

Transmission models in R

- We need to integrate the system of the ordinary differential equation.
- deSolve package in R.
- Numerical integration using of ODE system.

$$\left. \begin{aligned} \frac{dS(t)}{dt} &= -\lambda S(t) \\ \frac{dI(t)}{dt} &= \lambda S(t) - \sigma I(t) \\ \frac{dR(t)}{dt} &= \sigma I(t) \end{aligned} \right\} \text{Closed population}$$

91

Transmission models in R

SIR model (open population)

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

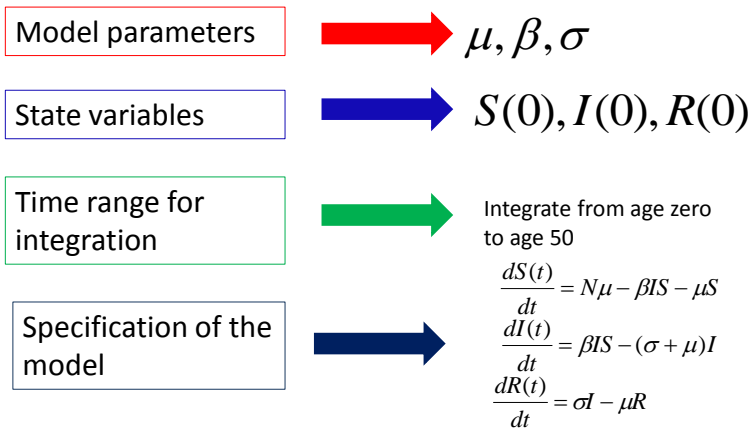
Specification in R

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

92

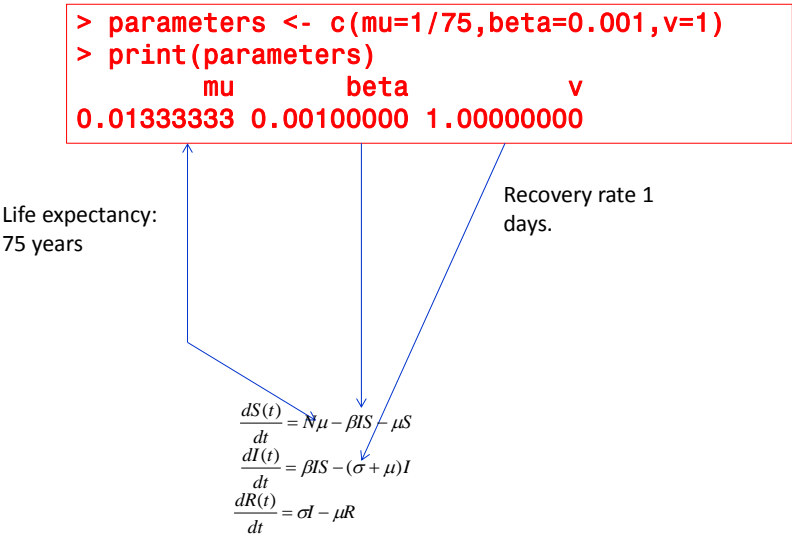
Transmission models in R

R program



93

Specification of the model parameters in R



94

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
```

95

SIR transmission model in open population

$$\left. \begin{aligned} \frac{dS(t)}{dt} &= N\mu - \beta IS - \mu S \\ \frac{dI(t)}{dt} &= \beta IS - (\sigma + \mu)I \\ \frac{dR(t)}{dt} &= \sigma I - \mu R \end{aligned} \right\}$$

```
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=)
```

96

Running the model

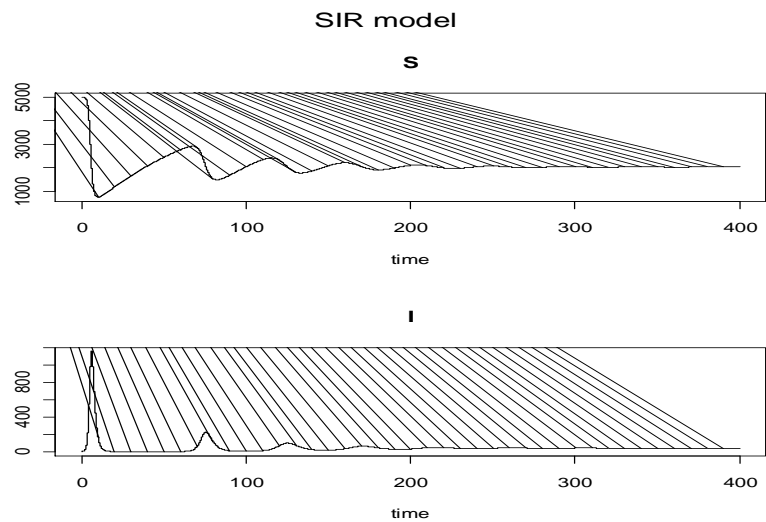
```
require(deSolve)
out<-as.data.frame(ode(y=state,times=times,func=SIR,parms=parameters))
```

Time range for integration. The model

Numerical integration using ordinary differential equation

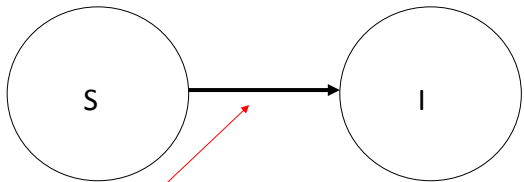
97

Solution for the model

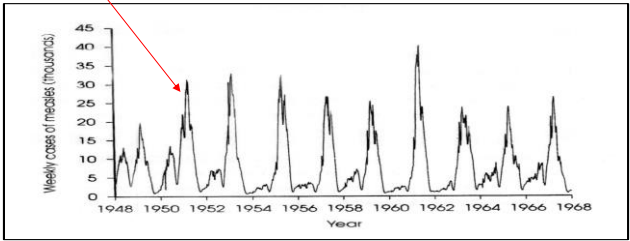


98

Incidence data : Measles in UK



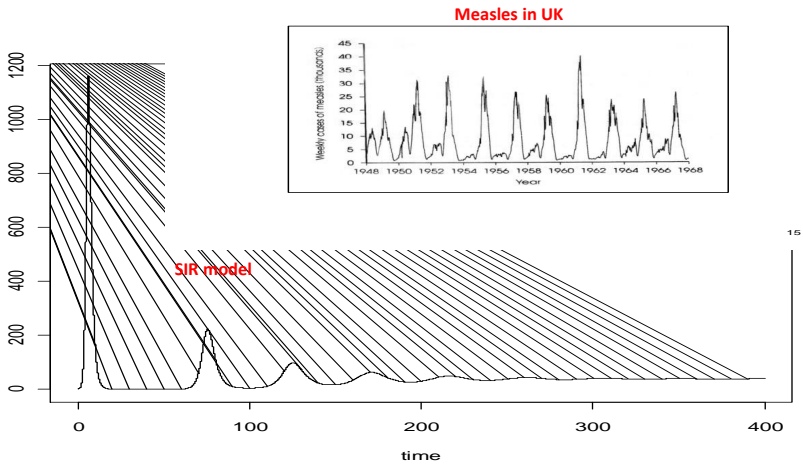
The *weekly* number of individuals who move from the susceptible to the infected class



Time unit=week

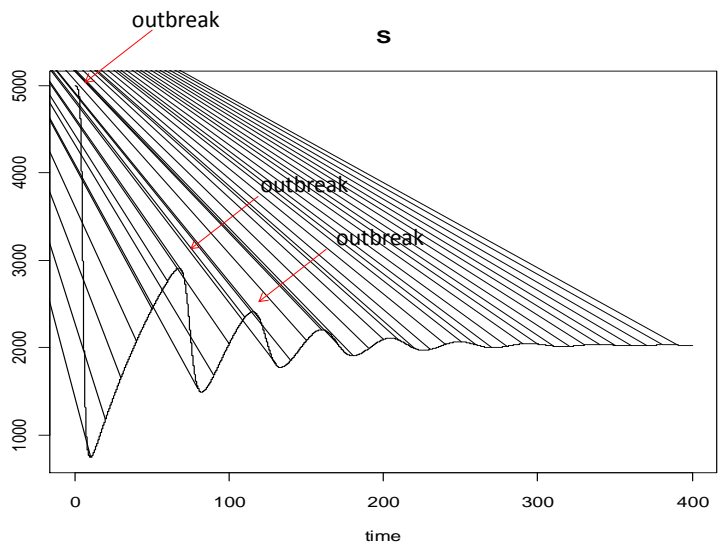
19

Observed outbreak and predicted outbreak



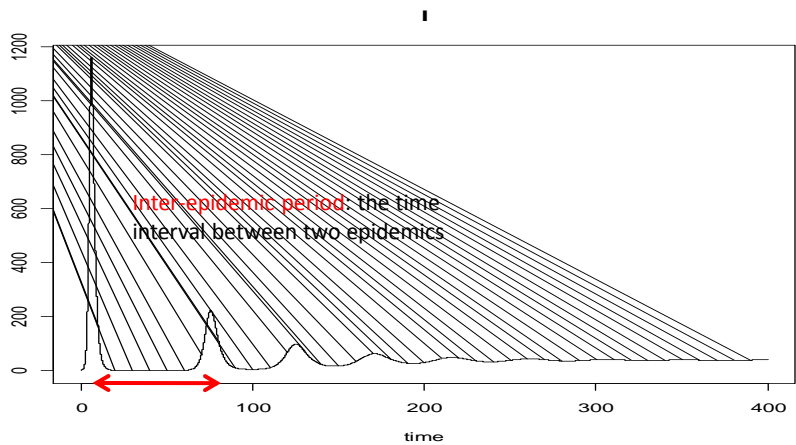
100

The susceptible class



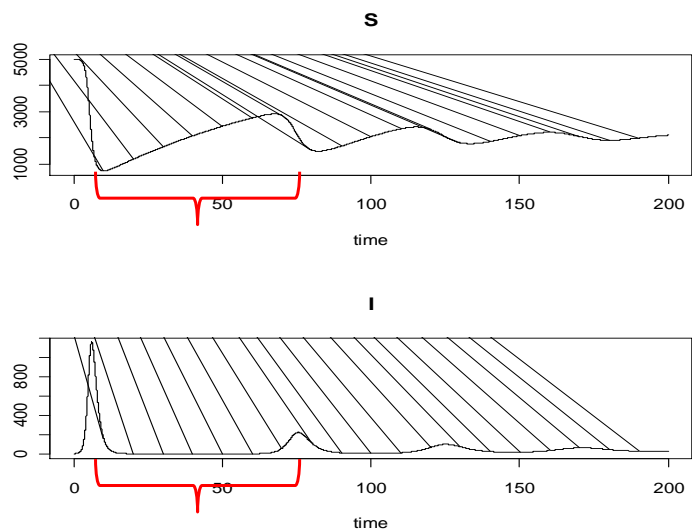
101

The infected class



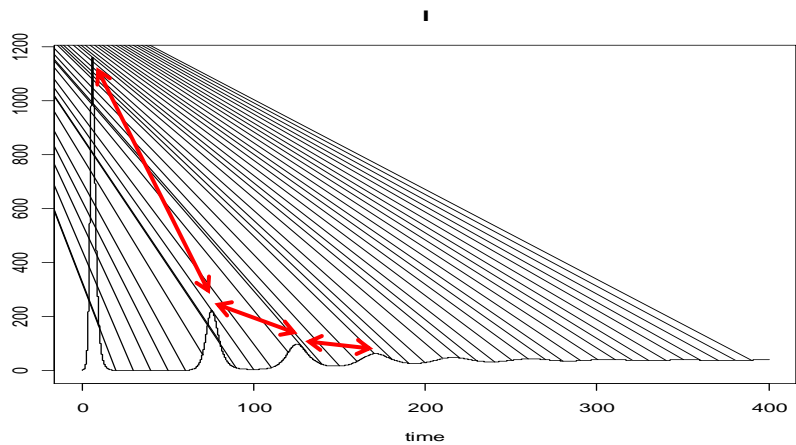
102

The Inter epidemic period



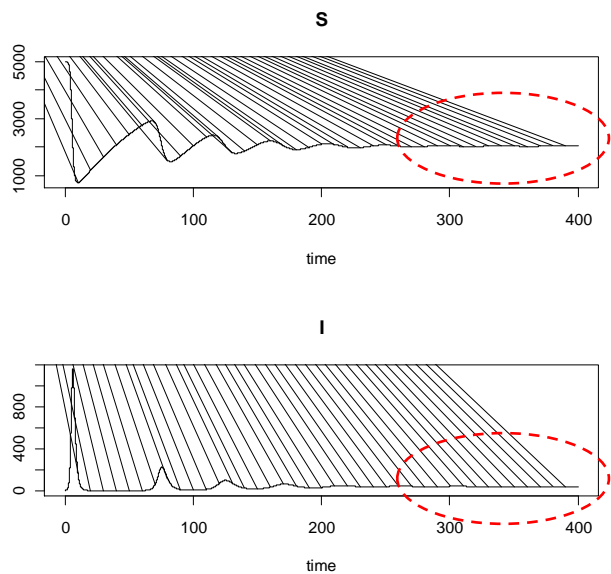
103

Damping effect ?



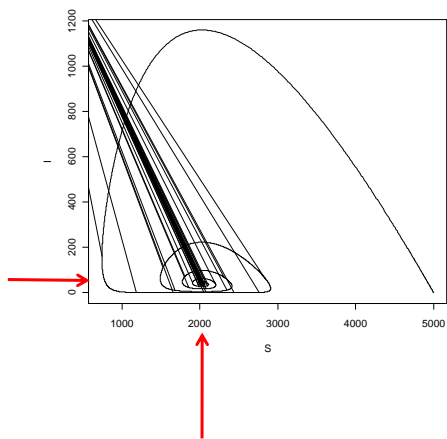
104

Equilibrium



105

Equilibrium



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

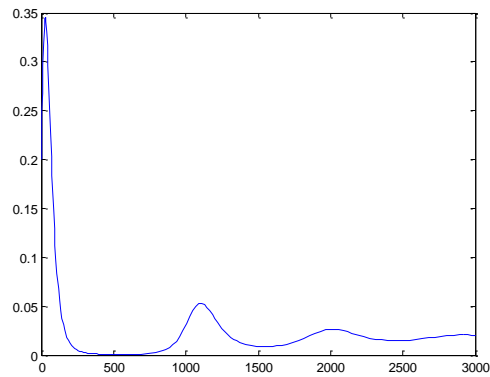
106

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

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

Patterns:

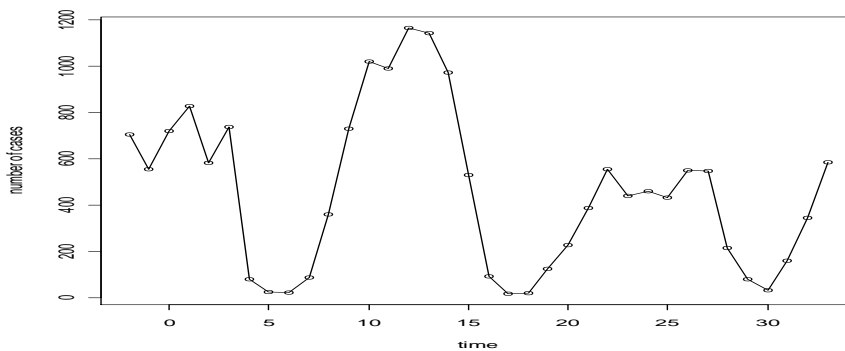
1. Oscillations.
2. Damping effect.
3. Equilibrium value.
4. Inter epidemic period.



107

Incidence Data varicella in Philadelphia 1941-1943

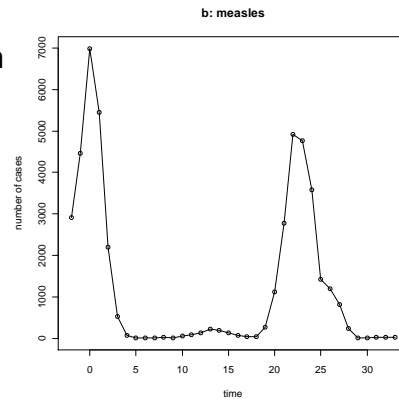
Oscillations seems to be symmetric around the equilibrium value.



108

Incidence Data Measles in Philadelphia 1941-1943

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



109

Understanding transmission

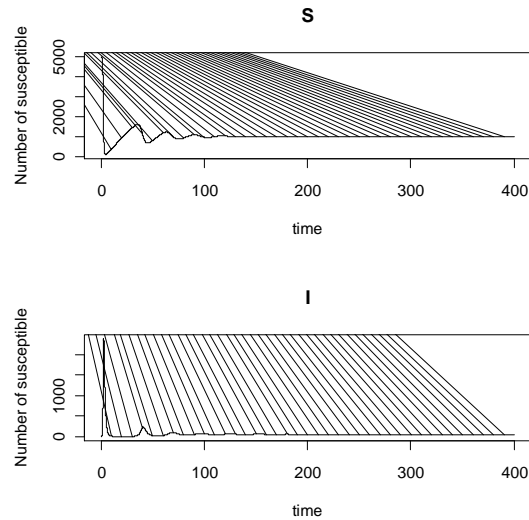
110

SIR model

Basic setting:

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

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



111

Effect of β

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

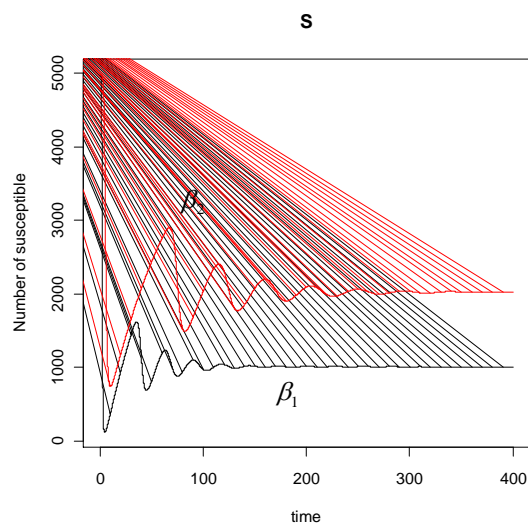


$$N = 5000, \beta = 0.0005, \nu = 1, L = 75$$

$$\beta_2 < \beta_1$$

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

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



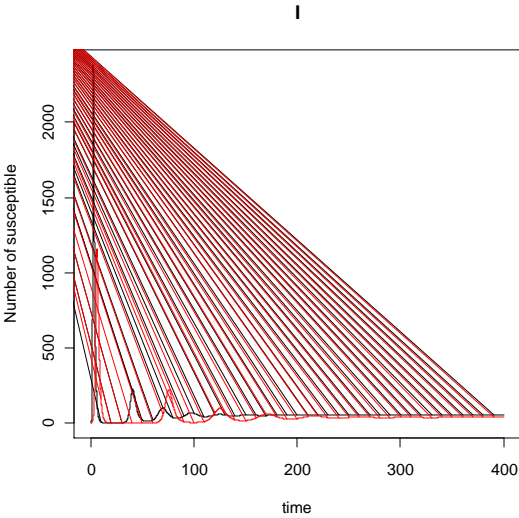
112

Effect of β

$\beta_2 < \beta_1$

Inter epidemic period.

Equilibrium values.

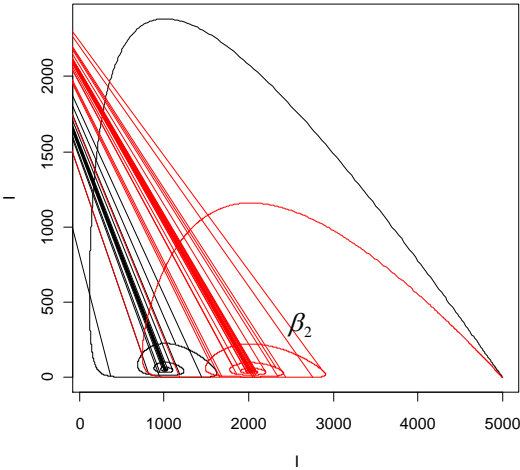


113

Effect of β

$\beta_2 < \beta_1$

Equilibrium values: more susceptible but the same number of infected individuals.



114

Effect of N

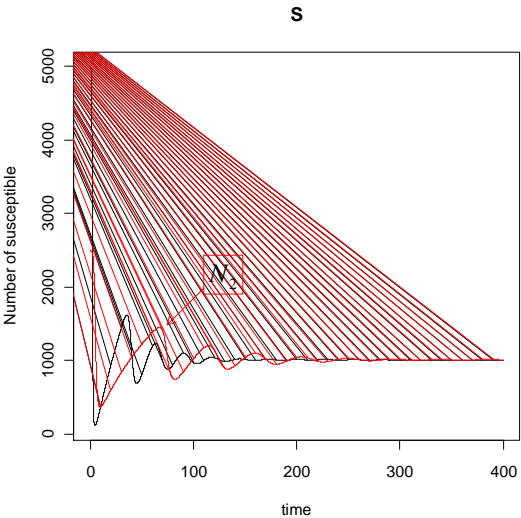
$N = 5000, \beta = 0.001, \nu = 1, L = 75$

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

$N_2 < N_1$

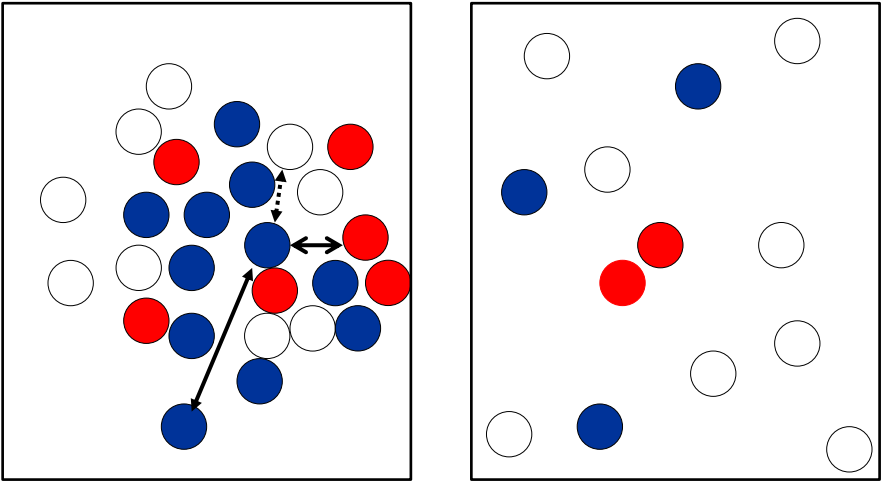
Inter epidemic period.

Equilibrium values.



115

The effect of N



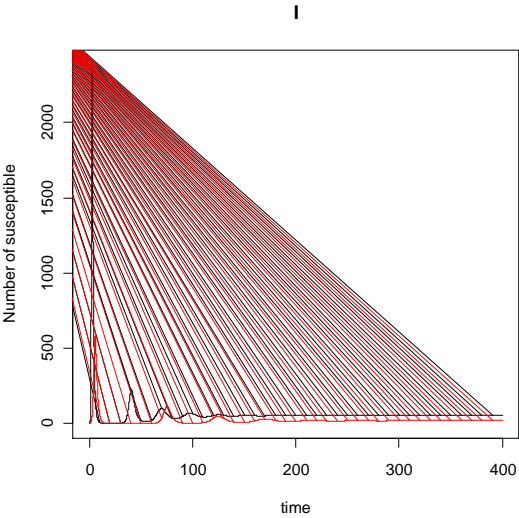
116

Effect of N

$N_2 < N_1$

Inter epidemic period is longer.

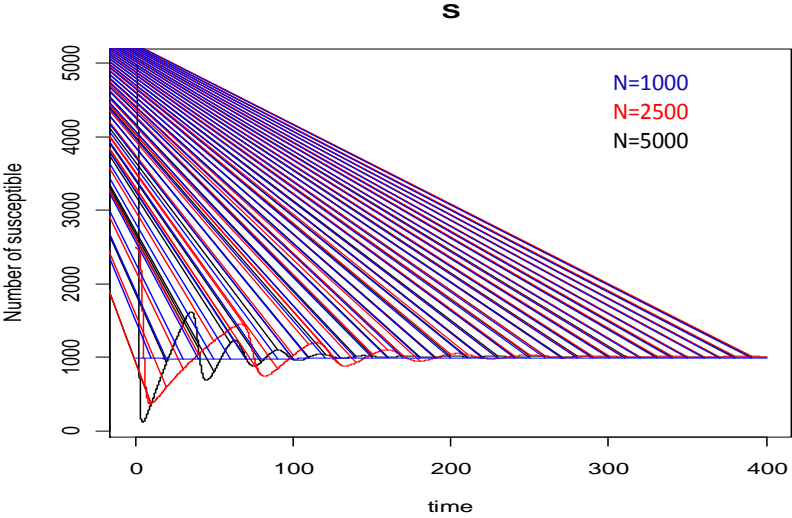
Susceptible class is built slowly



117

Effect of N

The population is too small to start an epidemic



118

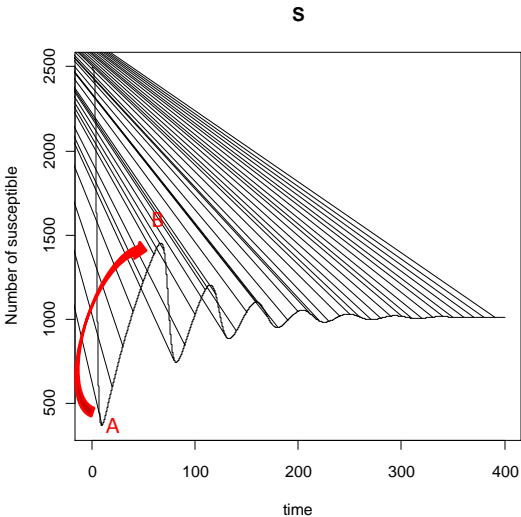
The build up of the susceptible class

Susceptible=the “fuel”
for an epidemic.

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

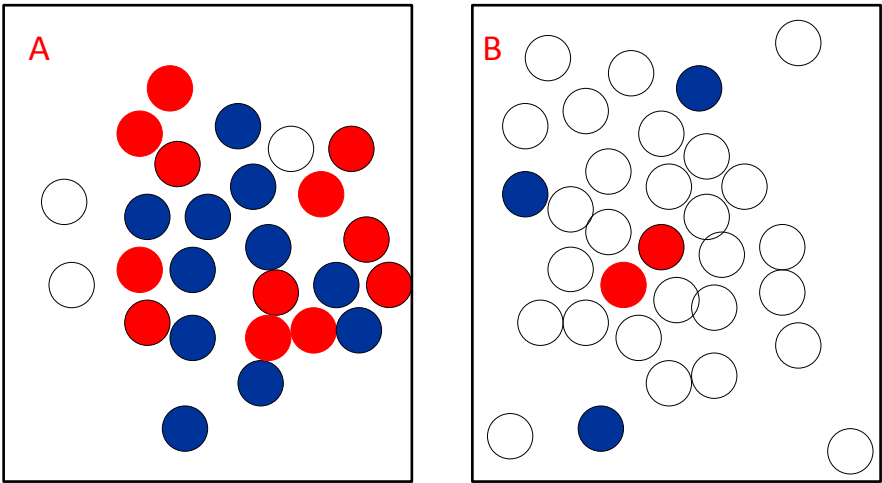
B: number of susceptible
is large enough for an
outbreak.

A to B: the build up of
the susceptible class



119

The build up of the susceptible class

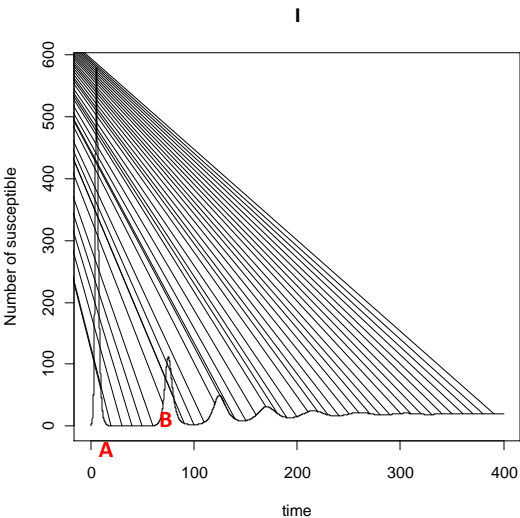


t_0 \longleftrightarrow t_1

Low number of cases

120

The build up of the susceptible class



121

Transmission parameters

122

The basic reproductive number

The fractions of S, I and R

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

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

Equilibrium

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

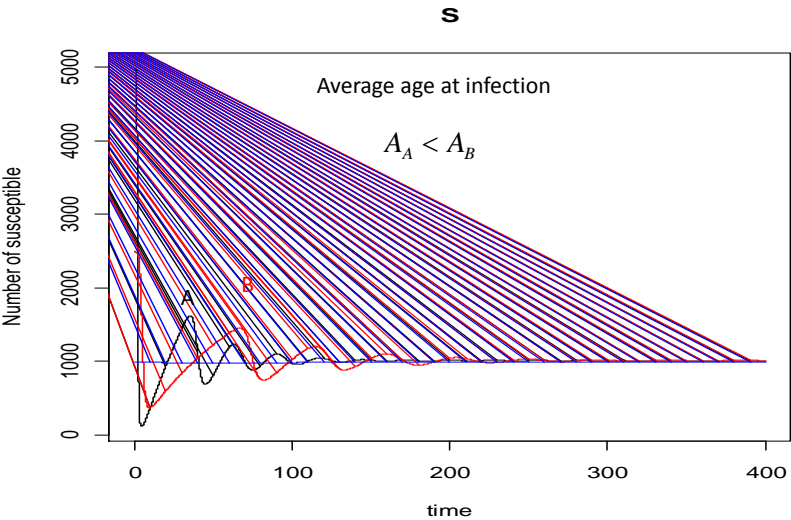


Condition for transmission

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

123

The average age at infection



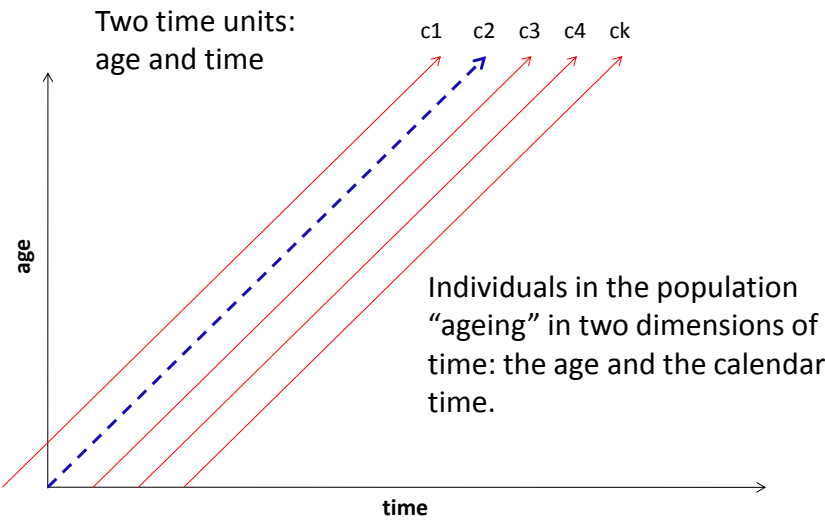
124

The SIR model in time homogeneity setting

R program: ModelingIDinR1_V1_Stat&Dynam_Sep2019.R

125

Transmission over age and time



126

SIR model: transmission over age and time

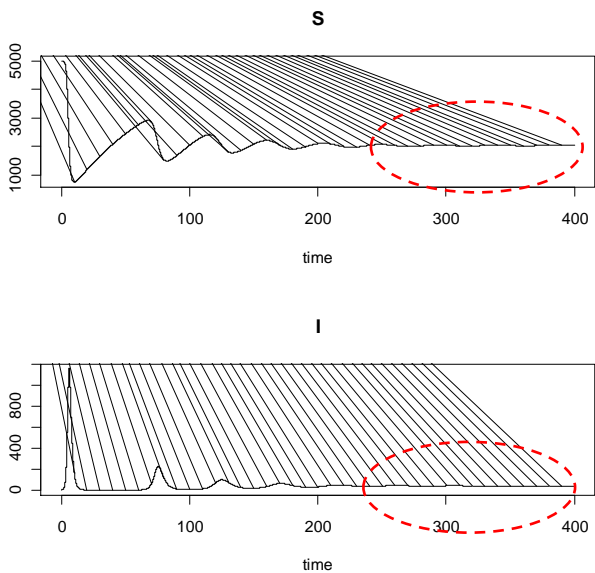
The change in each compartment with respect of age and time.

Age and time dependent force of infection.

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

127

Endemic equilibrium – time homogeneity



$$\begin{aligned}\frac{dS(t)}{dt} &= 0 \\ \frac{dI(t)}{dt} &= 0 \\ \frac{dR(t)}{dt} &= 0\end{aligned}$$

128

SIR model: transmission over age and time

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

Time homogeneity

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

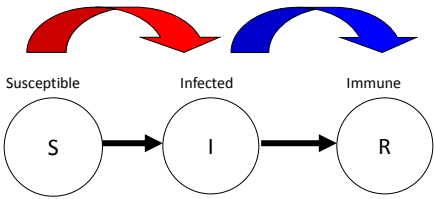
$$\frac{dS(t)}{dt} = 0$$
$$\frac{dI(t)}{dt} = 0$$
$$\frac{dR(t)}{dt} = 0$$

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

129

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

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



The SIR model

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

130

The Static model and serology

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

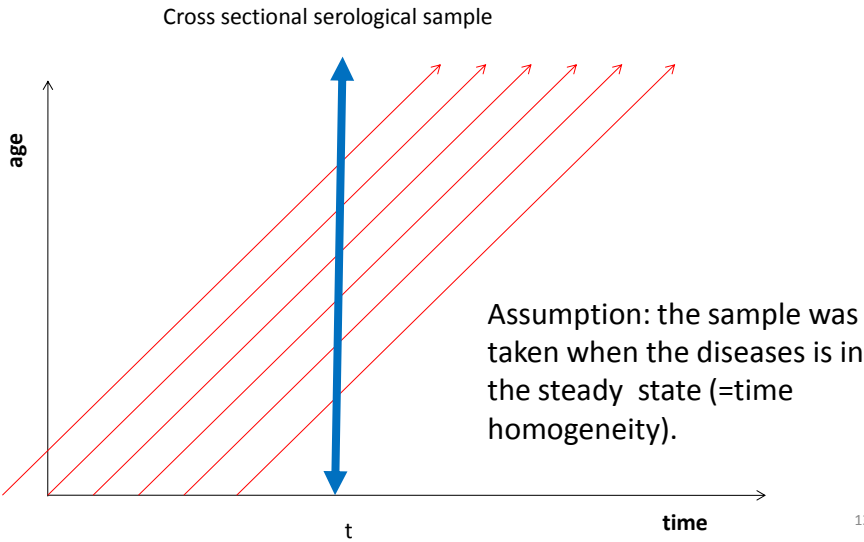
The time scale of primary interest is age.

How can we estimate the unknown parameters ?

Which type of data we need ?

131

Cross-sectional sample



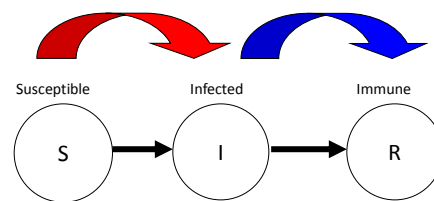
132

Models for closed population and SIR model in time homogeneity setting

The static model

133

The SIR model for closed population



The SIR model

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

134

SIR model (time homogeneity)

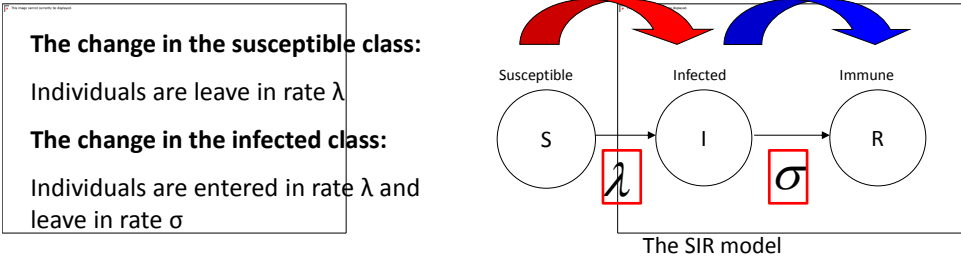
$$\frac{dS(a)}{da} = -\lambda S(a)$$
$$\frac{dI(a)}{da} = \lambda S(a) - \sigma I(a)$$
$$\frac{dR(a)}{da} = \sigma I(a)$$

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.

135

A simple Transmission Model SIR (time homogeneity)



136

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

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

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

The recovery rate: 10 days.

The unit of the parameters are in years

137

Transmission models in R

- We need to integrate the system of the ordinary differential equation.
- deSolve package in R.
- Numerical integration using of ODE system.

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

138

Transmission models in R

SIR model

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

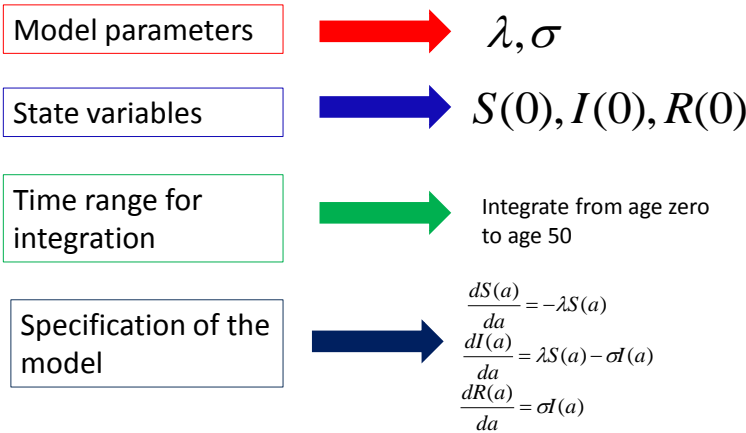
Specification in R

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

139

Transmission models in R

R program



140

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.

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

Recovery rate 10
days.

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

The unit of the
parameters are
in years⁻¹

141

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
```

142

Specification of the model in R

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

```
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

143

Specification of the time units for the integration

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

- 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
```

144

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
days)

145

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

146

Solution

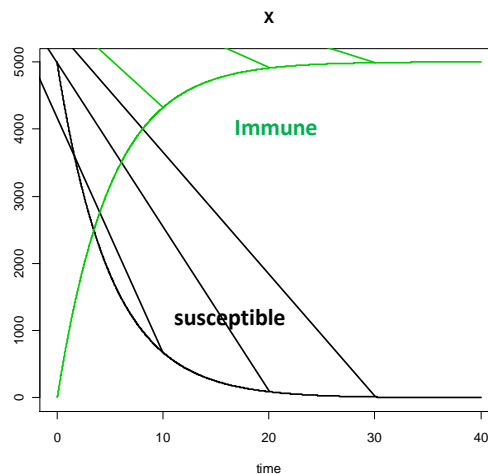
```
> require(deSolve)
> out <-
as.data.frame(ode(y=state,times=times,func=SIR,parms=
parameters))
> head(out)
```

	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

147

Graphical output

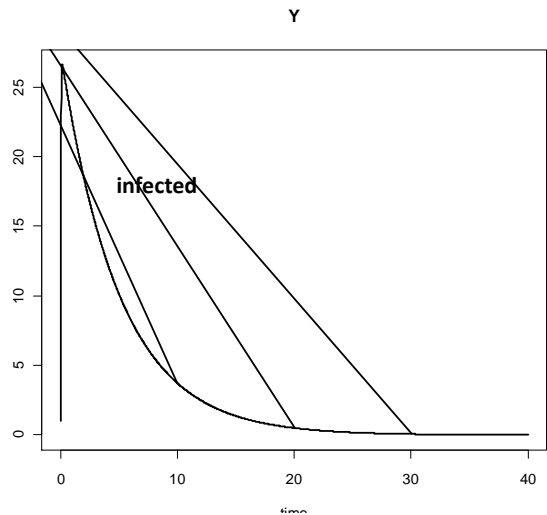
```
> plot (times,out$X ,type="l",main="X", xlab="time", ylab="-",lwd=2)
> lines(times,out$Z,col=3,lwd=2)
```



148

Graphical output

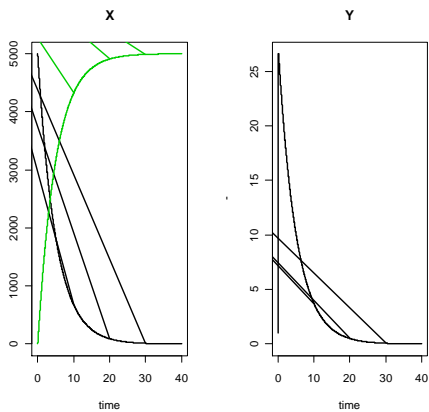
```
> plot (times,out$Y ,type="l",main="Y", xlab="time", ylab="-",lwd=2)
```



149

Graphical output

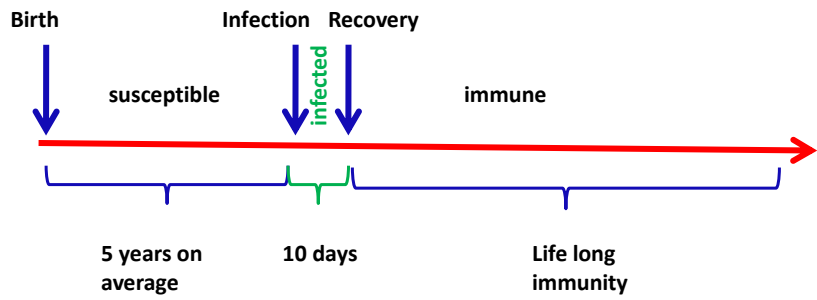
SIR model



What do we see here ?
Number of infected
individuals at each age.

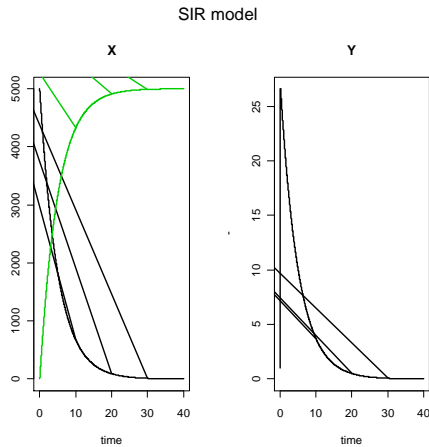
150

Duration of stay in the different compartments of the models



151

Graphical output



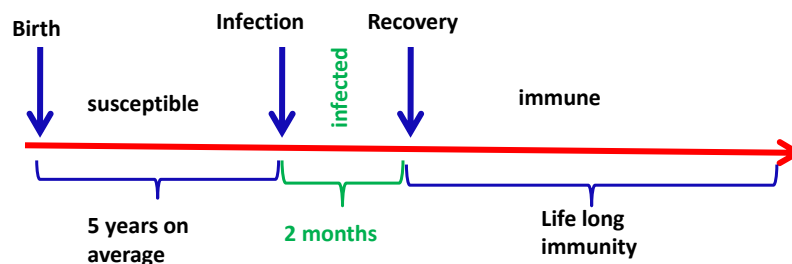
We expect to see only few infected individuals at each age (compared to the number of susceptible and immune).

152

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 ?



153

The model with recovery rate of 2 months

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

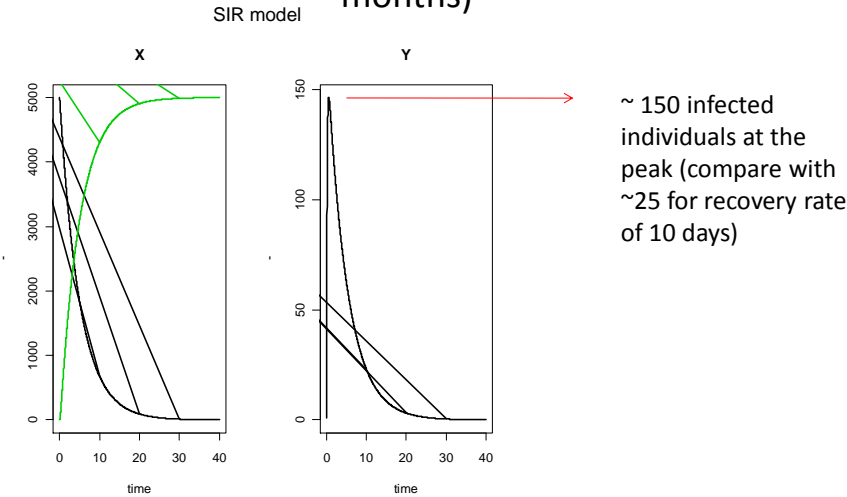
state <- c(X=4999,Y=1,Z=0)
state
SIR<-function(t,state,parameters)
{
  with(as.list(c(state, parameters)),
  {
    dX <- -lambda*X
    dY <- lambda*X - v*Y
    dZ <- v*Y
    list(c(dX, dY, dZ))
  })
}
times<-seq(0,40,by=0.01)
times
require(deSolve)
out <- as.data.frame(ode(y=state,times=times,func=SIR,parms=parameters))
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)

154

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



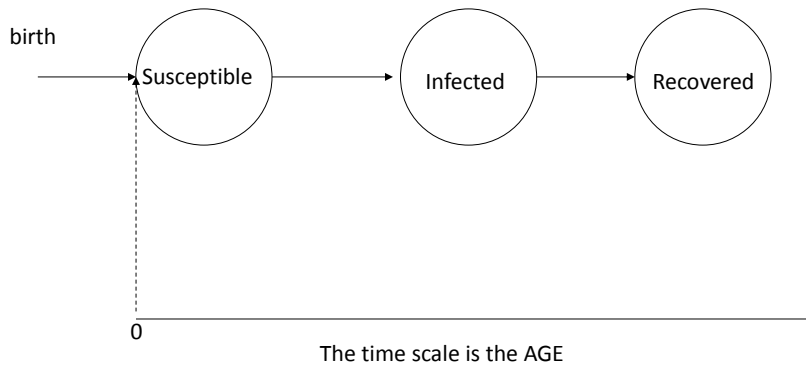
155

Transmission parameters

156

The average age at infection

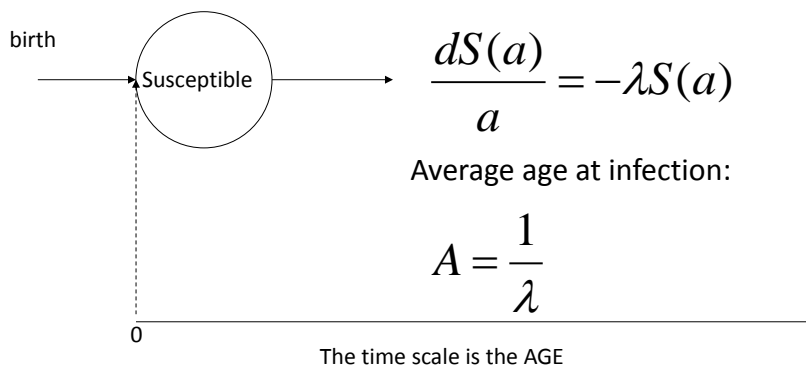
On average, how long individuals stay in the susceptible class ?
Average duration in the susceptible class.



157

The average age at infection

The change in the susceptible class:



158

Basic reproductive number

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

$$\left. \begin{array}{l} L > A \Rightarrow R_0 > 1 \\ L < A \Rightarrow R_0 < 1 \end{array} \right\} \begin{array}{l} R_0 < 1: \text{the disease will die out (} L > A \\ \text{means that, on average, individuals} \\ \text{will die before infection)} \end{array}$$

159

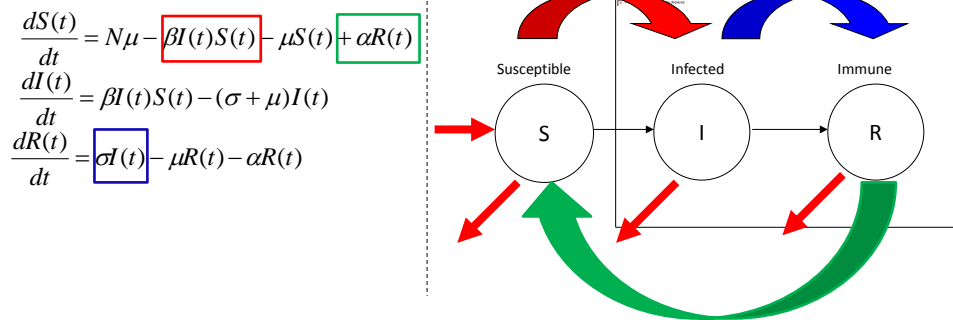
More about modeling

SIR model with temporary immunity
SIR model with carriers

Transmission models for multiple and sub populations.

160

SIRS model with temporary immunity

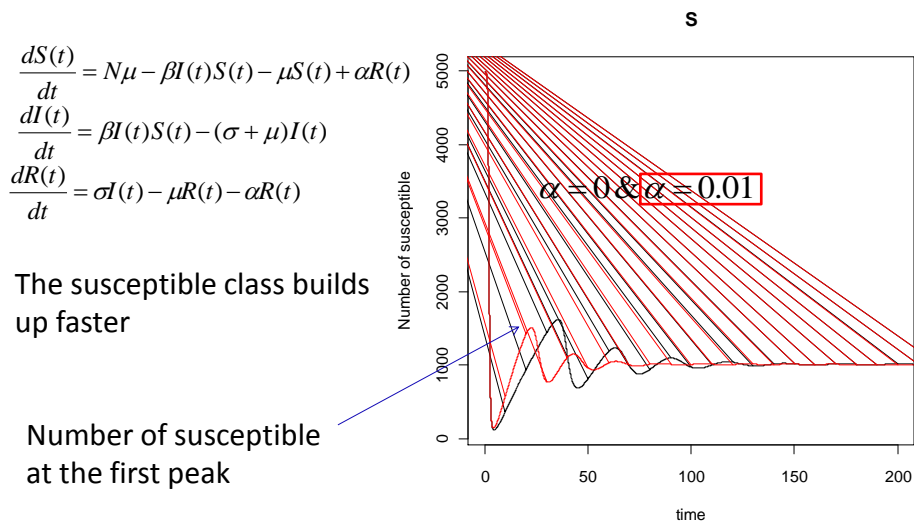


$\alpha = 0 \Rightarrow$ SIR with life long immunity

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

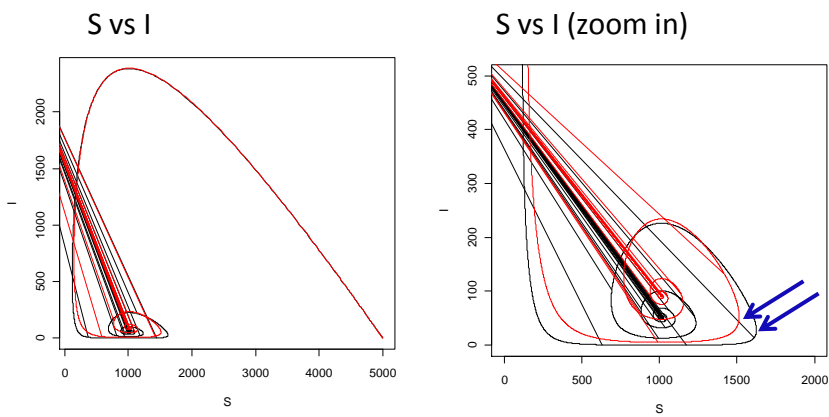
161

The susceptible class



162

Number of susceptible in the first peak



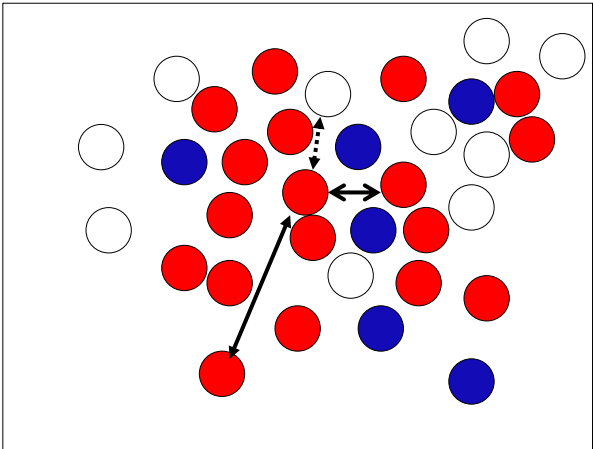
163

Multiple populations

R program: ModelingIDinR1_V1_MultiPop_Sep2019.R

164

The Mass-Action Principle and the force of infection



Contacts are made in random.
Number of new cases:

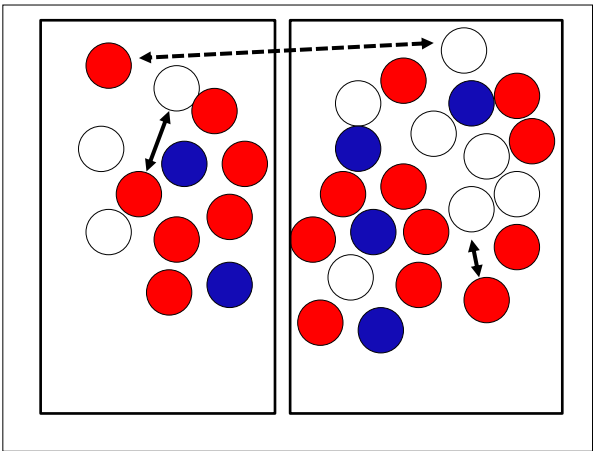
$$\beta \times I \times S$$

Transmission probability per contact

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

165

Transmission within/between sub populations



Contacts are **NOT** made in random.

Transmission between and within the sub population

166

Transmission revisited

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

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

- 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!

167

Transmission and mixing pattern

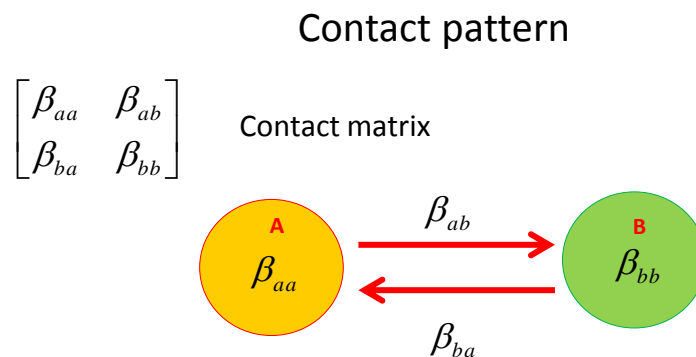
- In general, the "mixing pattern" within the population will **NOT be homogeneous**.
- The population is structured with respect to contacts.
- Examples:
 - Childhood infections: measles, mumps, rotavirus, ...: greater risk between infants: in day care centre, school, ..
 - Sexually transmitted infections: contact only possible within a sexual partnership.

168

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.

169

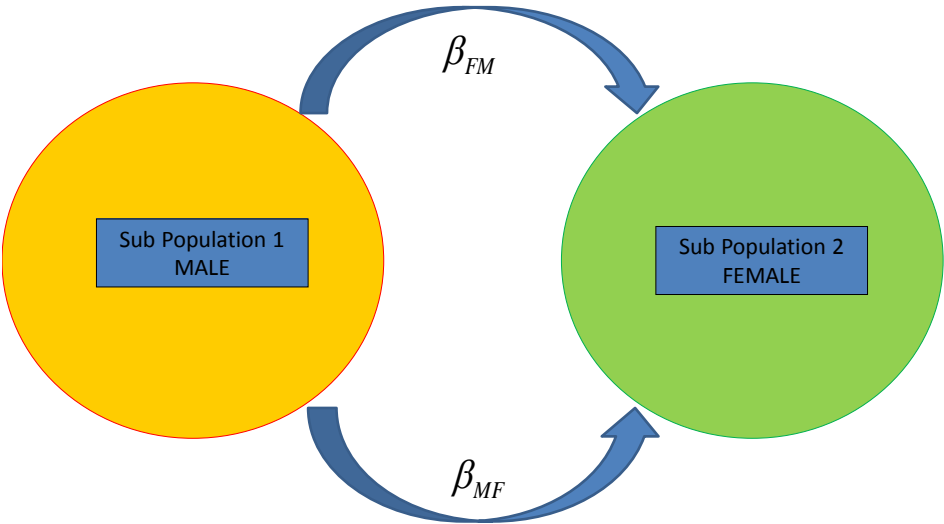


β_{ab} contact between susceptible from sub population A and infected from subpopulation B

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

170

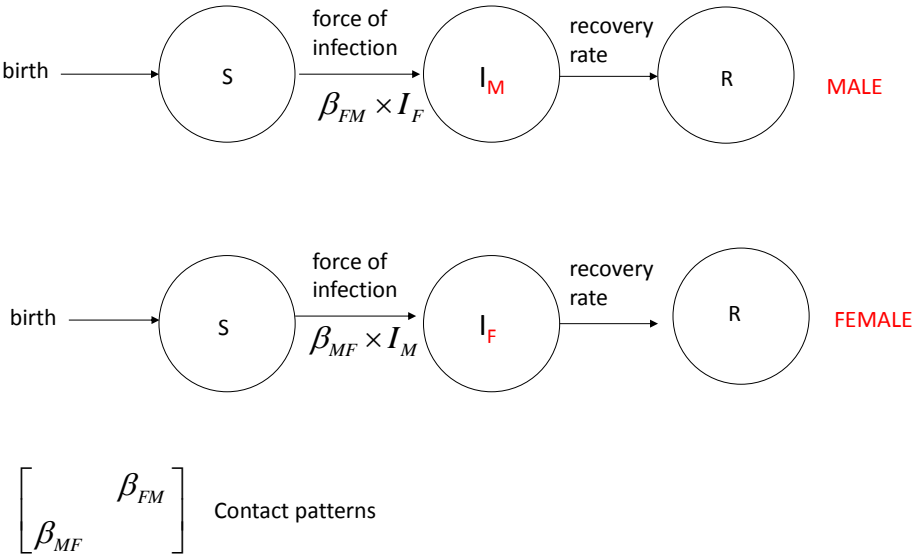
Sexually transmission diseases: Gonorrhea



Capasso 2008

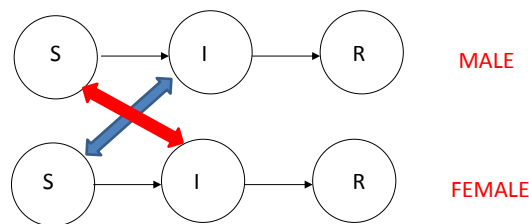
171

Model structure



172

Contact pattern: positive feedback



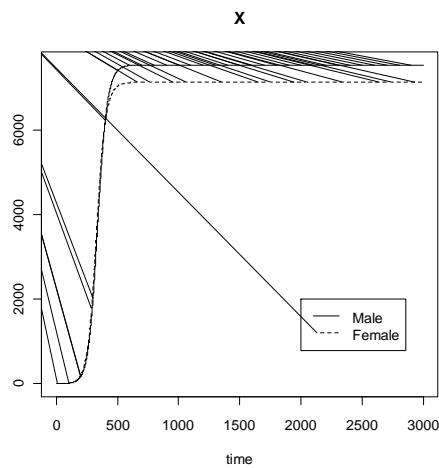
$$\begin{bmatrix} \beta_{MF} & \beta_{FM} \end{bmatrix}$$

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

Positive feedback: one population influence the transmission of the other population

173

Example



Parameter setting

$$\beta_{FM} =$$

$$\beta_{MF} =$$

$$N_M =$$

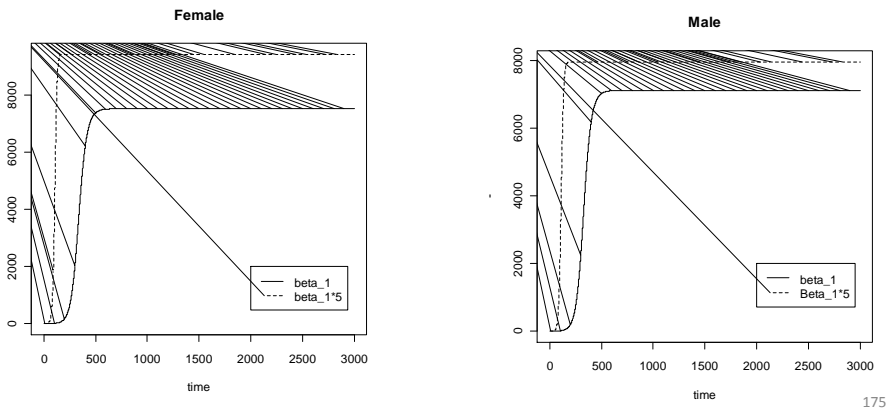
$$N_F =$$

174

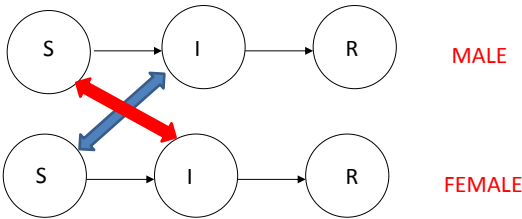
Example

Parameter setting

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



Transmission model for gonorrhea in R



THE ODE system

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

176

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)
```

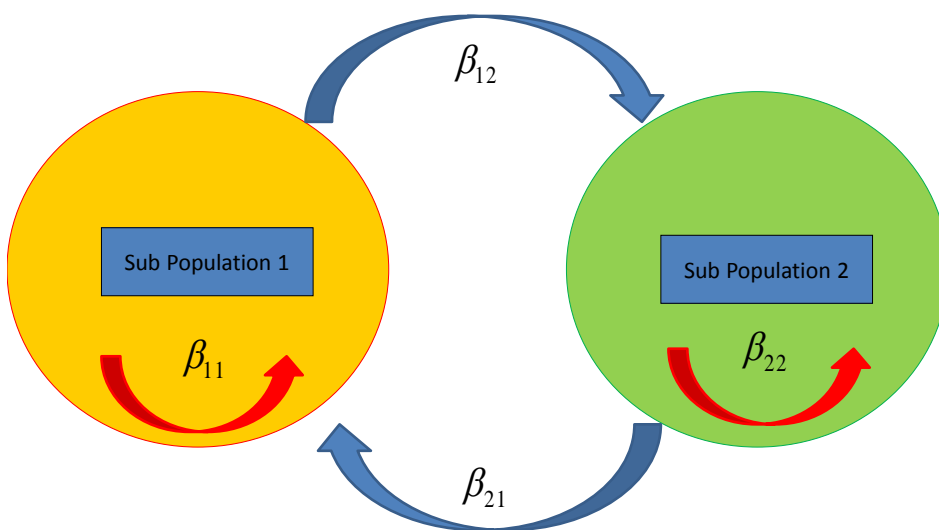
```
Gonorrhea<-function(t,state,parameters)
{
  with(as.list(c(state, parameters)),
  {
    dY1 <- beta1*(N1-Y1)*Y2-v1*Y1
    dY2 <- beta2*(N2-Y2)*Y1-v2*Y2
    list(c(dY1,dY2))
  })
}
```

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

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

177

Two interacting sub population



178

Contact pattern

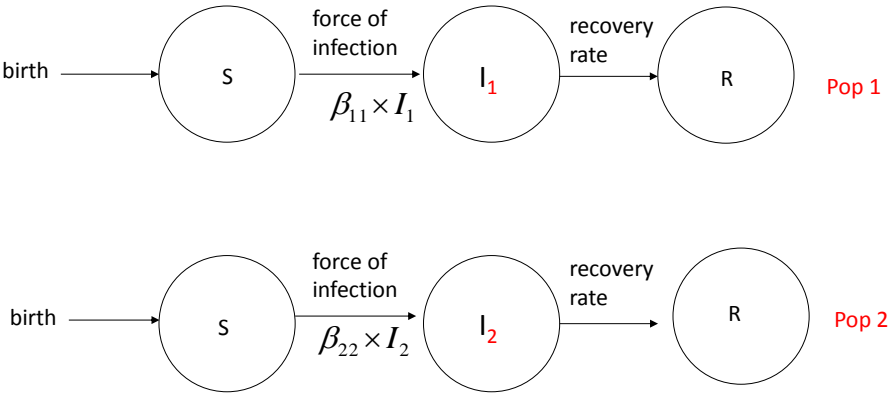
$$\begin{bmatrix} \beta_{11} & \beta_{12} \\ \beta_{12} & \beta_{22} \end{bmatrix}$$

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

Within population and within and between transmission.

179

Model structure 1

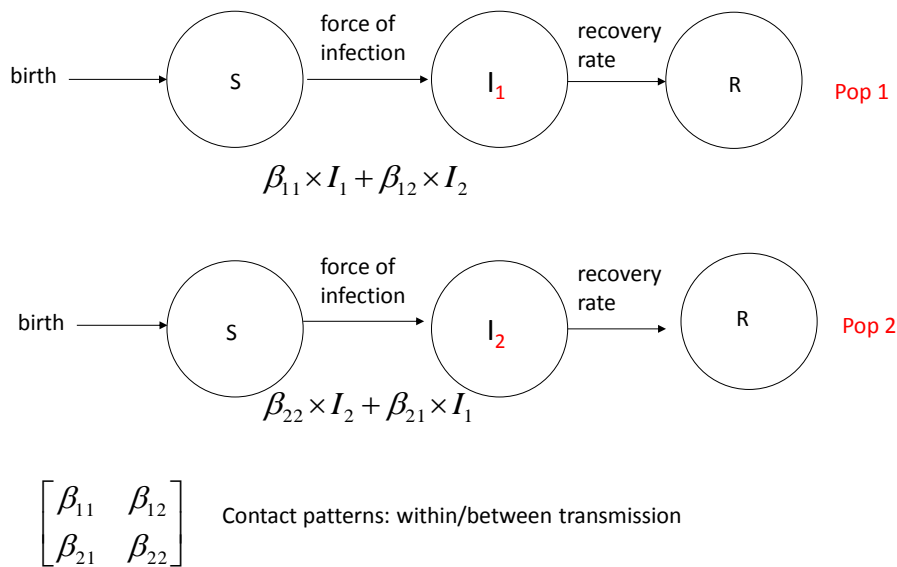


$$\begin{bmatrix} \beta_{11} & 0 \\ 0 & \beta_{22} \end{bmatrix}$$

Contact patterns: only within group transmission

180

Model structure 2



181

Model Structure

$$\left. \begin{aligned} \frac{dS_1(t)}{dt} &= \mu - (\beta_{11}I_1 + \beta_{12}I_2)S_1 - \mu S_1 \\ \frac{dI_1(t)}{dt} &= (\beta_{11}I_1 + \beta_{12}I_2)S_1 - \nu_1 I_1 - \mu I_1 \\ \frac{dR_1(t)}{dt} &= \nu_1 I_1 - \mu R_1 \\ \frac{dS_2(t)}{dt} &= \mu - (\beta_{21}I_1 + \beta_{22}I_2)S_2 - \mu S_2 \\ \frac{dI_2(t)}{dt} &= (\beta_{21}I_1 + \beta_{22}I_2)S_2 - \nu_2 I_2 - \mu I_2 \\ \frac{dR_2(t)}{dt} &= \nu_2 I_2 - \mu R_2 \end{aligned} \right\} \text{Contact patterns}$$

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

182

Example

Susceptible in population 1

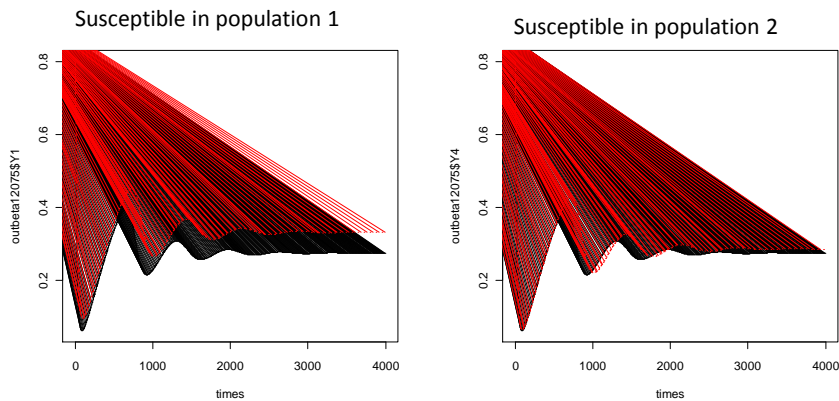
Parameter setting

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

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

183

Susceptible in the two sub population



184

Example

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:

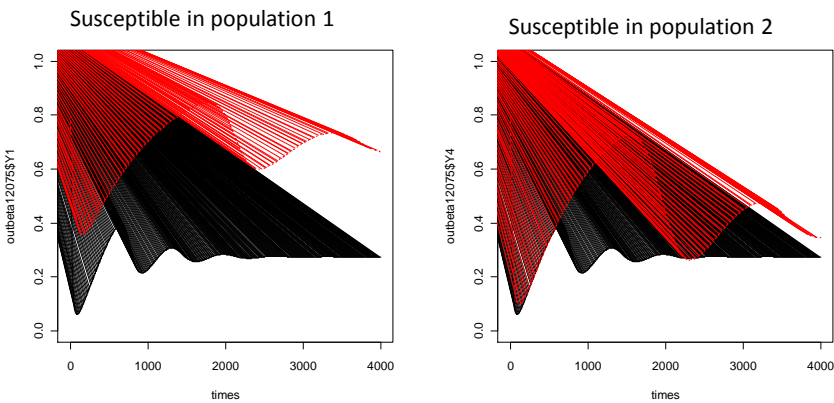
Per contact:

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

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

185

Susceptible in the two sub population



186

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:

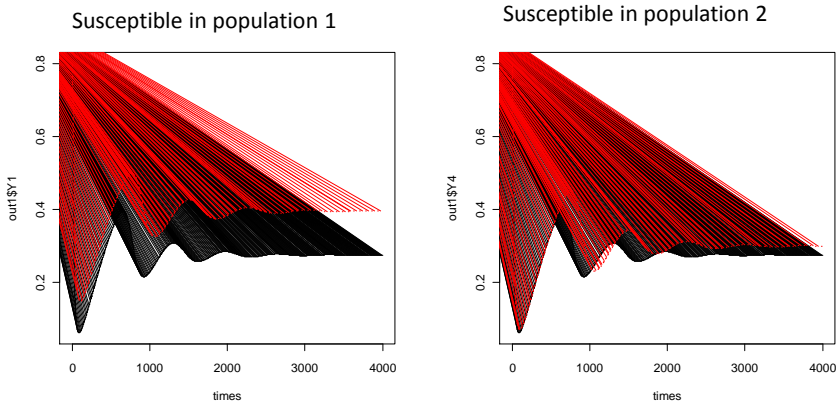
All transmission via contact between the population

Second population:

Transmission within / between the populations.

187

Susceptible in the two sub population



188

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)

```

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

189

Age Structured population

R program: ModelingIDinR1_V1_MultiPop_Sep2019.R

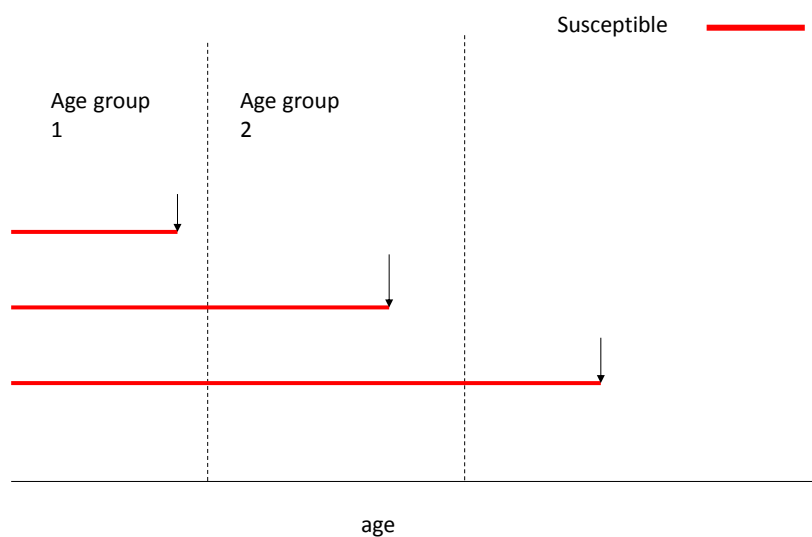
190

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).

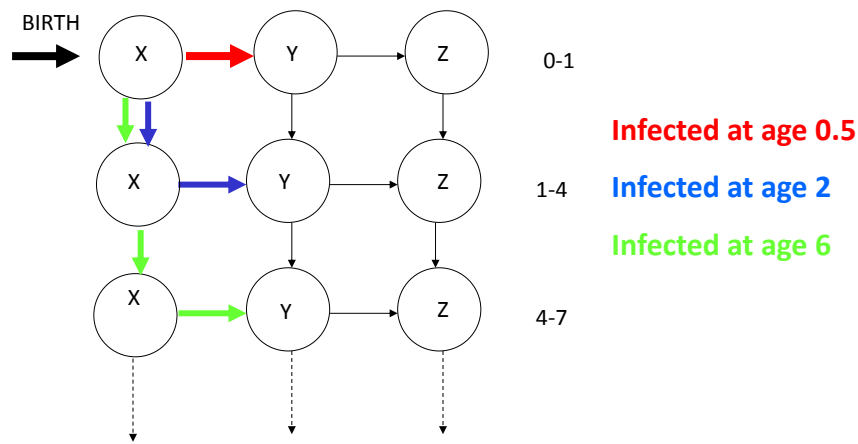
191

Age Structured population



192

Age Structured population



193

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

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

194

Model Structure: two age groups

$$\begin{aligned}\frac{dS_1(t)}{dt} &= N\mu - (\beta_{11}I_1 + \beta_{12}I_2)S_1 - \mu S_1 - \eta S_1 \\ \frac{dI_1(t)}{dt} &= (\beta_{11}I_1 + \beta_{12}I_2)S_1 - \nu_1 I_1 - \mu I_1 - \eta I_1 \\ \frac{dR_1(t)}{dt} &= \nu_1 I_1 - \mu R_1 - \eta R_1 \\ \frac{dS_2(t)}{dt} &= \eta S_1 - (\beta_{21}I_1 + \beta_{22}I_2)S_2 - \mu S_2 \\ \frac{dI_2(t)}{dt} &= \eta I_1 + (\beta_{21}I_1 + \beta_{22}I_2)S_2 - \nu_2 I_2 - \mu I_2 \\ \frac{dR_2(t)}{dt} &= \eta R_1 + \nu_2 I_2 - \mu R_2\end{aligned}$$

Contact patterns

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

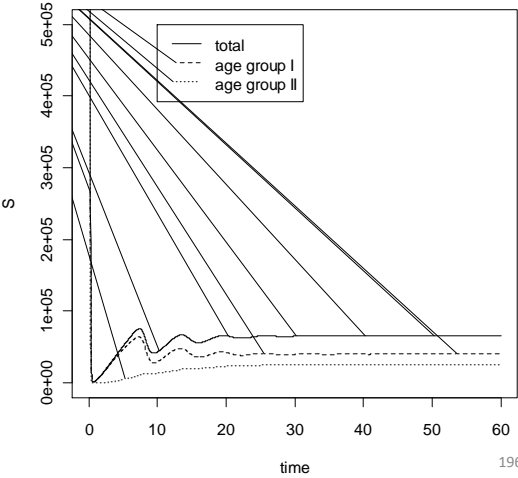
195

Example

Susceptible in the population

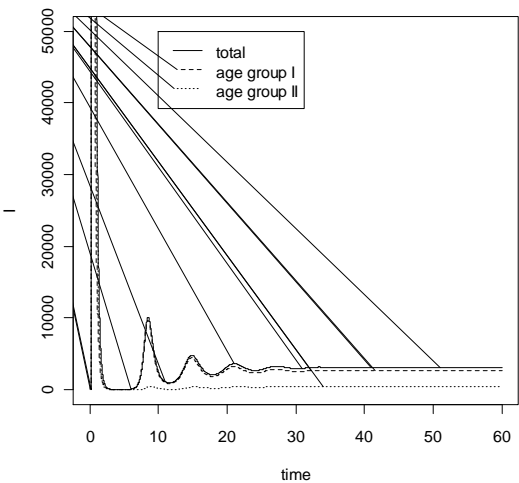
Parameter setting

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



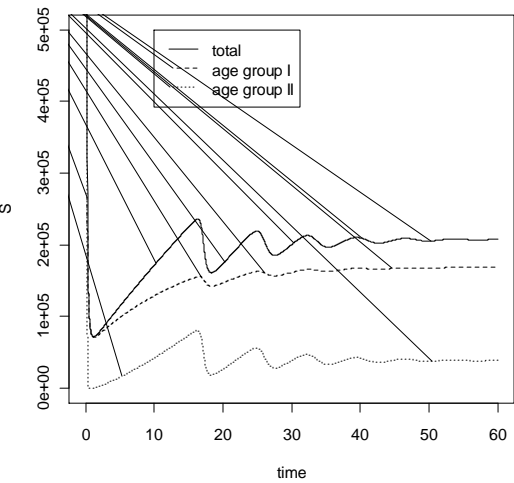
Example

Infected in the population



Example

Susceptible in the population



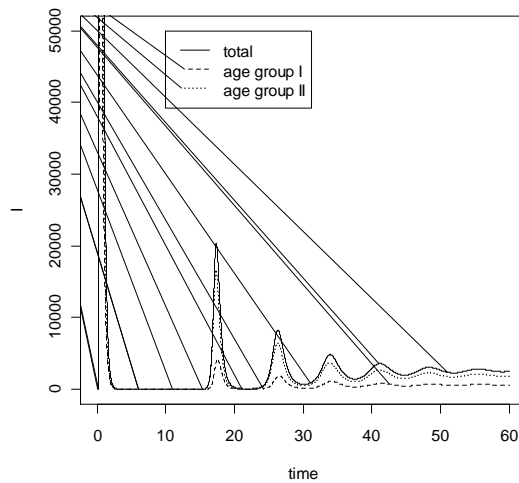
New parameter setting

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

Less within group transmission in pop. 1

Example

Infected in the population



199

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))
  })
}
```

$$\begin{bmatrix} \beta_{11} = 0.0001 & \beta_{12} = 0.0000075 \\ \beta_{21} = 0.0000075 & \beta_{22} = 0.0001 \end{bmatrix}$$

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

200

More about transmission models

201

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)

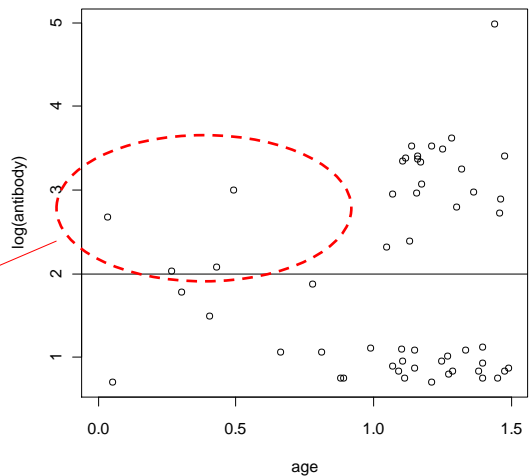


202

Maternal antibody for VZV in Belgium

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

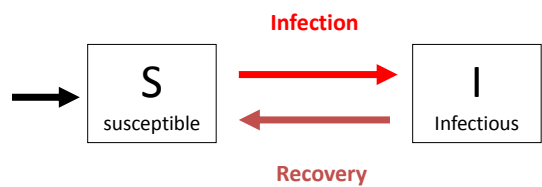
Not infected yet due to maternal antibody.



203

SIS model

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



Such a model is called a **S I S model**

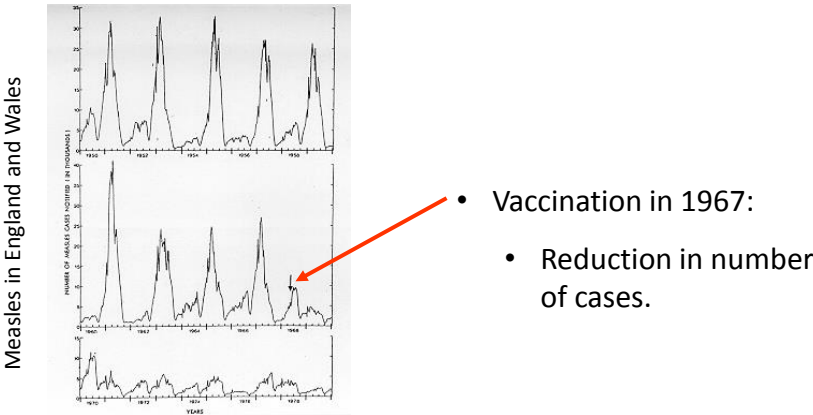
204

Vaccination: Intervention and Control

R program: ModelingIDinR1_V1_Vaccination_Sep2019.R

205

Measles in England and Wales

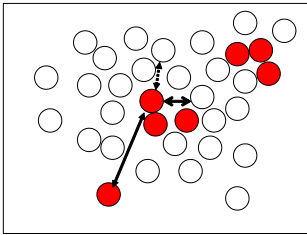


206

Intervention and control

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

The Mass-Action Principle



Contacts are made in random.

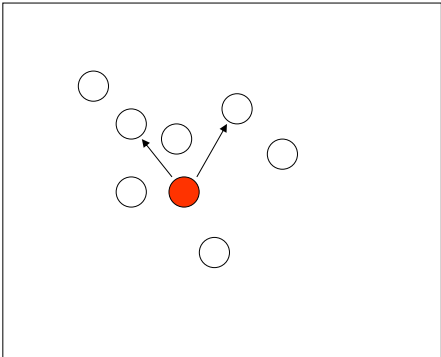
Stop the contacts
between infectious and
susceptible individuals.
It is not so easy to do!!!

Number of new cases= $P(\text{transmission}) \times \# \text{ of infectious} \times \# \text{ of susceptible}$

207

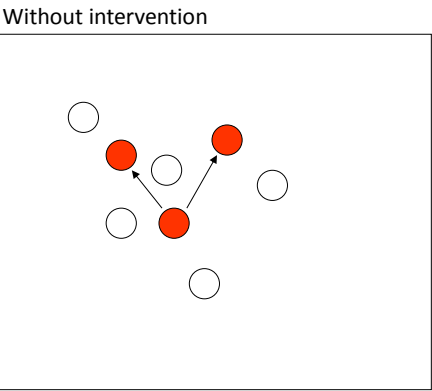
Intervention and control

First case



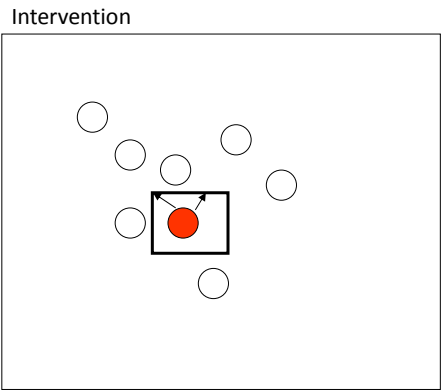
208

Intervention and control



209

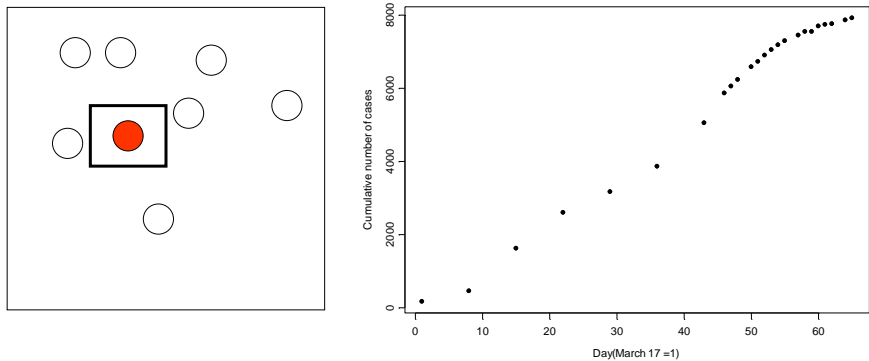
Intervention and control



210

Intervention and control

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

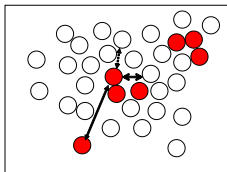


211

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= $P(\text{transmission}) \times \# \text{ of infectious} \times \# \text{ of susceptible}$

Stop the contacts between the **infectious** and susceptible individuals.

↓

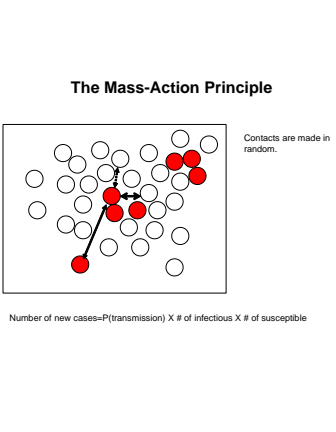
Stop the contacts between the **virus** and the susceptible individuals.

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

212

Intervention and control

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



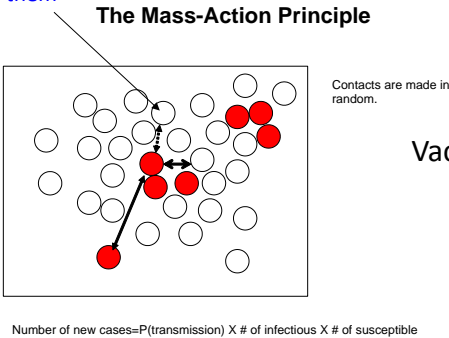
In order to control the number of contacts we need to understand how the disease spread....
...or what is the transmission process.

213

Intervention and control

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

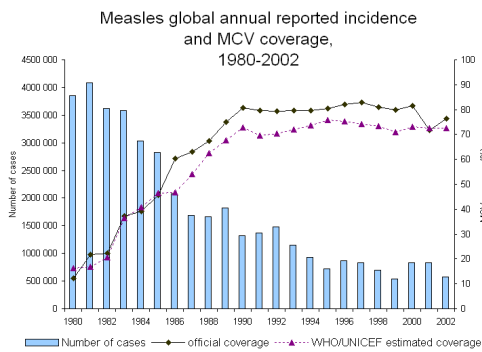
Focus of susceptible and protected them



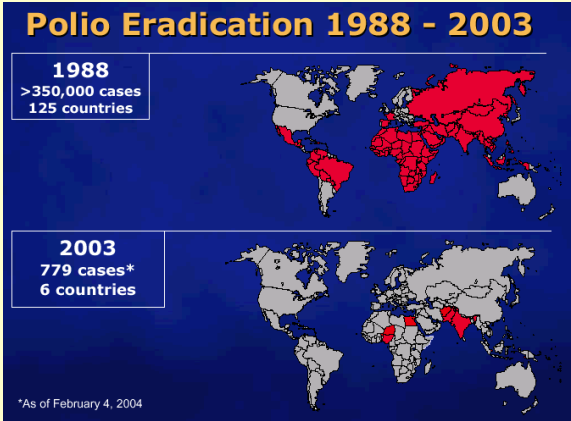
Vaccinate the susceptible.

214

Vaccination against measles

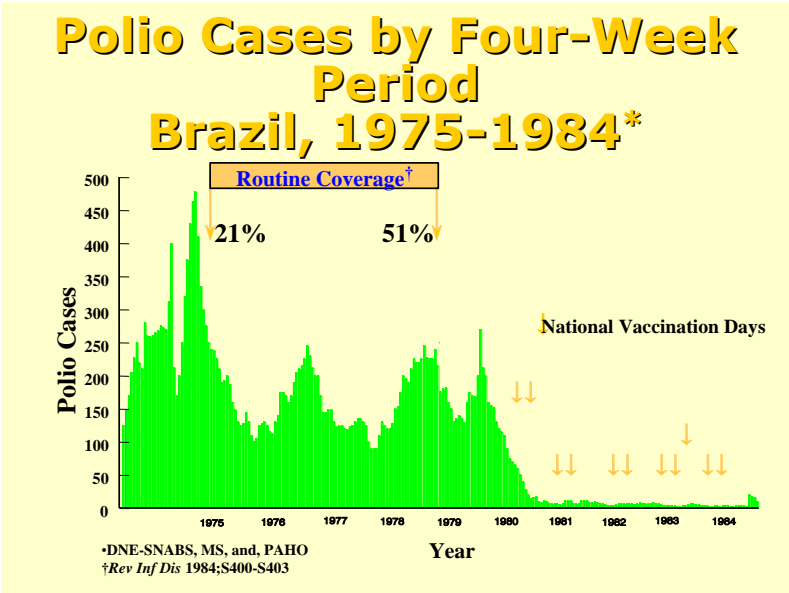


215



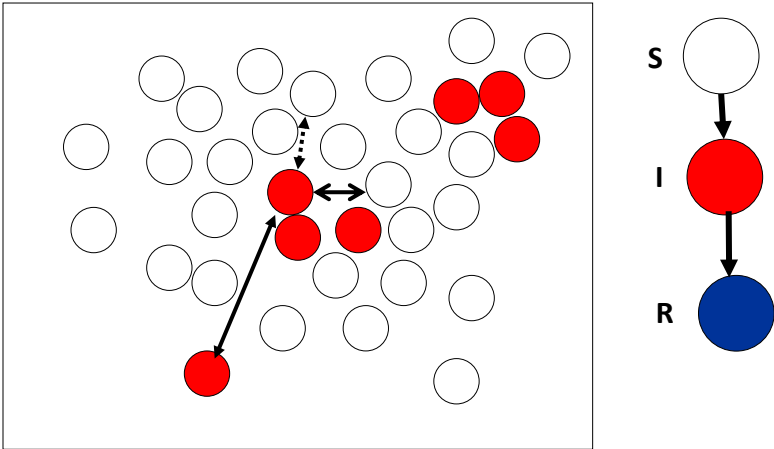
1

216



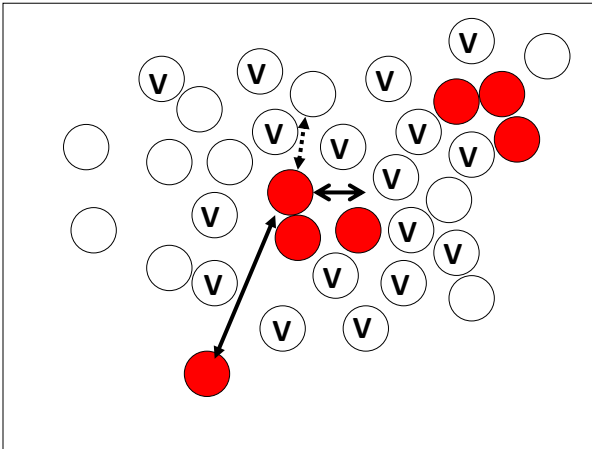
217

Vaccination



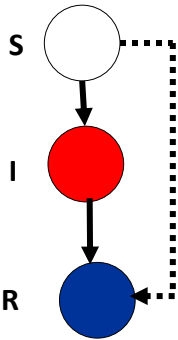
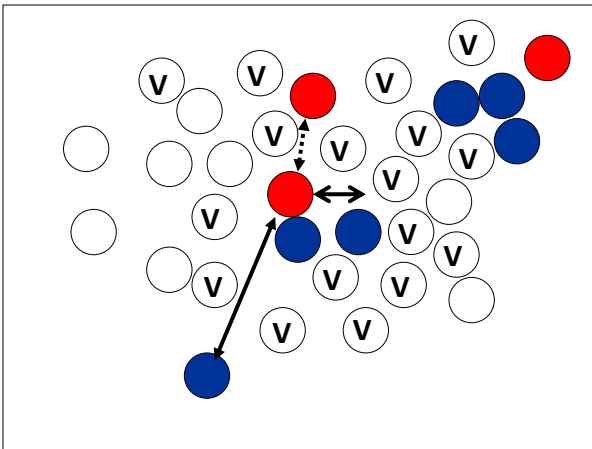
218

Vaccination



219

Vaccination

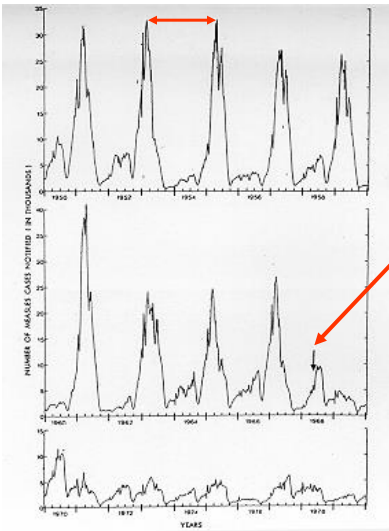


220

Example: vaccination of measles in UK

221

Measles in England and Wales



1978-1979

Vaccination
1967

222

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

223

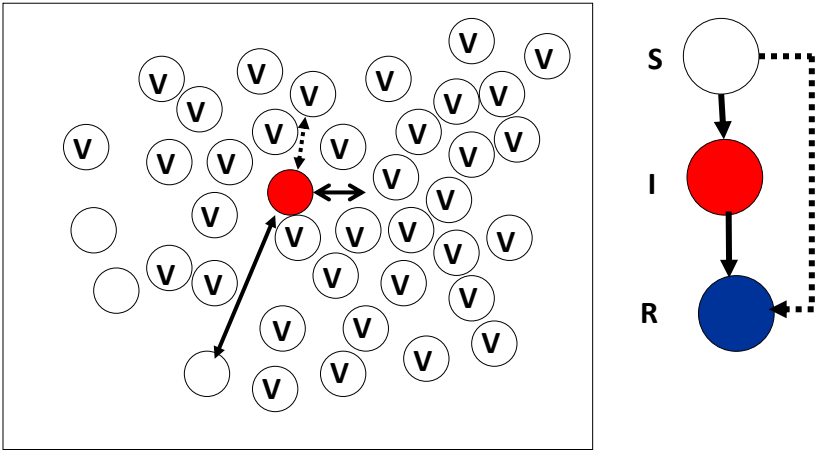
THE INDEPENDENT ON SUNDAY Saturday, 21 June 2008

- 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.



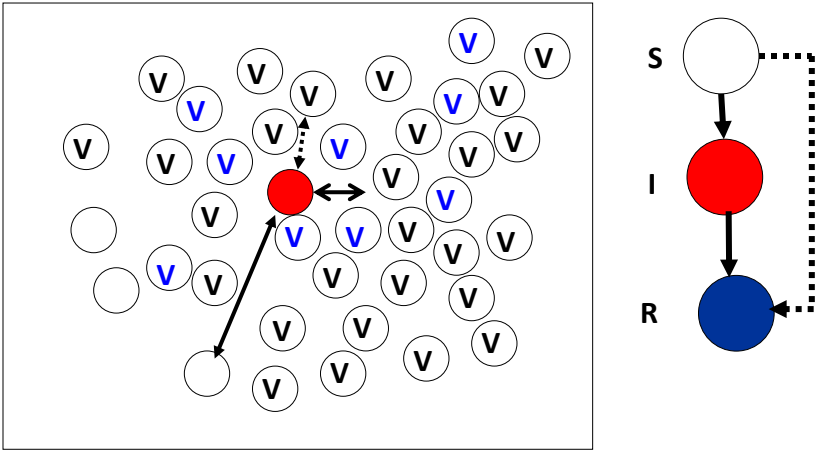
<http://www.independent.co.uk/life-style/health-and-wellbeing/health-news/official-warning-measles-endemic-in-britain-851584.html>

Vaccination rates ~92%



225

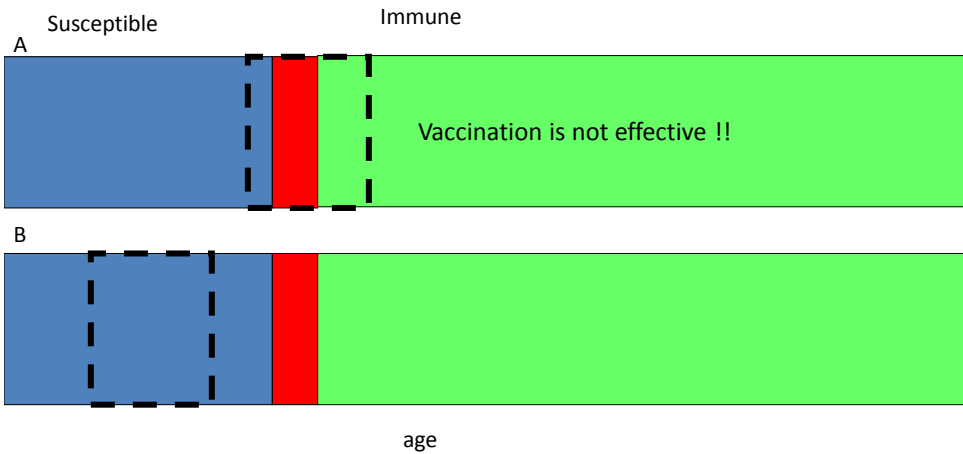
Vaccination rates ~70%



226

The time window for vaccination

When do we need to vaccinate ?



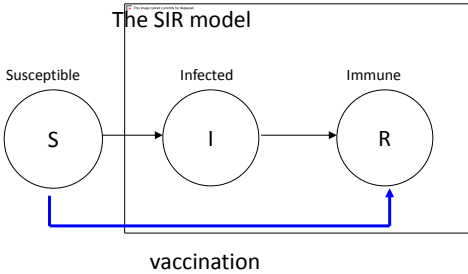
227

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.

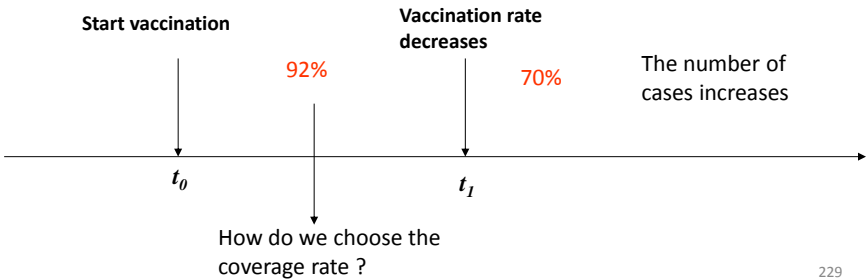


228

The “fuel” for an epidemic

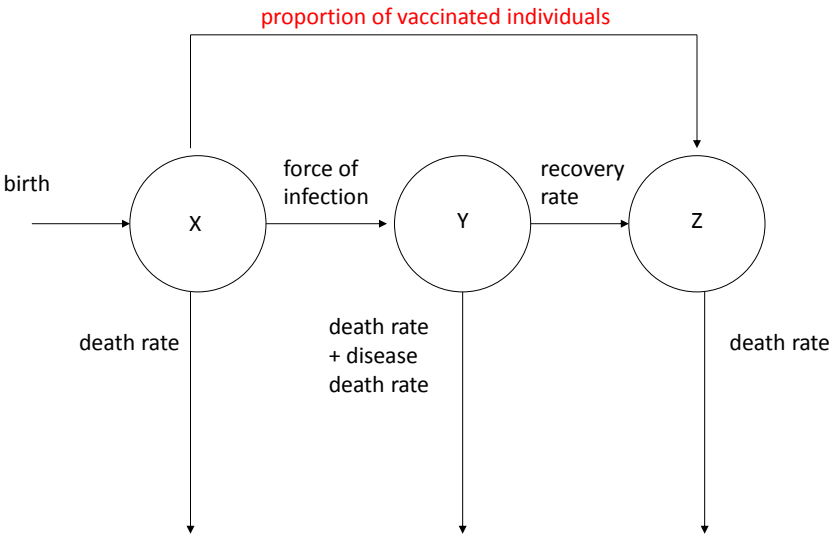
THE  ON SUNDAY
INDEPENDENT Saturday, 21 June 2008

- 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.



229

Model Structure: Vaccination in SIR model



230

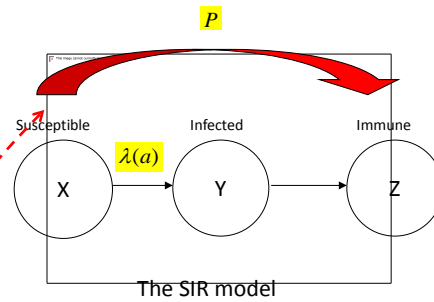
Model Structure: Vaccination in SIR model

- Open population:

$$\frac{dS(a)}{da} = (1 - P) \times B\mu - \lambda S(a)$$

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

$$\frac{dR(a)}{da} = P \times B\mu + \sigma I(a)$$



231

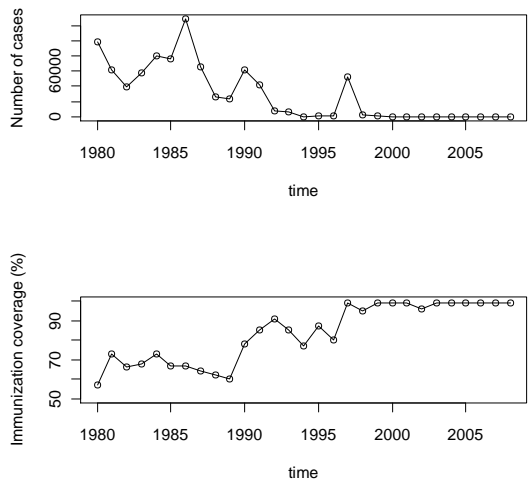
Effect of Vaccination

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

232

Effect of Vaccination

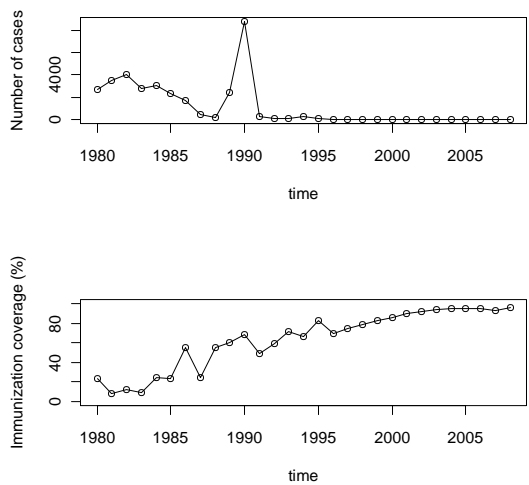
Number of measles cases in Brazil and coverage.



233

Effect of Vaccination

Number of measles cases in Guatemala and coverage.



234

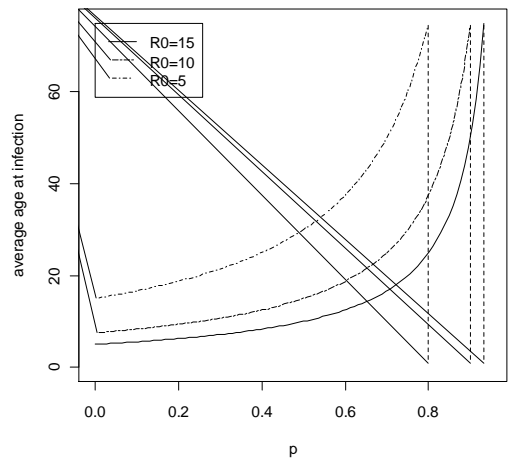
Effect of Vaccination: average age at infection

Critical proportion of vaccination:

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

New average age at infection:

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



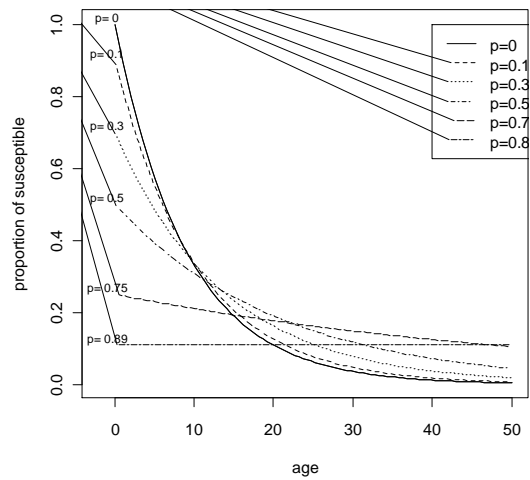
235

Effect of Vaccination: proportion of susceptible at equilibrium

Critical proportion of vaccination:

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

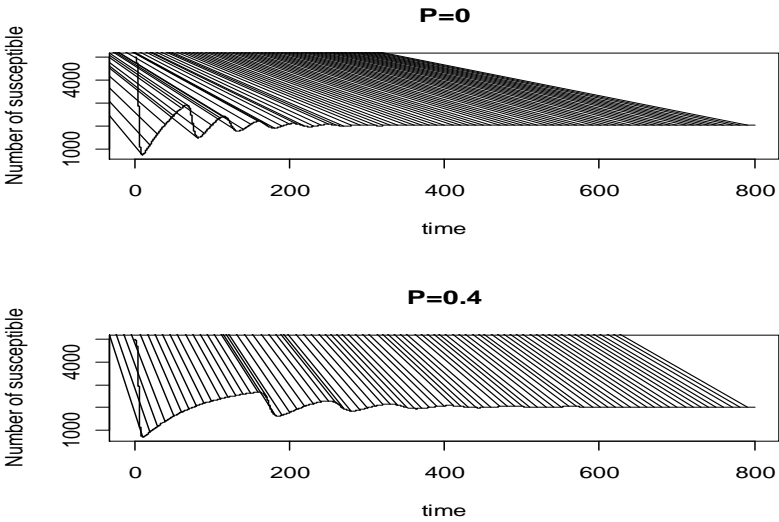
$$s(a) \rightarrow (1 - P)e^{-\lambda a}$$



236

Effect of Vaccination: Dynamic

Number of susceptible

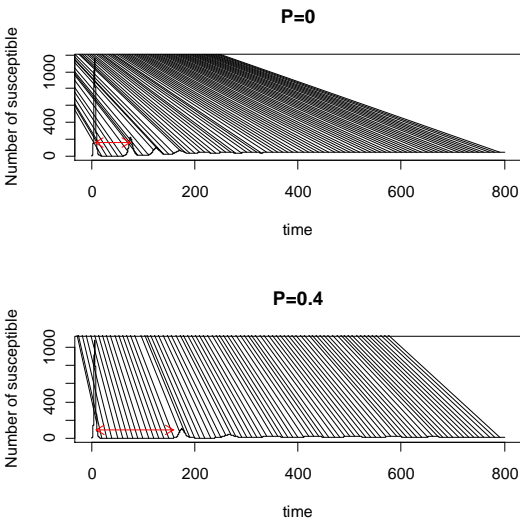


237

Effect of Vaccination: Dynamic

Number of infected

Inter-epidemic period.



238

Effect of Vaccination: Dynamic

Critical proportion of vaccination

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

Force of infection in the new equilibrium

$$\lambda' = \mu R_0 (P_c - P) \quad \longrightarrow \quad P \rightarrow P_c \Rightarrow \lambda' \rightarrow 0$$

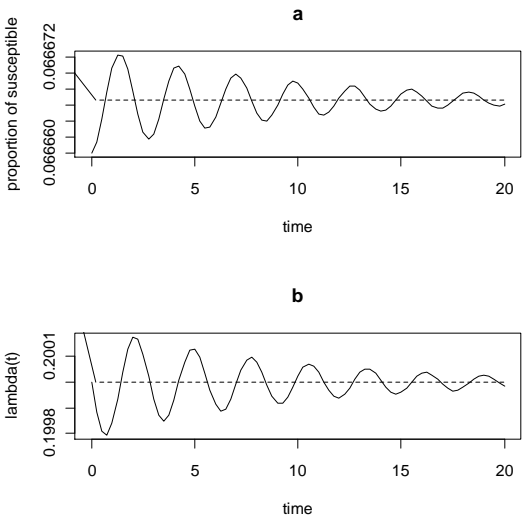
239

Effect of Vaccination: Dynamic

Proportion of susceptible and force of infection.

Parameter setting:

$\lambda_0 = 0.2$
 $\frac{1}{\mu} = 70$
 $\frac{1}{\nu} = 25$
 $R_0 = 15$
 $P = 0.0$



240

Effect of Vaccination: Dynamic

Proportion of susceptible and force of infection.

Parameter setting:

$$\lambda_0 = 0.2$$

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

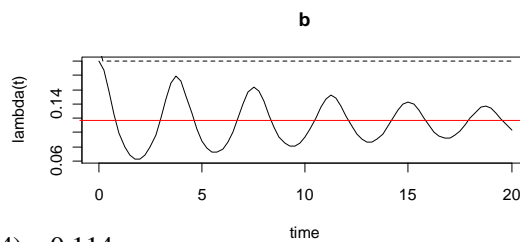
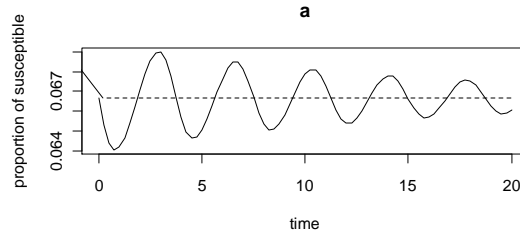
$$\mu$$

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

$$R_0 = 15$$

$$P = 0.4$$

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



241

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))
  })
}
```

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

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

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

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

242

Outbreak data Transmission model for HIV/AIDS

R program: ModelingIDinR1_V1_HIV&HCV_Sep2019.R

243

What are we looking for ?

Transmission
models



Data

Transmission model
for HIV/AIDS.

Very simple model
(just for illustration) ?

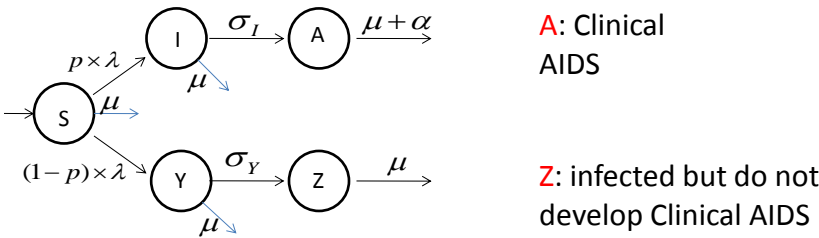
Can we observed the
“transmission
process” in the data ?

What can we estimate
from the data ?

244

Transmission model for HIV/AIDS

Transmission model for AIDS



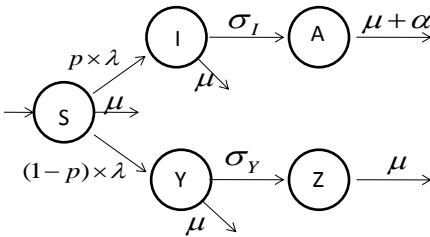
The time unit : exposure time – the time from entering to the population.

Capasso 2008, Anderson and May 1991, Anderson 1988

245

Transmission model for HIV/AIDS

Transmission model for AIDS



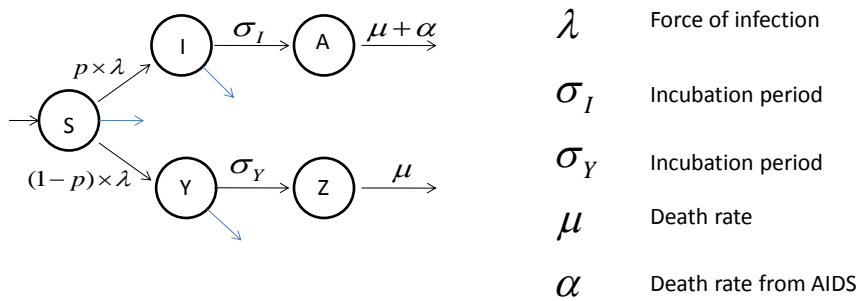
THE ODE system

$$\begin{aligned}\frac{dS(t)}{dt} &= B\mu - \lambda S(t) - \mu S(t) \\ \frac{dI(t)}{dt} &= P\lambda S(t) - (\sigma_I + \mu)I(t) \\ \frac{dY(t)}{dt} &= (1-P)\lambda S(t) - (\sigma_Y + \mu)Y(t) \\ \frac{dA(t)}{dt} &= \sigma_I I(t) - (\mu + \alpha)A(t) \\ \frac{dZ(t)}{dt} &= \sigma_Y Y(t) - \mu Z(t)\end{aligned}$$

Capasso 2008, Anderson and May 1991, Anderson 1988

246

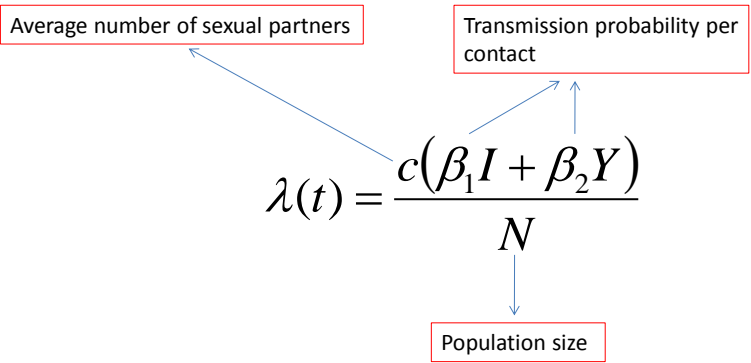
Model parameters



Capasso 2008, Anderson and May 1991, Anderson 1988

247

The force of infection



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

248

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

249

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
```

250

State variables

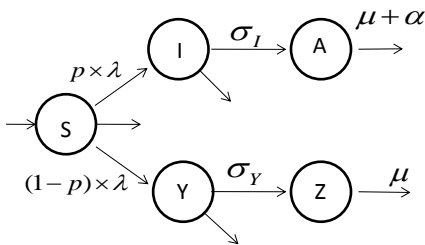
Population size of 10000.
At t=0, 5 individuals are infected.

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

251

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))
  })
}
```

252

Specification of the model in R

$$\begin{aligned}\frac{dS(t)}{dt} &= B\mu - \lambda S(t) - \mu S(t) \\ \frac{dI(t)}{dt} &= P\lambda S(t) - (\sigma_I + \mu)I(t) \\ \frac{dY(t)}{dt} &= (1-P)\lambda S(t) - (\sigma_Y + \mu)I(t) \\ \frac{dA(t)}{dt} &= \sigma_I I(t) - (\mu + \alpha)A(t) \\ \frac{dZ(t)}{dt} &= \sigma_Y Y(t) - \mu Z(t)\end{aligned}$$

```
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))
  })
}
```

253

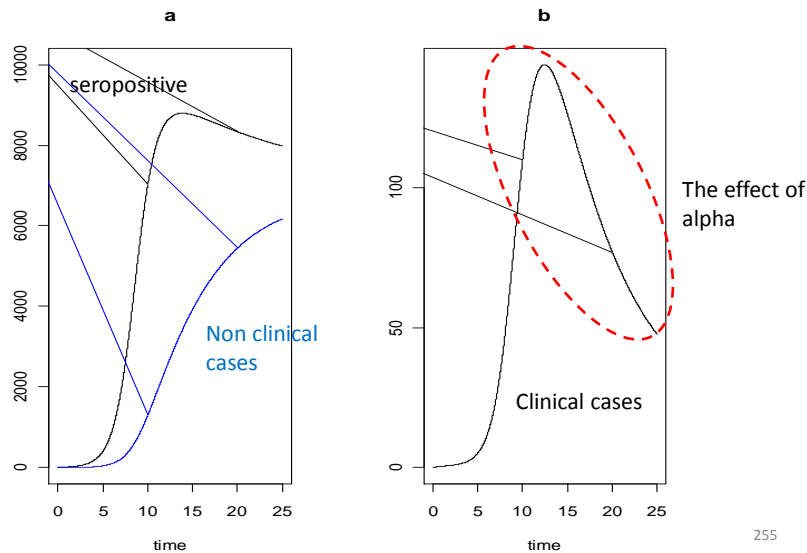
Running the model in R

```
times<-seq(0,20,by=0.01)
require(deSolve)
out <- as.data.frame(ode(y=state,times=times,func=AIDS,parms=parameters))
```

Time range for integration
state variables The model model parameters

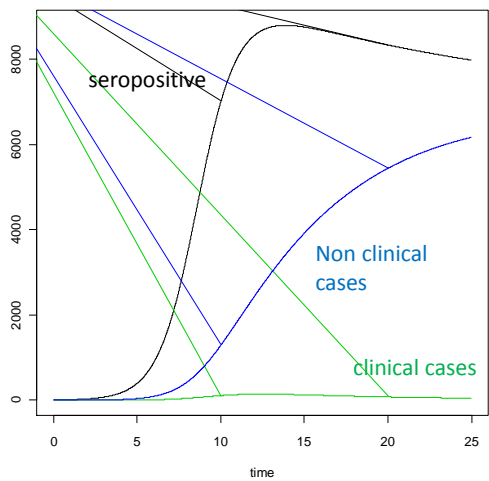
254

Solution



255

Solution



Why we do not see so many clinical cases ?

256

Model parameters in R

Model parameters:

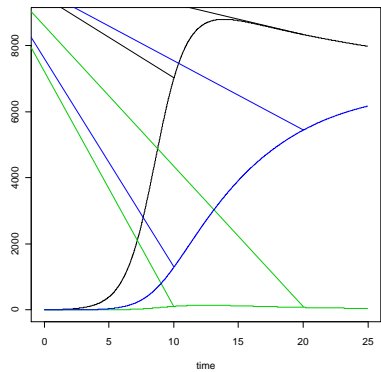
- 1. Life expectancy: 75 years.
- 2. Incubation period: 8 years.
- 3. Proportion of individuals develop clinical AIDS 20%.
- 4. life expectancy with clinical AIDS: 1 year ➡ 10 years.

```
> 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
```

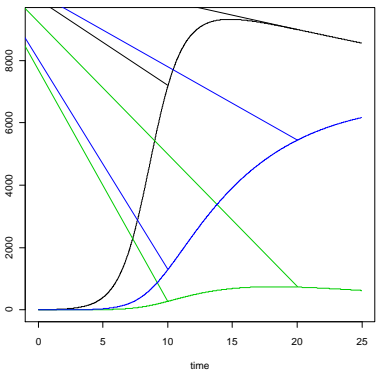
257

solution

life expectancy with clinical AIDS: 1 year



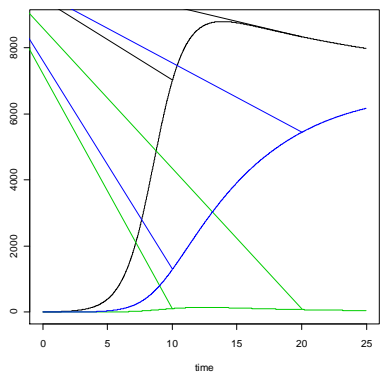
life expectancy with clinical AIDS: 10 years



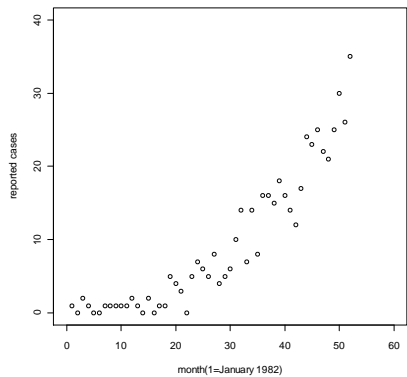
258

Modeling the initial outbreak of HIV/AIDS

Transmission model



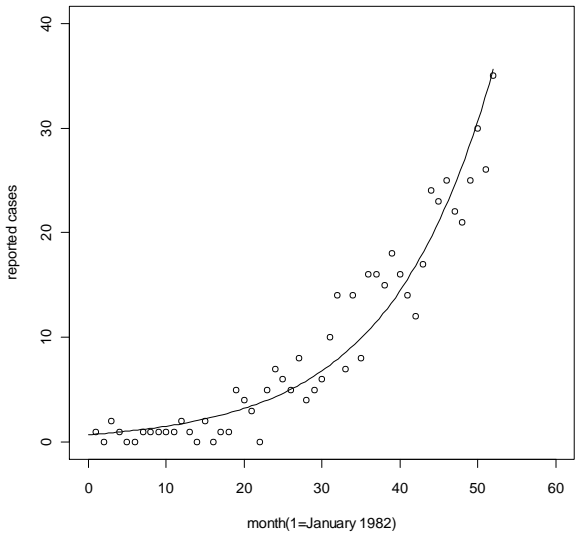
HIV positive in UK
(from Jan. 1982)



Which compartment we observed ?
Do we see the same pattern ?

259

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 ?

260

Transmission models for HCV among injecting drug users

R program: ModelingIDinR1_V1_Sep2017.R

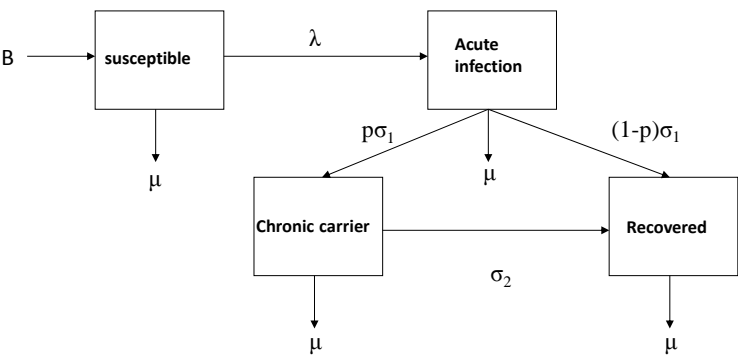
261

Part 1: Transmission models

262

PART 1
Transmission model for HCV

Mathematical model for transmission



263

The ODE system

The model

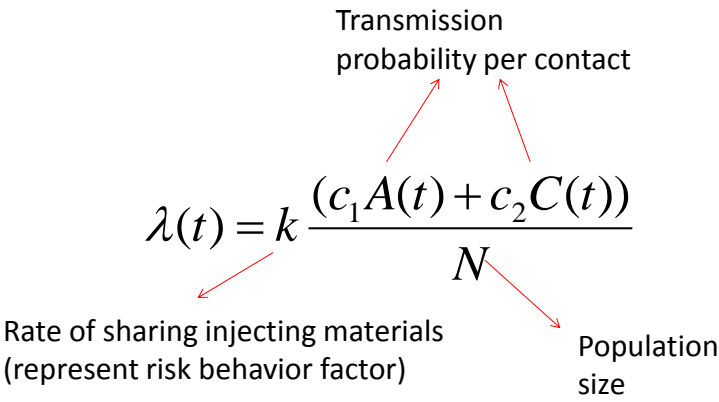
$$\begin{aligned}\frac{dS(t)}{dt} &= B\mu - \lambda(t)S(t) - \mu S(t) \\ \frac{dA(t)}{dt} &= \lambda(t)S(t) - (P\sigma_1 + \mu)A(t) \\ \frac{dC(t)}{dt} &= P\sigma_1A(t) - \sigma_2C(t) - \mu C(t) \\ \frac{dR(t)}{dt} &= (1-P)\sigma_1A(t) + \sigma_2C(t) - \mu R(t)\end{aligned}$$

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.

264

The force of infection



265

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%

```
>parameters <- 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
```

266

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.

267

Specification the transmission model in R

```
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))
  })
}
```

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

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

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

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

268

Specification the transmission model in R

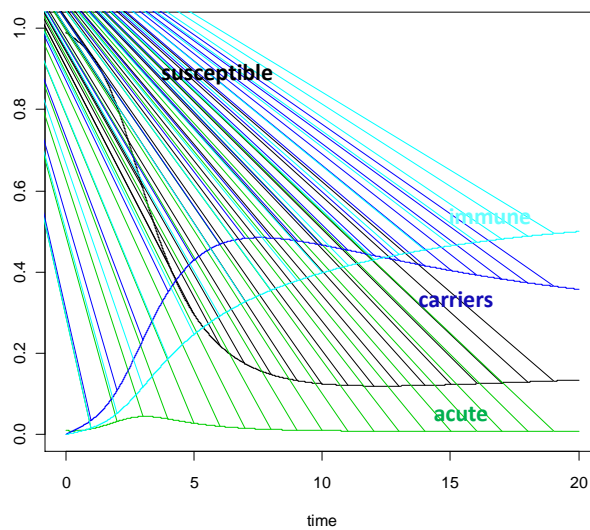
The force of infection depends on the duration of injection.

```
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))
  })
}
```

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

269

Solution



270