2013•2014
FACULTY OF SCIENCES
Master of Statistics

Master's thesis

Using stochastic simulation models to reconstruct B19 sero-epidemiology.

Promotor :
Prof. dr. Niel HENS

Kendra Houben

Thesis presented in fulfillment of the requirements for the degree of Master of Statistics

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Acknowledgements

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Contents

1 Introduction

In 1975, the first human parvovirus was accidently discovered. It was called parvovirus B19 (PVB19) which belongs to the family Parvoviridae and genus Erythrovirus (Cennimo, 2014). PVB19 can cause erythema infectiosum, also known as the fifth disease of childhood or slapped cheek syndrome. It mainly spreads through the respiratory route but transmission through blood or saliva droplets is also possible (Thyssen and Van Loock, 2002). The infection is common in children and teenagers, which transmit it to the parents. Usually, the disease is mild but acute arthritis can occur in adults, especially females (Cennimo, 2014). Currently, no vaccine against PVB19 is available.

Immunoglobulin G (IgG) antibodies are produced during PVB19 infection. These antibodies stay in the system and protects against secondary infections (Heegaard and Brown, 2002). Goeyvaerts et al. (2010) noticed that the assumption of lifelong immunity is not supported by the seroprevalence profiles of five European countries. Their goal was to find a transmission model that fits best to the data. The results showed that even the best transmission model was not able to fully capture the PVB19 sero-epidemiology. A reason could be that deterministic models are easier to analyze, but are not always realistic.

Stochastic models are often a more natural way to describe the spread of a disease (Andersson and Britton, 2000), but there is less literature about these models. One goal is to develop codes for different stochastic models, starting from the SIR model and extending it to the SIRS model. These stochastic simulation models can then be used to reconstruct the PVB19 sero-epidemiology of Belgium. In the future, this can be used to reconstruct the PVB19 sero-epidemiology of other countries as well as for other infections.

2 Methodology - Stochastic Simulation Models

The deterministic transmission models were used as basis to develop the stochastic models. The used transmission models consist of three compartments: susceptible (S), infected (I) and recovered (R). Assuming lifelong immunity after being infected, results in an SIR model which is the basic model. Goeyvaerts et al. (2010) noticed that the assumption of lifelong immunity was not supported by the data. Another possibility then is the SIRS model, where after recovery one can be susceptible again.

Both models were made stochastic under several assumptions in an age homogeneous and age heterogeneous setting, with and without vital dynamics.

2.1 Age Homogeneous

Both SIR and SIRS models can be described as a system of ordinary differential equations under the assumption of age homogeneity (Hens et al., 2012).

SIR model

$$\begin{aligned}
\frac{dS(t)}{dt} &= B(t) - \lambda(t)S(t) - \mu S(t), \\
\frac{dI(t)}{dt} &= \lambda(t)S(t) - gI(t) - \mu I(t), \\
\frac{dR(t)}{dt} &= gI(t) - \mu R(t),
\end{aligned}$$

where $S(t)$, $I(t)$ and $R(t)$ are respectively the number of susceptibles, infected and recovered individuals at time t. $B(t) = \mu N(t)$ is the number of births with μ the birth and death rate. If we assume that there is no disease-related mortality and because of equal birth and death rates, $B = \mu N$ which is constant. The force of infection can be expressed as $\lambda(t) = \beta I(t)$ from which the mass-action principle follows. The rate of becoming recovered after being infected is g.

SIRS model

$$\frac{dS(t)}{dt} = B(t) - \lambda(t)S(t) + \omega R(t) - \mu S(t),$$
$$\frac{dI(t)}{dt} = \lambda(t)S(t) - gI(t) - \mu I(t),$$
$$\frac{dR(t)}{dt} = gI(t) - \omega R(t) - \mu R(t),$$

where ω is the rate of becoming susceptible again after being recovered. All other parameters are the same as for the SIR model.

2.1.1 Without Vital Dynamics

First, the stochastic version of the deterministic SIR (SIRS) model under the assumption of age homogeneity and without vital dynamics was made.

A population of size $N = 1.000.000$ with $S(0) = N - 1$, $I(0) = 1$ and $R(0) = 0$ was considered. For simulation, the parameters were assumed to be $R_0 = 2.48$ (2.84) for SIR (SIRS), $g = 1/6$ days, $\omega = 0.013$ year and $\beta = \frac{gR_0}{N}$. These numbers were the estimates of Goeyvaerts et al. (2010).

Poisson distribution

S, I and R are the number of individuals at time 0. The newly infected/recovered/susceptible individuals were drawn from a poisson distribution.

- $I_{new} \sim Poisson(\beta I_t S_t)$
- $R_{new} \sim Poisson(gI_t)$
- $S_{new} \sim Poisson(\omega R_t)$

These numbers were then used to get S, I and R at time t according to the following equations for the SIR and SIRS model.

$$S_{t+1} = S_t - I_{new} \qquad S_{t+1} = S_t - I_{new} + S_{new}$$

$$I_{t+1} = I_t + I_{new} - R_{new} \qquad I_{t+1} = I_t + I_{new} - R_{new}$$

$$R_{t+1} = R_t - R_{new} \qquad R_{t+1} = R_t - R_{new} - S_{new}$$

Those numbers are kept in seperate vectors for S, I and R. This will be repeated until $I_t = 0$ or $S_t = 0$. The R-codes are given below for the SIR and SIRS model respectively.

_1_ SIR & SIRS - Pois - age homo.R

```
## S->I->R ##
-------------
Sold = S
Iold = I
Rold = R
Svec = NULL
Ivec = NULL
Rvec = NULL
stop = FALSE
while (!stop){
    Ih = rpois(1,b*Iold*Sold)
      print(Ih)
    Rh = rpois(1,g*Iold)
      if ((Iold+Ih-Rh)<=0) break
    Sold = Sold-Ih
      if (Sold<=0){Rold=N; break}
    Iold = Iold+Ih-Rh
    Rold = Rold+Rh
    Svec = c(Svec,Sold)
    Ivec = c(Ivec,Iold)
    Rvec = c(Rvec,Rold)
      if (Iold==0){stop=T}
}
```

_1_ SIR & SIRS - Pois - age homo.R

```
## S->I->R->S ##
----------------
Sold = S
Iold = I
Rold = R
Svec = NULL
Ivec = NULL
Rvec = NULL
stop = FALSE
while (!stop){
    Ih = rpois(1,b*Iold*Sold)
      print(Ih)
    Rh = rpois(1,g*Iold)
      if ((Iold+Ih-Rh)<=0) break
    Sh = rpois(1,w*Rold)
    Sold = Sold-Ih+Sh
      if (Sold<=0){Rold=N; break}
    Iold = Iold+Ih-Rh
    Rold = Rold+Rh-Sh
    Svec = c(Svec,Sold)
    Ivec = c(Ivec,Iold)
    Rvec = c(Rvec,Rold)
      if (Iold==0){stop=T}
}
```

Binomial distribution

Instead of using the poisson distribution to draw from, one could also use the binomial distribution. The relationship between rates (poisson) and probabilities (binomial) is $P = 1 - e^{-rate}$. Therefor, the newly infected/recovered/susceptible individuals were drawn from:

- $I_{new} \sim Bin(S_t, 1 - e^{-\beta I_t})$
- $R_{new} \sim Bin(I_t, 1 - e^{-g})$
- $S_{new} \sim Bin(R_t, 1 - e^{-\omega})$

An advantage of sampling from the binomial distribution is that it is restricted by a maximum. The breaks that were necessary with the Poisson, can now be removed. The program will run until a given point in time, TT. The R-codes with these changes are given below for the SIR and SIRS model respectively.

_1b_ SIR & SIRS - Bin - age homo.R

```
TT = 200

## S->I->R ##
-------------
Sold = S
Iold = I
Rold = R
Svec = NULL
Svec = c(Svec,Sold)
Ivec = NULL
Ivec = c(Ivec,Iold)
Rvec = NULL
Rvec = c(Rvec,Rold)
tt = 1
while (tt<TT){
    print(tt)
    Ih = rbinom(1,Sold,(1-exp(-b*Iold)))
      print(Ih)
    Rh = rbinom(1,Iold,(1-exp(-g)))
    Sold = Sold-Ih
    Iold = Iold+Ih-Rh
    Rold = Rold+Rh
    Svec = c(Svec,Sold)
    Ivec = c(Ivec,Iold)
    Rvec = c(Rvec,Rold)
    tt = tt+1
}
```

_1b_ SIR & SIRS - Bin - age homo.R

```
## S->I->R->S ##
----------------
Sold = S
Iold = I
Rold = R
Svec = NULL
Svec = c(Svec,Sold)
Ivec = NULL
Ivec = c(Ivec,Iold)
Rvec = NULL
Rvec = c(Rvec,Rold)
tt = 1
while (tt<TT){
    print(tt)
    Ih = rbinom(1,Sold,(1-exp(-b*Iold)))
      print(Ih)
    Rh = rbinom(1,Iold,(1-exp(-g)))
    Sh = rbinom(1,Rold,(1-exp(-w)))
    Sold = Sold-Ih+Sh
    Iold = Iold+Ih-Rh
    Rold = Rold+Rh-Sh
    Svec = c(Svec,Sold)
    Ivec = c(Ivec,Iold)
    Rvec = c(Rvec,Rold)
    tt = tt+1
}
```

2.1.2 With Vital Dynamics

Second, the model from section 2.1.1 when sampling from the binomial distribution was extended by adding vital dynamics. Birth and death were also sampled from a distribution.

- $birth \sim Poisson((S_t + I_t + R_t)\mu_B)$
- $S_{death} \sim Bin(S_t, 1 - e^{-\mu_D})$
- $I_{death} \sim Bin(I_t, 1 - e^{-\mu_D})$

- $R_{death} \sim Bin(R_t, 1 - e^{-\mu_D})$

Both birth and death were assumed to happen on a daily basis. All births start in the susceptible compartment. Mortality happens in each compartment with the same rate and disease-related mortality is ignored. Assume a life expectancy of 80 years, thus $\mu_B = \mu_D = 1/80$. The R-code for both SIR and SIRS models are given below.

_1c_ SIR & SIRS - Bin - age homo - vital dynamics.R

```
TT = 200

## S->I->R ##
-------------
Sold = S
Iold = I
Rold = R
Svec = NULL
Svec = c(Svec,Sold)
Ivec = NULL
Ivec = c(Ivec,Iold)
Rvec = NULL
Rvec = c(Rvec,Rold)
tt = 1
while (tt<TT){
    print(tt)
    Ih = rbinom(1,Sold,(1-exp(-b*Iold)))
      print(Ih)
    Rh = rbinom(1,Iold,(1-exp(-g)))
    muN = rpois(1,sum(Sold,Iold,Rold)*muB)
    muS = rbinom(1,Sold,(1-exp(-muD)))
    muI = rbinom(1,Iold,(1-exp(-muD)))
    muR = rbinom(1,Rold,(1-exp(-muD)))
    Sold = muN+Sold-Ih-muS
    Iold = Iold+Ih-Rh-muI
    Rold = Rold+Rh-muR
    Svec = c(Svec,Sold)
    Ivec = c(Ivec,Iold)
    Rvec = c(Rvec,Rold)
    tt = tt+1
}
```

_1c_ SIR & SIRS - Bin - age homo - vital dynamics.R

```
## S->I->R->S ##
----------------
Sold = S
Iold = I
Rold = R
Svec = NULL
Svec = c(Svec,Sold)
Ivec = NULL
Ivec = c(Ivec,Iold)
Rvec = NULL
Rvec = c(Rvec,Rold)
tt = 1
while (tt<TT){
    print(tt)
    Ih = rbinom(1,Sold,(1-exp(-b*Iold)))
      print(Ih)
    Rh = rbinom(1,Iold,(1-exp(-g)))
    Sh = rbinom(1,Rold,(1-exp(-w)))
    muN = rpois(1,sum(Sold,Iold,Rold)*muB)
    muS = rbinom(1,Sold,(1-exp(-muD)))
    muI = rbinom(1,Iold,(1-exp(-muD)))
    muR = rbinom(1,Rold,(1-exp(-muD)))
    Sold = muN+Sold-Ih+Sh-muS
    Iold = Iold+Ih-Rh-muI
    Rold = Rold+Rh-Sh-muR
    Svec = c(Svec,Sold)
    Ivec = c(Ivec,Iold)
    Rvec = c(Rvec,Rold)
    tt = tt+1
}
```

2.2 Age Heterogeneous

Both SIR and SIRS model can be described as a system of three partial differential equations in age and time (Hens et al., 2012).

SIR model

$$\begin{aligned}
\frac{\partial S(a,t)}{\partial a} + \frac{\partial S(a,t)}{\partial t} &= -\lambda(a,t)S(a,t) - \mu(a,t)S(a,t),\\
\frac{\partial I(a,t)}{\partial a} + \frac{\partial I(a,t)}{\partial t} &= \lambda(a,t)S(a,t) - \sigma(a,t)I(a,t) - \mu(a,t)I(a,t),\\
\frac{\partial R(a,t)}{\partial a} + \frac{\partial R(a,t)}{\partial t} &= \sigma(a,t)I(a,t) - \mu(a,t)R(a,t),
\end{aligned}$$

where $S(a,t)$, $I(a,t)$ and $R(a,t)$ are respectively the number of susceptibles, infected and recovered individuals at time t and age a. The number of births at time t is $B(t) = S(0,t)$, while under the assumption of no vertical transmission $I(0,t) = R(0,t) = 0$. The assumption of no disease-related mortality still counts. Only the natural death rate remains, which can depend on age and time $\mu(a,t)$. The force of infection is often assumed to be age and time dependent ($\lambda(a,t)$), while the revovery rate is often assumed to be constant ($\sigma(a,t) = \sigma$).

SIRS model

$$\begin{aligned}
\frac{\partial S(a,t)}{\partial a} + \frac{\partial S(a,t)}{\partial t} &= -\lambda(a,t)S(a,t) + \omega(a,t)R(a,t) - \mu(a,t)S(a,t),\\
\frac{\partial I(a,t)}{\partial a} + \frac{\partial I(a,t)}{\partial t} &= \lambda(a,t)S(a,t) - \sigma(a,t)I(a,t) - \mu(a,t)I(a,t),\\
\frac{\partial R(a,t)}{\partial a} + \frac{\partial R(a,t)}{\partial t} &= \sigma(a,t)I(a,t) - \omega(a,t)R(a,t) - \mu(a,t)R(a,t).
\end{aligned}$$

Like the recovery rate, the rate to become susceptible again is often assumed to be constant ($\omega(a,t) = \omega$). Again, the other parameters are the same as in the SIR model.

2.2.1 Without Vital Dynamics

The stochastic version of the age homogeneous SIR (SIRS) model was extended to be age heterogeneous without vital dynamics.

The difference with the age homogeneous model is that the population is divided in 80 agegroups of one year. So S, I and R will become vectors instead of numbers. Assume that each agegroup

consists of 100.000 individuals whereof 10 individuals are infected and none are in the recovered compartment at time 0. The same values for R_0, g, ω and β were considered, except that β now becomes a 80x80 matrix which leads to homogeneous mixing. The chance to become infected is the same within and between agegroups.

Poisson distribution

S, I and R are the vectors with the initial number of individuals as stated before. Again the newly infected/recovered/susceptible individuals in each agegroup were sampled from a poisson distribution.

- $I_{new} \sim Poisson(\beta I_t S_t)$
- $R_{new} \sim Poisson(gI_t)$
- $S_{new} \sim Poisson(\omega R_t)$

The vector of S, I and R at time t are changed according to the SIR or SIRS model. The number of individuals in each compartment for each agegroup and at each time are kept in a matrix. These steps will be repeated until the vector of S or I contains a value that is smaller or equal to 0. The R-code of this model is given below.

_2_ SIR & SIRS - Pois - age hetero - homo mixing.R

```
TT = 200

## S->I->R ##
-------------
Sold = S
Iold = I
Rold = R
Smat = matrix(0,TT,80)
Smat[1,] = S
Imat = matrix(0,TT,80)
Imat[1,] = I
Rmat = matrix(0,TT,80)
Rmat[1,] = R
tt = 1
while(tt < TT){
    print(tt)
    Ih = rpois(80,Sold*(bmat%*%(Iold)))
      print(c(sum(Ih)))#,Ih))
    Rh = rpois(80,g*Iold)
      if (sum(Iold+Ih-Rh<0)>0) break
    Sold = Sold-Ih
      if (sum(Sold<0)>0) break
    Iold = Iold+Ih-Rh
    Rold = Rold+Rh
    Smat[tt+1,] = Sold
    Imat[tt+1,] = Iold
    Rmat[tt+1,] = Rold
      if (sum(Iold<0)>0) break
    tt = tt+1
}
```

_2_ SIR & SIRS - Pois - age hetero - homo mixing.R

```
## S->I->R->S ##
----------------
Sold = S
Iold = I
Rold = R
Smat = matrix(0,TT,80)
Smat[1,] = S
Imat = matrix(0,TT,80)
Imat[1,] = I
Rmat = matrix(0,TT,80)
Rmat[1,] = R
tt = 1
while(tt < TT){
    print(tt)
    Ih = rpois(80,Sold*(bmat%*%(Iold)))
      print(c(sum(Ih)))#,Ih))
    Rh = rpois(80,g*Iold)
      if (sum(Iold+Ih-Rh<0)>0) break
    Sh = rpois(80,w*Rold)
    Sold = Sold-Ih+Sh
      if (sum(Sold<0)>0) break
    Iold = Iold+Ih-Rh
    Rold = Rold+Rh-Sh
    Smat[tt+1,] = Sold
    Imat[tt+1,] = Iold
    Rmat[tt+1,] = Rold
      if (sum(Iold<0)>0) break
    tt = tt+1
}
```

Binomial distribution

The poisson distribution can be replaced by the binomial distribution as done with the age homogeneous model. In each agegroup the newly infected/recovered/susceptible individuals were sampled from:

- $I_{new} \sim Bin(S_t, 1 - e^{-\beta I_t})$
- $R_{new} \sim Bin(I_t, 1 - e^{-g})$

- $S_{new} \sim Bin(R_t, 1 - e^{-\omega})$

As with the age homogeneous model, the program will run until a given point in time, TT.

_4_ SIR & SIRS - Bin - age hetero - homo mixing.R

```
TT = 200

## S->I->R ##
-------------
Sold = S
Iold = I
Rold = R
Smat = matrix(0,TT,80)
Smat[1,] = S
Imat = matrix(0,TT,80)
Imat[1,] = I
Rmat = matrix(0,TT,80)
Rmat[1,] = R
tt = 1
while(tt < TT){
    print(tt)
    Ih = rbinom(80,Sold,(1-exp(-bmat%*%Iold)))
      print(c(sum(Ih)))#,Ih))
    Rh = rbinom(80,Iold,(1-exp(-g)))
    Sold = Sold-Ih
    Iold = Iold+Ih-Rh
    Rold = Rold+Rh
    Smat[tt+1,] = Sold
    Imat[tt+1,] = Iold
    Rmat[tt+1,] = Rold
    tt = tt+1
}
```

_4_ SIR & SIRS - Bin - age hetero - homo mixing.R

```
## S->I->R->S ##
----------------
Sold = S
Iold = I
Rold = R
Smat = matrix(0,TT,80)
Smat[1,] = S
Imat = matrix(0,TT,80)
Imat[1,] = I
Rmat = matrix(0,TT,80)
Rmat[1,] = R
tt = 1
while(tt < TT){
    print(tt)
    Ih = rbinom(80,Sold,(1-exp(-bmat%*%Iold)))
      print(c(sum(Ih)))#,Ih))
    Rh = rbinom(80,Iold,(1-exp(-g)))
    Sh = rbinom(80,Rold,(1-exp(-w)))
    Sold = Sold-Ih+Sh
    Iold = Iold+Ih-Rh
    Rold = Rold+Rh-Sh
    Smat[tt+1,] = Sold
    Imat[tt+1,] = Iold
    Rmat[tt+1,] = Rold
    tt = tt+1
}
```

2.2.2 With Vital Dynamics

Now the model from section 2.2.1 when sampling from the binomial distribution was extended by stochasticly incorporating vital dynamics. The same distributions as in section 2.1.2 for birth and death were used. All births are susceptibles entering the first agegroup. Mortality happens in each agegroup and compartment with the same death rate. Both birth and death was assumed to happen on a daily basis. The life expectancy is still assumed to be 80 years and thus $\mu_B = \mu_D = 1/80$. g and ω are the values $1/6$ and 0.013 respectively.

Instead of using preset values for S, I and R, estimates close to the endemic equilibrium were used according to the formulas of Hens et al. (2012, p.41).

$$
\begin{aligned}
S(a) &= e^{-\int_0^a \lambda(u)\mathrm{d}u} \cdot N(a) \\
I(a) &= \frac{\int_0^a \lambda(u)\mathrm{d}u}{\int_0^a \lambda(u)\mathrm{d}u - g} \cdot (e^{-g} - e^{-\int_0^a \lambda(u)\mathrm{d}u}) \cdot N(a) \\
R(a) &= N(a) - S(a) - I(a)
\end{aligned}
$$

The distributions for I_{new}, R_{new} and S_{new} stays the same as in the previous model. One should keep in mind that individuals in a population grow older. This important concept should be programmed as well. After 365 days or 1 year, all individuals move to the next agegroup. For simplicity, we assumed that the last agegroup dies completely, otherwise a new agegroup will be created each year. To keep the population size constant, the last agegroup will re-enter in the susceptible compartment of the first agegroup. The R-code for this model is given below.

_11b_ SIR & SIRS - Bin - time & ageing - homo mixing.R

```
TT = 365; vv = 365*c(1:100)

## S->I->R ##
-------------
Sold = S
Iold = I
Rold = R
Smat = matrix(0,TT,80)
Smat[1,] = S
Imat = matrix(0,TT,80)
Imat[1,] = I
Rmat = matrix(0,TT,80)
Rmat[1,] = R
tt = 1
while(tt < TT){
    print(tt)
    Ih = rbinom(80,Sold,(1-exp(-bmat%*%Iold)))
      print(c(sum(Ih)))#,Ih))
    Rh = rbinom(80,Iold,(1-exp(-g)))
    muS = rbinom(80,Sold,(1-exp(-muD)))
    muI = rbinom(80,Iold,(1-exp(-muD)))
    muR = rbinom(80,Rold,(1-exp(-muD)))
    muN = rpois(1,sum(Sold,Iold,Rold)*muB)
    geb = c(muN,rep(0,79))
      if (tt %in% vv){
       Sold = c(muN+(Sold-Ih-muS)[80]+(Iold+Ih-Rh-muI)[80]+
                  (Rold+Rh-muR)[80],(Sold-Ih-muS)[-80])
       Iold = c(0,(Iold+Ih-Rh-muI)[-80])
       Rold = c(0,(Rold+Rh-muR)[-80])
      }
      else {
       Sold = geb+Sold-Ih-muS
       Iold = Iold+Ih-Rh-muI
       Rold = Rold+Rh-muR
      }
    Smat[tt+1,] = Sold
    Imat[tt+1,] = Iold
    Rmat[tt+1,] = Rold
    tt = tt+1
}
```

```
## S->I->R->S ##
----------------
Sold = S
Iold = I
Rold = R
Smat = matrix(0,TT,80)
Smat[1,] = S
Imat = matrix(0,TT,80)
Imat[1,] = I
Rmat = matrix(0,TT,80)
Rmat[1,] = R
tt = 1
while(tt < TT){
    print(tt)
    Ih = rbinom(80,Sold,(1-exp(-foid)))
      print(c(sum(Ih)))#,Ih))
      if (sum(Iold<0)>0) {Iold = (Iold+abs(Iold))/2}
    Rh = rbinom(80,Iold,(1-exp(-g)))
    Sh = rbinom(80,Rold,(1-exp(-w)))
    muS = rbinom(80,Sold,(1-exp(-muD)))
    muI = rbinom(80,Iold,(1-exp(-muD)))
    muR = rbinom(80,Rold,(1-exp(-muD)))
    muN = rpois(1,sum(Sold,Iold,Rold)*muB)
    geb = c(muN,rep(0,79))
      if (tt %in% vv){
       Sold = c(muN+(Sold-Ih+Sh-muS)[80]+(Iold+Ih-Rh-muI)[80]+
                  (Rold+Rh-Sh-muR)[80],(Sold-Ih+Sh-muS)[-80])
       Iold = c(0,(Iold+Ih-Rh-muI)[-80])
       Rold = c(0,(Rold+Rh-Sh-muR)[-80])
      }
      else {
       Sold = geb+Sold-Ih+Sh-muS
       Iold = Iold+Ih-Rh-muI
       Rold = Rold+Rh-Sh-muR
      }
    Smat[tt+1,] = Sold
    Imat[tt+1,] = Iold
    Rmat[tt+1,] = Rold
    tt = tt+1
}
```

2.2.3 Impact of Contact Patterns

Assuming homogeneous mixing is often not realistic because individuals tend to have more contact with individuals of the same age. Mossong et al. (2008) provided a large-scale study about contact patterns relevant for the transmission of infections (POLYMOD). Such contact patterns can be incorporated in the model via $\beta = q \cdot c$ with q a proportionality factor and c contact rates (Goeyvaerts et al., 2010).

2.3 Age Heterogeneous in Endemic Equilibrium

A system is in endemic equilibrium when the variables do not depend on time. Such a model can represent a cohort of individuals, followed from birth to death. The system of ordinary differential equations can be derived from the models in section 2.2 (Hens et al., 2012).

SIR model

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

SIRS model

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

2.3.1 Without Vital Dynamics

For the cohort model, the parameters g, ω and force of infection are expressed in years. This means that after one iteration, the population moves to the next agegroup.

_6_ SIR & SIRS - Bin - age homo - cohort model.R

```
TT = 81

## S->I->R ##
-------------
Sold = S
Iold = I
Rold = R
Svec = NULL
Svec = c(Svec,Sold)
Ivec = NULL
Ivec = c(Ivec,Iold)
Rvec = NULL
Rvec = c(Rvec,Rold)
tt = 1
while(tt < TT){
    print(tt)
    Ih = rbinom(1,Sold,(1-exp(-foi[tt])))
      print(Ih)
    Rh = rbinom(1,Iold,(1-exp(-g)))
    Sold = Sold-Ih
    Iold = Iold+Ih-Rh
    Rold = Rold+Rh
    Svec = c(Svec,Sold)
    Ivec = c(Ivec,Iold)
    Rvec = c(Rvec,Rold)
    tt = tt+1
}
```

_6_ SIR & SIRS - Bin - age homo - cohort model.R

```
## S->I->R->S ##
----------------
Sold = S
Iold = I
Rold = R
Svec = NULL
Svec = c(Svec,Sold)
Ivec = NULL
Ivec = c(Ivec,Iold)
Rvec = NULL
Rvec = c(Rvec,Rold)
tt = 1
while(tt < TT){
    print(tt)
    Ih = rbinom(1,Sold,(1-exp(-foi[tt])))
      print(Ih)
    Rh = rbinom(1,Iold,(1-exp(-g)))
    Sh = rbinom(1,Rold,(1-exp(-w)))
    Sold = Sold-Ih+Sh
    Iold = Iold+Ih-Rh
    Rold = Rold+Rh-Sh
    Svec = c(Svec,Sold)
    Ivec = c(Ivec,Iold)
    Rvec = c(Rvec,Rold)
    tt = tt+1
}
```

2.3.2 With Vital Dynamics

The basis for the model described here is the model from section 2.2.2. By importation of infected individuals, the infection stays in the population. To keep the popolution constant, the same amount of individuals that came in will leave the population. The R-code with importation is given below.

_11c_ SIR & SIRS - Bin - time & ageing - homo mixing - importation.R

```
TT = 365*100; vv = 365*c(1:100)

## S->I->R ##
-------------
Sold = S
Iold = I
Rold = R
Smat = matrix(0,TT,80)
Smat[1,] = S
Imat = matrix(0,TT,80)
Imat[1,] = I
Rmat = matrix(0,TT,80)
Rmat[1,] = R
tt = 1
while(tt < TT){
    print(tt)
    Ih = rbinom(80,Sold,(1-exp(-bmat%*%Iold)))
      print(c(sum(Ih)))#,Ih))
    Rh = rbinom(80,Iold,(1-exp(-g)))
    muS = rbinom(80,Sold,(1-exp(-muD)))
    muI = rbinom(80,Iold,(1-exp(-muD)))
    muR = rbinom(80,Rold,(1-exp(-muD)))
    muN = rpois(1,sum(Sold,Iold,Rold)*muB)
    geb = c(muN,rep(0,79))
      if (tt %in% vv){
       Sold = c(muN+(Sold-Ih-muS)[80]+(Iold+Ih-Rh-muI)[80]+
                  (Rold+Rh-muR)[80],(Sold-Ih-muS)[-80])
       Iold = c(0,(Iold+Ih-Rh-muI)[-80])
       Rold = c(0,(Rold+Rh-muR)[-80])
      }
      else {
       Sold = geb+Sold-Ih-muS
       Iold = c(rep(5,80))+Iold+Ih-Rh-muI
       Rold = Rold+Rh-muR-c(rep(5,80))
      }
      if (sum(Rold<0)>0) {Rold=(Rold+abs(Rold))/2}
    Smat[tt+1,] = Sold
    Imat[tt+1,] = Iold
    Rmat[tt+1,] = Rold
    tt = tt+1
}
```

```
## S->I->R->S ##
----------------
Sold = S
Iold = I
Rold = R
Smat = matrix(0,TT,80)
Smat[1,] = S
Imat = matrix(0,TT,80)
Imat[1,] = I
Rmat = matrix(0,TT,80)
Rmat[1,] = R
tt = 1
while(tt < TT){
    print(tt)
    Ih = rbinom(80,Sold,(1-exp(-foid)))
      print(c(sum(Ih)))#,Ih))
      if (sum(Iold<0)>0) {Iold = (Iold+abs(Iold))/2}
    Rh = rbinom(80,Iold,(1-exp(-g)))
    Sh = rbinom(80,Rold,(1-exp(-w)))
    muS = rbinom(80,Sold,(1-exp(-muD)))
    muI = rbinom(80,Iold,(1-exp(-muD)))
    muR = rbinom(80,Rold,(1-exp(-muD)))
    muN = rpois(1,sum(Sold,Iold,Rold)*muB)
    geb = c(muN,rep(0,79))
      if (tt %in% vv){
       Sold = c(muN+(Sold-Ih+Sh-muS)[80]+(Iold+Ih-Rh-muI)[80]+
                  (Rold+Rh-Sh-muR)[80],(Sold-Ih+Sh-muS)[-80])
       Iold = c(0,(Iold+Ih-Rh-muI)[-80])
       Rold = c(0,(Rold+Rh-Sh-muR)[-80])
      }
      else {
       Sold = geb+Sold-Ih+Sh-muS
       Iold = c(rep(5,80))+Iold+Ih-Rh-muI
       Rold = Rold+Rh-Sh-muR-c(rep(5,80))
      }
      if (sum(Rold<0)>0) {Rold=(Rold+abs(Rold))/2}
    Smat[tt+1,] = Sold
    Imat[tt+1,] = Iold
    Rmat[tt+1,] = Rold
    tt = tt+1
}
```

Another option to arrive at endemic equilibrium is to use a given force of infection instead of relying on the mass-action principle (βI_t). When using this option, importation is not necessary. The newly infected individuals are now sampled from $I_{new} \sim Bin(S_t, 1 - e^{-\lambda(a)})$.

2.3.3 Other Models of Recovery

In all previous models, the recovery (from I to R) was assumed to be $g \cdot I$. This could be replaced by other models of recovery. The logistic recovery and two compartments of infected individuals were considered here as possibilities.

Logistic recovery

The logistic recovery can be expressed as $gI(1 - \frac{I}{K})$ with K the carrying capacity. The code for the SIR and SIRS models is given in the appendix (6.1).

Two compartments of infected individuals

Another possibility is that the infectious compartment is replaced by two compartments for I with different transmission rates, I_1 and I_2.

- $I_1 \sim Exp(h)$
- $I_2 \sim Exp(g)$

Both I_1 and I_2 have 1 individual in the beginning, so $S = N - 2$. The rate of going from I_1 to I_2 is taken to be 1/3 days (h) and the rate of going from I_2 to R stays 1/6 days (g). The code of this model is given in the appendix (6.2).

3 Results

3.1 Age Homogeneous

3.1.1 Without Vital Dynamics

The program for the models in this section can be expressed in years or in days. One should only change the parameters so that they are in the right unit.

Poisson distribution

When running the program in days, two outcomes are possible. One is that the epidemic will not start because the initial infected individual is recovered before it can infect other individuals. The second possibility is that the epidemic starts. Figure 1 is an example of when the epidemic happens for both SIR and SIRS models. In this case, the epidemic fades out after approximately 100 days. The difference between SIR and SIRS is that the maximum number of infected individuals is somewhat higher in the SIRS model. When running the program in years, the epidemic stops after three iterations (years).

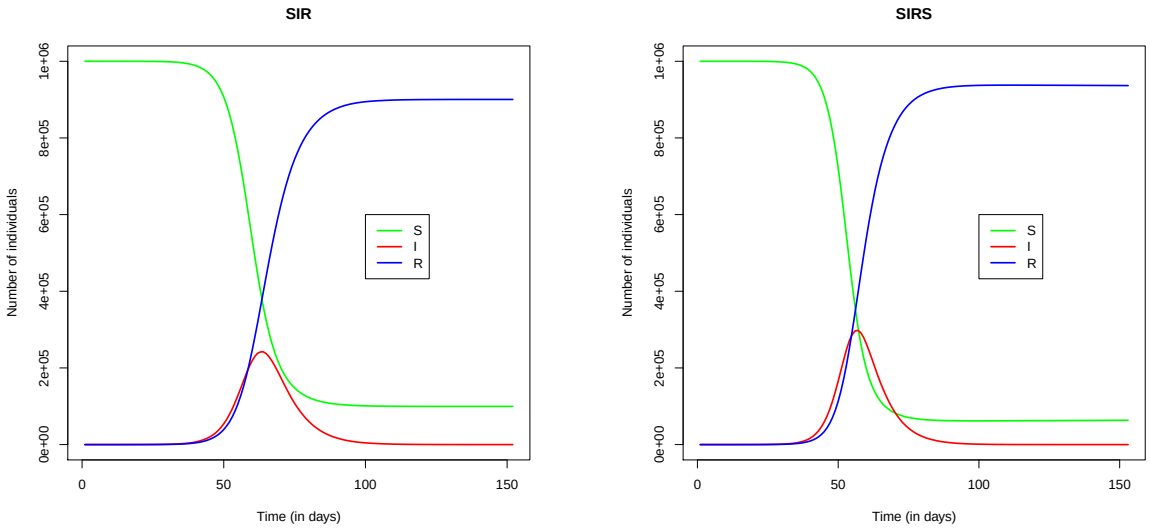

Figure 1: The number of susceptible, infected and recovered individuals over time (days). Left: SIR; Right: SIRS

Binomial distribution

The model with binomial distribution (figure 2) gives almost the same result as with the poisson distribution. When the program is in days and the epidemic starts, it lasts for approximately 100 days. When it is in years, it holds for three years.

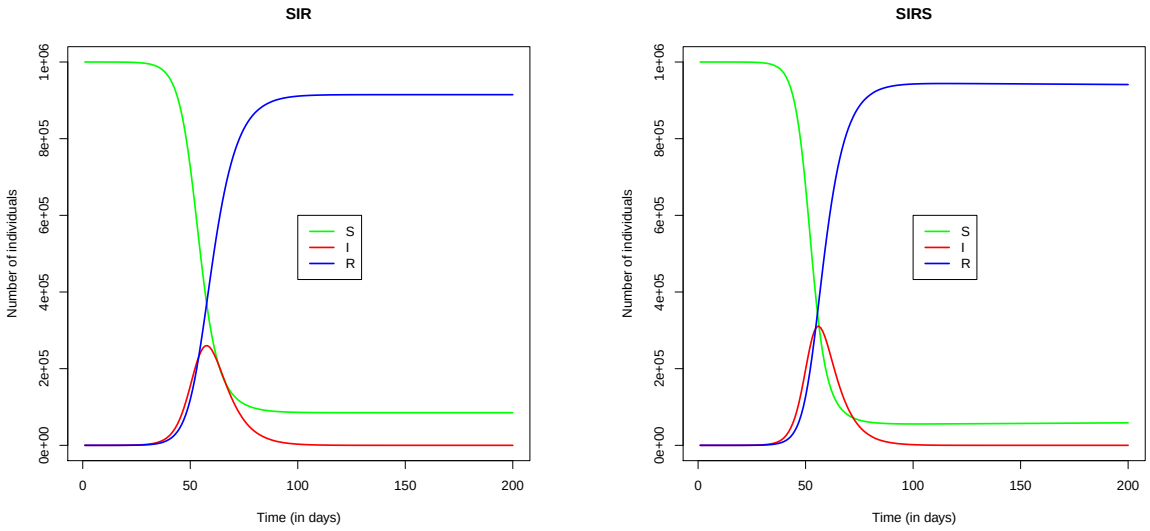

Figure 2: The number of susceptible, infected and recovered individuals over time (days). Left: SIR; Right: SIRS

3.1.2 With Vital Dynamics

Due to the assumption that birth and death happen on a daily basis, the model will be run in days. Even wih vital dynamics, the epidemic fades out around 100 days (figure 3). However, the chance still exists that the epidemic will not start.

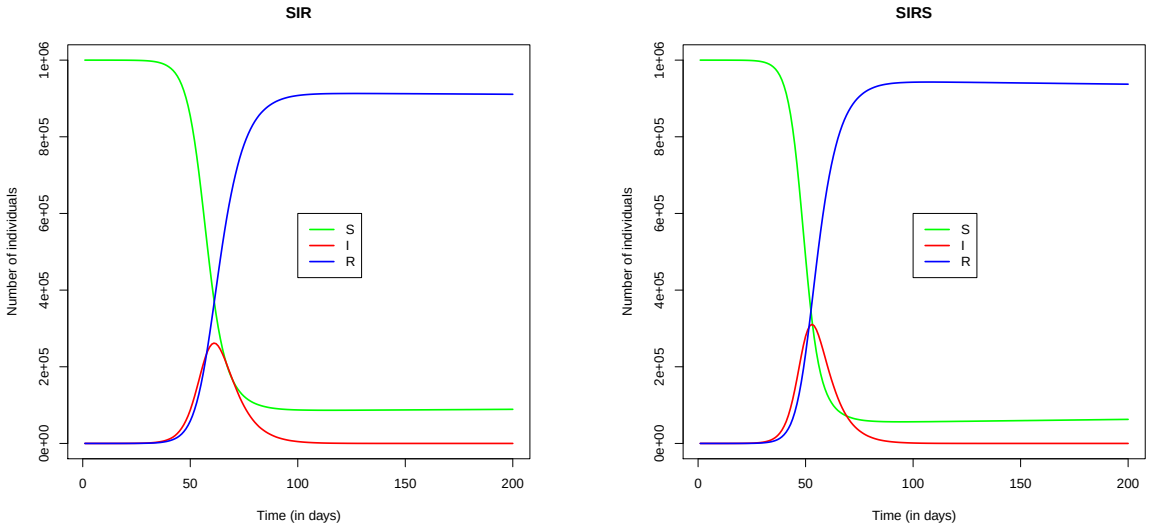

Figure 3: The number of susceptible, infected and recovered individuals over time (days). Left: SIR; Right: SIRS

3.2 Age Heterogeneous

In all models of this section, the iterations correspond to days.

3.2.1 Without Vital Dynamics

Poisson distribution

As for the age homogeneous model, the total number of susceptible, infected and recovered individuals are plotted over time (figure 4). The epidemic fades away around 100 days for both SIR and SIRS model. Within each agegroup, the number of infected individuals over time is approximately the same because of the homogeneous mixing.

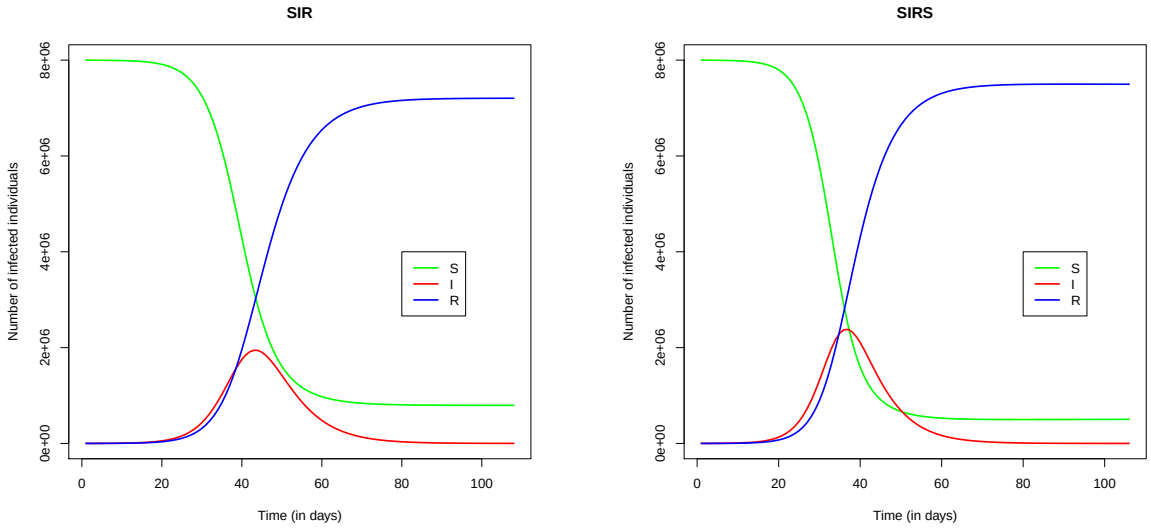

Figure 4: The number of susceptible, infected and recovered individuals over time (days). Left: SIR; Right: SIRS

Binomial distribution

The number of infected individuals over time within each agegroup is approximately the same due to the homogeneous mixing. For the total population, figure 5 is similar to figure 4.

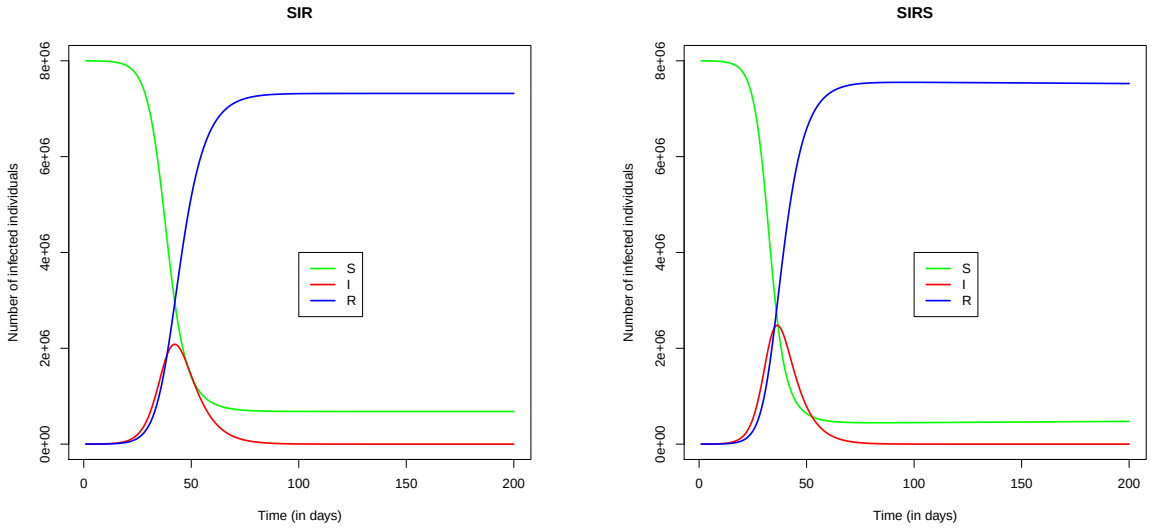

Figure 5: The number of susceptible, infected and recovered individuals over time (days). Left: SIR; Right: SIRS

3.2.2 With Vital Dynamics

As expected, figure 6 is similar to figure 5 despite the incorporation of vital dynamics.

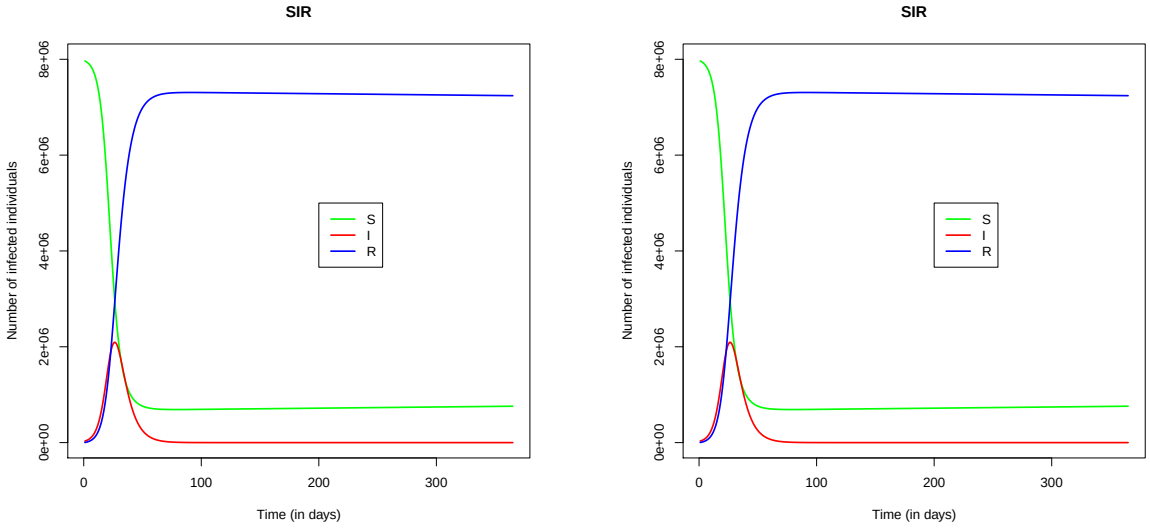

Figure 6: The number of susceptible, infected and recovered individuals over time (days). Left: SIR; Right: SiRS

3.2.3 Impact of Contact Patterns

Small differences can be observed when using contact patterns instead of homogeneous mixing. Figure 7 and 8 show the number of infected individuals over time at the age of 7, 35 and 75 with homogeneous and heterogeneous mixing, respectively in the SIR and SIRS model. When using a contact pattern, the number of infected individuals is different in the three agegroups, compared to approximately the same number of infected individuals when mixing is homogeneous.

Here, only one contact pattern was used to show its impact. It could be that other contact patterns have other effects.

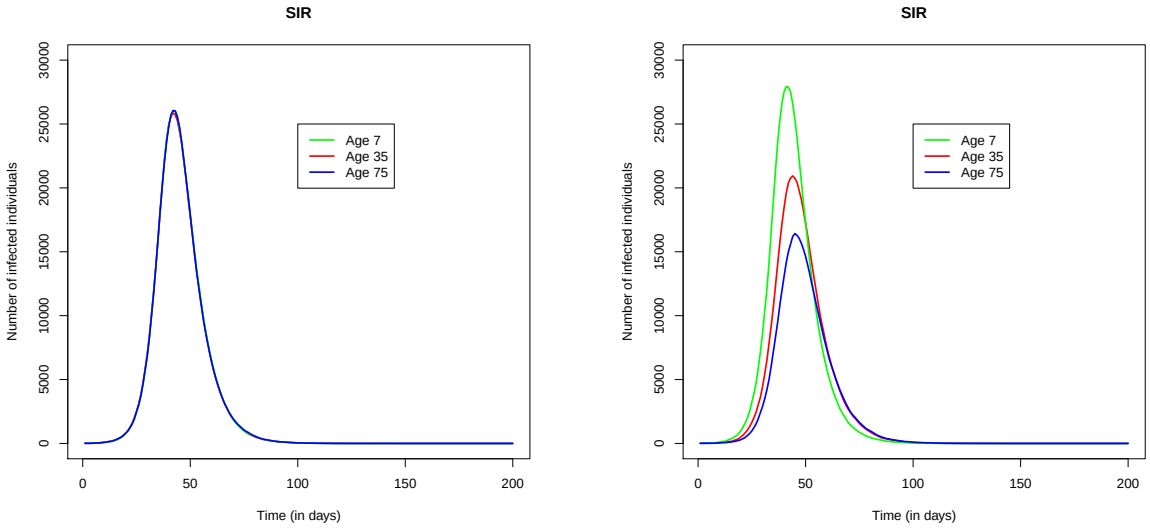

Figure 7: The number of infected individuals in three agegroups over time (days) for the SIR model. Left: homogeneous mixing; Right: heterogeneous mixing

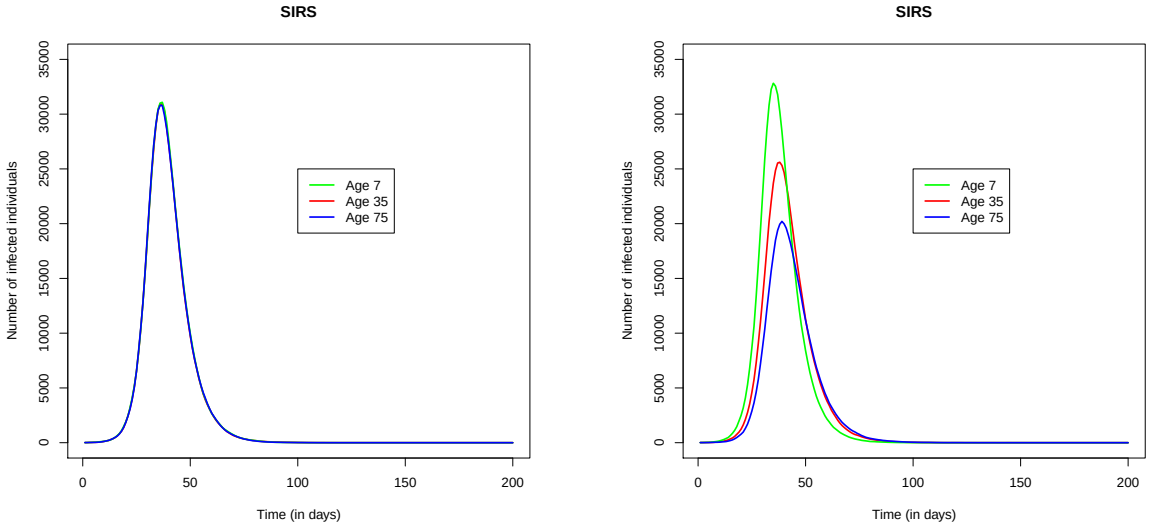

Figure 8: The number of infected individuals in three agegroups over time (days) for the SIRS model. Left: homogeneous mixing; Right: heterogeneous mixing

3.3 Age Heterogeneous in Endemic Equilibrium

3.3.1 Without Vital Dynamics

The plot in figure 9 shows two peaks, one around age 7 and the other around age 35. These peaks can be explained by the fact that young children are more vulnerable for the infection. If the child is infected, it is most likely that the parents will also get infected.

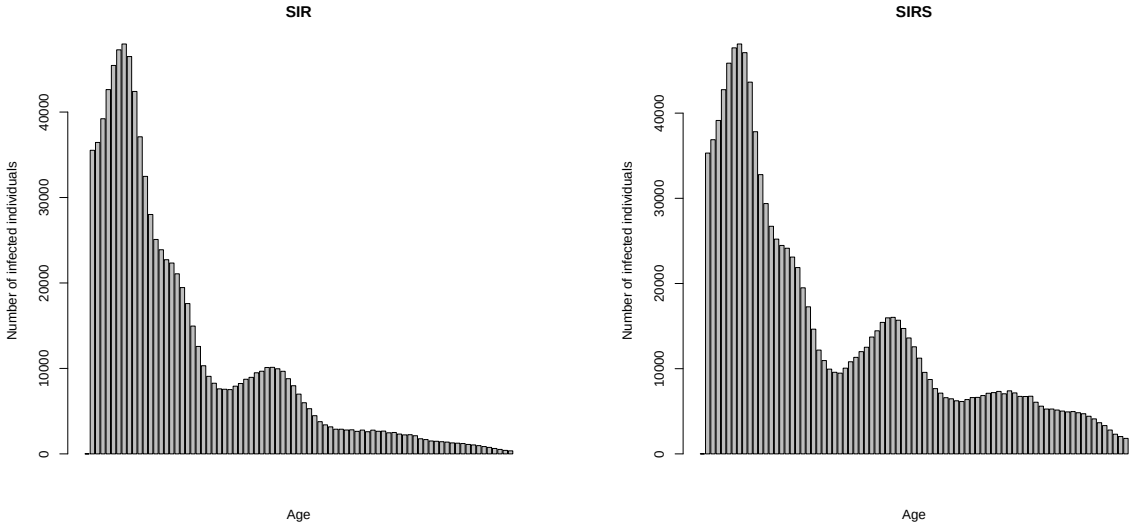

Figure 9: The number of infected individuals versus age. Left: SIR; Right: SIRS

The seroprevalence profile (figure 10) is what could be expected. All individuals that were infected will recover and thus a monotone increasing seroprofile is expected for the SIR model. The decrease in the seroprofile of the SIRS model can be explained by the fact that recovered individuals can become susceptible again.

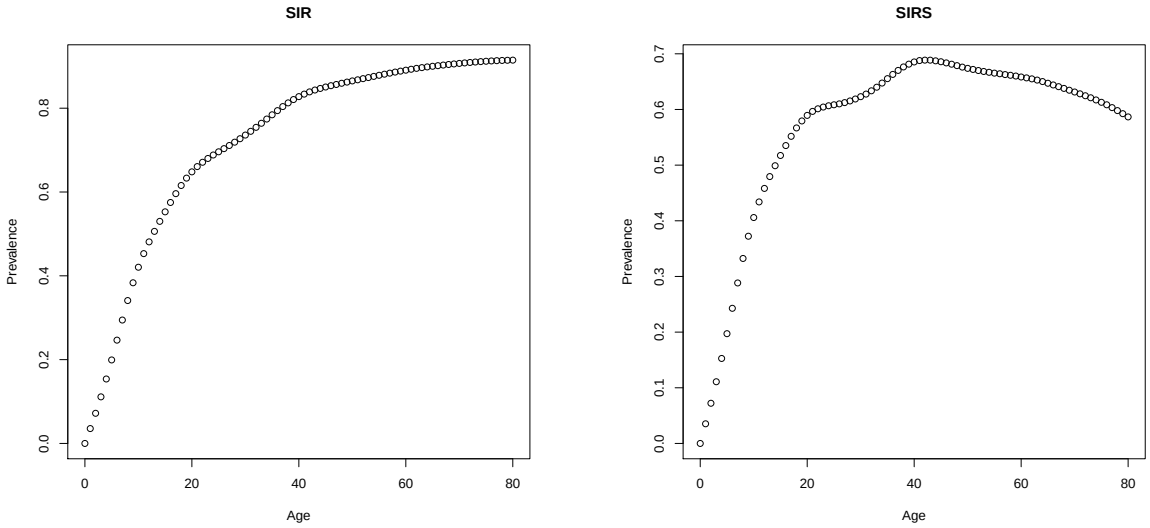

Figure 10: The seroprevalence (I+R/N) versus age. Left: SIR; Right: SIRS

3.3.2 With Vital Dynamics

The seroprevalence profiles of the SIR and SIRS model of section 2.3.2, taken at a time point in endemic equilibrium, are similar to the ones in figure 10.

3.3.3 Other Models of Recovery

Logistic recovery

The value for K should be taken large enough such that it will always be larger than I. However, several values for K were used, none of them has an effect on the seroprevalence.

Two compartments of infectious individuals

Incorporating two compartments of I has no effect on the prevalence.

4 Discussion

Deterministic transmission models are often a good approximation of the underlying stochastic model if the population is large enough (Andersson and Britton, 2000). Whereas these models are easier to analyze and more popular, they are not always realistic. Because less information is available about stochastic models, the development of such models was of interest.

The deterministic SIR and SIRS models were first extended to the stochastic version. Sampling was done from the poisson and binomial distribution. Sampling is done from a poisson distribution with a certain mean. Therefor, the sampled value can be larger than the value to sample from. Of course this is a disadvantage which can be avoided by sampling from the binomial distribution. The binomial distribution uses a certain probability and it is restricted by a maximum. Thus sampling from the binomial distribution is preferred over the poisson distribution.

A lot of infectious diseases are known to be age dependent, e.g. PVB19, rubella. That is why age heterogeneous models are of great interest. Under the assumption of homogeneous mixing, the results of age heterogeneous models are similar to age homogeneous models (figure 2 and 5). Homogeneous mixing is not a good assumption, because individuals tend to have more contact with individuals of the same age. When children are infected, the parents have more chance also to be infected. A large-scale study about contact patterns for transmission of infection (POLYMOD) is provided by Mossong et al. (2008). Incorporating a contact pattern proved to have an effect as shown in figure 7 and 8.

The cohort model is in endemic equilibrium, i.e. the calender time is not of primary interest (Hens et al., 2012). The prevalence in each agegroup was plotted in figure 10. For the SIR model, the prevalence is monotonically increasing with age. For the SIRS model, the prevalence increases first, reaches a maximum and then decreases.

The two other models of recovery in the cohort model considered here, have no effect on the prevalence.

4.1 Future Research

The main goal for the future is to fit a stochastic model to the data of PVB19. When the best model is found, that model can still be extended. First, protection of newborns by maternal antibodies can be included in the model. Second, one can look for the contact pattern that fits best to that of the PVB19 infection. These contact rates can then be included in the mass-action principle $\beta I_t = q \cdot cI_t$ with q a proportionality factor and c the contact rates. At last, other models of recovery can be examined to improve the fit.

5 References

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6 Appendix

6.1 Logistic Recovery

_12_SIR & SIRS - logistic recovery.R

```
TT = 80*365
vv = 365*c(1:100)
K = 10000

## S->I->R ##
-------------
Sold = S
Iold = I
Rold = R
Svec = NULL
Svec = c(Svec,Sold)
Ivec = NULL
Ivec = c(Ivec,Iold)
Rvec = NULL
Rvec = c(Rvec,Rold)
d = 1
tt = 1
while(tt < TT){
    print(tt)
      if (tt %in% vv){d = d+1}
    muN = rpois(1,N*muB)
    muS = rbinom(1,Sold,(1-exp(-muD)))
    muI = rbinom(1,Iold,(1-exp(-muD)))
    muR = rbinom(1,Rold,(1-exp(-muD)))
    Ih = rbinom(1,Sold,(1-exp(-foid[d])))
      print(Ih)
    Rh = rbinom(1,Iold,(1-exp(-g*(1-(Iold/K)))))
    Sold = muN+Sold-Ih-muS
    Iold = Iold+Ih-Rh-muI
    Rold = Rold+Rh-muR
    Svec = c(Svec,Sold)
    Ivec = c(Ivec,Iold)
    Rvec = c(Rvec,Rold)
    tt = tt+1
}
```

```
## S->I->R->S ##
----------------
Sold = S
Iold = I
Rold = R
Svec = NULL
Svec = c(Svec,Sold)
Ivec = NULL
Ivec = c(Ivec,Iold)
Rvec = NULL
Rvec = c(Rvec,Rold)
d = 1
tt = 1
while(tt < TT){
    print(tt)
      if (tt %in% vv){d = d+1}
    muN = rpois(1,N*muB)
    muS = rbinom(1,Sold,(1-exp(-muD)))
    muI = rbinom(1,Iold,(1-exp(-muD)))
    muR = rbinom(1,Rold,(1-exp(-muD)))
    Ih = rbinom(1,Sold,(1-exp(-foid[d])))
      print(Ih)
    Rh = rbinom(1,Iold,(1-exp(-g*(1-(Iold/K)))))
    Sh = rbinom(1,Rold,(1-exp(-w)))
    Sold = muN+Sold-Ih+Sh-muS
    Iold = Iold+Ih-Rh-muI
    Rold = Rold+Rh-Sh-muR
    Svec = c(Svec,Sold)
    Ivec = c(Ivec,Iold)
    Rvec = c(Rvec,Rold)
    tt = tt+1
}
```

6.2 Two Compartments of Infected Individuals

_13_SIR & SIRS - Two compartments I1 & I2.R

```
## S->I->R ##
-------------
Sold = S
Iold1 = I1
Iold2 = I2
Rold = R
Svec = NULL
Svec = c(Svec,Sold)
Ivec1 = NULL
Ivec1 = c(Ivec1,Iold1)
Ivec2 = NULL
Ivec2 = c(Ivec2,Iold2)
Rvec = NULL
Rvec = c(Rvec,Rold)
d = 1
tt = 1
while(tt < TT){
    print(tt)
      if (tt %in% vv){d = d+1}
    muN = rpois(1,N*muB)
    muS = rbinom(1,Sold,(1-exp(-muD)))
    muI1 = rbinom(1,Iold1,(1-exp(-muD)))
    muI2 = rbinom(1,Iold2,(1-exp(-muD)))
    muR = rbinom(1,Rold,(1-exp(-muD)))
    Ih1 = rbinom(1,Sold,(1-exp(-foid[d])))
    Ih2 = rbinom(1,Iold1,(1-exp(-h)))
      print(c(Ih1,Ih2))
    Rh = rbinom(1,Iold2,(1-exp(-g)))
    Sold = muN+Sold-Ih1-muS
    Iold1 = Iold1+Ih1-Ih2-muI1
    Iold2 = Iold2+Ih2-Rh-muI2
    Rold = Rold+Rh-muR
    Svec = c(Svec,Sold)
    Ivec1 = c(Ivec1,Iold1)
    Ivec2 = c(Ivec2,Iold2)
    Rvec = c(Rvec,Rold)
    tt = tt+1
}
```

```
## S->I->R->S ##
----------------
Sold = S
Iold1 = I1
Iold2 = I2
Rold = R
Svec = NULL
Svec = c(Svec,Sold)
Ivec1 = NULL
Ivec1 = c(Ivec1,Iold1)
Ivec2 = NULL
Ivec2 = c(Ivec2,Iold2)
Rvec = NULL
Rvec = c(Rvec,Rold)
d = 1
tt = 1
while(tt < TT){
    print(tt)
      if (tt %in% vv){d = d+1}
    muN = rpois(1,N*muB)
    muS = rbinom(1,Sold,(1-exp(-muD)))
    muI1 = rbinom(1,Iold1,(1-exp(-muD)))
    muI2 = rbinom(1,Iold2,(1-exp(-muD)))
    muR = rbinom(1,Rold,(1-exp(-muD)))
    Ih1 = rbinom(1,Sold,(1-exp(-foid[d])))
    Ih2 = rbinom(1,Iold1,(1-exp(-h)))
      print(c(Ih1,Ih2))
    Rh = rbinom(1,Iold2,(1-exp(-g)))
    Sh = rbinom(1,Rold,(1-exp(-w)))
    Sold = muN+Sold-Ih1+Sh-muS
    Iold1 = Iold1+Ih1-Ih2-muI1
    Iold2 = Iold2+Ih2-Rh-muI2
    Rold = Rold+Rh-Sh-muR
    Svec = c(Svec,Sold)
    Ivec1 = c(Ivec1,Iold1)
    Ivec2 = c(Ivec2,Iold2)
    Rvec = c(Rvec,Rold)
    tt = tt+1
}
```

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Using stochastic simulation models to reconstruct B19 sero-epidemiology.

Richting: **Master of Statistics-Epidemiology & Public Health Methodology**
Jaar: **2014**

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Datum: **10/09/2014**