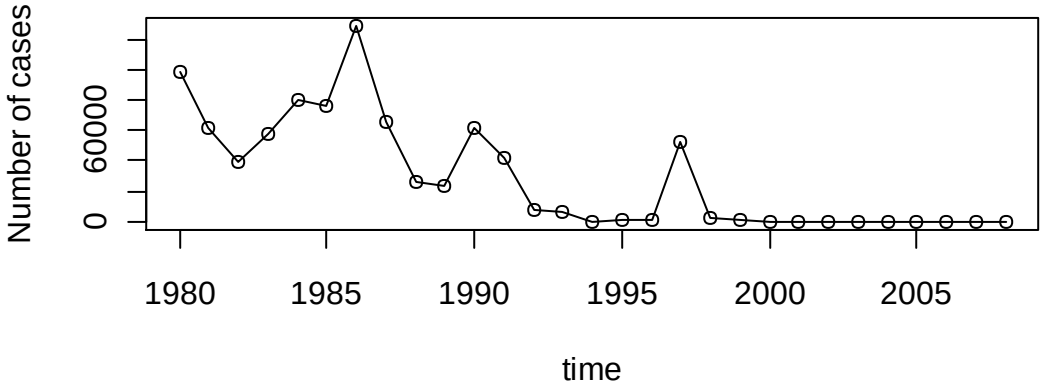
- Vaccination at birth.
- P: proportion of vaccinated individuals.

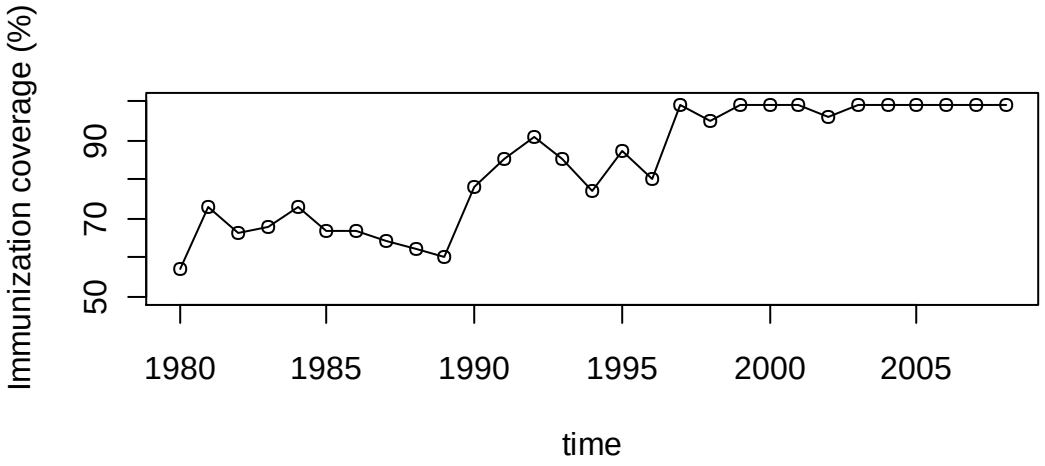
Effect of Vaccination

- Number of cases.
- Average age at infection.
- Proportion of susceptible.
- Inter-epidemic period.
- Force of infection.

Effect of Vaccination

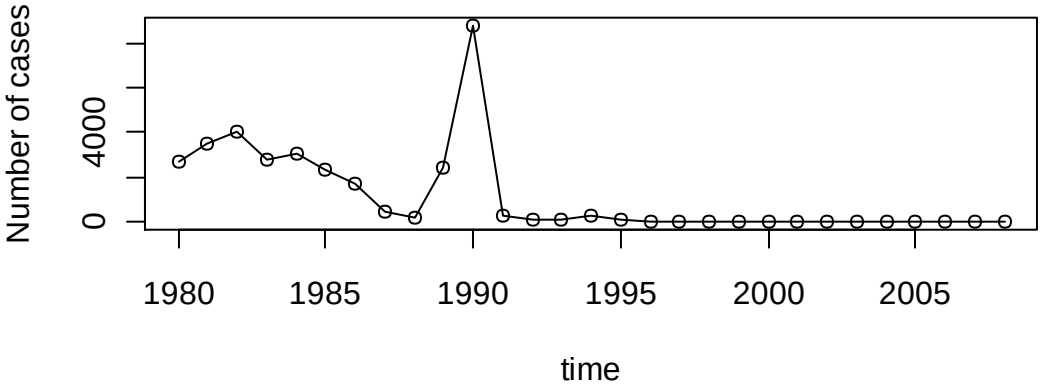
Number of measles cases in Brazil and coverage.

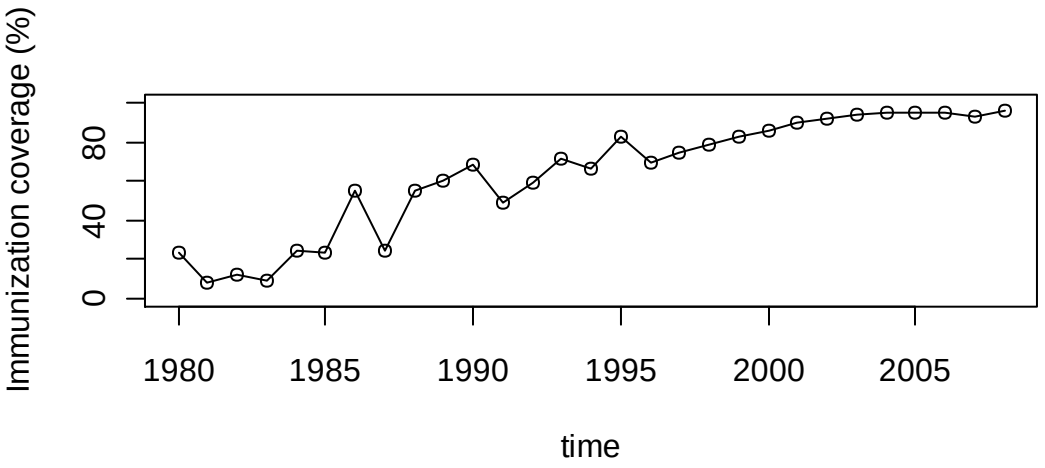




Effect of Vaccination

Number of measles cases in Guatemala and coverage.





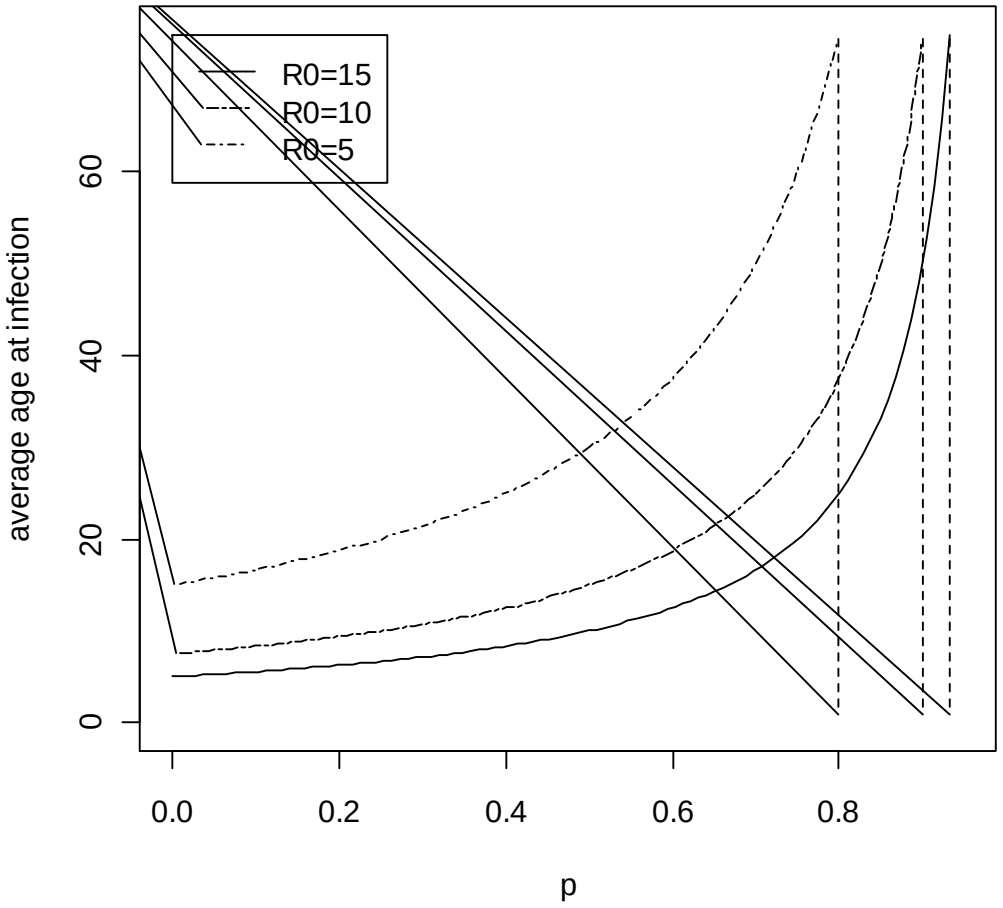
Effect of Vaccination: average age at infection

Critical proportion of vaccination:

$$P_c = \frac{1}{R_0}$$

New average age at infection:

$$A' = \frac{A}{1-P}$$

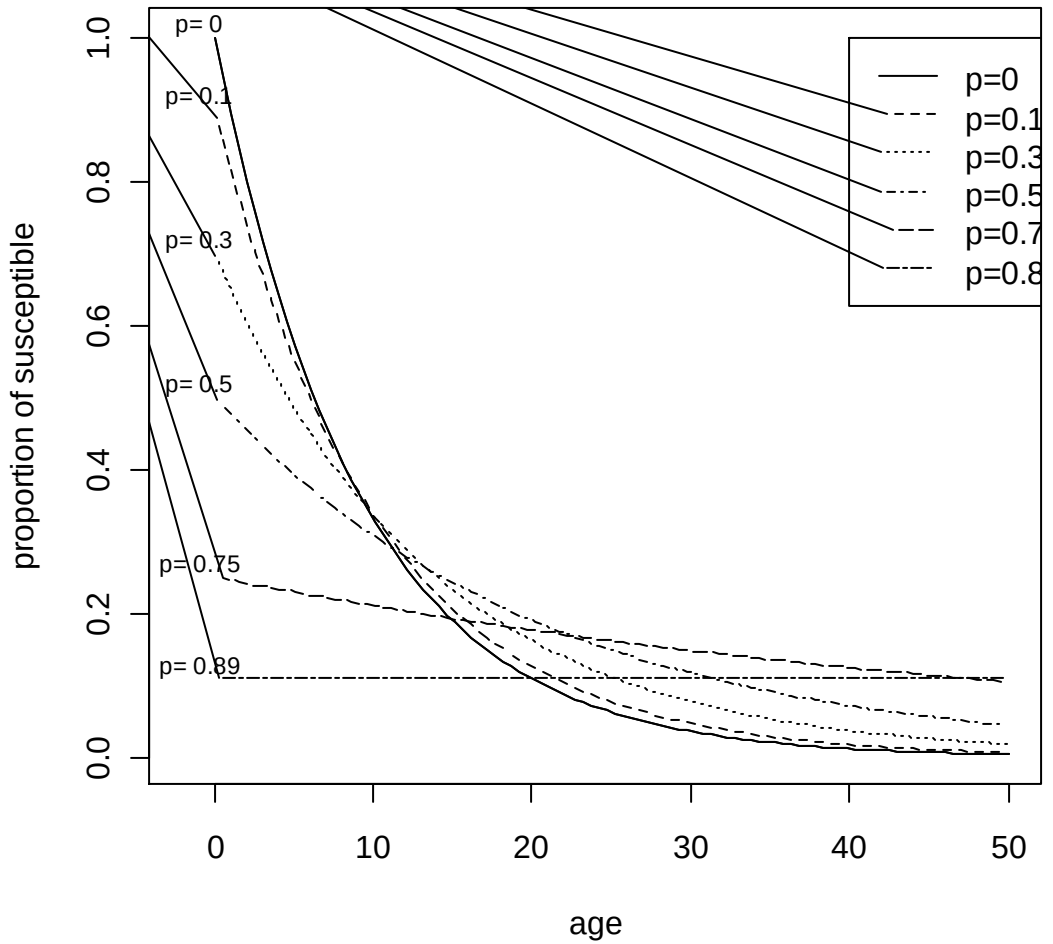


Effect of Vaccination: proportion of susceptible at equilibrium

Critical proportion of vaccination:

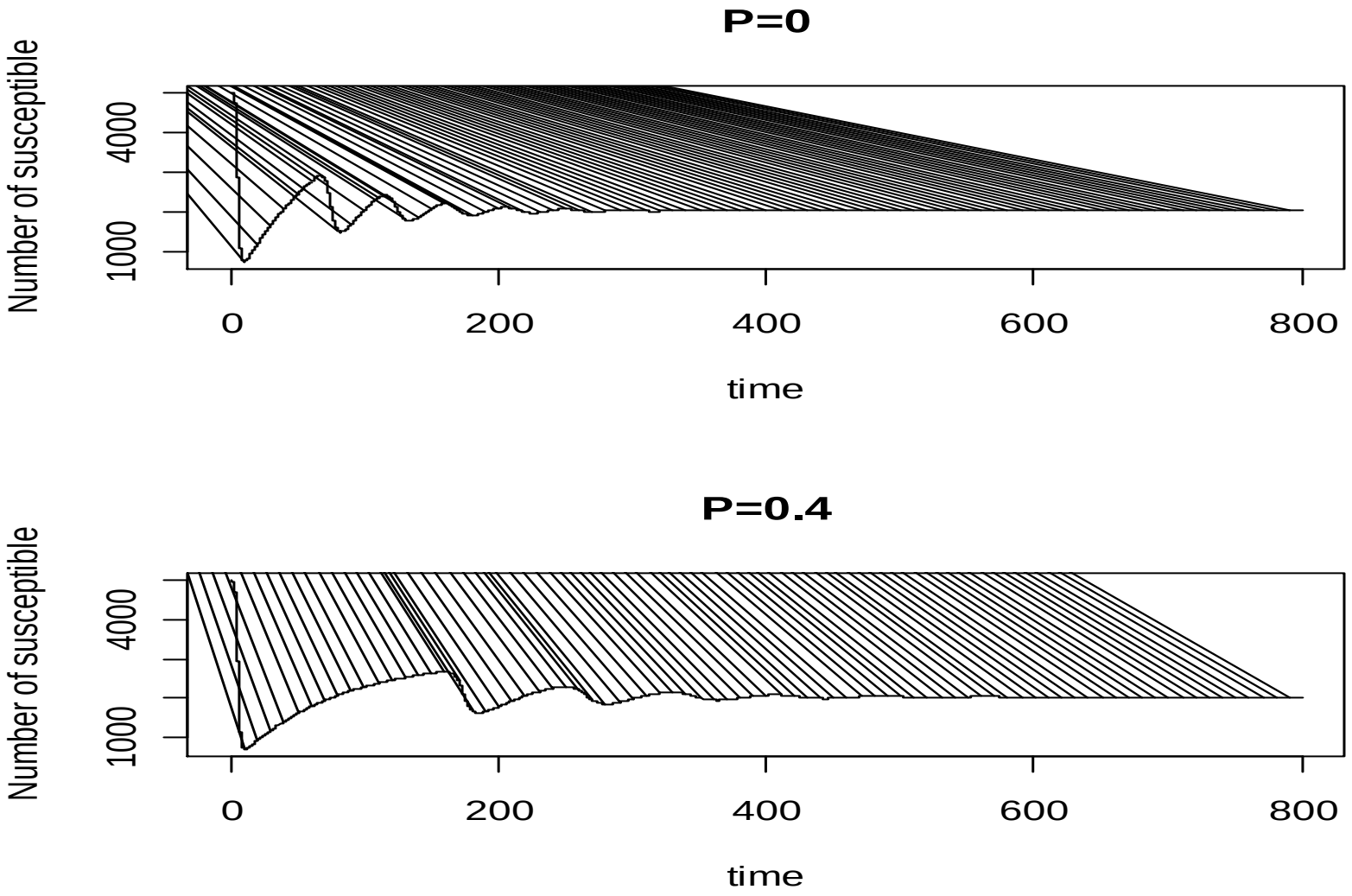
$$P_c = \frac{1}{R_0}$$

$$s(a) \rightarrow (1-P)e^{-\lambda' a}$$



Effect of Vaccination: Dynamic

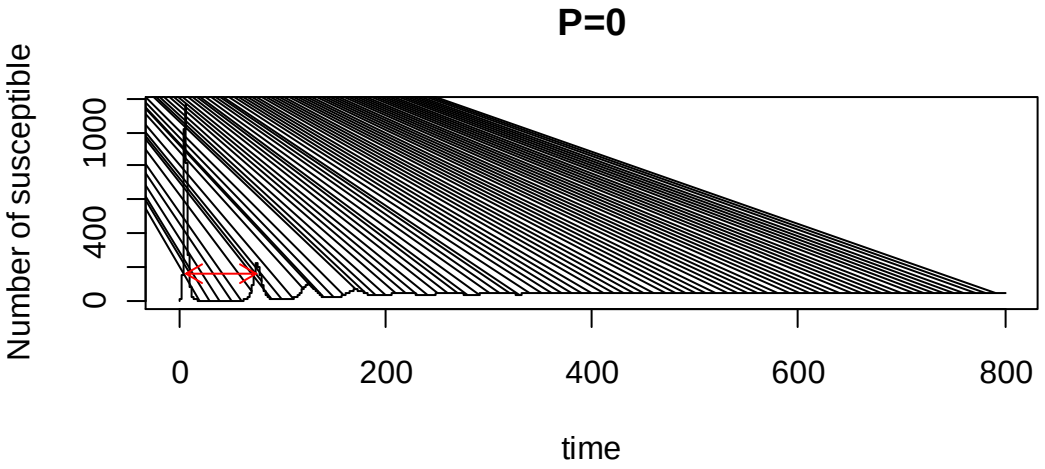
Number of susceptible

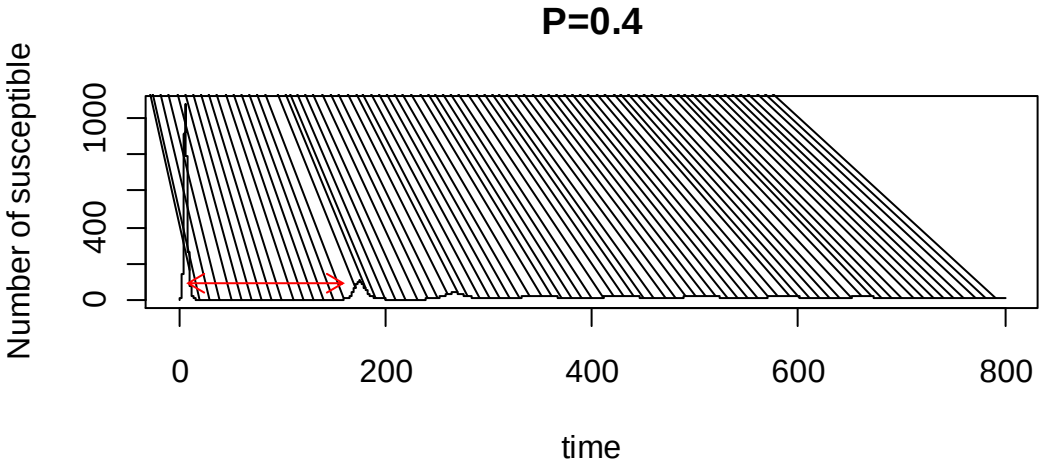


Effect of Vaccination: Dynamic

Number of infected

Inter-epidemic period.





Effect of Vaccination: Dynamic

Critical proportion of vaccination

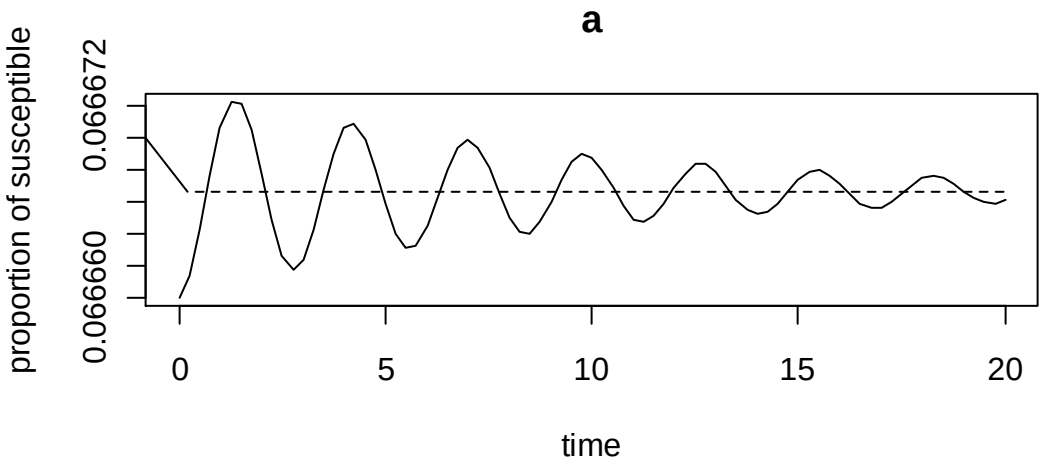
$$P_c = \frac{1}{R_0}$$

Force of infection in the new equilibrium

$$\lambda' = \mu R_0 (P_c - P) \Rightarrow P \to P_c \Rightarrow \lambda' \to 0$$

Effect of Vaccination: Dynamic

Proportion of susceptible and force of infection.



Parameter setting:

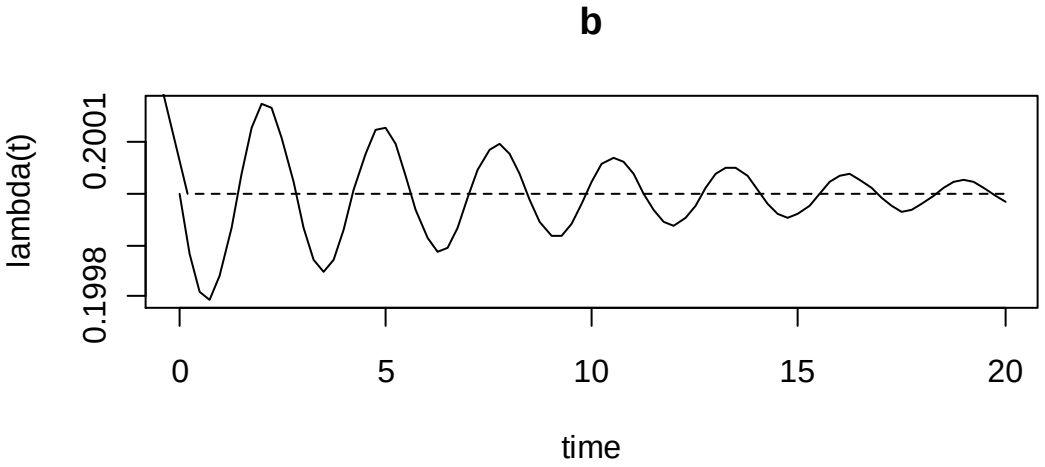
$\lambda_0 = 0.2$

$\frac{1}{\mu} = 70$

$\frac{1}{\nu} = 25$

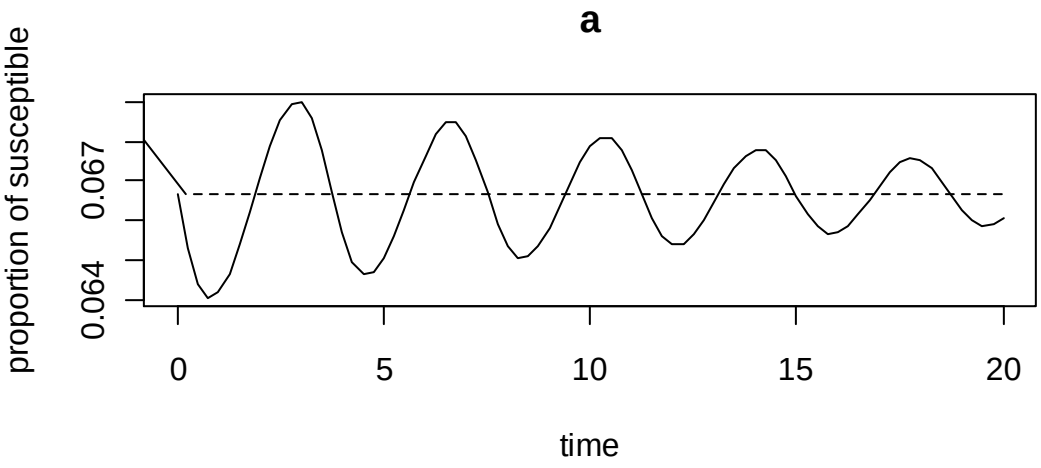
$R_0 = 15$

$P = 0.0$



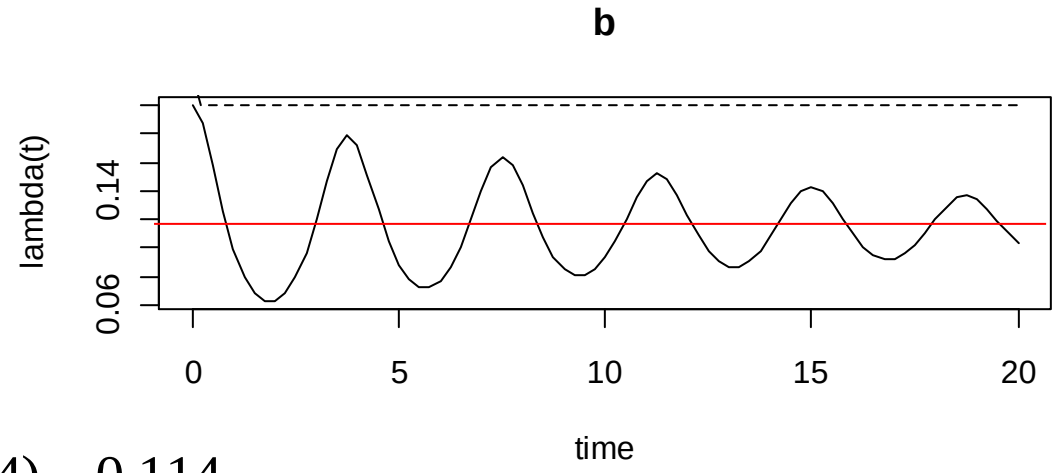
Effect of Vaccination: Dynamic

Proportion of susceptible and force of infection.



Parameter setting:

$$\lambda_0 = 0.2$$
$$\frac{1}{\mu} = 70$$
$$\frac{1}{\nu} = 25$$
$$R_0 = 15$$
$$P = 0.4$$



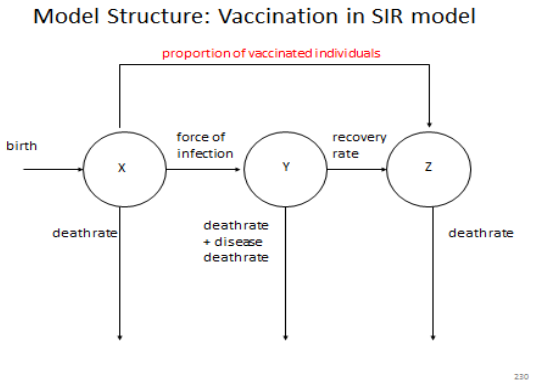
$$\lambda' = \frac{1}{70} \times 15 \times (0.9333 - 0.4) = 0.114$$

Vaccination in SIR model in R (open population)

```
parameters <- c(mu=1/75,beta=0.001/2,v=1)
state <- c(X=4999,Y=1,Z=0)
times<-seq(0,800,by=0.01)
p<-0.0
N<-5000

SIR<-function(t,state,parameters)
{
with(as.list(c(state, parameters)),
{
dX <- N*mu*(1-p)-beta*Y*X - mu*X
dY <- beta*Y*X - v*Y - mu*Y
dZ <- v*Y -mu*Z+N*mu*p
list(c(dX, dY, dZ))
})
}

require(deSolve)
out <- as.data.frame(ode(y=state,times=times,func=SIR,parms=parameters))
```



$$\frac{dS(t)}{dt} = N\mu(1-P) - \beta I(t)S(t) - \mu S(t)$$

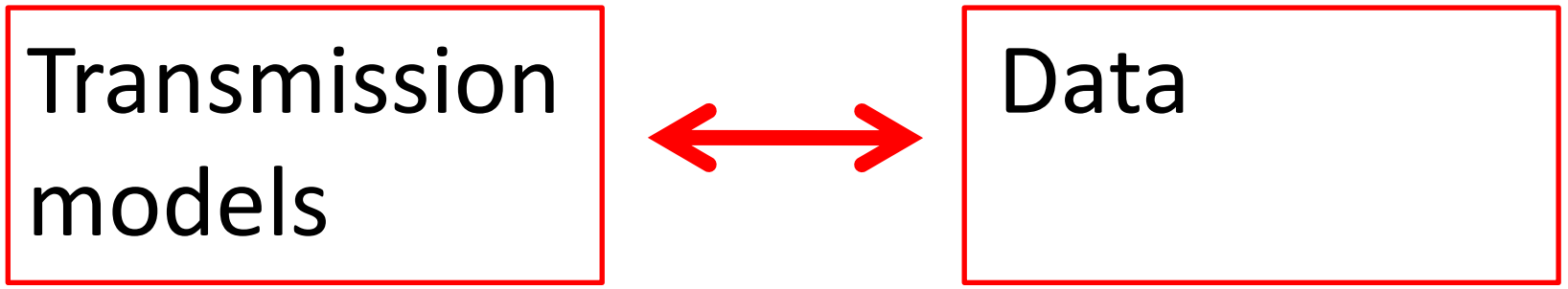
$$\frac{dI(t)}{dt} = \beta I(t)S(t) - \sigma I(t) - \mu I(t)$$

$$\frac{dR(t)}{dt} = N\mu \times P + \sigma I(t) - \mu R(t)$$

Outbreak data
Transmission model for HIV/AIDS

R program: ModelingIDinR1_V1_HIV&HCV_Sep2019.R

What are we looking for ?



Transmission model for HIV/AIDS.

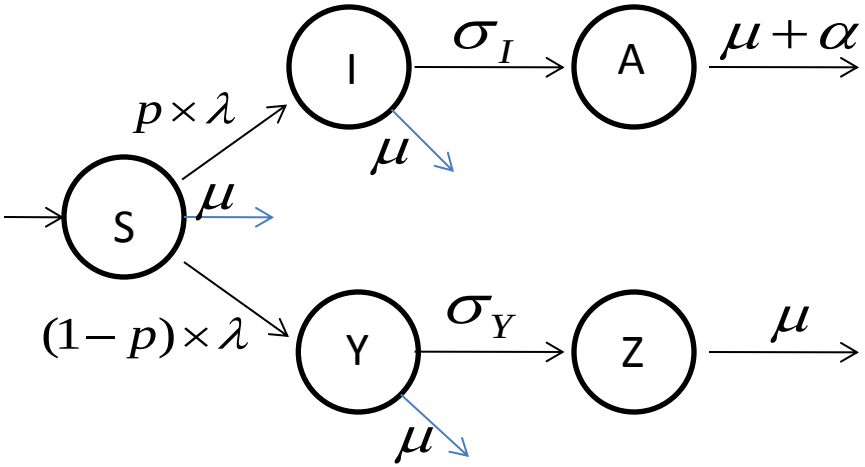
Very simple model (just for illustration) ?

Can we observed the "transmission process" in the data ?

What can we estimate from the data ?

Transmission model for HIV/AIDS

Transmission model for AIDS



A: Clinical AIDS

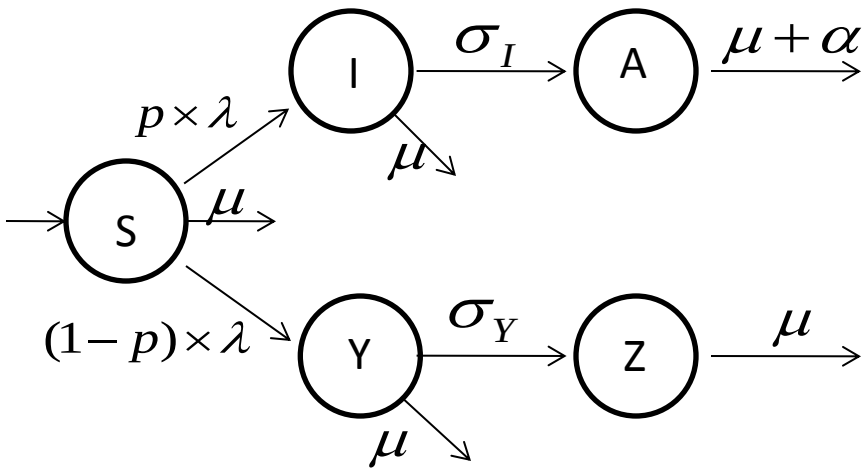
Z: infected but do not develop Clinical AIDS

The time unit : exposure time – the time from entering to the population.

Capasso 2008, Anderson and May 1991, Anderson 1988

Transmission model for HIV/AIDS

Transmission model for AIDS



THE ODE system

$$\frac{dS(t)}{dt} = B\mu - \lambda S(t) - \mu S(t)$$

$$\frac{dI(t)}{dt} = P\lambda S(t) - (\sigma_I + \mu) I(t)$$

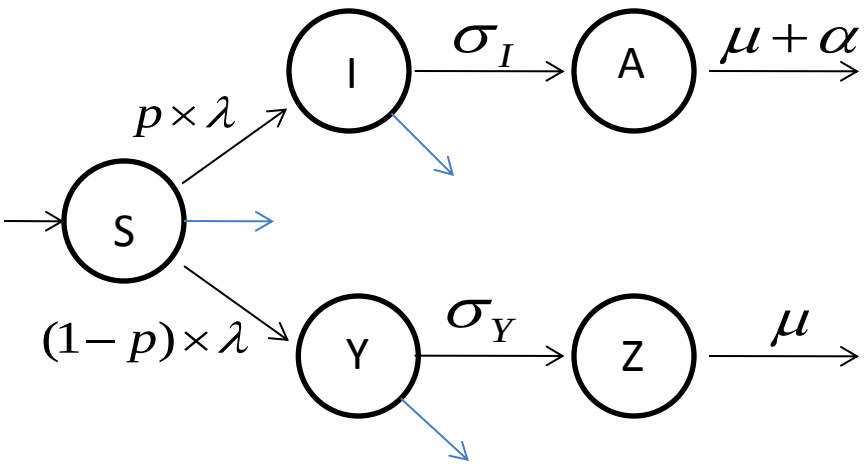
$$\frac{dY(t)}{dt} = (1-P)\lambda S(t) - (\sigma_Y + \mu) Y(t)$$

$$\frac{dA(t)}{dt} = \sigma_I I(t) - (\mu + \alpha) A(t)$$

$$\frac{dZ(t)}{dt} = \sigma_Y Y(t) - \mu Z(t)$$

Capasso 2008, Anderson and May 1991, Anderson 1988

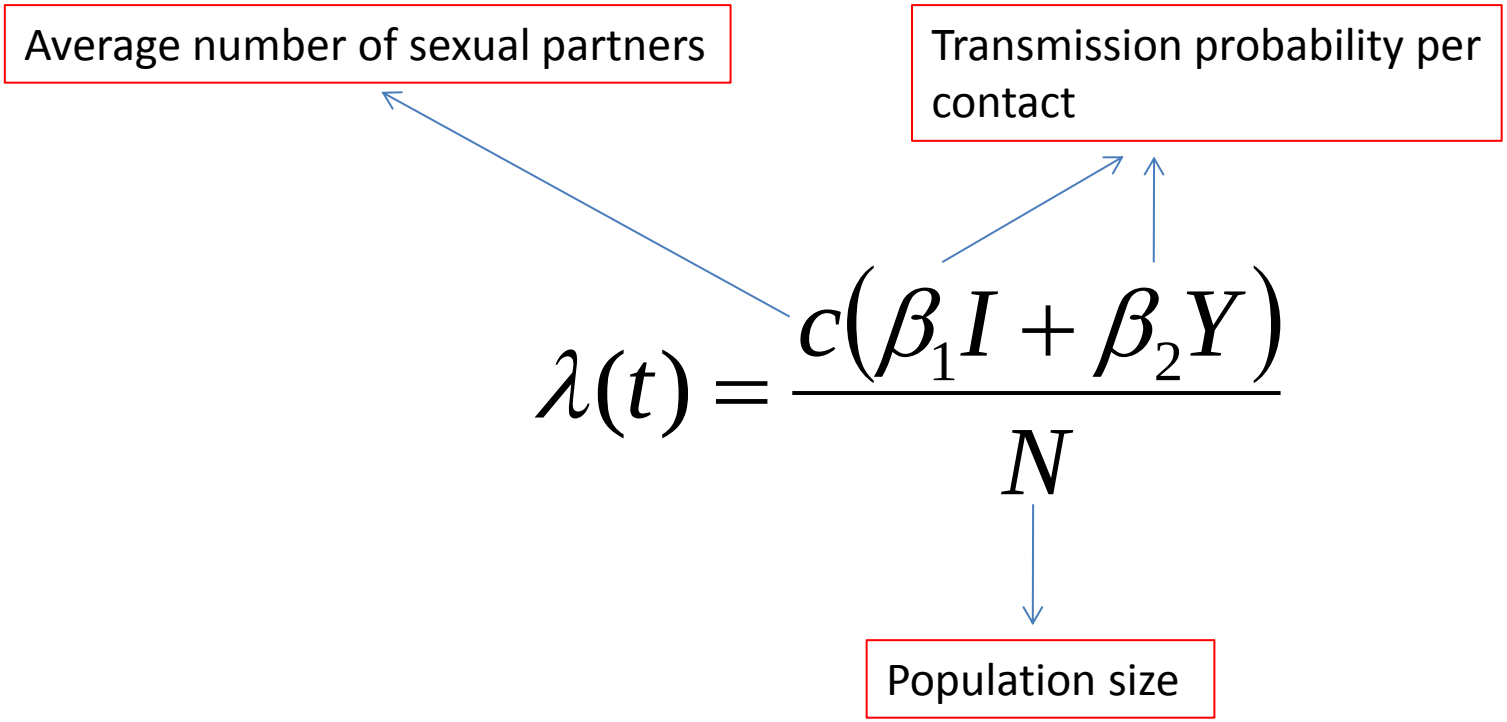
Model parameters



λ	Force of infection
σ_I	Incubation period
σ_Y	Incubation period
μ	Death rate
α	Death rate from AIDS

Capasso 2008, Anderson and May 1991, Anderson 1988

The force of infection



The force of infection is assumed to be proportional for the number of sexual partners of an individuals

The force of infection

Assumption:

$$c\beta_1 = c\beta_2 = 1$$

$$\lambda(t) = \frac{c(\beta_1 I + \beta_2 Y)}{N} = \frac{(I + Y)}{N}$$

Number of infected individuals

Population size

Model parameters in R

Model parameters:

1. Life expectancy: 75 years.
2. Incubation period: 8 years.
3. Proportion of individuals develop clinical AIDS 20%.
4. life expectancy with clinical AIDS: 1 year.

```
> parameters <- c(B=10000,mu=1/75,v1=1/8,v2=1/8,f=0.2,alpha=1)
> parameters
           B            mu            v1            v2             f
alpha
1.000000e+04 1.333333e-02 1.250000e-01 1.250000e-01 2.000000e-01
1.000000e+00
```

State variables

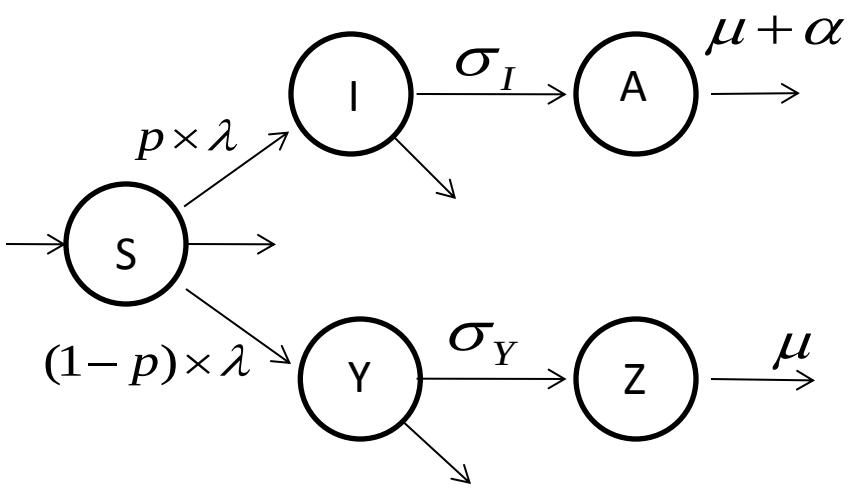
Population size of 10000.

At t=0, 5 individuals are infected.

```
> state <- c(y1=9995,y2=5,y3=0,y4=0,y5=0)
> state
  y1   y2   y3   y4   y5
9995    5    0    0    0
```

Specification of the model in R

The transmission model



The transmission model in R

```
AIDS<-function(t,state,parameters)
{
with(as.list(c(state, parameters)),
{
dy1 = B*mu-(mu+((y2+y3)/10000))*y1
dy2 = f*((y2+y3)/10000)*y1-(mu+v1)*y2
dy3 = (1-f)*((y2+y3)/10000)*y1-(mu+v2)*y3
dy4 = v1*y2-(mu+alpha)*y4
dy5 = v2*y3-mu*y5
list(c(dy1,dy2,dy3,dy4,dy5))
})
}
```

Specification of the model in R

$$\frac{dS(t)}{dt} = B\mu - \lambda S(t) - \mu S(t)$$

$$\frac{dI(t)}{dt} = P\lambda S(t) - (\sigma_I + \mu) I(t)$$

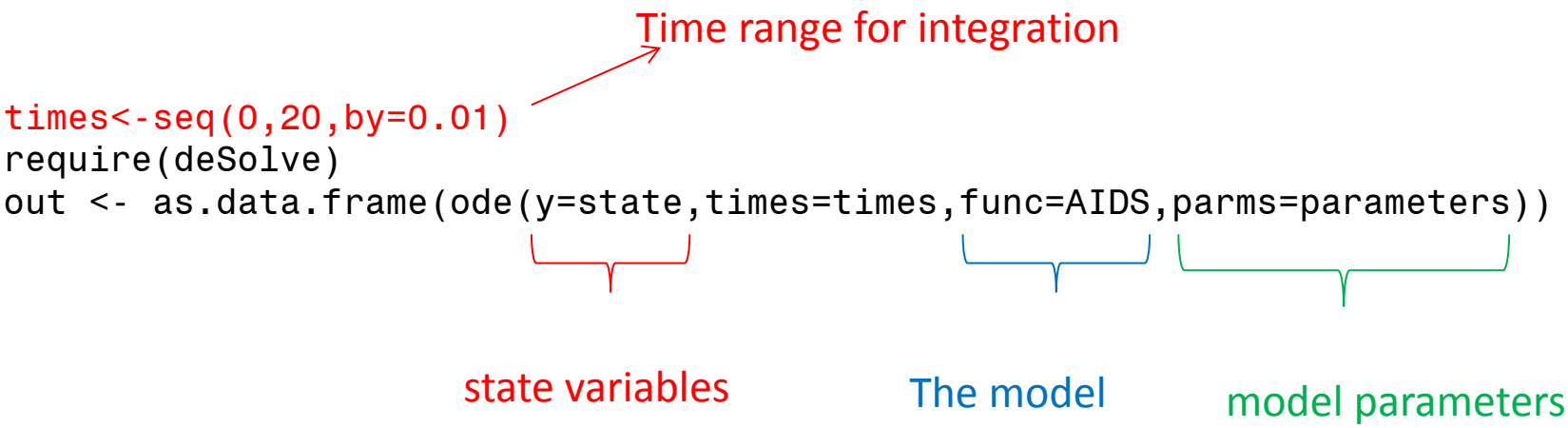
$$\frac{dY(t)}{dt} = (1-P)\lambda S(t) - (\sigma_Y + \mu) I(t)$$

$$\frac{dA(t)}{dt} = \sigma_I I(t) - (\mu + \alpha) A(t)$$

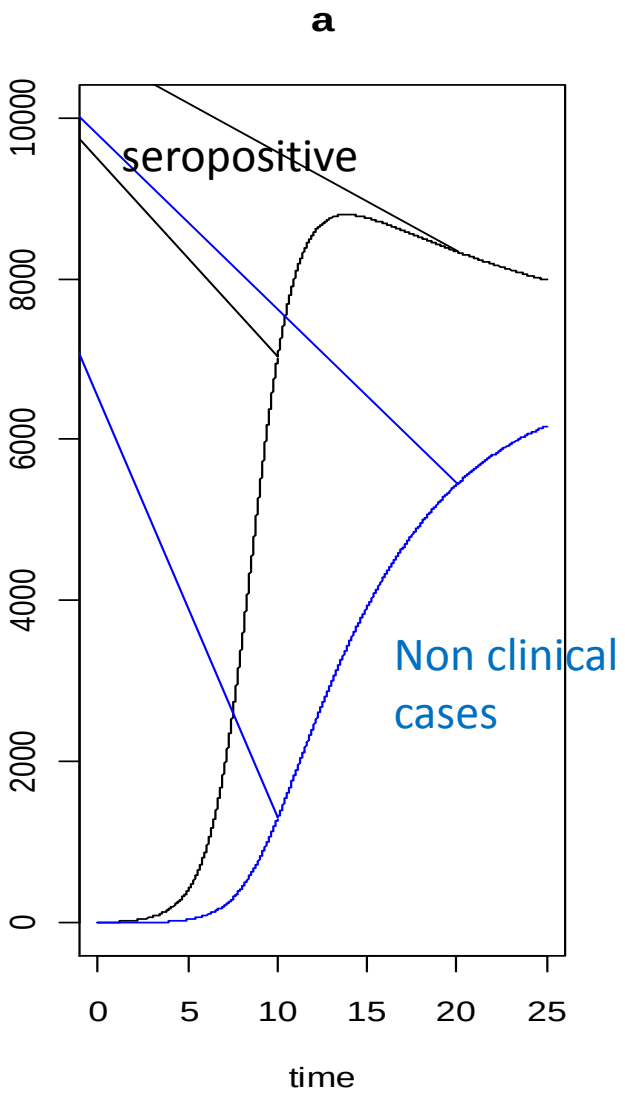
$$\frac{dZ(t)}{dt} = \sigma_Y Y(t) - \mu Z(t)$$

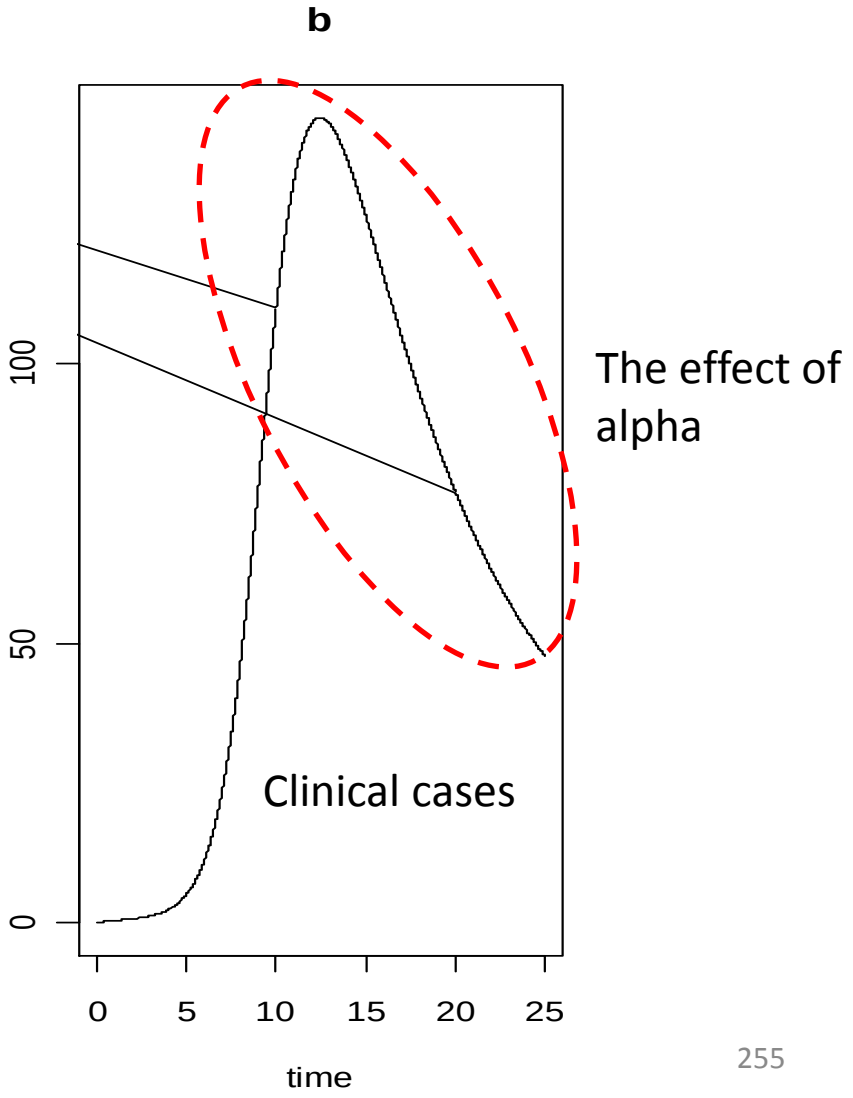
```
AIDS<-function(t,state,parameters)
{
with(as.list(c(state, parameters)),
{
dy1 = B*mu-(mu+((y2+y3)/10000))*y1
dy2 = f*((y2+y3)/10000)*y1-(mu+v1)*y2
dy3 = (1-f)*((y2+y3)/10000)*y1-(mu+v2)*y3
dy4 = v1*y2-(mu+alpha)*y4
dy5 = v2*y3-mu*y5
list(c(dy1,dy2,dy3,dy4,dy5))
})
}
```

Running the model in R

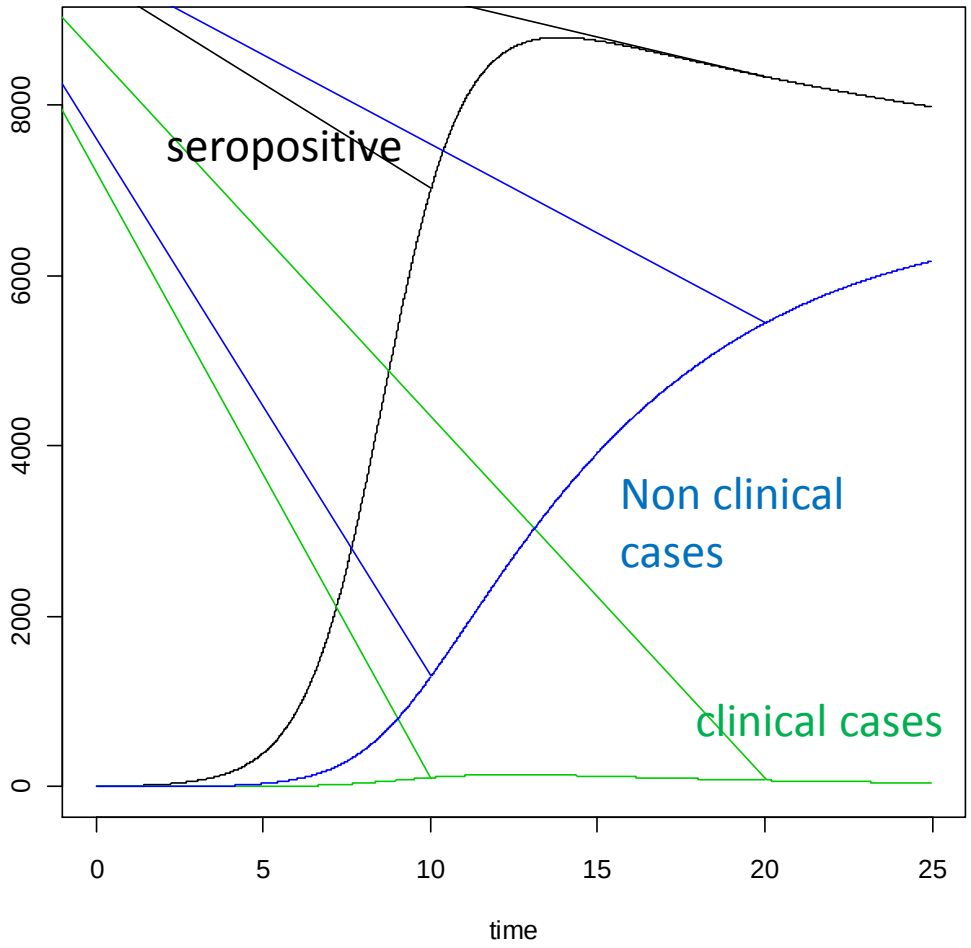


Solution


a
seropositive
Non clinical cases
0
2000
4000
6000
8000
10000
0
5
10
15
20
25
time


b
The effect of alpha
Clinical cases
0
50
100
0
5
10
15
20
25
time

Solution



Why we do not see so many clinical cases ?

Model parameters in R

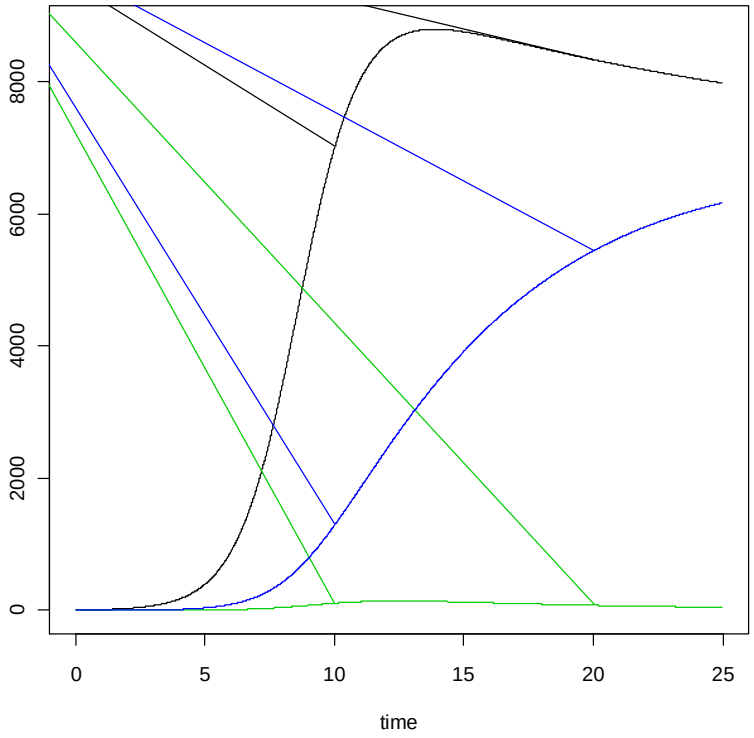
Model parameters:

1. Life expectancy: 75 years.
2. Incubation period: 8 years.
3. Proportion of individuals develop clinical AIDS 20%.
4. life expectancy with clinical AIDS: 1 year ➡ 10 years.

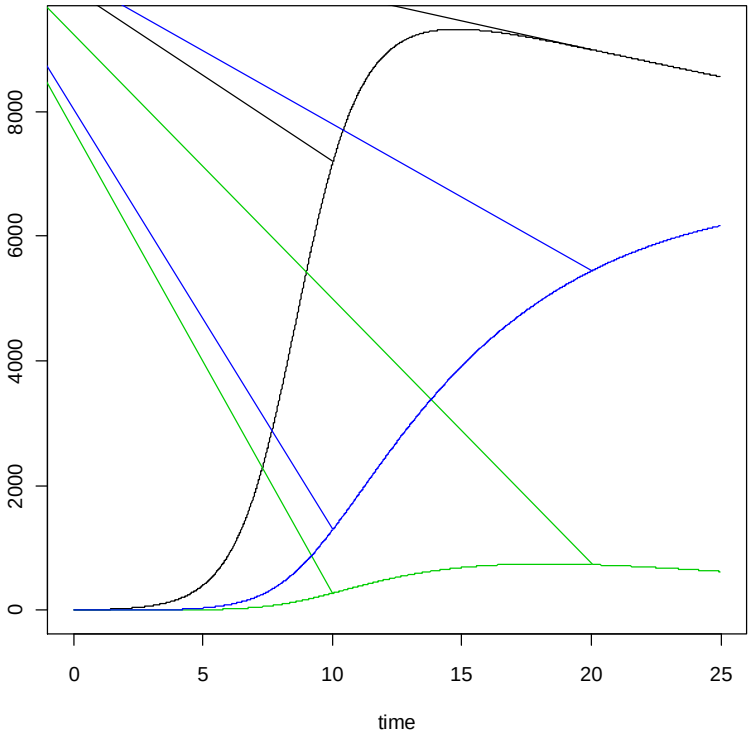
```
> parameters <- c(B=10000,mu=1/75,v1=1/8,v2=1/8,f=0.2,alpha=0.1)
> parameters
            B            mu            v1            v2             f
alpha
1.000000e+04 1.333333e-02 1.250000e-01 1.250000e-01 2.000000e-01
1.000000e-01
```

solution

life expectancy with clinical AIDS: 1 year

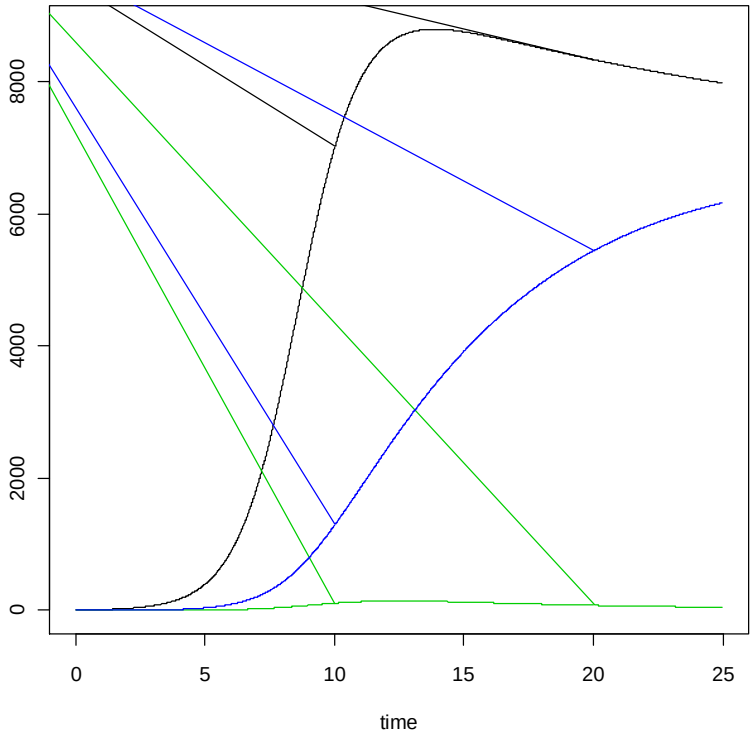


life expectancy with clinical AIDS: 10 years

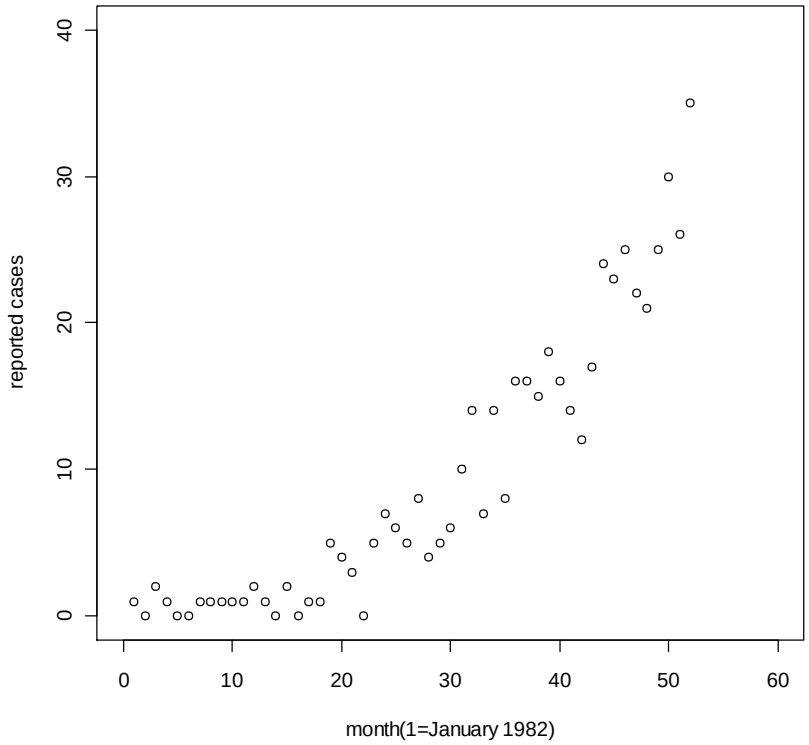


Modeling the initial outbreak of HIV/AIDS

Transmission model



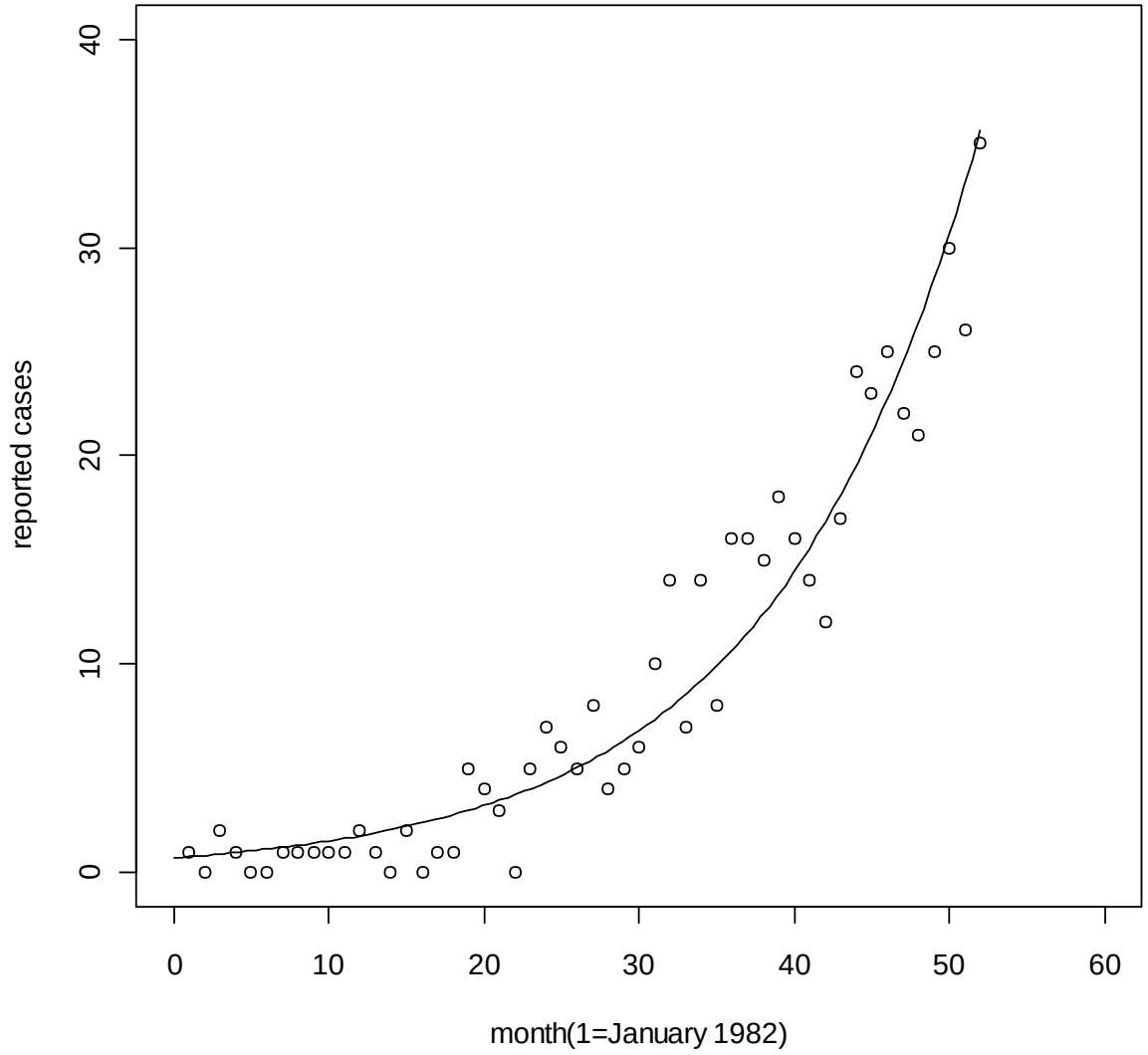
HIV positive in UK
(from Jan. 1982)



Which compartment we observed ?

Do we see the same pattern ?

Data and fitted model: outbreak of HIV/AIDS in UK



Long term prediction:

Can we use this model for prediction outside the range of the data ?

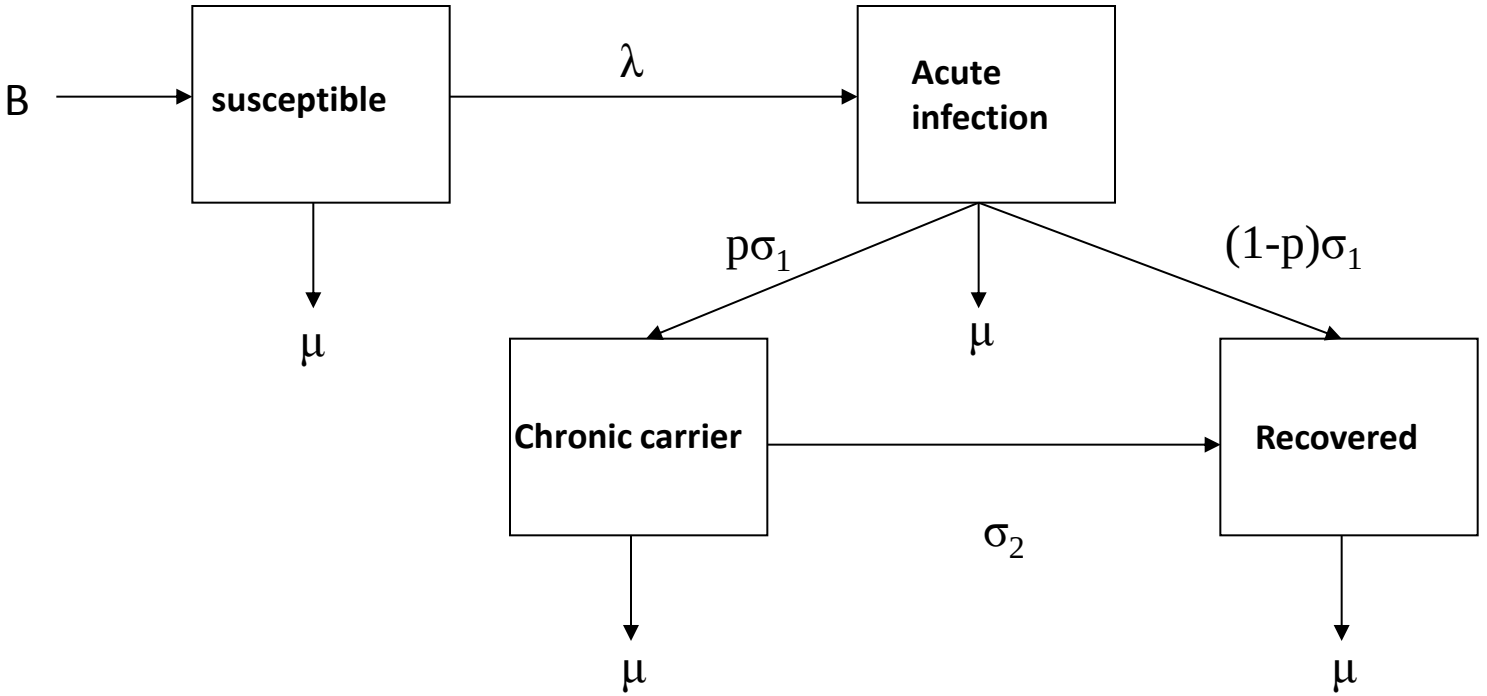
Transmission models for HCV among injecting drug users

R program: ModelingIDinR1_V1_Sep2017.R

Part 1:
Transmission models

PART 1
Transmission model for HCV

Mathematical model for transmission



The ODE system

The model

$$\frac{dS(t)}{dt} = B\mu - \lambda(t)S(t) - \mu S(t)$$

$$\frac{dA(t)}{dt} = \lambda(t)S(t) - (P\sigma_1 + \mu)A(t)$$

$$\frac{dC(t)}{dt} = P\sigma_1 A(t) - \sigma_2 C(t) - \mu C(t)$$

$$\frac{dR(t)}{dt} = (1-P)\sigma_1 A(t) + \sigma_2 C(t) - \mu R(t)$$

Model parameters

B	Rate of entry to the IDU population.
$\lambda(t)$	Force of infection.
σ_1	Recover rate.
P	Proportion of IDUs with carrier state.
σ_2	Recovery rate (carriers).
μ	Death rate.

The force of infection

Transmission probability per contact

$$\lambda(t) = k\frac{(c_1 A(t) + c_2 C(t))}{N}$$

Rate of sharing injecting materials (represent risk behavior factor)

Population size

Specification of model parameters in R

Model parameters:

1. “Life expectancy” in the IDU population: 25 years.
2. Rate of sharing materials 15.
3. Transmission probabilities 0.3 (acute to susceptible)
4. Transmission probabilities 0.03 (carrier to susceptible)
5. Recovery rate (acute): ~2.5 months.
6. Duration as carrier: ~ 20 years.
7. Proportion of infected IDU that will be carrier: ~70%

```
>paraameters <- c(B=0.05,mu=0.05,k=15,ba=0.3,bc=0.05,sigma1=5,sigma2=0.05,rho=0.7)
> parameters
     B     mu      k     ba     bc sigma1 sigma2    rho
  0.05   0.05  15.00   0.30   0.05   5.00   0.05   0.70
```

State variables

```
> state <- c(y1=0.99,y2=0.01,y3=0,y4=0)
> state
  y1   y2   y3   y4
0.99 0.01 0.00 0.00
```

At time zero: 99% are susceptible and 1% are infected.

Specification the transmission model in R

$$\frac{dS(t)}{dt} = B\mu - \lambda(t)S(t) - \mu S(t)$$

$$\frac{dA(t)}{dt} = \lambda(t)S(t) - (P\sigma_1 + \mu)A(t)$$

$$\frac{dC(t)}{dt} = P\sigma_1 A(t) - \sigma_2 C(t) - \mu C(t)$$

$$\frac{dR(t)}{dt} = (1-P)\sigma_1 A(t) + \sigma_2 C(t) - \mu R(t)$$

```
SIR<-function(t,state,parameters)
{
with(as.list(c(state, parameters)),
{
dy1 = B-k*ba*y1*y2-k*bc*y3*y1-mu*y1
dy2 = k*ba*y1*y2+k*bc*y3*y1-sigma1*y2-mu*y2
dy3 = rho*sigma1*y2-sigma2*y3-mu*y3
dy4= (1-rho)*sigma1*y2+sigma2*y3-mu*y4;
list(c(dy1,dy2,dy3,dy4))
})
}
```

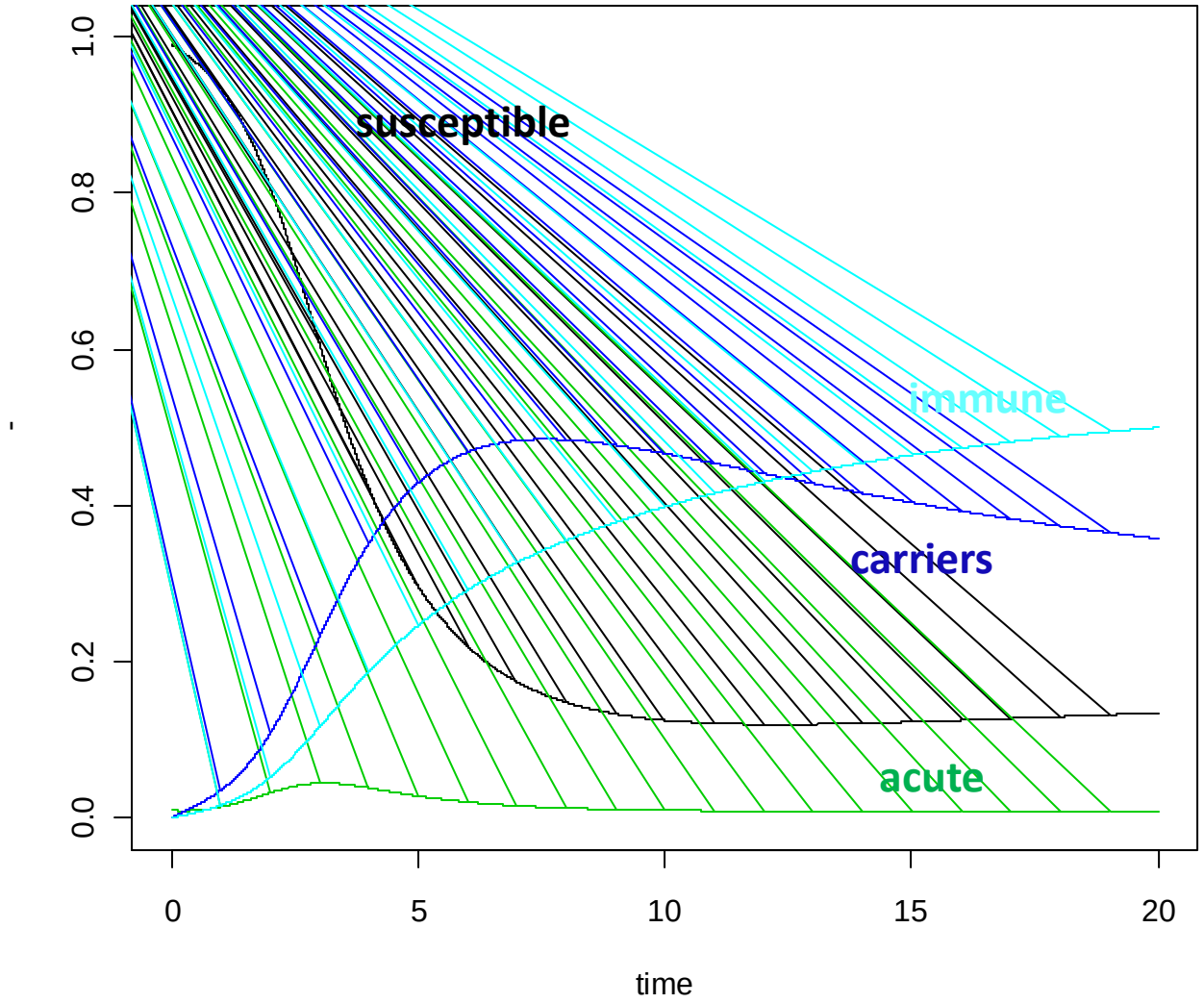
Specification the transmission model in R

The force of infection depends on the duration of injection.

```
SIR<-function(t,state,parameters)
{
with(as.list(c(state, parameters)),
{
dy1 = B-k*ba*y1*y2-k*bc*y3*y1-mu*y1
dy2 = k*ba*y1*y2+k*bc*y3*y1-sigma1*y2-mu*y2
dy3 = rho*sigma1*y2-sigma2*y3-mu*y3
dy4= (1-rho)*sigma1*y2+sigma2*y3-mu*y4;
list(c(dy1,dy2,dy3,dy4))
})
}
```

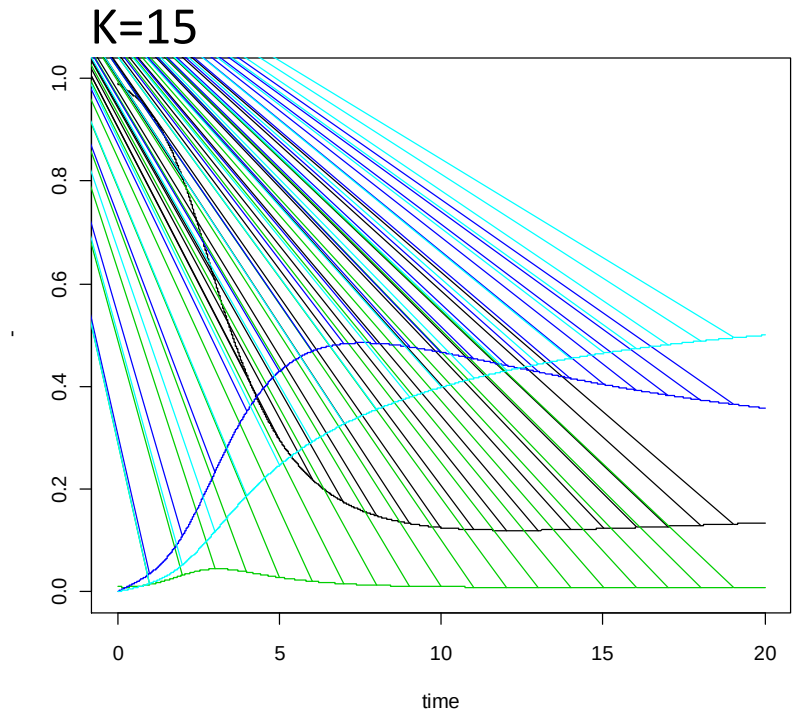
$$\lambda(t) = k\frac{(c_1 A + c_2 C)}{N}$$

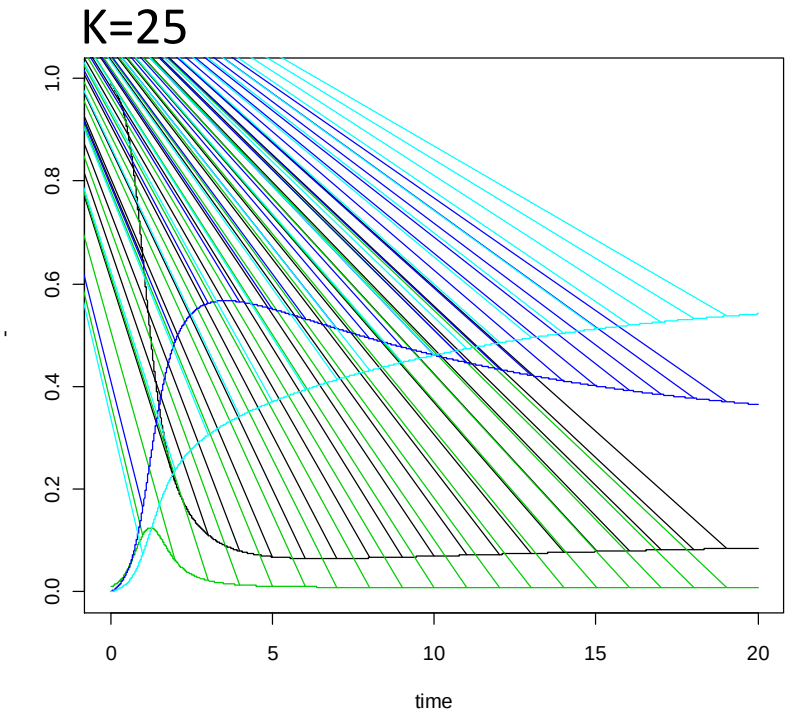
Solution


susceptible
immune
carriers
acute
1.0
0.8
0.6
0.4
0.2
0.0
-
0
5
10
15
20
time

Change in sharing rate

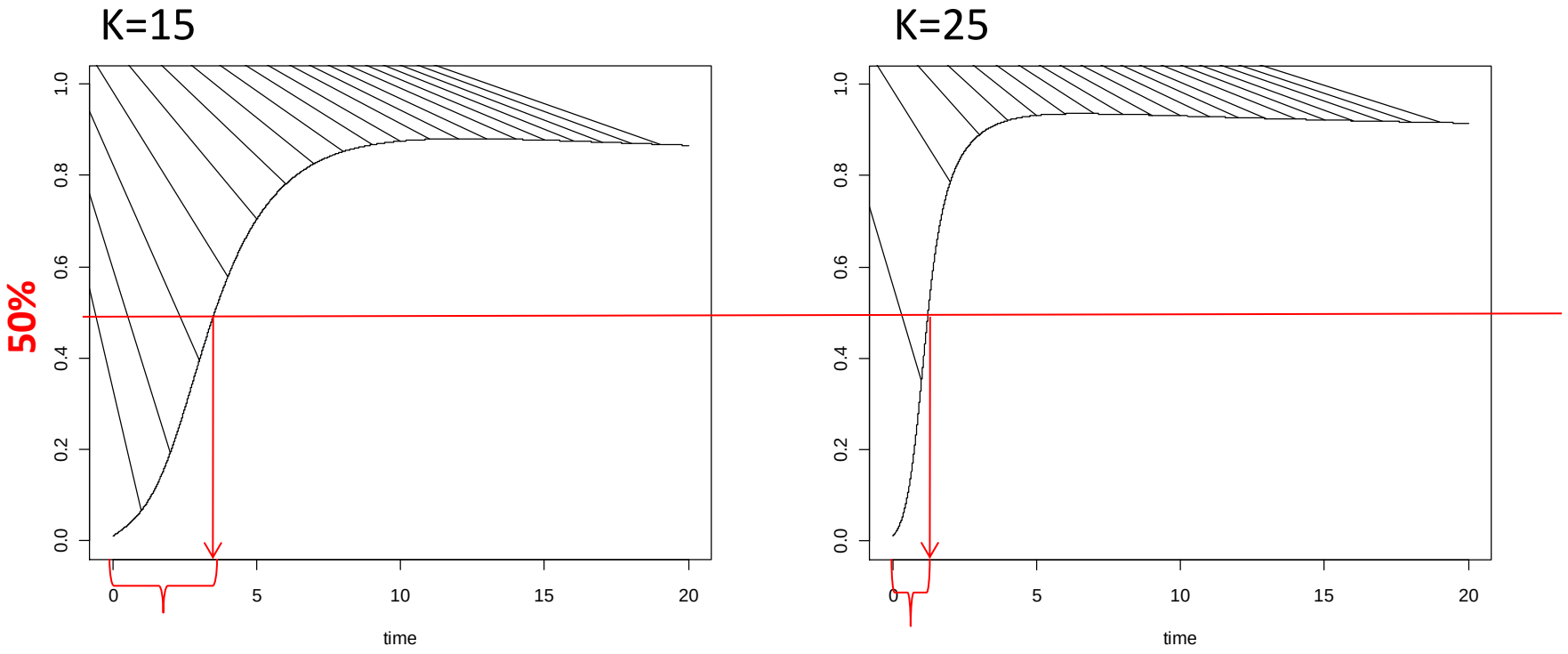
The sharing rate increase from 15 to 25 (represent a population with higher risk behavior).





The prevalence

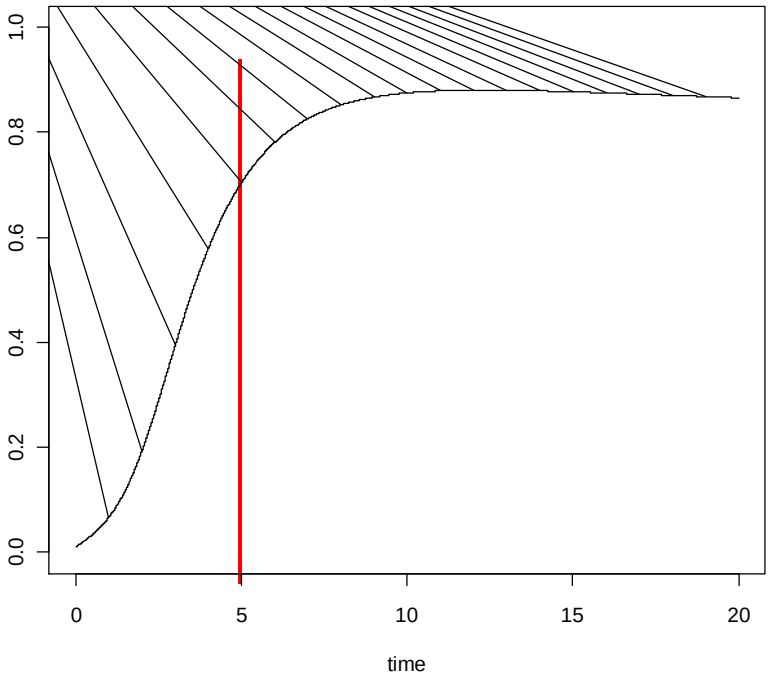
The duration of injected for a prevalence of 50% in the population.



Model based prediction for the prevalence

K=25.

Predicted prevalence after 5 years of injection: ~ 70%.



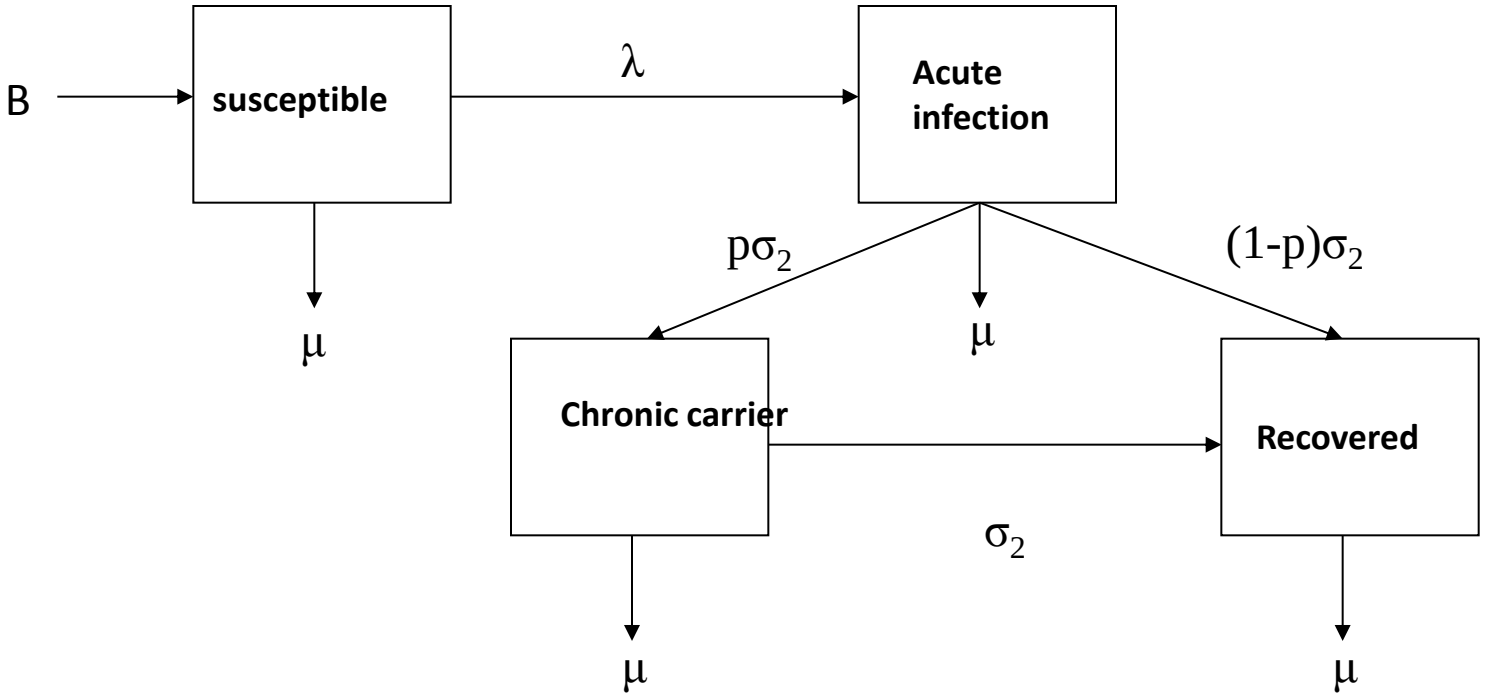
Part 2

Case study: Hepatitis C in Belgium

Based on the paper of Catharina Mathei et al. (2006)

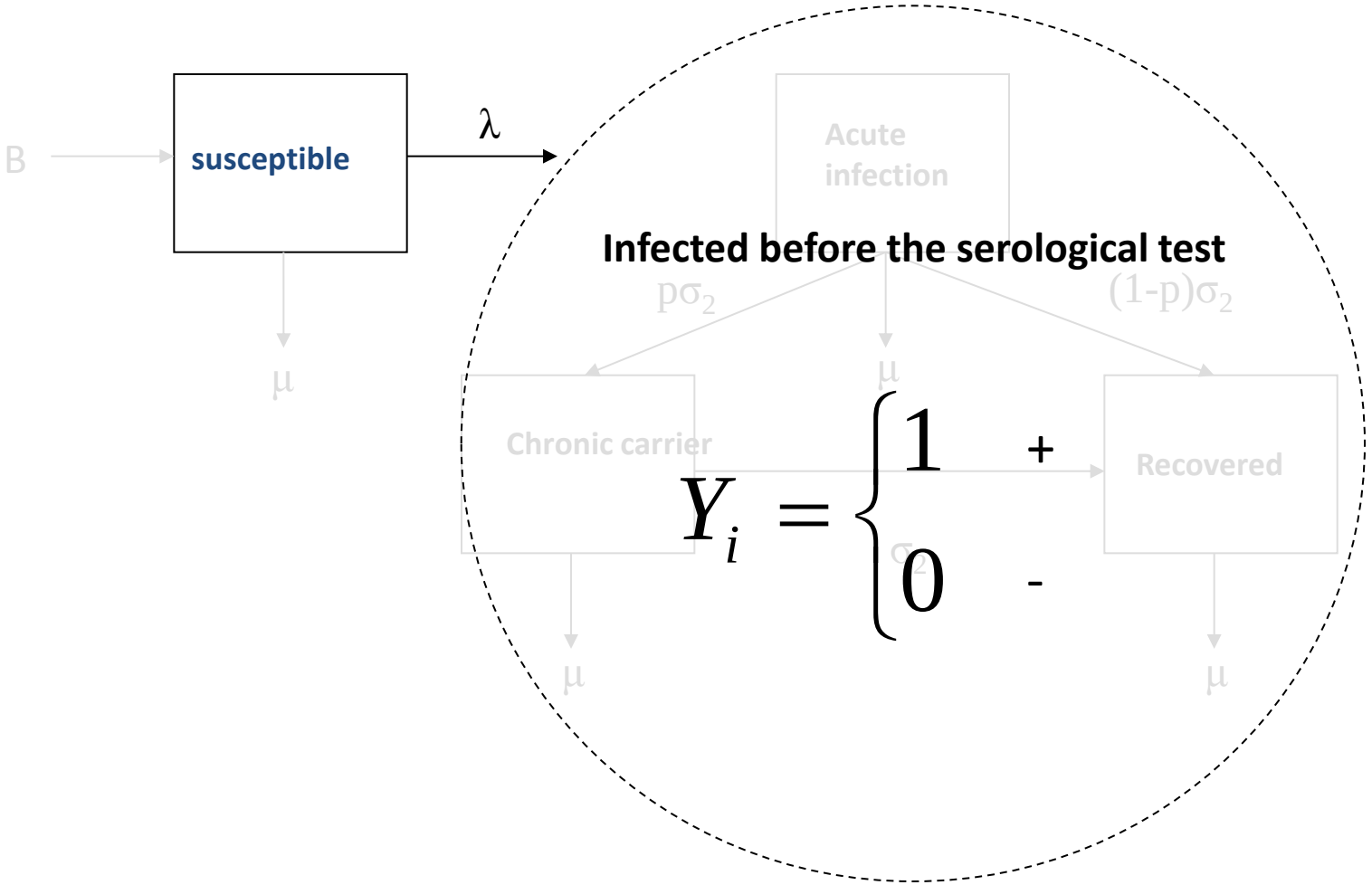
Statistical and mathematical models: the connection

Mathematical model for transmission



Statistical and mathematical models: the connection

Statistical model



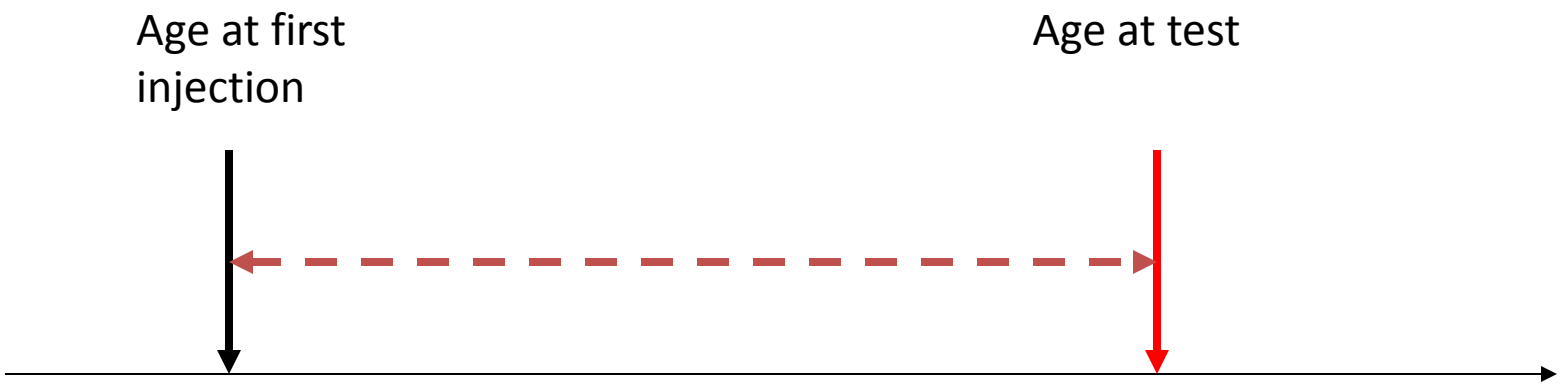
The study

- Seroprevalence study of HCV among injecting drug users (421 IDUs).
- Three different locations: Charleroi, Antwerp, Limburg.
- All injecting drug users were interviewed by means of a standardized face-face interview and information on their socio-demographic status, drug use history, drug use and related risk behaviour was available.
- Overall 325 IDUs (77.2 %) were found to be seropositive.

The aim of the analysis

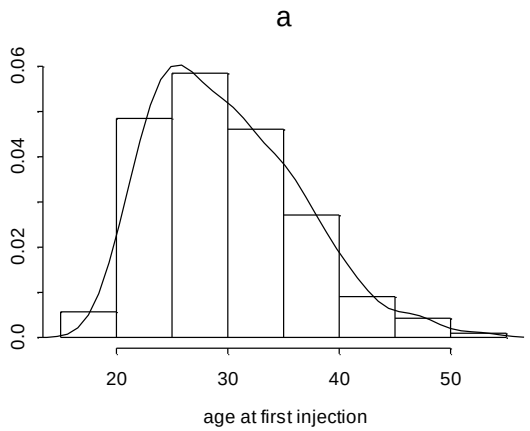
- To identify risk factors and to estimate the change in force of infection over the exposure time.
- For many diseases the exposure time is the age of the individual.
- The age is the time in which the individual spend in the susceptible state.

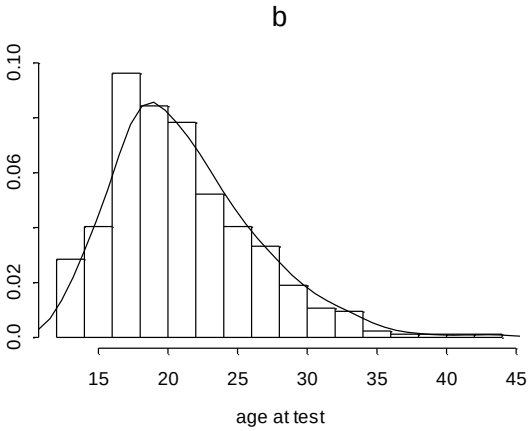
Exposure time

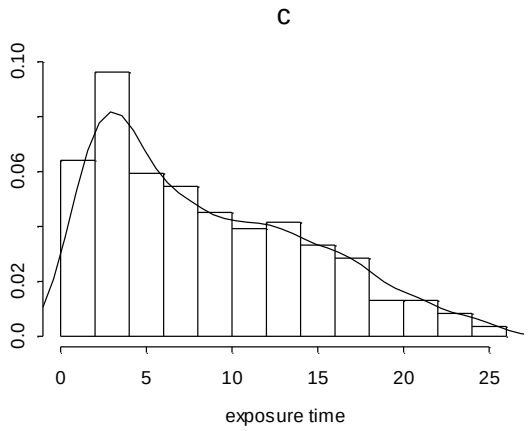


The time scale is the exposure time: the difference between the age at first injection and the age at test.

Density estimate for the exposure time



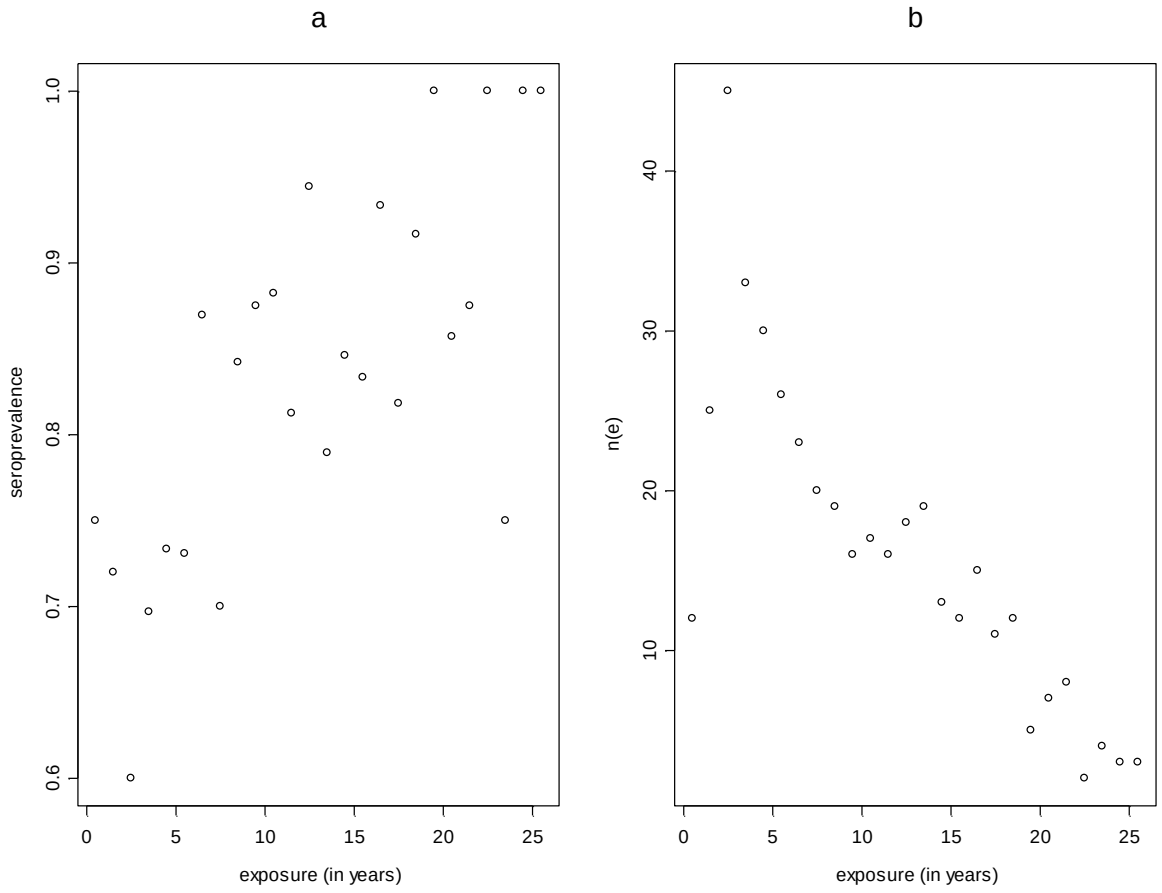




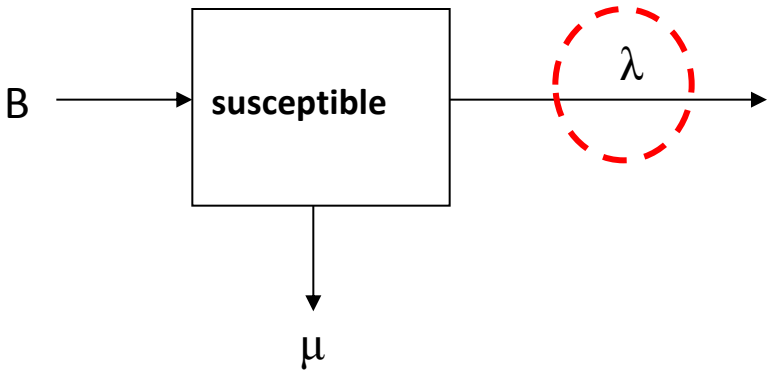
Exposure time=age at test – age at first injection.

Measurement error

Prevalence and sample size at each duration group



Models for the force of infection



$$\frac{dS(t)}{dt} = B - \lambda S(t) - \mu(t)S(t)$$

λ: constant force of infection.

$\lambda(t)$: exposure dependent force of infection

$\lambda_R(t)$: exposure dependent force of infection with different rates for subgroups in the IDU population (the sub groups define by the risk behaviour factors)

Risk Behaviour Factors

- Sharing Syringes.
- Sharing other paraphernalia materials.
- Frequency of injections.
- Age at first injection.

Other risk factors:

- Gender (not significant).
- Location of injection (was not considered in the models).

The current status of the IDU

$$Y_i = \begin{cases} 1 & \text{Sero positive} \\ 0 & \text{Sero Negative} \end{cases}$$

Binomial likelihood

$$L(\beta) = \sum_{i=1}^{N} Y_i \log[\pi(t_i)] + (1 - Y_i)\log[1 - \pi(t_i)]$$

The prevalence of HCV

The Weibull model

Weibull Model for the prevalence

$$\pi(t) = 1 - \exp\left(-\alpha t^{\beta}\right)$$

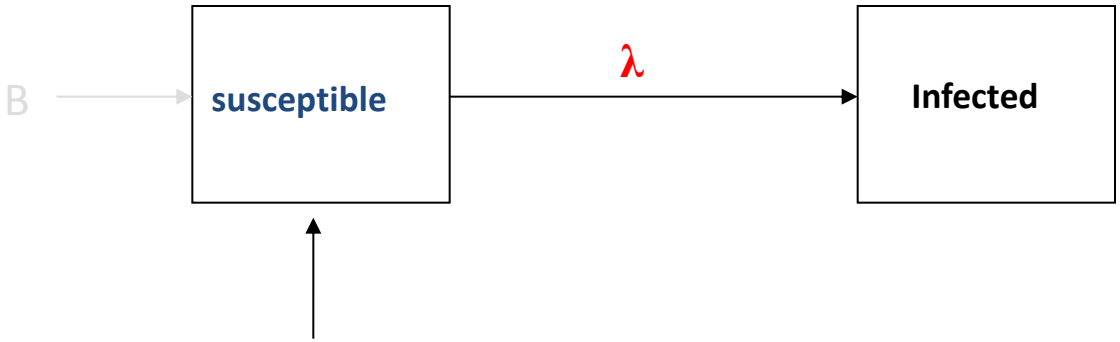
P(0)=0, the prevalence at t=0 is zero.

The model implies an underlying Weibull distribution in the susceptible class.

$$\lambda(t) = \alpha\beta t^{\beta-1}$$

t: the exposure time

Statistical and mathematical models: the connection



- We focus on the time that each IDU stays in the susceptible class.
- The duration that each IDU stays as a susceptible is a random variable which assume to follow a Weibull distribution.
- The force of infection is a parameter of the distribution.

Why Weibull model ?

Weibull Model for the prevalence

$$\pi(t) = 1 - \exp\left(-\alpha t^{\beta}\right)$$

P(0)=0, the prevalence at t=0 is zero.

All the models for the force of infection (constant, exposure dependent and exposure dependent with different rates for subgroups) can be formulated as a Weibull model.

The Setting

$$Y_i = \begin{cases} 1 & \text{Sero positive} \\ 0 & \text{Sero Negative} \end{cases}$$

Binomial likelihood

$$L(\beta) = \sum_{i=1}^{N} Y_i \log[\pi(t_i)] + (1 - Y_i)\log[1 - \pi(t_i)]$$

$$\pi(t) = 1 - \exp(-\alpha t^{\beta})$$

The prevalence of HCV

MODEL 1

- The first model includes only the exposure time as a risk factor.
- Logistic regression model was used on order to estimate the prevalence and the force of infection.

The Weibull model

Weibull Model for the prevalence

$$\pi(t) = 1 - \exp\left(-\alpha t^{\beta}\right)$$

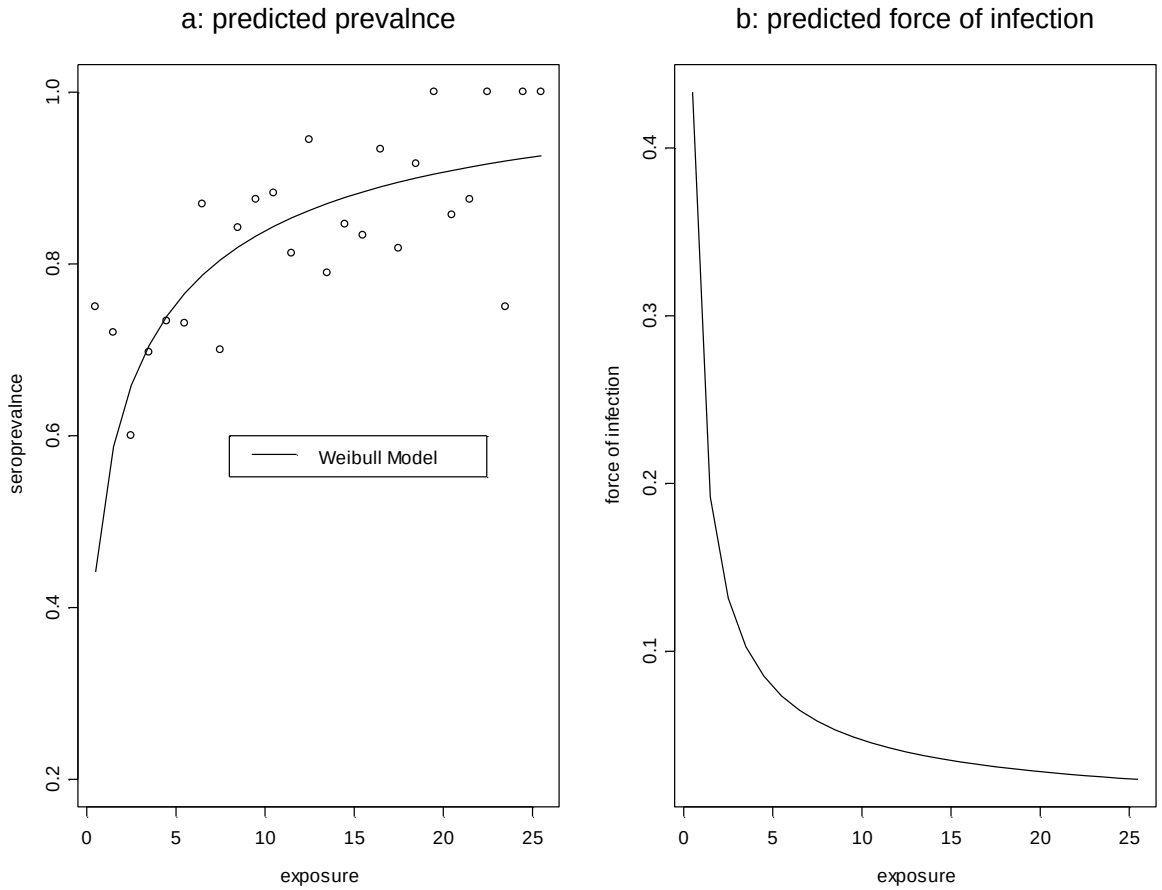
P(0)=0, the prevalence at t=0 is zero.

The model implies an underlying Weibull distribution in the susceptible class.

$$\lambda(t) = \alpha\beta t^{\beta-1}$$

t: the exposure time

Predicted values for the prevalence and the force of infection (model 1)



Model 2: Identification of risk factors

- Potential risk factors

1. Sex.
2. Age at first injection.
3. Location of injection.
4. Exposure time.
5. Sharing needles.
6. Sharing other materials.

- Stepwise procedure was used for variable selection.

Identification of risk factors: the statistical model

PH model:

$$\pi(t) = 1 - \exp\left(-\alpha t^{\beta} \exp(Z\gamma)\right)$$

Force of infection:

$$\lambda(t \mid Z) = \alpha \exp(Z\gamma)\beta t^{\beta-1}$$

For binary covariate, such as sharing needles, the ratio between the force of infection across the covariate levels is time independent.

$$\frac{\lambda(t \mid Z=1)}{\lambda(t \mid Z=0)} = \exp(\gamma)$$

Model 2: final model

- Significant risk factors: exposure time, location, sharing needles, sharing other materials and the interaction between sharing needles exposure time.
- Sharing needles: increase the probability to be infected.
- Sharing other materials: increase the probability to be infected.

The interaction sharing needles X exposure time

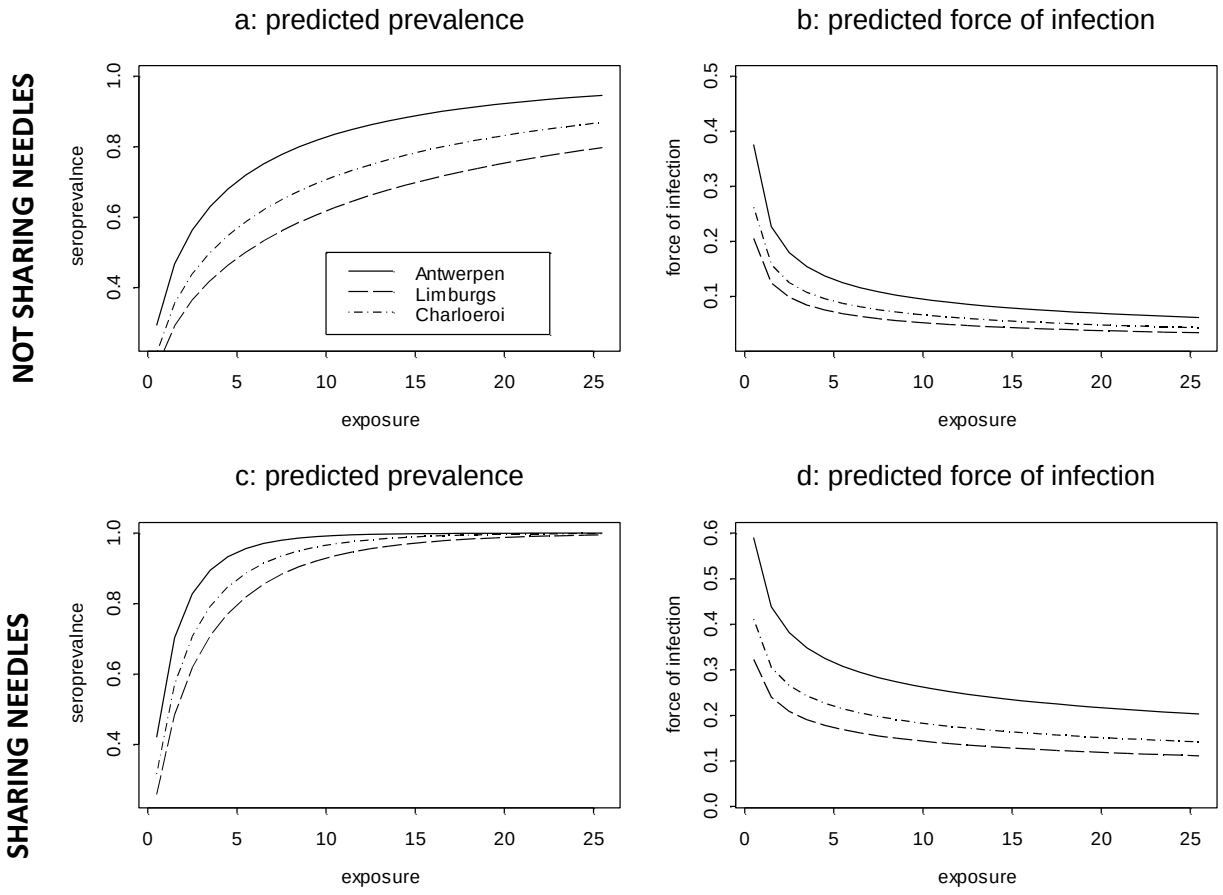
$$\frac{\lambda(t \mid \text{Sharing/ yes})}{\lambda(t \mid \text{Sharing/ no})} = g(t)$$

The ratio of the force of infection across the covariate level is time dependent

Model 2: final model

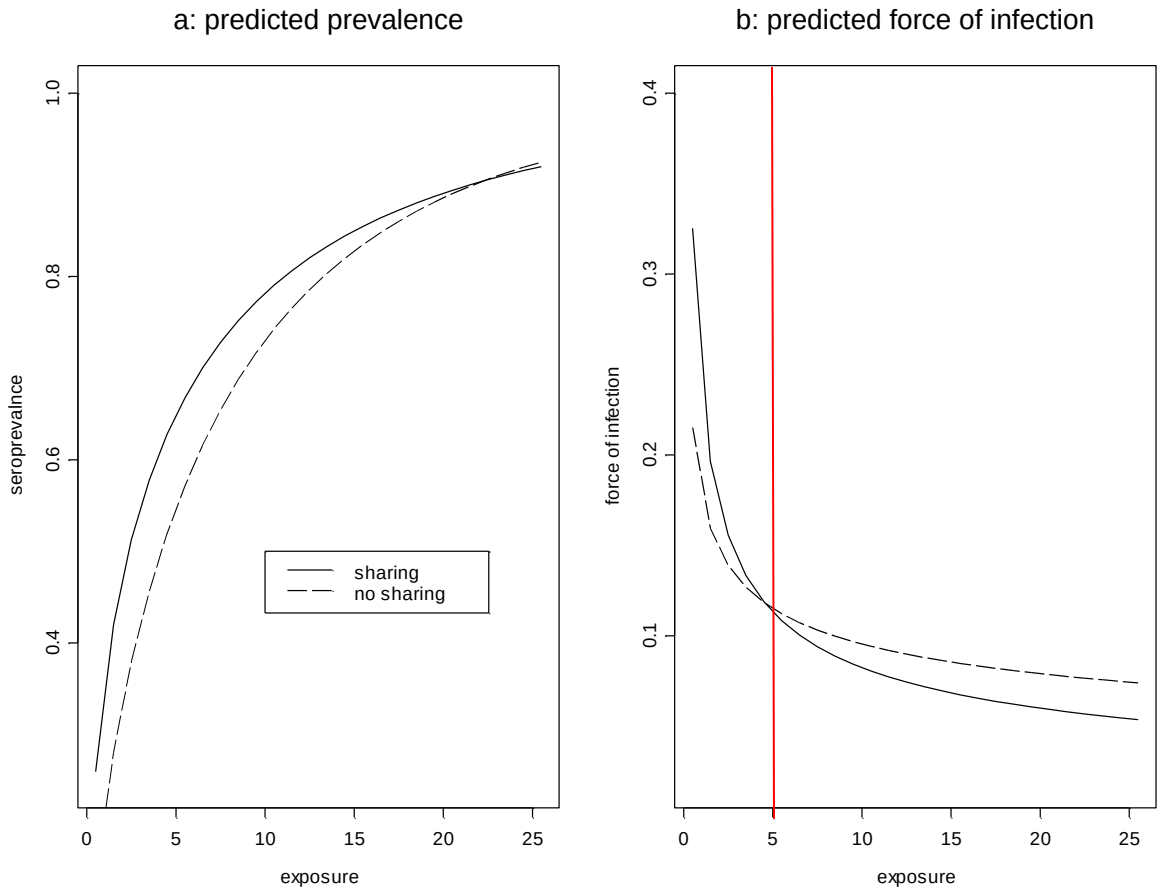
- Location: the risk in Antwerp is higher than the risk in Charleroi.
- The risk in Charleroi is higher than the risk in Limburg.

Location: effect on prevalence and the force of infection



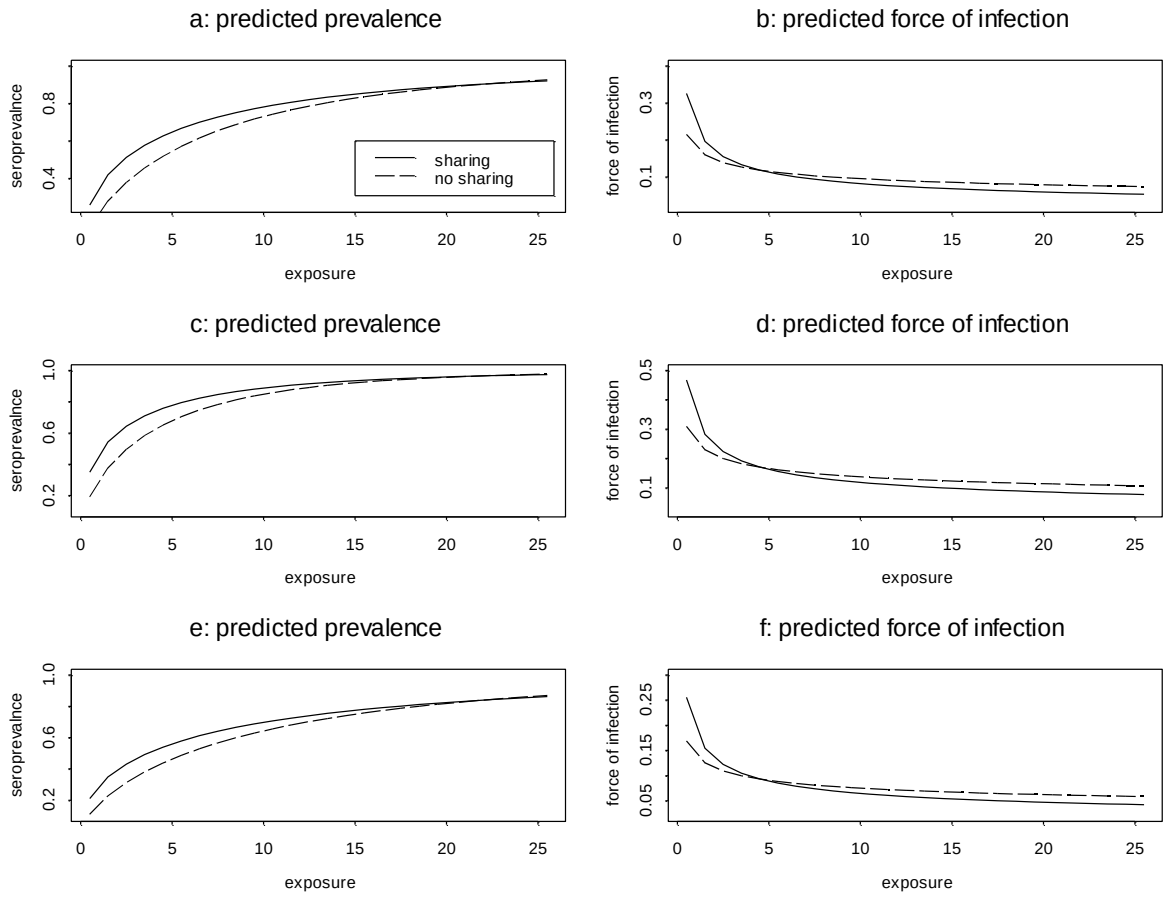
ESTIMATED MODELS FOR IDUs **WHO NOT SHARE** OTHER MATERIALS

Sharing needles: effect on prevalence and force of infection in Charleroi



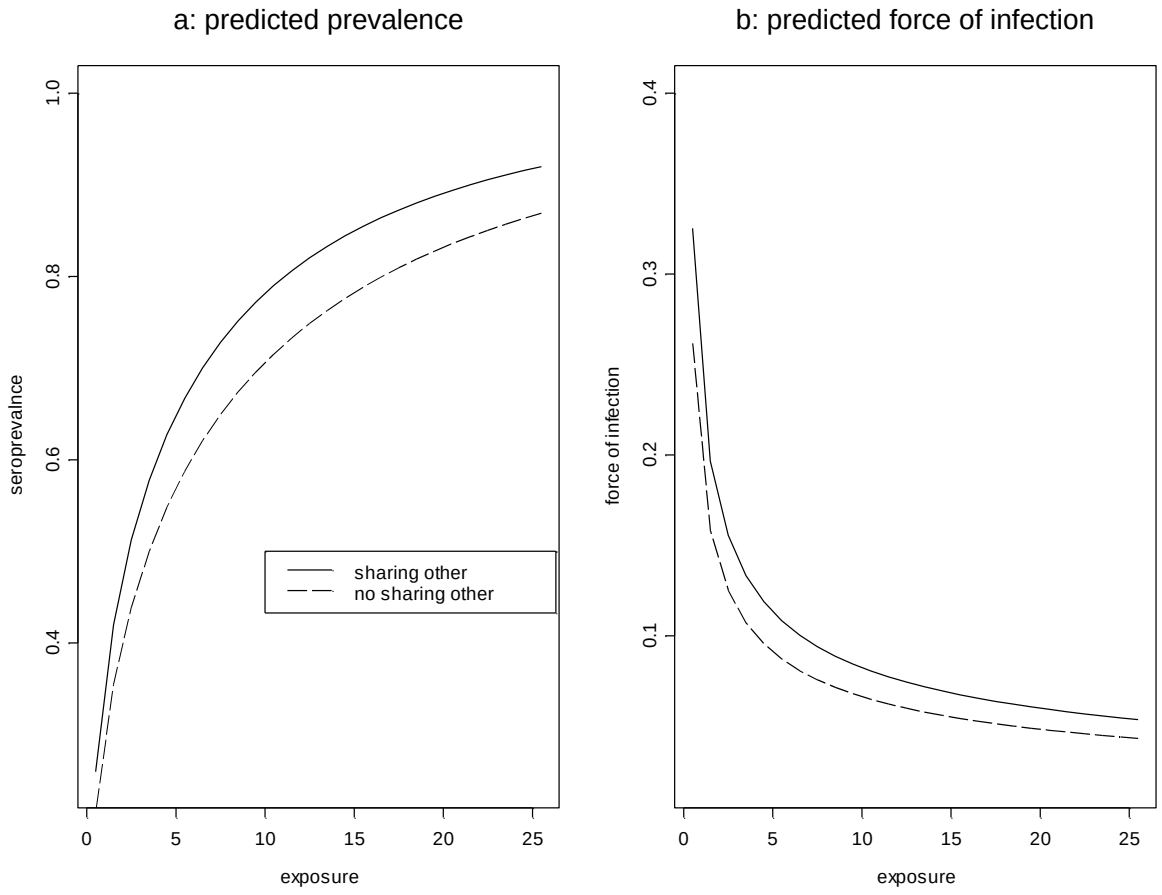
EFFECT OF SHARING OR NONSHRING

Sharing needles: effect on prevalence and the force of infection



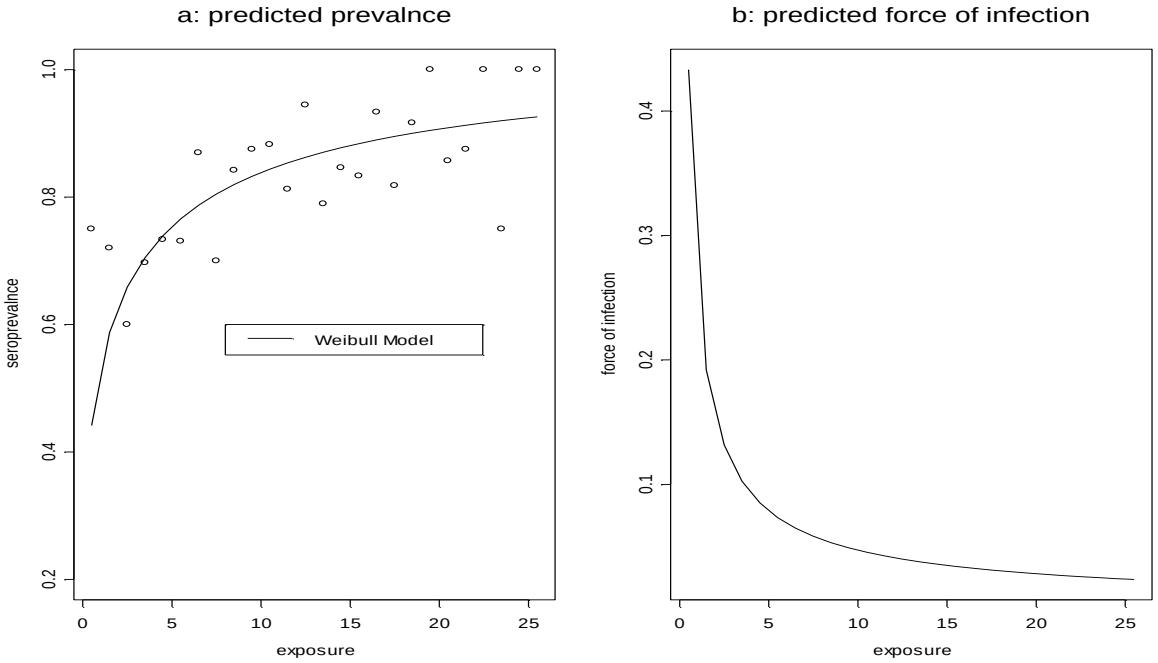
Panel a and b: Charleroi. Panel c and d: Antweprn. Panel e anf f: Limburg

Sharing other materials: effect on prevalence and force of infection in Charleroi



EFFECT OF SHARING OTHER MATERIALS

Predicted values for the prevalence and the force of infection

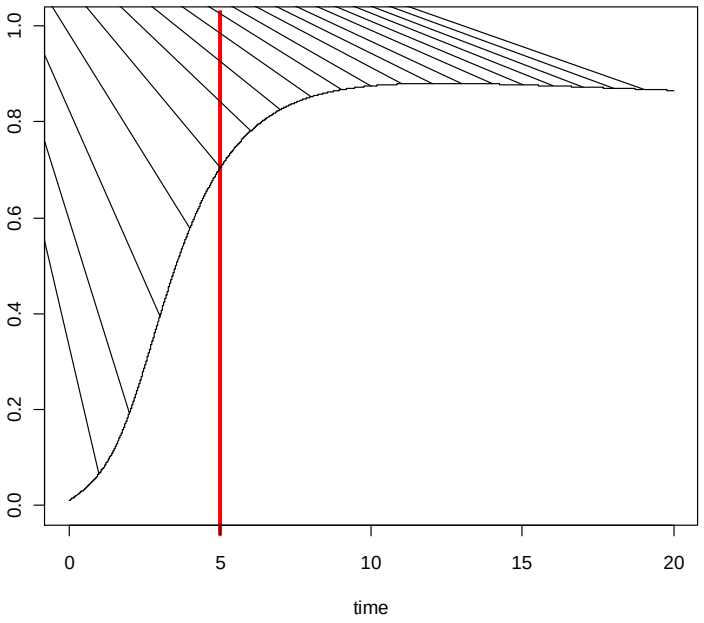


Criteria For Assessing Goodness Of Fit

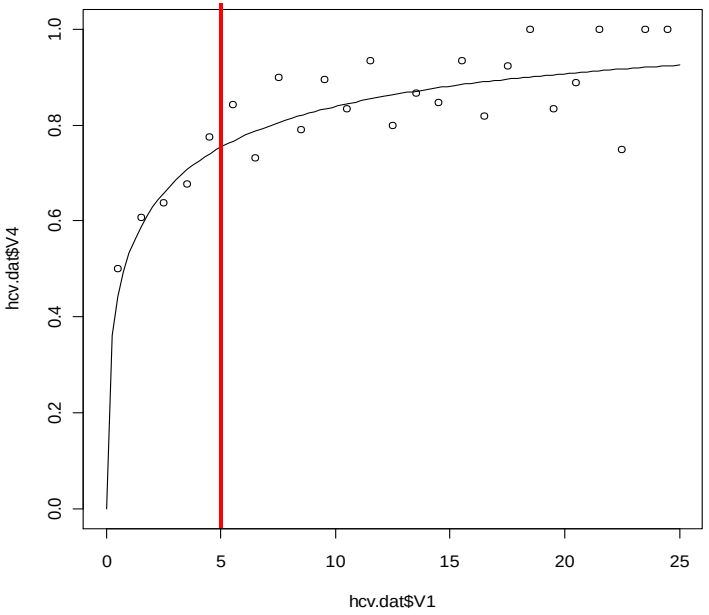
Criterion	DF	Value	Value/DF
Pearson Chi-Square	419	422.2240	1.0077

SIR Ronald Ross modeling framework for infectious diseases

Transmission model



Statistical model



Predicted prevalence after 5 years of injection: ~ 70%.