Chapter 3
R_0

3.1 Primacy of R_0

For directly transmitted pathogens, R_0 is, per definition, the expected number of secondary cases that arise from a typical infectious index-case in a completely susceptible host population. R_0 plays a critical role for a number of aspects of disease dynamics and is therefore the focus of much study in historical and contemporary infectious disease dynamics (Heesterbeek and Dietz 1996). For perfectly immunizing infections in homogeneously mixing populations these include (e.g., Anderson and May 1991):

- The threshold for pathogen establishment. When R_0 is greater than one, a pathogen can invade. When it is smaller than one, the chain of transmission will stutter and break (Lloyd-Smith et al. 2009). For directly transmitted wildlife diseases there is often an associated *critical host density* for disease invasion. This has for example been estimated to be 1 red fox per km^2 for rabies in Europe (Anderson et al. 1981) and 17 mice/ha for *Sin nombre* hantavirus in Montana (Luis et al. 2015).
- The threshold for vaccine-induced herd immunity: If a sufficient number of individuals are vaccinated, the effective reproductive ratio will be below one, and the population will be resistant to pathogen invasion. The threshold is $p_c = 1 - 1/R_0$. Thus, measles with a R_0 of up to 20 requires around 95% vaccine cover for elimination and smallpox ($R_0 \simeq 5$) 80%.

This chapter uses the following R-packages: `bbmle` and `statnet`.
A conceptual understanding of *reproductive ratios* and the *simple epidemic* is useful prior to this discussion. Five minute epidemics-MOOC intros can be watched from YouTube:
Reproductive number https://www.youtube.com/watch?v=ju26rvzfFg4.
Simple epidemic https://www.youtube.com/watch?v=sSLfrSSmJZM.

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- As discussed in Sect. 2.3, the final epidemic size is given by R_0 according to the approximate relationship $f \simeq \exp(-R_0)$.
- In a stable host population, the mean age of infection is approximately $\bar{a} \simeq L/(R_0 - 1)$, where L is host life-expectancy (Dietz and Schenzle 1985). In a changing population a more accurate calculation is $\bar{a} \simeq 1/(\mu(R_0 - 1))$, where μ is the host birth rate.
- As derived in Sect. 2.5, the susceptible fraction at equilibrium is $S^* = 1/R_0$. A consequence of this is that for competing strains that elicit cross-protecting immunity, R_0 will determine competitive dominance and strain replacement (Shrestha et al. 2014).[1]

A lot of attention has been given to measuring R_0 for various infectious diseases.

3.2 Preamble: Rates and Probabilities

When working with data, models, and "models-and-data" for infectious disease dynamics, it is important to keep a cool head in terms of keeping track of which quantities are **probabilities** and which quantities are **rates**, and how to move between these two mathematical currencies.[2] Confusion arises because the nomenclature of *epidemiology* and *mathematical epidemiology* is related but not always identical. In epidemiology the "case-fatality rate" is used to denote the fraction of infections that ends in death, which from a mathematical/statistical point of view is **not a rate** but a **probability**: the probability that an infection will lead to death (Dietz and Heesterbeek 2002). Likewise, in epidemiology, the seasonal influenza "attack rate" denotes the fraction of people that contracts the flu in a given influenza season. Again, from a mathematical/statistical/dynamical-systems point of view this quantity is **not a rate** but a **probability** representing the chance of any randomly chosen individual of unknown previous influenza infection-history getting infected during the season.

When considering events in modeling terms, a rate x per time unit is defined on $[0, \infty]$ and $1/x$ is the average time to an event (if the rate remains constant). If events are random and independent, the probability of no events in a time interval Δt is $1 - \exp(x\Delta t)$ and the number of events in Δt follows a Poisson-distribution with mean $x\Delta t$ (if the rate remains constant). A probability, in contrast, is defined on $[0, 1]$. If we observe a probability p of something happening in a time interval, we can back-calculate the associated (constant) rate as $x = -log(1 - p)/\Delta t$.

[1] This result is parallel to Tilman (1976)'s R^*-theory of resource-based competition of free-living organisms: whichever species can sustain positive growth at the lowest concentration of the limited resource will be competitively dominant.

[2] The disease dynamics literature has many example of how easy it is to confuse the two; cf some of the mathematical models of ebola dynamics published during the 2014 West Africa outbreak.

If we have two competing rates, x at which event one (e.g., recovery) happens and y at which event two (e.g., death) happens, the probability of ending up with outcome one is $x/(x+y)$ and the probability of ending up with outcome two is $y/(x+y)$. This scales such that with three competing rates the probability of outcome one is $x/(x+y+z)$.

3.3 Estimating R_0 from a Simple Epidemic

A variety of methods have been proposed to estimate R_0 (or the effective reproductive ratio, R_E[3]) in an epidemic setting (such as the 2014–15 West African ebola outbreak; Althaus 2014). Some are purely model based, others involve very elaborate model fitting exercises, and some use fairly simple ideas based on the closed epidemic and analogies to the ecology of free-living organisms (Dietz 1993).

The simplest idea is that during the initial spread phase susceptible depletion may be sufficiently negligible that the epidemic may be assumed to grow in a density-independent, exponential fashion. Basic ecology of free-living organisms tells us that the rate of exponential growth is $r = \log(R_0)/G$, where G is the generation time; thus $R_0 = \exp(rG)$.[4] Moreover, since an exponentially growing population grows according to $N(t) = N(0)exp(rt)$, the time for a population to double is $\log(2)/r$. We can apply these ideas to the early phase of an epidemic to get a rough value for R_0.

For pathogens, the Ns above would represent the *prevalence*. The G represents the *serial interval* (V) which is the average time between infection and reinfection. This interval will normally be a little shorter than the latent plus infectious period. Disease data, however, most often represents *incidence*—i.e., the number of new infections, not the number of current infections. However, incidence also grows at the same exponential rate. The simplest way to estimate R_0 is thus to regress log(cumulative incidence) on time to estimate the rate of exponential increase (r) and then calculate $R_0 = Vr + 1$ (e.g., Anderson and May 1991). The logic comes from the fact that in one serial interval each infected is expected to give rise to R_0 secondary cases and one removal (thus the total change is $R_0 - 1$).

Let us explore using weekly measles-data from the 2003 outbreak in Niamey, Niger (Grais et al. 2008). The data is available as `niamey` in the `epimdr`-package. The `tot_cases`-column represents the total incidence across the city for each week of the outbreak.[5]

[3] The effective reproductive ratio is the expected number of secondary cases in a partially immune population $R_E = sR_0$, where s is the fraction of the population that is susceptible.

[4] Unless explicitly stated otherwise, `log` will always be taken to mean the natural logarithm in this text.

[5] All data sets analyzed in this text are included in the `epimdr`-package. To get a more detailed description of each data set consult the `R` help-pages.

```
data(niamey)
head(niamey[, 1:5])

  ##   absweek week tot_cases tot_mort lethality
  ## 1       1   45        11        0  0.000000
  ## 2       2   46        12        1  8.333333
  ## 3       3   47        15        0  0.000000
  ## 4       4   48        14        1  7.142857
  ## 5       5   49        30        0  0.000000
  ## 6       6   50        41        1  2.439024
```

We can do a visual inspection to identify the initial period of exponential growth:

```
par(mar = c(5,5,2,5))
plot(niamey$absweek, niamey$tot_cases, type="b",
     xlab="Week", ylab="Incidence")
par(new=T)
plot(niamey$absweek, niamey$cum_cases, type="l",
     col="red", axes=FALSE, xlab=NA, ylab=NA, log="y")
axis(side = 4)
mtext(side = 4, line = 4, "Cumulative incidence")
legend("topleft", legend=c("Cases", "Cumulative"),
       lty=c(1,1), pch=c(1,NA), col=c("black", "red"))
```

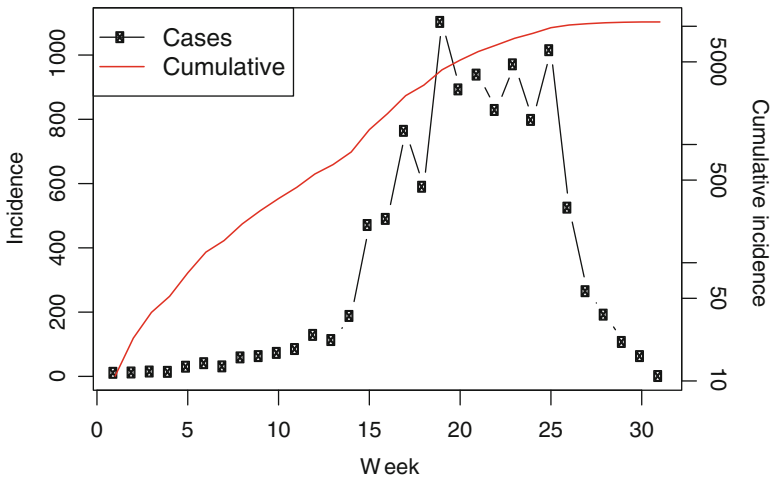

Fig. 3.1 Weekly incidence of measles in Niamey, Niger during the 2003–2004 outbreak

The cumulative incidence looks pretty log-linear for the first 6 weeks or so (Fig. 3.1). The data is weekly and the serial interval for measles is around 10–12 days, thus V is around 1.5–1.8 weeks; We calculate R_0 assuming either 1.5 or 1.8:

```
fit=lm(log(cum_cases)~absweek, subset=absweek<7,
     data=niamey)
r=fit$coef["absweek"]
V=c(1.5, 1.8)
V*r+1

  ## [1] 1.694233 1.833080
```

So a fast-and-furious estimate of the reproductive ratio for this outbreak places it in the 1.5–2 range. Measles exhibits recurrent epidemics in the presence of various vaccination campaigns in Niger, so this number represents an estimate of the *effective* reproductive ratio, R_E, at the beginning of this epidemic.

In their analysis of the SARS epidemics, Lipsitch et al. (2003) showed that for an infection with distinct latent and infectious periods a more refined estimate is given by $R = Vr + 1 + f(1-f)(Vr)^2$, where f is the ratio of infectious period to serial interval. For measles the infectious period is around 5 days:

```
V = c(1.5, 1.8)
f = (5/7)/V
V * r + 1 + f * (1 - f) * (V * r)^2

  ## [1] 1.814450 1.999198
```

Lipsitch et al.'s (2003) refined calculations thus produce slightly higher estimates of R_E in the range of 1.8–2. These simple methods based on initial growth are very handy because they are simple. However, they only use a portion of the data, and as pointed out by King et al. (2015a) it may be desirable to carry out more rigorous estimation.

3.4 Maximum Likelihood: The Chain-Binomial Model

Ferrari et al. (2005) proposed a maximum likelihood "removal" method for estimating R_0 for the simple epidemic based on the so-called "chain-binomial" model of infectious disease dynamics. The chain-binomial model, originally proposed by Bailey (1957), is a discrete-time, stochastic alternative[6] to the continuous-time, deterministic SIR model introduced in Chap. 2.

[6] This model also forms the foundation for the TSIR model (Bjørnstad et al. 2002a; Grenfell et al. 2002) which is the focus of Chap. 7.

In contrast to the S(E)IR models, the chain-binomial assumes that an epidemic is formed from a succession of discrete generations of infectious individuals in a coin-flip fashion. Just like in the SIR we assume that infectious individuals exert a force of infection on susceptibles of $\beta I/N$. In a generation, t, of duration given by the serial interval (which we use as the basic time unit). The probability that any given susceptible will escape an infectious contact will be $\exp(-\beta I/N)$. This comes from the basic result that if some event—such as contacts between a susceptible and the population of infectious individuals—is happening at rate, x, the number of events in Δt will be distributed according to a Poisson$(x\Delta t)$ distribution, so the probability of no events—no contacts—will be $e^{-x\Delta t}$. The converse outcome will happen with a probability $1-\exp(-\beta I/N)$, thus if there are S_t susceptibles we expect $S_t(1-\exp(-\beta I_t/N))$ new infecteds in generation $t+1$. Since we assume that contacts happen at random, the stochastic chain-binomial model is:

$$\begin{aligned} I_{t+1} &\sim \text{Binomial}(S_t, 1-\exp(-\beta I_t/N)). \\ S_{t+1} &= S_t - I_{t+1} = S_0 - \sum_{i=1}^{t} I_i \end{aligned} \tag{3.1}$$

If we ignore observational error, we thus have two unknown parameters: the initial number of susceptibles, S_0, and the transmission rate. The reproductive ratio is a composite of these two $R = S_0(1-\exp(-\beta/N))$, which for large populations is approximately $\beta S_0/N$ because $1-\exp(-x) \simeq x$ for $x << 1$. Thus β is approximately the reproductive ratio at the beginning of the epidemic, which makes sense, since infectious individuals are expected to transmit for exactly a time unit before recovering.

If we make the assumption that each epidemic generation depends only on the state of the system in the previous time step ("conditional independence"), the removal method estimates β and S_0 from a sequence of binomial likelihoods. The advantage of this method relative to the earlier methods is that we can use all the data and not just a few observations from the beginning of an epidemic.

We employ a standard recipe, for doing a "nonstandard" maximum likelihood analysis (see Bolker 2008, for an excellent discussion of this). The first step is to write a function for the likelihood. Conditional on some parameters, the function returns the negative log-likelihood of observing the data given the model. The likelihood, which is the probability of observing data given a model and some parameter values, is the working-horse of a large part of statistics. R has inbuilt `dxxxx`-functions to calculate the likelihood for any conceivable probability distribution. The function to calculate a binomial likelihood is `dbinom`. We can thus define a likelihood-function for the chain-binomial model [7]:

[7] Note that the `[-x]` subsetting in R means "drop the x'th observation"; thus the `[-n]` and `[-1]` make sure that adjacent pairs of observations are aligned correctly. We use the `floor`-function for the vector of S's because `dbinom` requires the denominator and numerator to be integers.

```
llik.cb = function(S0, beta, I) {
    n = length(I)
    S = floor(S0 - cumsum(I[-n]))
    p = 1 - exp(-beta * (I[-n])/S0)
    L = -sum(dbinom(I[-1], S, p, log = TRUE))
    return(L)
}
```

For the real statistical analysis (below), the two parameters will be estimated simultaneously. However, in order to ease into the idea of likelihood estimation we will consider the two sequentially and visualize the likelihood by plotting it over a grid of potential values. We illustrate with the data on measles from one of the three different reporting centers in Niamey, Niger from 2003 (Grais et al. 2008). We first need to aggregate the data into 2-week intervals which is roughly the serial interval for measles. The epidemic in district 1 lasted for 30 weeks (the 31st week is a zero)[8]:

```
twoweek = rep(1:15, each = 2)
y = sapply(split(niamey$cases_1[1:30], twoweek), sum)
sum(y)
```

```
## [1] 5920
```

In district 1 there were 5920 cases during the epidemics, so S_0 needs to be at least that number. In the above parameterization $R_E \simeq \beta$, lets initially assume a candidate value of 6500 for S_0 and calculate the likelihood for each candidate value of β between 1 and 10 by 0.1 (Fig. 3.2):

```
S0cand=6500
betacand=seq(0,10, by=.1)
ll=rep(NA, length(betacand))
for(i in 1:length(betacand)){
     ll[i]=llik.cb(S0=S0cand, beta=betacand[i], I=y)
}
plot(ll~betacand, ylab="Neg log-lik", xlab=
     expression(beta))
betacand[which.min(ll)]
```

```
## [1] 2.3
```

We follow the convention of using the negative log-likelihood in the profile. Intuitively, one may think that it would be more natural to consider the *likelihood* itself (i.e., the probability of observing the data, given particular parameter values). How-

[8] The function `split` splits a vector into a list based on some grouping variable, and `sapply` applies a function—in this case `sum`—to the list.

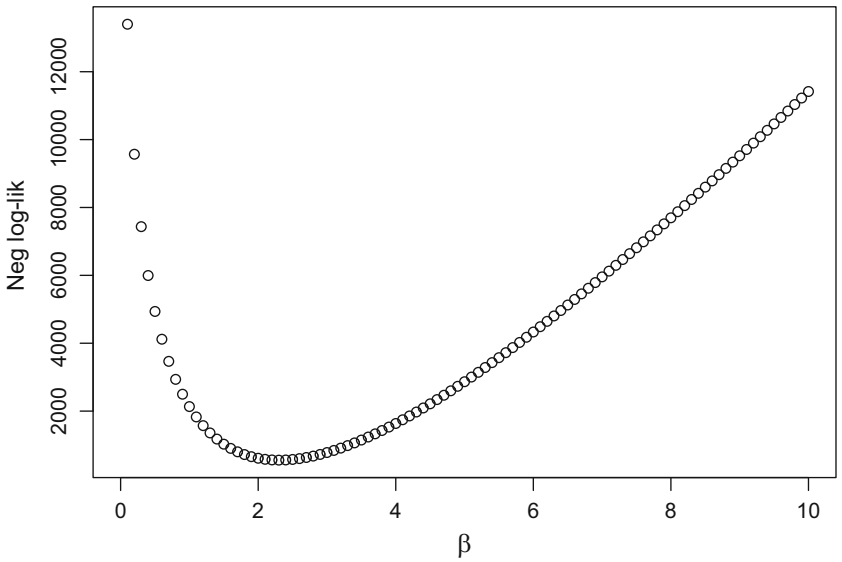

Fig. 3.2 The conditional profile log-likelihood of β for Niamey's district 1 assuming $S_0 = 6500$

ever, since this would be a product of small numbers (one for each observation), computers are not precise enough to distinguish the joint probability from zero if the data set is large.

If our S_0 guess is right, then β should be around 2.3. We can do a similar check for S_0 (assuming β is 2.3). The grid-value associated with the highest likelihood value is 7084.8 (Fig. 3.3), so our original S_0 guess was good but not perfect.

```
betacand=2.3
S0cand=seq(5920,8000, length=101)
ll=rep(NA, length=101)
for(i in 1:101){
     ll[i]=llik.cb(S0=S0cand[i], beta=betacand, I=y)
}
plot(ll~S0cand, ylab="Neg log-lik", xlab=
     expression(S[0]))
S0cand[which.min(ll)]

  ## [1] 7084.8
```

For a proper analysis we minimize the negative log-likelihood by varying both parameters simultaneously. We can do this using the generic `optim`-function or the `mle2`-function in the `bbmle`-package. The `mle2`-function uses `optim` to find

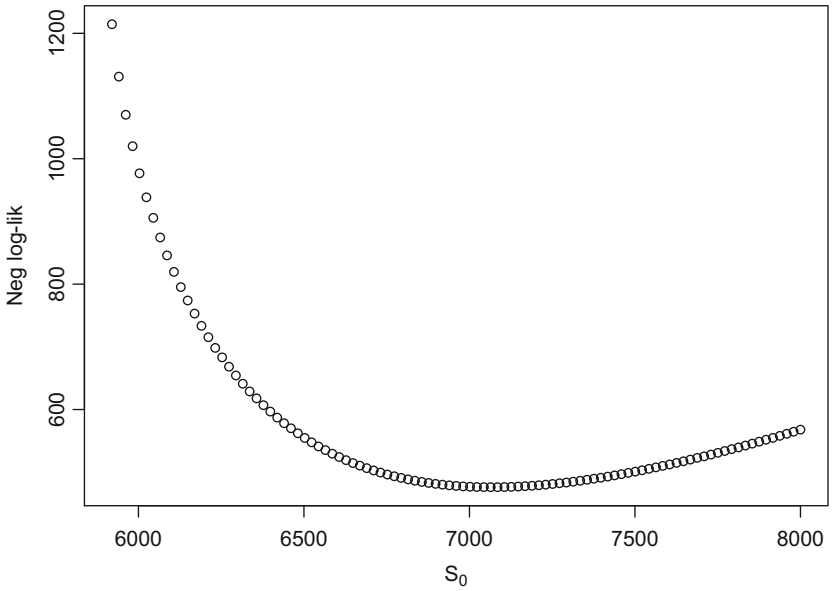

Fig. 3.3 The conditional profile log-likelihood of S_0 for Niamey's district 1 assuming $\beta = 2.3$

maximum likelihood estimates, but also provides confidence intervals, profile likelihoods, and a variety of other useful measures (Bolker 2008). We summarize the basic pertinent likelihood theory for these other measures in Sect. 8.4.

```
require(bbmle)
fit=mle2(llik.cb, start=list(S0=7085, beta=2.3),
    method="Nelder-Mead",data = list(I = y))
summary(fit)
```

```
## Maximum likelihood estimation
##
## Call:
## mle2(minuslogl = llik.cb, start = list(S0 = 7085,
##     beta = 2.3), beta = 2), data = list(I = y))
##
## Coefficients:
##        Estimate Std. Error z value     Pr(z)
## S0   7.8158e+03 1.3022e+02  60.019 < 2.2e-16 ***
## beta 1.8931e+00 3.6968e-02  51.209 < 2.2e-16 ***
## ---
## Signif. codes:
## 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## -2 log L: 841.831
```

```
confint(fit)

## Profiling...

  ##             2.5 %       97.5 %
  ## S0    7577.967212 8088.641095
  ## beta     1.820943    1.966336
```

So the joint MLE estimates are $S_0 = 7816$ (CI: 7578, 8088) and $\beta = 1.89$ (CI: 1.82, 1.7).

Applying statistical tools to biological models—like the chain-binomial—can usefully highlight uncertainties due to parametric interdependencies. In the case of a "simple epidemic" like the measles outbreak considered here, for example, it is conceivable that similar epidemic trajectories can arise from having a large number of initial susceptibles and a low transmission rate, or a more moderate number of susceptibles and a higher transmission rate. We can quantify this through considering the correlation matrix among the parameters of our likelihood analysis; `vcov` calculates their variance-covariance matrix from which we can calculate standard errors according to `sqrt(diag(vcov(fit)))` and `cov2cor` converts this to a correlation matrix. As intuition suggested there is a strong negative correlation between the estimates of the β and S_0 parameters.

```
cov2cor(vcov(fit))

  ##               S0       beta
  ## S0    1.0000000 -0.7444261
  ## beta -0.7444261  1.0000000
```

3.5 Stochastic Simulation

The chain-binomial is both a statistical model for estimation and a stochastic model for dynamics. We can thus write a function to simulate dynamics using the estimated parameters.[9]

```
sim.cb=function(S0, beta, I0){
   I=I0
   S=S0
   i=1
   while(!any(I==0)){
```

[9] In contrast to the loop introduced in Sect. 2.3, where the number of iterations is constant and known, the number of epidemic generations may vary among realizations because disease extinction is a stochastic process. We therefore use `while` instead of `for` when looping; `!` means "not" in R.

```
        i=i+1
        I[i]=rbinom(1, size=S[i-1], prob=1-
           exp(-beta*I[i-1]/S0))
        S[i]=S[i-1]-I[i]
    }
    out=data.frame(S=S, I=I)
    return(out)
}
```

We superimpose 100 stochastic simulations on the observed epidemic. The simulations from the chain-binomial model brackets the observed epidemic nicely (Fig. 3.4), suggesting that the model is a reasonable first approximation to the underlying dynamics. We will revisit on this case study in the context of outbreak-response vaccination in Sect. 8.8.

```
plot(y, type="n", xlim=c(1,18),
   ylab="Predicted/observed", xlab="Week")
for(i in 1:100){
     sim=sim.cb(S0=floor(coef(fit)["S0"]),
     beta=coef(fit)["beta"], I0=11)
     lines(sim$I, col=grey(.5))
}
points(y, type="b", col=2)
```

3.6 Further Examples

3.6.1 Influenza A/H1N1 1977

The `flu` data set in the `epimdr`-package represents the number of children confined to bed each day during a 1978 outbreak of the reemerging influenza A/H1N1 strain in a boarding school in North England (Fig. 3.5). This subtype of influenza had been absent from human circulation after the A/H2N2 pandemic of 1957 but reemerge (presumably from some laboratory freezer) in 1977. The school had 763 boys of which 512 boys were confined to bed sometime during the outbreak. None of the boys would have had previous exposure to A/H1N1.

The typical time of illness was 5–7 days. Since the data is number confined to bed each day, the data is not incidence but (a proxy for) *prevalence*. The data looks pretty log-linear for the first 5 days. Family studies have been used to estimate the serial interval for flu between 2 and 4 days (most between 2 and 3; Cowling et al.

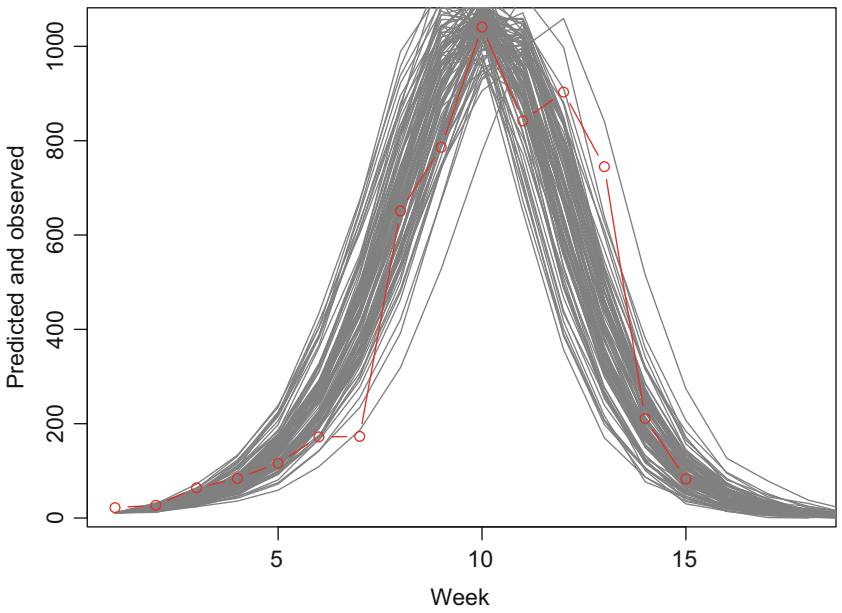

Fig. 3.4 Observed (red) and 100 simulated (gray) epidemics using the chain-binomial model and ML parameters for S_0 and β from Niamey's district 1 data

2009; Vink et al. 2014). Volunteer studies show the mean infectious period around 5 days (Carrat et al. 2008).

```
data(flu)
plot(flu$day, flu$cases, type="b", xlab="Day",
     ylab="In bed", log="y")
tail(flu)
```

```
##    day cases
## 9    9   192
## 10  10   126
## 11  11    70
## 12  12    28
## 13  13    12
## 14  14     5
```

The "fast-and-furious" estimate of R_0 is thus:

```
fit=lm(log(cases)~day, subset=day<=5,
     data=flu)
lambda=fit$coef["day"]
V=c(2,3)
V*lambda+1
```

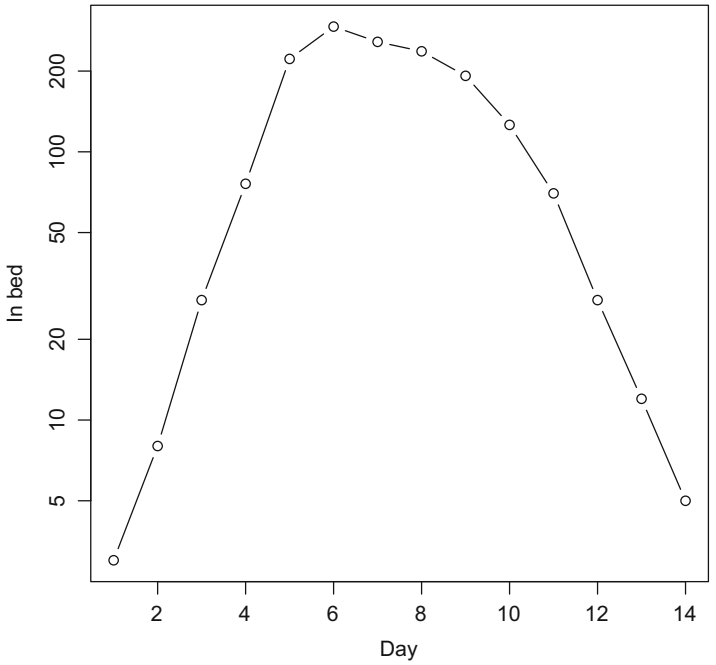

Fig. 3.5 Daily number of children confined to bed in a boarding school in North England during an outbreak in 1978 of the reemerging A/H1N1 strain

```
## [1] 3.171884 4.257827
```

This is higher than most estimates of R_0 of pandemic flu (which typically lies in the 1.5–2.5 interval). However, contact rates within a boarding school is likely to be higher than average across human populations as a whole.

3.6.2 Ebola Sierra Leone 2014–2015

The CDC's record for the 2014–2015 ebola outbreak in Sierra Leone is in the `ebola`-data set. The serial interval for ebola is estimated at around 15 days with an incubation period of 11 days. The mean time to hospitalization is 5 days and mean time to death or dismissal was 5 and 11 days, respectively (WHO Ebola Response Team 2014; White and Pagano 2008). The data is the back-calculated incidence as the difference of the cumulative cases reported by the CDC. Because of the complexities of reporting and revisions of case-load through time, this leads to some negative numbers for certain dates. These were set to zero as a crude fix (Fig. 3.6).

```
data(ebola)
par(mar = c(5,5,2,5))
plot(ebola$day, ebola$cases, type="b", xlab="Week",
     ylab="Incidence")
par(new=T)
plot(ebola$day, ebola$cum_cases, type="l", col="red",
      axes=FALSE, xlab=NA, ylab=NA, log="y")
axis(side = 4)
mtext(side = 4, line = 4, "Cumulative incidence")
legend("right", legend=c("Cases", "Cumulative"),
     lty=c(1,1), pch=c(1,NA), col=c("black", "red"))
tail(ebola)
```

```
##         date day cum_cases cases
## 98    7/8/15 468     13945    34
## 99   7/15/15 475     13982    37
## 100 7/22/15 482     14001    19
## 101 7/29/15 489     14061    60
## 102  8/5/15 496     14089    28
## 103 8/12/15 503     14122    33
```

We first use the regression method with Lipsitch's correction:

```
V = 15
f = 0.5
V * lambda + 1 + f * (1 - f) * (V * lambda)^2
```

```
##     day
## 1.6988
```

We next aggregate the data in 2-week increments roughly corresponding to the serial interval, so we can apply the removal method.[10]

```
#Data aggregation
cases=sapply(split(ebola$cases,
     floor((ebola$day-.1)/14)), sum)
sum(cases)
```

```
## [1] 14721
```

```
#Removal MLE
fit=mle2(llik.cb, start=list(S0=20000, beta=2),
        method="Nelder-Mead",data = list(I = cases))
```

[10] Because of the difference in magnitude of the estimates of S_0 (in the ten thousands) and R_0 (around 1.4), the numerical method used to calculate confidence intervals struggles, so we suggest starting standard errors for the `confint`-function.

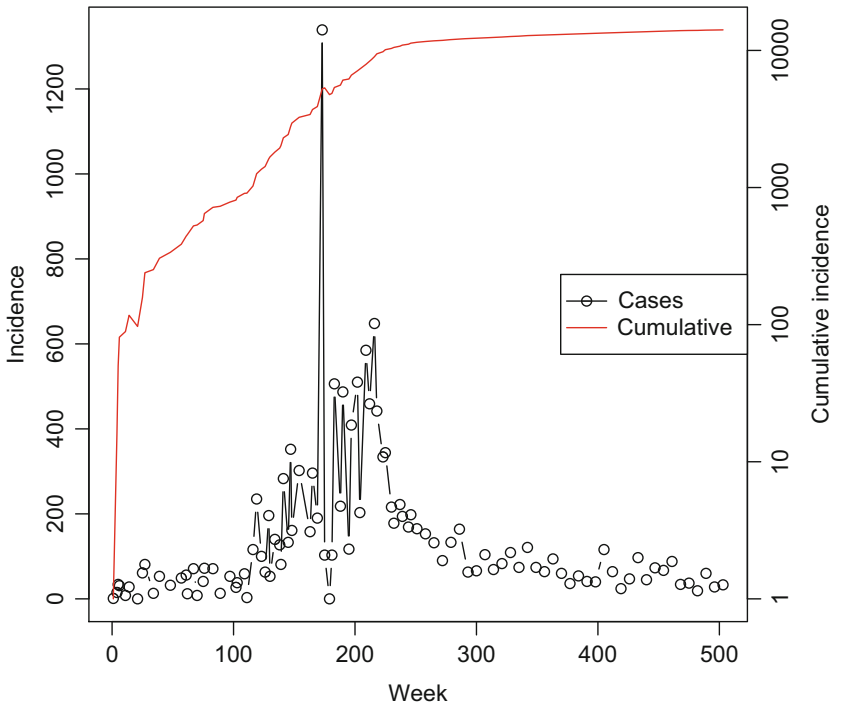

Fig. 3.6 Incidence and cumulative incidence of ebola during the 2014–2015 outbreak in Sierra Leone

```
summary(fit)

  ## Maximum likelihood estimation
  ##
  ## Call:
  ## mle2(minuslogl = llik.cb, start = list(S0 = 20000,
  ##     beta = 2), data = list(I = cases))
  ##
  ## Coefficients:
  ##        Estimate Std. Error    z value     Pr(z)
  ## S0   2.7731e+04 2.5949e-07 1.0687e+11 < 2.2e-16 ***
  ## beta 1.4237e+00 1.1783e-02 1.2083e+02 < 2.2e-16 ***
  ## ---
  ## Signif. codes:
  ## 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
  ##
  ## -2 log L: 5546.683

confint(fit, std.err=c(100,0.1))
```

```
## Profiling...
  ##              2.5 %       97.5 %
  ## S0    26393.579452 29287.725327
  ## beta      1.384683     1.463184
```

The removal and Lipsitch methods provide comparable estimates that are somewhat lower than those concluded by more elaborate analyses by the WHO team for the Sierra Leone outbreak (WHO Ebola Response Team 2014).

3.6.3 Ebola DRC 1995

The `ferrari`-data set holds the incidence data for a number of outbreaks—Ebola DRC '95, Ebola Uganda '00, SARS Hong Kong '03, SARS Singapore '03, Hog Cholera Netherlands '97, and Foot-and-mouth UK '00—aggregated by disease-specific serial intervals (Table 3.1; Ferrari et al. 2005).

Table 3.1 Serial intervals for each outbreak in the `ferrari` data set

Disease	Serial interval	Location	Year
Ebola	14d	DRC	1995
		Uganda	2000
SARS	5d	Hong Kong	2003
		Singapore	
Hog cholera	7d	Netherlands	1997
FMD	21d	UK	2000

```
names(ferrari)

  ## [1] "Eboladeaths00" "Ebolacases00"  "Ebolacases95"
  ## [4] "FMDfarms"      "HogCholera"    "SarsHk"
  ## [7] "SarsSing"

ferrari$Ebolacases95

  ##  [1]  4  6  5 18 36 99 40 17  4  1 NA NA NA NA NA

sum(ferrari$Ebolacases95, na.rm = TRUE)

  ## [1] 230

y = c(na.omit(ferrari$Ebolacases95))
```

The number of initial susceptibles must be larger than the summed incidence, so we make an initial guess of 300.

```
fit=mle2(llik.cb, method="Nelder-Mead",
    start=list(S0=300, beta=2), data = list(I = y))
fit
```

```
  ##
  ## Call:
  ## mle2(minuslogl = llik.cb, start = list(S0 = 300,
  ##     beta = 2), data = list(I = y))
  ##
  ## Coefficients:
  ##          S0        beta
  ## 241.118108   3.181465
  ##
  ## Log-likelihood: -48.3
```

```
confint(fit, std.err=2)
```

```
## Profiling...
```

```
  ##            2.5 %     97.5 %
  ## S0   233.973778 254.051292
  ## beta   2.692505   3.718357
```

The estimated R_0 is 3.2. It thus appears that the Ebola outbreak in DRC in 1995 was more explosive than in Sierra Leone in 2014. This could be due to aggregation across a larger geographic area of the latter and/or the more intensive public health interventions. We will revisit on the DRC outbreak using the "next-generation matrix" method in Sect. 3.9.2.

3.7 R_0 from S(E)IR Flows

As discussed in Sect. 2.1, $R_0 = \beta/(\gamma+\mu)$ for the simple SIR model. This is the correct quantity assuming that the force-of-infection (the rate at which susceptibles are infected) is $\beta I/N$, there is no latent period and no disease-induced mortality, so the index case is expected to be infectious for a period of $1/(\gamma+\mu)$ time units during which it will transmit at a rate of $\beta * N/N$. The numerator comes about because all the N individuals in the population is by definition susceptible when we consider the basic reproductive ratio.

Different SIR-like flows will produce different definitions of R_0 but we can use the same logic for all linear SIR-like flows. Consider, for example, the SEIR model (Fig. 3.7) of the flow of hosts between **S**usceptible, **E**xposed (but not yet infectious), **I**nfectious, and **R**ecovered compartments in a randomly mixing population:

$$\frac{dS}{dt} = \mu(N[1-p]-S) - \frac{\beta IS}{N} \tag{3.2}$$

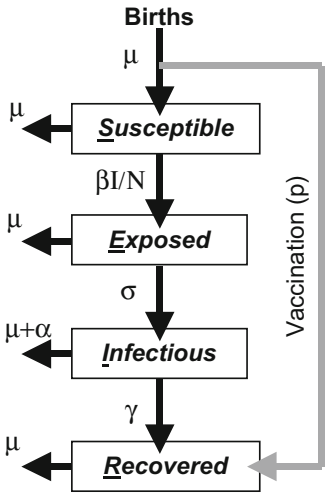

Fig. 3.7 The SEIR flow diagram. Apart from vaccination, flows represent *per capita* rates of flow from the donor compartment. Vaccination is assumed to be a fraction of children vaccinated at birth

$$\frac{dE}{dt} = \frac{\beta IS}{N} - (\mu + \sigma)E \tag{3.3}$$

$$\frac{dI}{dt} = \sigma E - (\mu + \gamma + \alpha)I \tag{3.4}$$

$$\frac{dR}{dt} = \gamma I - \mu R + \mu N p, \tag{3.5}$$

where susceptibles are either vaccinated at birth (fraction p) or infected at a rate $\beta I/N$. Infected individuals will remain in the latent class for an average period of $1/(\sigma + \mu)$ and subsequently (if they escape natural mortality at a rate μ) enter the infectious class for an average time of $1/(\gamma + \mu + \alpha)$; α is the *rate* of disease induced mortality (*not* case fatality rate). By the rules of competing rates (Sect. 3.2), the case fatality rate is $\alpha/(\gamma + \mu + \alpha)$ because during the time an individual is expected to remain in the infectious class the disease is killing them at a rate α. By a similar logic, the probability of recovering with immunity (for life in the case of the SEIR model) is $\gamma/(\gamma + \mu + \alpha)$. Putting all these pieces together, the expected number of secondary cases in a completely susceptible population is thus: probability of making it through latent stage without dying * expected infectious period * transmission rate while infectious. Thus, $R_0 = \frac{\sigma}{\sigma+\mu}\frac{1}{\gamma+\mu+\alpha}\frac{\beta N}{N} = \frac{\sigma}{\sigma+\mu}\frac{\beta}{\gamma+\mu+\alpha}$.

3.8 Other Rules of Thumb

3.8.1 Mean Age of Infection

For endemic, fully immunizing infections, in a constant-sized host population R_0 is related to mean age of infection, $\bar{a}$, according to $R_0 \simeq 1 + L/\bar{a}$ where L is the life expectancy of the host (e.g., Dietz and Schenzle 1985). This rule of thumb is often used in conjunction with seroprevalence-by-age profiles to get ballpark estimates of R_0. Chapter 4 discusses age-incidence patterns in more detail.

3.8.2 Final Epidemic Size

In principle, the reproductive ratio can be estimated from the final epidemic size according to the equations discussed in Sect. 2.3. If there is some preexisting immunity and there is homogeneous mixing, then R_0 can be quantified according to $\frac{\log(s_0)-\log(s_\infty)}{s_0-s_\infty}$, where s_0 and s_∞ are the fractions of the population that is susceptible at the beginning and end of the epidemic, respectively (Heesterbeek and Dietz 1996). However, this is unlikely to be very reliable because the final epidemic size calculations assume that the epidemic is progressing according to the deterministic model (and all its assumptions) including no changes in host behavior in the face of the epidemic. For example, ebola is thought to have an R_0 in the 2–3.5 range, which is what lead CDC to warn that the West-African outbreak could result in millions of cases. In the end the total number of cases in Guinea, Liberia, and Sierra Leone was a far lower number, around 25,000, because of extensive public health interventions and changes to dangerous funeral practices.

For certain common infections like seasonal influenza the rule of thumb may hold; The annual *attack rate* for the flu is around 10–15% which is probably close to that expected from its R_0 (around 1.5–2) and the typical fraction of susceptible of around a quarter (pre-vaccination; assuming immunity following infection lasted around 4 years).

3.8.3 Contact Tracing

Contact tracing can provide direct estimates of R_0. Blumberg and Lloyd-Smith (2013) showed that this together with size-distributions of subcritical transmission-chains can provide estimates in important low R settings, such as human monkey pox in the face of eroding smallpox herd-immunity. They estimated the human-to-human reproductive ratio to be 0.32. Given that the smallpox vaccine is likely to

be cross-protective against monkey pox, the worry is that this effective reproductive ratio will increase over time since smallpox vaccination is no longer carried out. Contact tracing was also used to estimate R_0 during the early spread of SARS during the 2003 outbreak (Riley et al. 2003).

De et al. (2004) did a contact-tracing study of the spread of gonorrhea across a sexual network in Alberta, Canada. The directional transmission graph among the 89 individuals is in the `gonnet`-data set. The initial cluster of 17 cases all frequented the same bar, each infected between 0 and 7 other partners with 2.17 as the average. We can use the `statnet`-package to visualize the chains of transmission (Fig. 3.8):

```
require(statnet)
data(gonnet)
nwt = network(gonnet, directed = TRUE)
plot(nwt, vertex.col = c(0, rep(1, 17), rep(2, 71)))
```

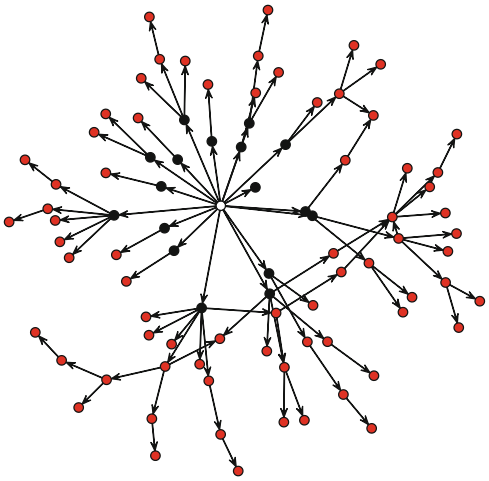

Fig. 3.8 Network of spread of gonorrhea as studied by De et al. (2004). The initial 17 cases (in black) frequented the same bar (white) were ultimately responsible for a cluster of 89 cases identified through contact tracing

The subsequent infections, in turn, infected between 0 and 6 partners with an average of 0.62. The drop is (1) due to the sexual network being depleted of susceptibles, and (2) because infection across heterogenous networks will differentially infect individuals according to their number of contacts (Ferrari et al. 2006a). Epidemics across social networks is the topic of Chap. 12 and we will revisit on this network therein.

3.9 Advanced: The Next-Generation Matrix

For models that are not simple linear chains, it is less straightforward to calculate R_0 from parameterized models using the "logical method." The next-generation matrix is the general approach that work for all compartmental models of any complexity (Diekmann et al. 1990). It is done in a sequence of steps:

1. Identify all n infected compartments,
2. Construct a $n \times 1$ matrix, $\mathbf{F}$, that contains expressions for all *completely new* infections entering each infected compartment,
3. Construct a $n \times 1$ matrix, $\mathbf{V}^-$, that contains expressions for all losses out of each infected compartment,
4. Construct a $n \times 1$ matrix, $\mathbf{V}^+$, that contains expressions for all gains into each infected compartment that does *not* represent *new* infections but transfers among infectious classes,
5. Construct a $n \times 1$ matrix, $\mathbf{V} = \mathbf{V}^- - \mathbf{V}^+$,
6. Generate two $n \times n$ Jacobian matrices $\mathbf{f}$ and $\mathbf{v}$ that are the partial derivatives of $\mathbf{F}$ and $\mathbf{V}$ with respect to the n infectious state variables,
7. Evaluate the matrices at the disease free equilibrium (dfe), and finally
8. R_0 is the greatest eigenvalue of $\mathbf{fv}^{-1}|_{dfe}$.

3.9.1 SEIR

This is quite an elaborate scheme, so we will try it out first for the SEIR model for which we already know the answer. Unfortunately, `R` cannot do vectorized *symbolic* calculations, so we need to do this, one matrix element at a time.[11] In Chap. 2, we discussed how to use `expression` to do symbolic calculations in `R`. The `quote`-function is an alternative way to define mathematical expressions; `substitute` allows some simple additional manipulations.

Step 1: Infected classes are E and I, let us label them 1 and 2.
Step 2: All new infections: $dE/dt = \beta SI/N$, $dI/dt = 0$

```
F1 = quote(beta * S * I/N)
F2 = 0
```

Step 3: All losses $dE/dt = (\mu + \sigma)E$, $dI/dt = (\mu + \alpha + \gamma)I$

```
Vm1 = quote(mu * E + sigma * E)
Vm2 = quote(mu * I + alpha * I + gamma * I)
```

Step 4: All gained transfers $dE/dt = 0$, $dI/dt = (\sigma)E$

[11] Though it is possible to do calculations more compactly using a `list` of equations.

```
Vp1 = 0
Vp2 = quote(sigma * E)
```

Step 5: Subtract Vp from Vm

```
V1 = substitute(a - b, list(a = Vm1, b = Vp1))
V2 = substitute(a - b, list(a = Vm2, b = Vp2))
```

Step 6: Generate the partial derivatives for the two Jacobians

```
f11 = D(F1, "E"); f12 = D(F1, "I")
f21 = D(F2, "E"); f22 = D(F2, "I")

v11 = D(V1, "E"); v12 = D(V1, "I")
v21 = D(V2, "E"); v22 = D(V2, "I")
```

Step 7: Assuming N=1, the disease free equilibrium (dfe) is $S = 1, E = 0, I = 0, R = 0$. We also need values for other parameters. Assuming a weekly time-step and something chickenpox-like we may use $\mu = 0$, $\alpha = 0$, $\beta = 5$, $\gamma = .8$, $\sigma = 1.2$, and $N = 1$.

```
paras=list(S=1, E=0, I=0, R=0, mu=0, alpha=0,
     beta=5, gamma=.8, sigma=1.2, N=1)

f=with(paras,
matrix(c(eval(f11),eval(f12),eval(f21),
     eval(f22)), nrow=2, byrow=TRUE))

v=with(paras,
matrix(c(eval(v11),eval(v12),eval(v21),
     eval(v22)), nrow=2, byrow=TRUE))
```

Step8: Calculate the largest eigenvalue of $f \times$ inverse(v). Note that the function for inverting matrices in `R` is `solve`.

```
max(eigen(f %*% solve(v))$values)

  ## [1] 6.25
```

Let us check that the next-generation method and the "flow" method are in agreement recalling that for the SEIR-flow $R_0 = \frac{\sigma}{\sigma+\mu}\frac{\beta}{\gamma+\mu+\alpha}$.

```
with(paras, sigma/(sigma + mu) * beta/(gamma + mu + alpha))

  ## [1] 6.25
```

3.9.2 SEIHFR

Legrand et al. (2007) forms the foundation for many of the recent Ebola models. The model has five compartments corresponding to Susceptible, Exposed, Infectious in community, Infectious in hospital, Dead but not yet buried, and removed (either buried or immune). The model is more complex than previous compartmental models and cannot be represented by a simple linear chain (Fig. 3.9). The parameterization used here is motivated by the original formulation of Legrand et al. (2007), but the notation conforms to the other sections of this book; Each infectious compartment contributes to the force of infection through their individual βs. There are two branching-points in the flow: The hospitalization of a fraction Θ of the infectious cases after an average time of $1/\gamma_h$ days following onset of symptoms, and the death of a fraction Λ of the I- and H-class after an average time of $1/\gamma_f$ days and $1/\eta_f$ days, respectively. For the 1995 DRC outbreak, Legrand et al. (2007) assumed that hospitalization affected transmission rates but not duration of infection or probability of dying. Model parameters are given in Table 3.2, and the model equations are:

$$\frac{dS}{dt} = -(\beta_i I + \beta_h H + \beta_f F)S/N \tag{3.6}$$

$$\frac{dE}{dt} = (\beta_i I + \beta_h H + \beta_f F)S/N - \sigma E \tag{3.7}$$

$$\frac{dI}{dt} = \sigma E - \Theta\gamma_h I - (1-\Theta)(1-\Lambda)\gamma_r I - (1-\Theta)\Lambda\gamma_f I \tag{3.8}$$

$$\frac{dH}{dt} = \Theta\gamma_h I - \Lambda\eta_f H - (1-\Lambda)\eta_r H \tag{3.9}$$

$$\frac{dF}{dt} = (1-\Theta)(1-\Lambda)\gamma_r I + \Lambda\eta_f H - \chi F \tag{3.10}$$

$$\frac{dR}{dt} = (1-\Theta)(1-\Lambda)\gamma_r I + (1-\Lambda)\eta_r H + \chi F \tag{3.11}$$

There are four infected compartments (E, I, H, and F), thus $\mathbf{F}$, $\mathbf{V}^-$, and $\mathbf{V}^+$ will be 4×1 matrices, and $\mathbf{f}$ and $\mathbf{v}$ will be 4×4 matrices.

Step 1: Infected classes are E, I, H, and F, and let us label them 1–4.

Step 2: All new infections $dE/dt = \beta SI/N$, $dI/dt = 0$

```
F1=expression(betai * S * I / N + betah* S * H / N +
   betaf * S * F / N)
F2=0
F3=0
F4=0
```

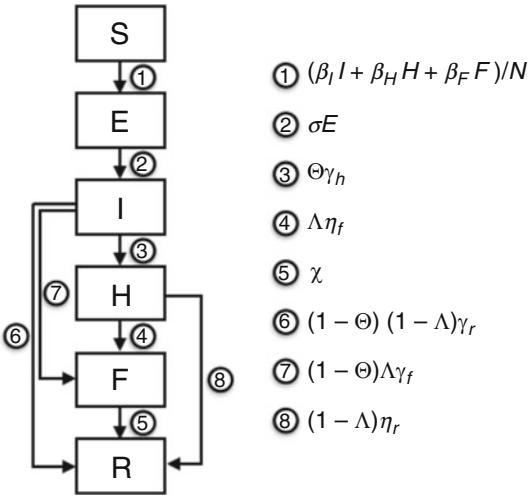

Fig. 3.9 The SEIHFR flow diagram for ebola dynamics

Table 3.2 Parameters for Legrand et al. (2007)'s Ebola model using the data from the 1995 DRC epidemic

Parameter	Meaning	Value
N	Population size	
$1/\sigma$	Incubation period	7d
$1/\gamma_h$	Onset to hospitalization	5d
$1/\gamma_f$	Onset to death	9.6d
$1/\gamma_r$	Onset to recovery	10d
$1/\eta_f$	Hospitalization to death	4.6d
$1/\eta_r$	Hospitalization to recovery	5d
$1/\chi$	Death to burial	2d
Θ	Proportion hospitalized	80%
Λ	Case fatality ratio	81%
β_i	Transmission rate in community	0.588
β_h	Transmission rate in hospital	0.794
β_f	Transmission rate at funeral	7.653

To avoid confusion, we use lowercase Greek for rates and uppercase for probabilities

Step 3: All losses

```
Vm1=quote(sigma * E)
Vm2=quote(Theta * gammah * I + (1 - Theta) * (1-
   Lambda) * gammar * I + (1 - Theta) * Lambda *
   gammaf * I)
Vm3=quote(Lambda * etaf * H + (1 - Lambda) * etar * H)
Vm4=quote(chi * F)
```

Step 4: All gained transfers

```
Vp1=0
Vp2=quote(sigma * E)
Vp3=quote(Theta * gammah * I)
Vp4=quote((1 - Theta) * (1 - Lambda) * gammar * I+
   Lambda * etaf * H)
```

Step 5: Subtract Vp from Vm

```
V1 = substitute(a - b, list(a = Vm1, b = Vp1))
V2 = substitute(a - b, list(a = Vm2, b = Vp2))
V3 = substitute(a - b, list(a = Vm3, b = Vp3))
V4 = substitute(a - b, list(a = Vm4, b = Vp4))
```

Step 6: Generate the partial derivatives for the two Jacobians

```
f11 = D(F1, "E"); f12 = D(F1, "I"); f13 = D(F1, "H")
     f14 = D(F1, "F")
f21 = D(F2, "E"); f22 = D(F2, "I"); f23 = D(F2, "H")
     f24 = D(F2, "F")
f31 = D(F3, "E"); f32 = D(F3, "I"); f33 = D(F3, "H")
     f34 = D(F3, "F")
f41 = D(F4, "E"); f42 = D(F4, "I"); f43 = D(F4, "H")
     f44 = D(F4, "F")

v11 = D(V1, "E"); v12 = D(V1, "I"); v13 = D(V1, "H")
     v14 = D(V1, "F")
v21 = D(V2, "E"); v22 = D(V2, "I"); v23 = D(V2, "H")
     v24 = D(V2, "F")
v31 = D(V3, "E"); v32 = D(V3, "I"); v33 = D(V3, "H")
     v34 = D(V3, "F")
v41 = D(V4, "E"); v42 = D(V4, "I"); v43 = D(V4, "H")
     v44 = D(V4, "F")
```

Step 7: Disease free equilibrium: the dfe is $S = 1, E = 0, I = 0, H = 0, F = 0, R = 0$. We also need values for other parameters. We use the estimates from the DRC 1995 outbreak scaled as weekly rates from tables and appendices of Legrand et al. (2007).

```
gammah = 1/5 * 7
gammaf = 1/9.6 * 7
gammar = 1/10 * 7
chi = 1/2 * 7
etaf = 1/4.6 * 7
etar = 1/5 * 7
```

```
paras=list(S=1,E=0, I=0, H=0, F=0,R=0,
     sigma=1/7*7, Theta=0.81, Lambda=0.81, betai=0.588,
     betah=0.794, betaf=7.653,N=1, gammah=gammah,
     gammaf=gammaf, gammar=gammar, etaf=etaf,
     etar=etar, chi=chi)

f=with(paras,
matrix(c(eval(f11),eval(f12),eval(f13),eval(f14),
     eval(f21),eval(f22),eval(f23),eval(f24),
     eval(f31),eval(f32),eval(f33),eval(f34),
     eval(f41),eval(f42),eval(f43),eval(f44)),
     nrow=4, byrow=T))

v=with(paras,
matrix(c(eval(v11),eval(v12),eval(v13),eval(v14),
     eval(v21),eval(v22),eval(v23),eval(v24),
     eval(v31),eval(v32),eval(v33),eval(v34),
     eval(v41),eval(v42),eval(v43),eval(v44)),
     nrow=4, byrow=T))
```

Step 8: Calculate the largest eigenvalue of $f \times \text{inverse}(v)$

```
max(eigen(f %*% solve(v))$values)

  ## [1] 2.582429
```