CHAPTER 11

Epidemiology

In the medical literature, ‘epidemiology’ is a field that seeks to identify key correlates for a particular disease. For example, is leukaemia more common in the vicinity of high-voltage power lines, or is heart failure associated with smoking (Greenberg et al. 2004)? This kind of study overlaps sometimes with the approach taken in the context of this book (Giesecke 2002). In this book, ‘epidemiology’ is the study of host–parasite population dynamics as a branch of population biology and population genetics. Epidemiology in this sense started with the Swiss mathematician Daniel Bernoulli who, in 1766, used a mathematical model to analyse the dynamics of a smallpox epidemic in Paris and to evaluate the effect of vaccination (‘variolization’) (Box 11.1).

11.1 Population biology of host–parasitoid systems

Parasitoids are an important and rich group of parasites. Parasitoids grow inside (or attached to) a host, and typically kill the host as an obligate part of their life-cycle. Therefore, the ecology and population dynamics of parasitoids is somewhere in between those of predators and ‘true’ infectious parasites, such as bacteria or protozoa (Hassell 2000). Figure 11.1 shows the dynamics of such a system, which is characterized by strong fluctuations in numbers in this particular example. Observations from the field, as well as experiments in the laboratory, demonstrate that host populations can be drastically reduced by the presence of parasitoids (Hassell and Godfray 1992; Godfray 1994).

A classical approach to model the dynamics of a host–parasitoid system is the Nicholson–Bailey model (Nicholson and Bailey 1935) (Box 11.2). The model generates a non-stable equilibrium that tends to lead to oscillations with ever increasing amplitudes in population sizes. In fact, the Nicholson–Bailey model ignores biologically more realistic scenarios. For example, it is typically observed that parasitoid attacks are not random as assumed in the basic model; rather, attacks are aggregated. Furthermore, parasitoids may begin to interfere with each other’s search, as more and more parasitoids are present and compete for access to the same hosts. Such interference would affect the attack rate and make it density-dependent. The dynamics can even be completely spatial; that is, unfold in a meta-population (a set of interconnected sub-populations or patches). Hosts and parasites may encounter themselves at random within a patch, but otherwise they are interacting over all patches, where varying fractions of hosts and parasitoids are present. Further complications arise as individual hosts vary in their susceptibility to parasitism due to, for example, differences in genotypes, local environmental conditions, or variable microhabitats. Such complications can be taken into account by modifying the basic Nicholson–Bailey model and adding extra terms. In general, the Nicholson-Bailey model is a useful start, though.
In 1766, Daniel Bernoulli (1700–82) (Figure 1) published a mathematical analysis of the epidemic behaviour of smallpox infections (Variola major) and considered the effects of immunity (Bernoulli 1766). During Bernoulli’s lifetime, in the eighteenth century, smallpox was endemic and recurred frequently in Europe. Smallpox took a heavy toll, perhaps being responsible for one-tenth of all deaths at the time. According to Bernoulli’s calculations, about three-quarters of all people must have had become infected at least once during their life. Bernoulli’s interest was aroused by the observation that smallpox was primarily a childhood disease. On average, children died from smallpox at an age of perhaps 3 to 4 years but adults were more or less protected. Furthermore, he calculated from the available data a case-mortality rate of 12–14% and noticed that this rate varied across countries and epidemics. Similarly, Bernoulli was aware of the fact that a host that has survived an infection would become protected to some degree against another infection by smallpox. Although this was not the modern concept of immunization, the fact of protection after previous exposure was known.

He constructed his analysis in a very modern way with numerical estimates of the degree of immune protection, and of the case-mortality rates at different ages of individuals. In this way, he essentially derived a model that we would now recognize as belonging to the larger class of SIR-models. From this, he estimated how many lives could be saved by vaccination with cowpox. In particular, he estimated that an additional 25,000 ‘useful lives’ could be given to the society of France as a whole, by which criterion he understood that a person would reach the age of 17 and lead a working life.

Bernoulli also applied sensitivity analyses because he realized that the uncertainty about the exact value of model parameters is the most serious problem when theories are applied to real cases. When presenting his analyses, just as in our days, Bernoulli had to deal with opponents to vaccination that feared an ‘artificial smallpox’ would be caused by the vaccine itself. But Bernoulli’s calculation showed that, when the population is entirely or even only partially vaccinated, the number of fatalities would still be much lower than if vaccinations were not carried out, and that with no vaccination, the natural infections would still be 32-times more common than a possible breakthrough of the vaccine (i.e. a case resulting from the vaccine) (Bernoulli and Blower 2004). Vaccination (from the Latin, ‘vacca’, the cow) against smallpox was gaining momentum after 1750–70 in England and Germany. In 1796, Edward Jenner (1749–1823) finally demonstrated that inoculation with cowpox could protect against human smallpox. Most remarkably, at this time, the nature of the causative agent, the smallpox virus, remained a deep mystery. The nature of viruses was only discovered in the late-nineteenth century, when Adolf Eduard Mayr (1843–1942) in 1879 first demonstrated the transmissibility of the tobacco mosaic disease in plants, and later Dimitri Iwanowski (1864–1920) in 1892, and Martinus Beijerinck (1851–1931; who coined the term ‘virus’) in 1898 demonstrated that this occurred by particles that could not be removed by a porcelain bacterial filter and, therefore, must be smaller.

Figure 1  Daniel Bernoulli (1700–82).
Host–parasitoid interactions can be simulated by the Nicholson–Bailey model (Nicholson and Bailey 1935), assuming discrete generations and random encounters in large populations. The dynamics is as follows:

\[ H_{t+1} = RH_t e^{-at} \]
\[ P_{t+1} = cH_t (1 - e^{-at}) \]

where \( H_t \) is the number of hosts at time \( t \), and \( R \) the rate of per capita increase in the host population (i.e. number of new hosts per existing host). If encounters are random, the fraction of hosts that remain non-parasitized is \( e^{-at} \), where the parameter \( a \) is the attack rate of the parasitoids. The attack rate is the probability of successful parasitization of a host upon encounter, per unit time. Therefore, a fraction of \( 1 - e^{-at} \) of hosts become parasitized and are converted into new parasitoids. Correspondingly, \( P_{t+1} \) is the number of parasitoids at time \( t + 1 \), where \( c \) = conversion efficiency of hosts into new parasitoids. The equilibrium point of this model is given by:

\[ \hat{H} = \left( \frac{R}{R - 1} \right) \left( \frac{\log R}{ac} \right) \]
\[ \hat{P} = \left( \frac{1}{a} \right) \cdot \log R \]

where \( \hat{H}, \hat{P} \) denote the equilibrium values for host and parasites, respectively. This equilibrium is not stable, however. The dynamics of this system will drift away from the equilibrium point of eqn 2 with ever increasing oscillations for host and parasitoids.
11.2 Epidemiology of infectious diseases: microparasites

Infectious diseases are among the most important causes of human suffering and human deaths. According to the 2004 data of the WHO World Health Report, malaria, with an estimated death toll of 0.9 millions, tuberculosis (1.5 millions), HIV (2.0 millions), diarrhea (2.2 millions), and respiratory diseases (4.2 millions) are major killers. They all have in common that the diseases are caused by infectious microparasites, such as viruses, bacteria, or protozoa. As the name implies, microparasites are generally small. But the main reason why epidemiology separates them from the macroparasites, is the way in which the epidemics is analysed. With macroparasites, parasite individuals can be tracked, but with microparasites it makes sense to shift the focus to the host, and to classify hosts as infected or not infected. This approach can also make sense for worm infections and, hence, micro- and macroparasites are distinguished by how their epidemiology is modelled, rather than by their size.

Current formulations of models for the dynamics of microparasites date back to models first developed in the 1920s (the Kermack–McKendrick general epidemiological model; Kermack and McKendrick 1927), and were later refined in the 1970s (May and Anderson 1979; Anderson and May 1981). A general important assumption of these models is that the processes of parasite infection and clearance unfold faster than processes governing the recruitment of new host individuals into a population. This simplifies the mathematical analysis of epidemics. Typically, this branch of epidemiology is interested in the dynamics of the infected and non-infected (‘susceptible’) individuals in the population, after the parasite has been introduced with a seed (an infected individual) into a wholly susceptible population of hosts. The epidemic spread of an infectious disease, starting from a few infected individuals, can be very dramatic, as is illustrated in the classical example of Rinderpest, caused by the rinderpest virus (Box 11.3).

Human diseases are much better documented than wildlife or even livestock diseases, and provide many helpful examples of how an epidemic unfolds. For example, measles (rubeola) is a typical childhood disease caused by the measles virus (MV). MV is a single-stranded RNA virus (ssRNA) belonging to the Paramyxoviridae (Morbillivirus) (Rall 2003). Measles virus is transmitted via droplets in aerosol and infects the respiratory tract. MV is highly contagious with an estimated 90% of exposed people actually contracting the infection (Rall 2003). MV first replicates in the epithelial cells from where it is eventually transported to the lymph nodes and starts to disseminate into other parts of the body. Further replication is in both epithelia and endothelia of various tissues. MV also lodges in immune cells, such as monocytes and macrophages. The incubation period is 8–12 days during which time flu-like symptoms with fever develop and the typical Koplik’s spots (small, irregular red spots with a white speck in the centre, named after the American paediatrician, Henry Koplik, 1858–1927, who first described these spots in 1896) appear in the oral cavity. Later, the typical skin rash appears accompanied by coughing, sneezing, and general malaise. In up to 30% of the cases, complications with different degrees of severity might result. These include diarrhoea, but also pneumonia, or infections of the middle ear (otitis media). In one out of 100,000 cases, severe infections of the central nervous system develop, resulting, for example, in sub-acute sclerosing panencephalitis (SSPE), which can occur months or years after the infection. It is associated with inflammation of brain tissue leading to progressive motor impairment and eventual death. Seizure and deafness is a more common result and is estimated to hit one out of 1000 cases.

According to data from the WHO (World Health Organization), there are approximately 40 million measles-infected people, of which one million die every year, primarily children in Third World countries. In the developed countries, the peak of infections is usually seen by late winter to early spring. In the USA, a vaccine was introduced in 1963. Subsequently, cases dropped by 98%. The average coverage of vaccination is around 90%, although it might be as low as 50% in poor areas (Rall 2003). Due to such high coverage, massive measles outbreaks have become less frequent but still occur. Examples are an epidemic with 3300 cases during 1999–2000 in the Netherlands. In 1989–91 an epidemic in the USA produced a reported 56,000 cases, mostly children below
Rinderpest is a disease of cattle that has been known since antiquity. It is caused by the rinderpest virus (RPV), a morbillivirus related to measles and distemper virus, the latter of which is known from wild cats, dogs, seals, and a variety of other carnivorous mammals. RPV originated presumably in Asia, from where it spread to Europe more than once, causing several epidemics, mainly in the eighteenth century. The most severe epidemic, however, was observed in the late-nineteenth century in Africa. Rinderpest had been prevalent in Egypt and was spreading southwards around the middle of the nineteenth century. However, the most likely account of the origins of the Great African Epidemic is as follows. By 1887, the Italian Army had invaded and occupied Ethiopia. To feed its soldiers, the authorities imported cattle from India to their camps. Some of the cattle were infected and carried the rinderpest virus. Subsequently, the imported animals transferred the disease to other livestock. The virus also jumped into populations of wild animals. Within a decade, the epidemic had spread from Ethiopia through the interior of Africa to reach the Cape, where around 2.5 million cattle died (Mack 1970) (Figure 1).

Figure 1 The great African rinderpest epizootic 1887–97. The epidemic was started in 1887–89 by infected, imported cattle at the Horn of Africa and swept to Capetown within 10 years. The Zambesi river is several kilometers wide and provided a natural barrier that halted the spread of the virus for about three years. Eventually, a herd of infected cattle was taken across the river and sold, which triggered the spread towards the south. Redrawn from Mack (1970) with permission from Springer Media.

(Continued)
In the course of the epidemic, an estimated 80–90% of livestock was killed. In addition, wild ungulates, such as antelopes, buffaloes, and giraffes were heavily affected, too. As a result of the loss of large herbivores, the vegetation changed and the landscape became covered with dense bush. This, in turn, allowed certain insect populations to flourish. Tsetse flies, in particular, were able to increase in numbers and spread to settled areas. Tsetse flies are the classical vector of human sleeping sickness (caused by the protozoan, *Trypanosoma brucei*), which, therefore, also increased in prevalence. The Masai people of East Africa starved and were severely reduced in numbers, as their livestock were killed. Together with a following smallpox epidemic, this resulted in large tracts of emptied land that probably favoured the European colonizers (Mack 1970). But also elsewhere many millions of people died due to loss of their livestock.

At the time, the Cape Colony had one of the few functioning medical services in Africa, and Arnold Theiler (a Swiss-born veterinarian, 1867–1936, and father of Max Theiler of yellow fever Nobel fame) was charged by the British Government to fight the disease. By first developing a culling strategy for cattle, and later developing a vaccine, he succeeded in containing the epidemic by 1897.

In Europe, the last large rinderpest epidemics were recorded in 1913 in Bulgaria as a consequence of the war in the Balkans, and in 1920 in Belgium. By the 1990s, rinderpest was still found in East Africa, Yemen, and on the Indian subcontinent. In Africa, the Pan-African Rinderpest Campaign (PARC), an organization active in 34 countries and launched in 1986 by the OAU (Organization of African Unity), seeks to eradicate the disease by information campaigns, vaccination programmes, and improved veterinary services. PARC coordinates information and expertise, maintains a vaccine bank, and finances national efforts. PARC is supported by the European Union (EU), FAO, USAID, and many other funding agencies. By the beginning of the twenty-first century, rinderpest was considered eradicated in Asia, and the FAO (the United Nations Food and Agricultural Organization) announced that the disease should be completely eliminated by 2011 (Platt 2009). Besides smallpox, rinderpest might, therefore, become the other great triumph of vaccination, leading to the eradication of a horrible disease by the efforts of many, by the investment of money, and the insights from science.
they include evolutionary change of hosts and, in particular, the parasites as the epidemic unfolds, or whether they restrict themselves to a purely ecological dynamics. Epidemic modelling furthermore depends on the actual biological details of the respective system. Consequently, the dynamics of measles has to be modelled in somewhat different ways from the dynamics of nematodes infecting birds, for example, even though the basic principles remain the same. For each system, the biological details, therefore, have to be studied and converted into an appropriate model. Here, we will first use the example of a simple, directly transmitted microparasitic infection to illustrate the basic characteristics of epidemiological models, in particular, the so-called SIR-models (Box 11.4). The complication added by vectors is discussed in Box 11.5. Nematode infections of birds serve as the example to illustrate the dynamics of macroparasites and their hosts (Box 11.6). Other cases could be analysed and modelled in similar ways by introducing and adding the necessary changes. Also, some basic concepts will be introduced in the example of the SIR-model.

11.2.1 The SIR-model

The SIR-model gives a good understanding of how an epidemic unfolds (Box 11.4; Figure 11.3). As an infected individual enters the population of wholly susceptible individuals, it infects on average $R_0$ others, which in turn transmit the parasite further to approximately another $R_0$ hosts. The basic reproductive number, $R_0$, is an essential characteristic of the parasite and the given environment. Its value varies widely and is indicative of the epidemic potential a given parasite has (Table 11.1). During the epidemics, as the disease spreads further, more individuals will have become infected, or will have turned into refractory ones that are immune to a second challenge. As the pool of susceptible individuals becomes smaller, the epidemic is slowed down, the number of new infections drops below the value of $R_0$, and the epidemics might eventually grind to a halt when everybody is infected or refractory. In the long run, therefore, the epidemic is only sustained when new individuals enter the pool of susceptibles, either as newborns, or when immune protection

Figure 11.2 The dynamics of measles before the age of vaccination. Shown are the numbers of clinical cases reported weekly for England and Wales in the period from 1948 to 1968. Redrawn from Anderson and May (1991) with permission from Oxford University Press.
The SIR-model (susceptible, infected, recovered) is the most widely used model in host–parasite epidemiology (Anderson and May 1981). It describes the dynamics of directly transmitted microparasites, where hosts can recover and remain protected for some time afterwards. This model can be visualized in a simple scheme (Figure 1) with $S$, $I$, and $R$ the number of susceptible, infected, and recovered hosts, respectively, at time $t$. The scheme and the flow of individuals from one compartment to another can be used to readily derive the formalized set of differential equations:

$$
\frac{dS}{dt} = b(S,I,R) - \mu S - \beta SI + qR
$$

$$
\frac{dI}{dt} = \beta SI - \mu I - \alpha I - vI = \beta SI - I(\mu + \alpha + v)
$$

$$
\frac{dR}{dt} = vI - \mu R - qR = vI - R(\mu + q)
$$

where $b(S,I,R)$ is the number of births into the population of susceptible hosts, $\mu$ the background mortality rate, $\alpha$ the infection-induced mortality rate (in this context called parasite ‘virulence’), $v$ the rate of recovery to immunity, and $q$ the rate at which immunity is lost again. The parameter $\beta$ is the transmission rate, which indicates the probability that the parasite infects the next host upon encounter. The number of newly infected individuals is assumed to be proportional to $SI$. This assumption reflects a scenario where infected and susceptible hosts meet at random and in proportion to their numbers; the assumption is known as the ‘mass action principle’, or a case of homogeneous mixing. With heterogeneous mixing, susceptible and infected individuals meet according to stratifications by age, sex, behaviour, spatial location, and so forth. In eqn 1, transmission assumes density-dependence, since new infections occur at a rate given by the numbers/densities of susceptibles and infecteds ($\beta SI$). It is also conceivable that new infections arise in relation to the frequency of infecteds in the population. In this case, the transmission term could be changed to $\beta S\left(I/N\right)$, the latter part being the proportion of infecteds among all individuals. This simple model, therefore, ignores a number of biological relevant situations. For example, direct recovery without the formation of lasting immunity (broken lines in Figure 1) is not included (but could be added). Populations are also assumed to lack an age structure or spatial heterogeneity. More complex models dealing with these additional factors have been formulated (Anderson and May 1991; Keeling and Rohani 2007; Otto and Day 2007).

The model of eqn 1 can be simplified by observing that the total population size is often approximately constant, if the parasite is not directly regulating population size. This happens when the parasite-induced mortality rate, virulence $\alpha$, is small. With a total population size $N = S + I + R$, and solving for the equilibrium:

$$
\hat{S} = \frac{\mu + \alpha + v}{\beta},
$$

$$
\hat{I} = \frac{(\beta N - \mu - \alpha - v)(\mu + q)}{\beta (\mu + v + q)}.
$$

where $\hat{S}, \hat{I}$ are the endemic equilibrium values for susceptible and infected individuals in the population, respectively. Note that the other equilibrium point would be $S = N$, i.e. no infection. The SIR-model typically unfolds as an epidemic with waves of infecteds. Eventually, the system converges to an endemic state, i.e. the equilibrium characterized by eqn 2, where the epidemic leaves a constant proportion, $\hat{I}$, of infected individuals in a population (Figure 11.3).

The SIR-mode also gives an insight into when an epidemic can unfold. With eqn 1, this is only the case when the number of infecteds increases, hence, when $dI/dt > 0$ and therefore:

$$
\beta SI - I(\mu + \alpha + v) > 0 \text{ which yields: } R = \frac{\beta S}{\mu + \alpha + v} > 1.
$$

**Box 11.4 The basic epidemic model (SIR)**
Of particular interest is the introduction of an infected individual into a population of susceptible individuals. In this case, $S$ approximately equals $N$, and we have:

$$R_0 = \frac{\beta N}{\mu + \alpha + \nu}$$

(3)

$R_0$ is the so-called basic reproductive number of the infection. It describes the number of newly (secondary) infected hosts resulting from one (primary) infected individual that enters a wholly susceptible host population (Diekmann et al. 1990). $R_0$ is thus the maximum potential of a parasite to spread, similar to the intrinsic rate of increase in classical population dynamics (the Malthusian parameter, $r$). The basic reproductive rate, $R_0$, can be understood as the product of the number of newly generated infections ($\beta N$) during the expected duration of the infection as given by $1/(\mu + \alpha + \nu)$. The value of $R_0$ varies widely among different parasites and has been estimated for a number of human infectious diseases (Table 11.2). Furthermore, given a number of $I$ infected individuals, the term $\lambda = \beta I$ is the ‘force of infection’. In other words, $\lambda$ describes the rate at which an uninfected individual becomes infected in this population.

From eqn 3, we can develop an argument for the average age at infection as follows:

$$R_0 = \frac{\beta N}{\mu + \alpha + \nu} = \frac{\beta (S + I + R)}{\mu + \alpha + \nu} = \frac{(\mu + \alpha + \nu) + \beta I + \beta R}{\mu + \alpha + \nu} = 1 + \frac{\beta I}{\mu} \frac{(\mu + \nu)}{(\mu + \alpha + \nu)},$$

because at equilibrium $S = (\mu + \alpha + \nu)/\beta$, and $R = \nu I/\mu$. This can be simplified further by assuming that $\nu \gg \mu$ and $\nu \gg \alpha$, which might be the case for many infections. Hence, $(\mu + \nu)/(\mu + \alpha + \nu) = 1$. With this, we have:

$$R_0 = 1 + \frac{\beta I}{\mu} = 1 + \frac{L}{A} = \frac{L}{A}$$

(4)

Note that $1/\mu$ is the average life expectancy, while the term, $\beta I$, is the rate at which susceptibles become infected and, therefore, $1/(\beta I)$ is the average age, $A$, at which infection occurs.
wanes, when the infection is cleared, and new infections become possible.

The average age at which an individual becomes infected is an important quantity for the application of epidemiological theory in practice. If \( L \) is the individual life-expectancy in a given host population, the basic reproductive number can be approximately written as
\[
R_0 \approx \frac{L}{A}
\]
such that the average age at infection, \( A \), is given by (Box 11.4):
\[
A = \frac{L}{R_0}.
\] (11.1)

These calculations assume that there is a single infection at age \( A \) followed by life-long immunity, and that the background and parasite-induced mortality rates are much lower than the rate of recovery from the infection. By and large, these conditions are met for most childhood diseases. Hence, the estimate of \( A \) is a useful indicator for this kind of infectious disease. Table 11.2 lists some numerical examples of \( A \) and shows that, in highly endemic areas, children become infected at a very early age. The estimate of eqn 11.1 again ignores a set of biologically reasonable conditions; for example, that the rates of infection or recovery are likely to vary with age. Furthermore, it assumes a type II survival curve, i.e. a constant risk of mortality independent of age. More realistically, a type I survivorship curve would have to be assumed where mortality is increasing with age. Nevertheless, it turns out that the estimate of eqn 11.1 remains a good approximation also with such changes.

The SIR-model is primarily a conceptual model that gives important general insights. Any given host–parasite system is likely to deviate from the standard model and this requires modifications in several ways (Box 11.6). Similarly, by changing parameter values and modifications to the standard model, a rich repertoire of dynamic behaviours for the host–parasite system results, reaching from the standard dampened oscillations towards an endemic state (Figure 11.3), to periodic outbreaks, chaotic dynamics, travelling waves of infection in space, and so forth. For extensions of this kind, consult the rapidly expanding, more specialized literature.

### 11.2.2 Vaccination

The SIR-model is very useful when it comes to devise rational vaccination strategies. This is because we can see that a condition under which a disease disappears is when the basic reproductive number of an infection drops below one, \( R_0 < 1 \). Box 11.5 shows that at least a proportion of \( p_{\text{crit}} = 1 - 1/R_0 \) of the population needs to be

**Box 11.5 SIR-model and vaccination**

The SIR-model shows that an epidemic is sustained as long as a sufficient number of susceptible individuals are available. More formally, an epidemic would die out and the parasite be eradicated when \( R_0 < 1 \). For the respective threshold condition, \( R_0 = 1 \), we can derive the number of susceptibles that are necessary to just allow the epidemic to exist. This condition yields:

\[
R_0 = \frac{\beta S}{\mu + \alpha + \nu} = 1
\]

and

\[
S_{\text{crit}} = \frac{\mu + \alpha + \nu}{\beta}
\]

for the critical number, \( S_{\text{crit}} \), to which the population of susceptibles needs to be reduced in order to eradicate the infection. Given a total population size, \( N \), this translates into a fraction of the population, \( p_{\text{crit}} \), that needs to be protected from infection:

\[
p_{\text{crit}} = \frac{N - S_{\text{crit}}}{N} = 1 - \frac{\mu + \alpha + \nu}{\beta N} = 1 - \frac{1}{R_0}.
\]

Hence, if it were possible to vaccinate at least \( p_{\text{crit}} \) of the population and protect them effectively against infection, the epidemic would die out and the population would be protected as a whole.
Figure 11.3 The time course of an infection according to the SIR-model. The graph shows the number of infected (I) and susceptible (S) individuals in a population of \( N = 200 \) individuals. Parameters for this numerical simulation (Box 11.4, eqn 1) were: initial population size plus one infected host entering at time zero. Birth rate of hosts \( b = 0.01 \), transmission rate \( \beta = 0.01 \), background mortality rate \( \mu = 0.001 \), virulence \( \alpha = 0.05 \), and recovery rate \( \nu = 0.2 \). In this case, the host population maintains a high number of infecteds (around 90%) at the endemic equilibrium, as the loss by parasites is compensated by births and a high recovery rate.

Table 11.1 Basic reproductive number, \( R_0 \), and critical vaccination coverage, \( p_{\text{crit}} \), for various infectious parasites of humans.

<table>
<thead>
<tr>
<th>Infection</th>
<th>Locality</th>
<th>Year</th>
<th>( R_0 )</th>
<th>Coverage ( p_{\text{crit}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>Nigeria, hyper-endemic regions (( P. falciparum ))</td>
<td>1970s</td>
<td>80</td>
<td>99%</td>
</tr>
<tr>
<td></td>
<td>Nigeria (( P. malariae ))</td>
<td>1970s</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Measles</td>
<td>England and Wales</td>
<td>1950–68</td>
<td>16–18</td>
<td>90–95%</td>
</tr>
<tr>
<td></td>
<td>Eastern Nigeria</td>
<td>1960–68</td>
<td>16–17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ghana</td>
<td>1960–68</td>
<td>14–15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cirencester, England;</td>
<td>1947–50</td>
<td>13–14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ontario, Canada</td>
<td>1912–13</td>
<td>11–12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Willesden, England</td>
<td>1912–13</td>
<td>11–12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kansas, USA</td>
<td>1918–21</td>
<td>5–6</td>
<td></td>
</tr>
<tr>
<td>Pertussis</td>
<td>England and Wales</td>
<td>1944–78</td>
<td>16–18</td>
<td>90–95%</td>
</tr>
<tr>
<td></td>
<td>Maryland, USA</td>
<td>1943</td>
<td>16–17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ontario, Canada</td>
<td>1912–13</td>
<td>10–11</td>
<td></td>
</tr>
<tr>
<td>Human parvovirus</td>
<td>Gambia</td>
<td>1976</td>
<td>15–16</td>
<td>90–95%</td>
</tr>
<tr>
<td>Rubella</td>
<td>Poland</td>
<td>1970–77</td>
<td>11–12</td>
<td>82–87%</td>
</tr>
<tr>
<td></td>
<td>Czechoslovakia</td>
<td>1970–77</td>
<td>8–9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>England and Wales</td>
<td>1960–70</td>
<td>6–7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>West Germany</td>
<td>1970–77</td>
<td>6–7</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
Table 11.2 Average age at infection for various childhood diseases and locations (after Anderson and May 1991).

<table>
<thead>
<tr>
<th>Infection</th>
<th>Locality</th>
<th>Year</th>
<th>(R_0)</th>
<th>Coverage (p_{\text{crit}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>USA</td>
<td>1955–58</td>
<td>5–6</td>
<td>85–90%</td>
</tr>
<tr>
<td></td>
<td>Morocco</td>
<td>1963</td>
<td>2–3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ghana</td>
<td>1960–68</td>
<td>2–3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Senegal</td>
<td>1964</td>
<td>1–2</td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>Nairobi, Kenya (female prostitutes)</td>
<td>1981–85</td>
<td>11–12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nairobi, Kenya (heterosexuals)</td>
<td>1981–85</td>
<td>10–11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>England and Wales (male homosexuals)</td>
<td>1981–85</td>
<td>2–5</td>
<td></td>
</tr>
<tr>
<td>Polio</td>
<td>Netherlands</td>
<td>1960</td>
<td>6–7</td>
<td>82–87%</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>1955</td>
<td>5–6</td>
<td></td>
</tr>
<tr>
<td>Mumps</td>
<td>England and Wales</td>
<td>1960–80</td>
<td>11–14</td>
<td>85–90%</td>
</tr>
<tr>
<td></td>
<td>Netherlands</td>
<td>1970–80</td>
<td>11–14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baltimore, USA</td>
<td>1943</td>
<td>7–8</td>
<td></td>
</tr>
<tr>
<td>Diphtheria</td>
<td>New York, USA</td>
<td>1918–19</td>
<td>4–5</td>
<td>82–87%</td>
</tr>
<tr>
<td></td>
<td>Maryland, USA</td>
<td>1908–17</td>
<td>4–5</td>
<td></td>
</tr>
<tr>
<td>Scarlet fever</td>
<td>New York, USA</td>
<td>1918–19</td>
<td>5–6</td>
<td>82–87%</td>
</tr>
<tr>
<td></td>
<td>Maryland, USA</td>
<td>1908–17</td>
<td>7–8</td>
<td></td>
</tr>
<tr>
<td>Smallpox</td>
<td>Globally</td>
<td></td>
<td></td>
<td>70–80%</td>
</tr>
</tbody>
</table>

Sources:
1 Anderson and May (1991), tables 4.1, 14.8.
2 Anderson and May (1991), table 5.1

Box 11.6 Extensions of the standard SIR-model

The standard SIR-model of microparasitic infections is a conceptual model, whose application to the real world needs a number of extensions (Grassly and Fraser 2008). Modifying the SIR-model also produces a rich repertoire of different dynamical behaviours, such as dampened or persistent oscillations, chaotic dynamics, propagating waves of infection in space, and so forth. For more details, see (Keeling and Rohani 2007).

**Age structure**

Transmission rate can depend on age class, for example, when an infection is not acquired below a certain age \(a_1\) and not above another age \(a_2\). With these
assumptions the basic reproductive number, $R_0$, changes to:

$$R'_0 = \frac{a_2 - a_1}{A - a_1} R_0, \quad (1)$$

where $A$ is the average age of infection. This formulation takes into account that the fraction of susceptible hosts in the population has become smaller in proportion to $a_1$, $a_2$, and $A$. As a consequence, $R'_0$ will be smaller than $R_0$ without age structure provided that $a_1$ is sufficiently small, and $a_2$ not too close to the life expectancy of the hosts. A smaller value of $R'_0$ means that an infection would be easier to eradicate. Partial immunization of the host population would be one process that increases the average age of infection and thus reduces $R_0$. The calculations furthermore depend on the type of cohort survival curves.

**Latency period**

Infections typically take some time to become transmissible to the next host. In the standard SIR-model, latency is assumed to be short relative to the epidemiological dynamics. If this assumption is not met, the newly infected individuals will no longer be susceptibles, but they enter the class of infecteds (that can infect others) only after a latency period, $\tau$. The effect depends on the survivorship curve of the host population. With Type II survival (i.e. the age-dependent rate of mortality is constant), latency will reduce $R_0$. A further effect of latency is that the time between recurrences of the epidemic waves is extended.

**Immunization**

Immunizing a fraction of the population removes susceptibles from the pool at a rate $c(a)$, where $c$ characterizes the effect of protection at age $a$. Hence, in the standard equations of Box 11.4, additional susceptibles would be removed with rate $c(a) S(a,t)$. These immunized individuals change into a class of the refractory/recovered hosts; $S(a,t)$ is the number of susceptibles in age class $a$ and at time $t$ of the process. Immunization might also get lost at a certain rate, such that the compartment of immunized hosts would slowly lose members that become susceptible again. Such complications are straightforward to formulate. The modified standard equations are typically age-dependent, and simplifying assumptions are needed to efficiently solve the problem.

**Sexually transmitted parasites**

This kind of parasitism primarily affects the transmission term of Box 11.4. In particular, the transmission of sexually transmitted diseases is frequency-dependent, since meeting an infected individual is proportional to their frequency in the population, and not to their density. In the basic equations the frequency-dependent transmission term is used, additionally weighted by a number, $z$, of sexual contacts between two individuals. With this, we have (leaving out the recovered class for simplicity):

$$\frac{dS}{dt} = b(S,I) - \mu S - z\beta S \frac{I}{N}, \quad (2)$$

$$\frac{dI}{dt} = z\beta S \frac{I}{N} - (\mu + \alpha)I$$

when using the same notations as in Box 11.4. This yields a basic reproductive number of:

$$R_0 = \frac{z\beta}{\mu + \alpha}, \quad (3)$$

which suggests that the spread of the infection is driven in direct proportion to the number of sexual contacts, $z$.

**Growth of the host population**

The population of susceptible hosts can grow independently, for example, in proportion to its size, such that in the simplest case:

$$\frac{dS}{dt} = -\beta SI + bS, \quad (4)$$

$$\frac{dI}{dt} = \beta SI - (\mu + \alpha)I$$

(Continued)
where \( b \) is the *per capita* growth rate of the susceptible population. This modification can lead to periodic oscillations because the number of susceptibles builds up, which then becomes rapidly infected in a spreading epidemic that leads to a crash in population size, and eventually recovers after a while.

**Analysis by cellular automata**

This is a class of discrete, computer-based models, where the world is divided into cells of a grid. Each cell can have various states, such as susceptible, infected, recovered, extinct, and so forth. Each cell interacts with its neighbourhood, e.g. by receiving or transmitting the infection to a neighbouring cell, either those immediately bordering the focus cell or those in some defined distance. The rules of the epidemiology decide the state of a cell in the next generation, e.g. it becomes infected with probability, \( p \), when at least one cell in the neighbourhood is infected, etc. Cellular automata are particularly suitable to model the spread of an epidemic in space.

**Analysis by network models**

The contact between susceptible and infected individuals can be modelled as a node in a network. If transmission happens, the infection will spread across the nodes in a network of contacts among host individuals. Network analysis takes into account that the particular contacts and the frequency of contacts varies considerably among host individuals, but that this variation follows certain patterns (Keeling 2005).

**Box 11.6  Continued**

...vaccinated to achieve this goal. Hence, parasites with a large \( R_0 \) require a high percentage of the population to be vaccinated. Estimated values of \( p_{\text{crit}} \) for various human diseases are listed in Table 11.1. If a population is protected, with the number of susceptibles reduced below the threshold, then it is said to enjoy the benefits of ‘herd immunity’.

Table 11.1 suggests that diseases with high values of \( R_0 \), such as malaria or measles, are hard to eradicate completely, since a critical vaccination coverage close to 100% is needed, i.e. almost all people need to be vaccinated. Such a high coverage is generally hard to achieve given the demands on infrastructure and logistics, and especially difficult in less-developed countries. Moreover, recurrent bouts of vaccination scepticism in developed countries (e.g. towards measles vaccination) have also added their share to the difficulties of reaching this goal.

As the concept of a critical vaccination coverage, \( p_{\text{crit}} \), in fact shows, vaccination is a classical example of a conflict between individual and group interests. An individual, even if not vaccinated, benefits from the entire population being vaccinated above the critical threshold, \( p_{\text{crit}} \), because the individual is protected by herd immunity. A given parent, for example, might value the risk of vaccination for the child higher than the risk of becoming infected in the first place, and therefore decides not to let his/her child be vaccinated. In this case, the benefits are still there but the cost of vaccination is transferred to others. This individual risk perception is objectively wrong, since with the high fatality rates of many childhood diseases, the consequences of becoming infected are clearly much worse than the expected side-effects of vaccination. Nevertheless, this disparity in risk perception is particularly strong when the vaccination programme has been so successful as to lower the individual risk of infection substantially. Risk perception is different if the disease is rampaging in a population; in this case, parents would worry more about the disease than about the vaccine.

There is a minimum population size, \( S_{\text{crit}} \), needed to sustain an epidemic infection. This suggests that a disease might not occur in small populations, such as found on real islands or in cities where most of the interactions are among the residents. Even though the model of a closed island or city population is not correct,
the prediction of a population-size effect is supported by the observations (Figure 11.4). In real cases, such as those depicted in Figure 11.4, the disappearance of the epidemic infections is also a process of stochastic fade-out (see below). Hence, the deterministic model of Box 11.4 does not apply fully. Various other extensions can be added to the standard SIR-model as shown in Box 11.6.

11.2.3 Stochastic epidemiology

Random (stochastic) processes can affect the course of an epidemic in many ways. In particular, the initial number of infecteds is presumably small; it is, therefore, possible that the epidemic dies out in the beginning, simply because the infecteds happen to die for other reasons and so take the parasite with them, or are able to clear

Figure 11.4 Host population size threshold for epidemic measles. (a) The larger the population of an island, the more often an epidemic occurs. Recurrent epidemics are caused by immigration and interactions with individuals from outside. However, a threshold population size of approximately 500,000 seems required to maintain measles permanently. (b) A permanent presence of measles in American cities does not occur below a minimum population size of roughly 200,000 people, with the data over the period of 1921–40. Redrawn from Nokes (1992) with permission from John Wiley & Sons, Inc.
The effect of stochasticity can best be seen when the course of an infection is depicted as a branching process. In this process, every infected host infects a number of other individuals with some probability. Therefore, the spread of the infection through a population can be illustrated by a tree whose root is the first infection introduced into a susceptible population (Figure 11.5). On average, the probabilities of transmission in this tree might add up to an average reproductive number of $R_0 > 1$, which would predict a sustained epidemic. However, chance events might lead to a situation where many encounters between hosts do not lead

**Figure 11.5** The branching process in epidemiology. Every infected individual (filled circles) encounters a number of susceptible individuals (open circles). Transmission occurs by chance in only a fraction of these encounters, with solid lines indicating successful transmission and dotted lines contacts with no transmission. In the case shown here, every primary infection leads to an average of 3.25 secondary infections. The branching process could be embedded in an analysis of contact networks.
to transmission, such that incidentally a value of \( R_0 \)  \( < 1 \) results for a given round of transmission steps. In this case, the infection would die out, despite the fact that the expected average \( R_0 \) at large is above one.

The chance that such a stochastic breakdown in the transmission chain actually occurs is surprisingly large. For example, extinction occurs in approximately half of all cases with an average \( R_0 \) = 1.5, and when the infection is started by a single, infected individual. Such extinctions primarily occur within the first generations, when the population of infecteds is still small and chance events have a larger effect. As one might expect, the probability of extinction decreases exponentially with an increase in the number of initially infected individuals entering a wholly susceptible host population. Calculations show that with \( R_0 \) = 1.5, and once an epidemic has grown to more than 20 infecteds, it will almost certainly persist. This pattern incidentally demonstrates how important it is to have a fast response to an emerging epidemic in order to benefit from this natural tendency towards extinction with stochastic effects. The early response requirement is actually generally true, as the final size of an epidemic depends critically on the early expansion of an epidemic.

11.2.4 Spatial heterogeneity

According to Box 11.4, the basic reproductive number of an epidemic infection, \( R_0 \), depends on the transmission rate \( b \) and on population size, \( N \) (where \( N = S \) at the beginning of an epidemic). Both parameters are affected by spatial heterogeneities; that is, differences among localities. Such spatial differences are visible, for example, from the fact that the mean age of infection for measles varies with location (Walsh 1983), which reflects both differences in population sizes of susceptibles, as well as transmission opportunities. In fact, the value of \( R_0 \) increases with population size in predictable ways (Anderson and May 1991).

Heterogeneity in transmission can be caused by various factors. Examples are the effects of social heterogeneity, where certain groups of individuals interact more commonly with one another, differences in individual behaviour that relates to transmission, variation in the standards of hygiene, microclimatic heterogeneity that affects the survival of spores, and so forth. The effect of such heterogeneity for the effective reproductive number, \( R'_0 \), in the overall population can be summarized as (Barbour 1978):

\[
R'_0 = R_0 (1 + \text{Var}(\beta)),
\]

where \( R_0 \) is the average basic reproductive number across all sub-populations that make up a meta-population in which an epidemic unfolds. \( \text{Var}(\beta) \) reflects the variance in the local transmission rates among the sub-populations. As can be seen from eqn 11.2, the higher this variance, the larger the effective \( R'_0 \) becomes for the overall meta-population. Using Box 11.5, the effect of spatial heterogeneity is to increase the effective \( R_0 \) and thus to make it more difficult to eradicate a parasite from the population, because a larger fraction of the population would have to be vaccinated (Anderson and May 1991).

11.3 Endemic infections and periodic outbreaks

Infections are endemic when they are maintained in a population (usually at low levels) for longer periods of time, without the need of being re-introduced from external sources. According to the SIR-model, once an epidemic has run its course, the system will settle to the equilibrium conditions of Box 11.4 (Figure 11.3), with a constant number of infecteds being maintained indefinitely, unless the system is disturbed. If disturbance occurs, theory suggests that the number of infecteds will afterwards show damped oscillations until the equilibrium values are reached again.

Such oscillations can develop into recurrent epidemic outbreaks that emerge out of an endemic situation. Outbreaks are driven by a number of processes, such as demographic stochasticity, seasonal variations, time lags, intervention, and control measures, and so forth. Periodic outbreaks, such as observed for measles in the pre-vaccination period (Figure 11.2), are especially interesting. Time series of infections, as those shown in Figure 11.2,
can be analysed by statistical methods, such as auto-correlation and spectral analyses. The latter partitions the observed waves of infections into a set of constituent sinoidal waves. This set has a distribution of frequencies for the constituent waves, which defines the frequency spectrum. Auto-correlation analyses the degree to which the observed infection at time $t$ is correlated with the infection in the same population at some earlier stages, i.e. at times $t-1$, $t-2$, and so forth.

For the case of the measles data for England and Wales 1948–68, shown in Figure 11.2, the auto-correlation shows an oscillation consisting of a major wave every two years and a minor wave every year. When decomposing this time series into a set of waves by spectral analysis, the same finding is made: the time series is made up of sinoidal waves that peak every 0.5 and every 1.0 year, respectively. With only two major contributing sinoidal waves, the epidemic time series of Figure 11.2 is said to have a narrow bandwidth (a large bandwidth would include a set of many different waves, peaking at different intervals). Such analyses reveal regular patterns also for other classical childhood diseases before vaccination was introduced. For example, for pertussis (whooping cough) a seasonal cycle combined with a dominant 3-year cycle was found. Similarly, mumps seems to be driven by a 2- to 3-year cycle (Anderson and May 1991). Auto-correlation and bandwidth provide insight into the possible underlying periodic phenomena that lead to recurrent outbreaks. Annual waves, for example, could result from simple seasonal effects, whereas periods of 2–3 years might reflect the periodic recruitment of children to school classes. The interpretation is complicated by the fact that, in an endemic situation, the period of outbreaks around the equilibrium value is not necessarily the same as the time scale at which the pool of susceptibles is replenished (but somewhere in between the two time scales; Anderson and May 1991).

### 11.4 Epidemiology of vectored microparasites

Many important infections are transmitted by vectors, especially by blood-sucking insects. Examples are malaria, yellow fever, sleeping sickness, and tick-borne encephalitis. Such a scenario can be implemented in the standard SIR-model by adding compartments for the uninfected and infected vectors, and by adjusting the transmission rates and other variables accordingly (Dye and Williams 1995). This was pioneered in early studies by Ronald Ross (1857–1932, who received the Nobel prize for his work on malaria in 1902), and was later extended by George Macdonald (1903–67) into what has become known as the Ross–Macdonald model (Macdonald 1957).

Vectors are usually short-lived compared to the final host of the parasite, such that the vector populations can be assumed to be at a numerical equilibrium with respect to the final host. For instance, the death rate of mosquitoes is higher than the recovery rate of the infected human host and, therefore, the turnover of the mosquito population balances out numbers, as compared to the slower processes on the side of the human population. Such considerations simplify the analysis and allow approximate solutions to a complex problem, sometimes making the dynamics of a vector-transmitted infectious disease similar to that of directly transmitted parasites for which the standard SIR-model applies (Dye and Williams 1995). Nevertheless, vectors are also intermediate hosts, where important steps for the parasite’s life-cycle happen. For example, malaria parasites (*Plasmodium* spp.) develop into gametocytes and then form oocysts that release sporozoites able to infect a vertebrate (human) host when the mosquito bites. In such systems, it is, therefore, often the case that the time the parasite needs to develop inside the vector and to become infective (the latency period) is comparable to the life span of the vector.

Furthermore, active manipulation of the mosquito by the parasite occurs to reduce the vector’s immune response and to limit the size of the blood meals, which in turn forces the mosquito to visit more hosts. This, in fact, occurs only during the presence of the transmissible stages (Boëte et al. 2002). The opposite effect occurs, i.e. mosquitoes becoming less inclined to visit hosts, when the parasite is not yet infective and still develops into a transmission stage (Koella et al. 2002). Few vectors normally live long enough to become infected, but in hyper-endemic areas, most vectors are infected and some carry more than one infection. Examples are blood-sucking
flies (Phlebotomus) that transmit the protozoan, Leishmania major, and where around 50% are carriers of the infection (Dye and Williams 1995). The biting rate might also be affected by the host’s behaviour or by its condition. For example, mosquitoes are twice as frequently attracted to humans harbouring gametocytes of the malaria parasite (Lacroix et al. 2005). In principle, the infection could also reduce the lifespan of vectors. At least for one of the best-investigated vectored diseases, malaria, mosquito mortality is decreased by the infection under artificial conditions (Dawes et al. 2009), but the empirical evidence is ambiguous for field situations, and generalities are not agreed upon (Ferguson and Read 2002). Such processes can introduce non-linearities in the standard equations describing the dynamics of vectored infections.

### 11.5 Epidemiology of macroparasites

To understand the epidemiology of macroparasites, it is more practical to track individual parasites, rather than infected hosts. Parasites, such as cestodes or trematodes, are not only large but they replicate relatively slowly, such that measures like parasite body size and fecundity, rather than the growth rate of the parasite population within the host, become useful quantities. Furthermore, macroparasites typically debilitate their hosts and reside inside hosts for prolonged periods of time. Hence, in epidemiological terms, macroparasites are defined as parasites that can be more conveniently analysed by tracking their individual life-history. One consequence of this approach is that the distribution of the number of parasites per host (i.e. infection intensity), which in this context is often referred to as ‘parasite load’ or ‘parasite burden’, is a much more prominent measure, too. Parasite load does correlate with an increased risk of host death or loss of fecundity (Figure 11.6). Note that none of these aspects—body size, fecundity, parasite load, or distribution of numbers across hosts—are unique features of macroparasites. Also, microparasite populations can be counted, their body size measured, or even individual variation in the rates of cell division estimated by modern techniques. The distinction of macro- and microparasites is, therefore, somewhat arbitrary and guided by practical considerations, rather than genuine differences in biology.
11.5.1 The distribution of macroparasites among hosts

Macroparasites and their final hosts at least are typically long-lived. The standing distribution of parasites across host ages, therefore, reflects the net result of new infections that have been acquired, the rate of parasite clearance from the host, and of age-dependent host mortality rate, either parasite-induced or by other causes. Data from a large number of different systems show that these population processes typically result in an increasing parasite load with age, sometimes combined with a decrease in old age (Figure 11.7). A pattern of monotonically increasing parasite load (Figure 11.7a) with age is indicative of a situation where infection rates exceed clearance or host mortality rates, and where there is no increased protection against successive infections. If parasites disappear from the population, by clearance or host mortality, a pattern of increasing parasite load reaching an asymptote should result. Finally, convex age–parasite load curves (Figure 11.7a) could result from a number of different processes, such as increasing host mortality with age, a decrease in infection rate (due to changed behaviour, etc.), by establishing immune protection, and so forth. In fact, immune protection is likely to play a major role in many cases (Anderson and May 1991; Quinnell et al. 2004).

Macroparasites typically show a more or less aggregated distribution over host individuals; that is, some hosts have

---

Figure 11.7 Macroparasite load varies with age. (a) The nematode *Heligmosomum polygyrus* in voles. (b) The tick *Ixodes ricinus* on red grouse chicks (*Lagopus lagopus scoticus*; with standard errors). Redrawn from Hudson (1992) with permission from Game & Wildlife Conservation Trust.
many more, and others have fewer parasites, than expected by chance. Such patterns are thus compared to the random (Poisson) distribution. With random distribution, the variance of parasite load among hosts is equal to the mean of parasite load over all hosts; with aggregation, variance exceeds the mean. Similar to the age-dependent variation, the pattern of distribution among hosts reflects the outcome of processes that affect infection, clearance, transmission, host deaths, and so forth. For example, the hosts themselves might not be distributed at random but aggregate at certain sites, which in turn could facilitate parasite transmission in these localities. Moreover, hosts vary in their susceptibility to an infection, either by their genotype, body condition, or by differences in acquired immune protection. There might also be a sampling bias in that weakly infected individuals might not be recognized as such, or when a parasite-induced change in behaviour makes a certain host class inaccessible for some time. It is also worth keeping in mind that males typically carry heavier parasite loads than females and, hence, a sex ratio bias in the sampling procedure would change the result, too. It is also quite commonly observed that, among younger hosts, the parasites are more or less randomly distributed; whereas in older age classes, the parasite distribution is aggregated. This can result from differences in individual host development.

Aggregated distributions are conveniently described by a negative binomial distribution that is characterized by a mean and an aggregation parameter (often termed $k$). Numerically, many macroparasite infections show negative-binomial aggregation indices of $k = 0.1$ to $k = 10$ (Hudson and Dobson 1995), where low values of $k$ mean an aggregated (clumped) distribution, and large values of $k$ tending to random distributions. In addition, the variance of the distributions generally increases faster than the mean, indicating that parasite infections become more aggregated as the average parasite load increases (Hudson and Dobson 1995).

### 11.5.2 Population dynamics and models for macroparasites

The populations of macroparasites show a range of dynamic behaviours, from more or less stable numbers, to fluctuating populations (in terms of parasite burden per host), and to host population crashes as the infections take hold (Figure 11.8). Because parasite abundances do not increase unboundedly, at least some form of population regulation must be in place; that is, some density-dependent processes must occur. For example, we might find decreased per capita fecundity and prolonged development with an increasing number of parasites within a host. Similarly, parasite mortality and clearance by the host is likely to depend on parasite load. But also, the increase of host mortality with increasing parasite burden regulates the population sizes of hosts, as well as of parasites. The result of such effects on the population dynamics of the host–parasite system depends strongly on the degree of aggregation. Models for the epidemiology of macroparasites keep track of different parasite classes; for example, juvenile and adult stages (Box 11.7). This is especially helpful when parasites pass through prolonged development or must produce specialized stages before they can be transmitted further. In addition, the system contains a separate compartment for the free-living stages of the parasite, which could also include spores and other durable stages that can infect a new host.

The population dynamics of red grouse (Lagopus lagopus scoticus) infected by the nematode Trichostrongylus tenuis is a well-studied example of a macroparasite–host interaction (Hudson 1986). The dynamics of the system is dominated by the presence of the nematodes, and their effects on host survival and fecundity. When, in particular, an increasing parasite load reduces fecundity, the population of host birds tends to oscillate (Hudson et al. 1992a). This is demonstrated by the experimental removal of the parasite that leads to the disappearance of the oscillations, suggesting that the host–parasite dynamics are the major cause of the population cycles. Population cycles are a classical problem of population biology, and macroparasites, as in the case of red grouse, might be an important factor driving such oscillations.

### 11.6 Immuno-epidemiology

The term ‘immuno-epidemiology’ seems to have been used for the first time in the late-1960s in connection with
Figure 11.8 Population dynamics of macroparasites. (a) The mean parasite load (infection intensity) of four helminth species (*Corrigia vitta*, *Hymenolepis hibernia*, *Taenia taeniformis*, *Syphacia stroma*) in a population of the wood mouse, *Apodemus sylvaticus* in Northern Ireland. (b) The effect of experimentally introducing, at week eight (arrow), the nematode *Heligmosomum polygyrus* in two laboratory populations of mice (open and closed symbols). In both cases, the host population sizes collapsed dramatically. Redrawn from Montgomery and Montgomery (1998), and Scott (1987) with permission from Cambridge University Press.
Models for the epidemiology of macroparasites keep track of different parasite classes, e.g. juvenile and adult stages. Figure 1 shows a simple scheme that might apply for nematode infections of birds and mammals (Hudson and Dobson 1989). Following this scheme, the changes in hosts (H), and the populations of adult (P), and free-living (W) parasites can be described by a set of differential equations. With the symbols of Figure 1, but ignoring the juvenile stage for simplicity, and in the standard notation:

\[
\frac{dH}{dt} = (b - \mu_H)H - \alpha P
\]

\[
\frac{dP}{dt} = \beta WH - (\mu_I + \mu_H + \alpha)P - \alpha \left( \frac{P^2}{H} \right) \frac{(k+1)}{k}.
\]

\[
\frac{dW}{dt} = \phi P - \mu_W W - \beta WH
\]

As before, \( \beta \) is the transmission rate but this time from the free-living stages to the hosts. The last, quadratic term and the parameter, \( k \), reflect the fact that parasites are aggregated among hosts; this term describes the average expected individual load, and the effect of load on host mortality beyond the linear effect. From these equations, the basic reproductive number of the parasite is:

\[
R_0 = \frac{\beta \phi H}{(\mu_I + \mu_H + \alpha)(\mu_W + \beta H)}
\]

Similar to the case of directly transmitted micro-parasites, the basic reproductive number, \( R_0 \), can be understood as the expected number of secondary parasites generated by a primary parasite. In eqn 2, this logic can be seen with the number of newly
different strains of malaria. The concept was expanded in the early 1990s especially for studies of helminth infections of humans (Hellriegel 2001). Immuno-epidemiology seeks to understand how immune responses, in particular the effect of acquired immunity, affect the population dynamics of host–parasites interactions and parasite population structure. The respective empirical studies use observational data from long-term longitudinal studies (especially in humans where data are most complete), the study of genetic or serotype variation of the parasites, the study of specific immune protection, and experimentation in appropriate systems. Obvious parameters that play a critical role are the extent of herd immunity in the population, the degree of cross-immunity, the genotypes of hosts and parasites, as well as stochastic effects. Therefore, given the complexity of immune-response repertoires, differences in the biology of various systems, and the highly non-linear nature of epidemic processes (Anderson 1994), immuno-epidemiology remains a daunting, albeit highly relevant task.

11.6.1 Effects of immune response on parasites

There can be little doubt that an immune response acts against parasitic infections, be it by an increase in resistance to infection, clearance, or by a reduction in parasite fecundity. We should, therefore, expect a negative relationship between parasite load and the strength of the immune response. Data to test these ideas suffer from many confounding variables, not the least from ignoring the age structure of the populations, wrong identification of the relevant immune responses, or the effects of immunosuppression by the parasite. Such confounding variables might explain that, sometimes, a positive association of immune response and parasite load is observed. But the expected negative correlation can indeed be observed, for example, for levels of immunoglobulins and helminth parasite load, or for anti-larval IgE and the success of re-infection by hookworms of humans (Quinnell et al. 2004) (Figure 11.9).

Another important effect of the immune system for the structure of parasite populations includes differential defence against co-infecting strains. In malaria (Plasmodium chabaudi), for example, experimental co-infections in mice suggest that the minority strains in the inoculum are suppressed, as compared to when they infect alone. However, the sexual gametocytes of the minority strain are represented at higher frequencies than expected in mosquitoes that had taken blood from the experimental mice (Taylor et al. 1997). Closer inspection suggests that these shifts are unlikely to be caused by direct parasite–parasite competition for resources. Rather, the shifts appear to be caused by

**Box 11.7 Continued**

generated parasites in the hosts (via parasite fecundity, $\beta \phi$), weighted by the expected stay of the parasite inside the host, i.e. the average infection lifetime, $1/(\mu_2 + \mu_1 + \alpha)$, and by the average lifetime of free-living stages, $1/(\mu_0 + \beta H)$. In the case of the nematode *Trichostrongylus tenuis* infecting red grouse, the value has been estimated to be in the order of $R_0 = 5$ to $R_0 = 10$ (Dobson et al. 1992), thus reaching similar values as infectious diseases of humans (Table 11.1). Like in the standard SIR-model, it is possible to estimate the minimum number of hosts, $H_{\text{crit}}$, that allow an epidemic to unfold with the boundary condition $R_0 \geq 1$. Any treatment to eradicate the parasite would likewise require measures to reduce the number of susceptible hosts, $H$, below this threshold, i.e. to $R_0 < 1$. For this model, equilibrium values for $H$, $P$, and $W$ have been mathematically derived (Anderson and May 1978). The respective equations suggest that the equilibrium host numbers are directly proportional to the degree of parasite aggregation (as given by $(k+1)/k$) and inversely correlated with parasite fecundity ($\phi$) and transmission rate ($\beta$).
strain-specific immune responses that favour the initially rare clone during development into the transmission stages, the gametocytes. Transmission success for the rarer strain is vastly greater (up to 20-fold in the experiments) than when it infects alone. Such rarity advantage can play a major role for host–parasite co-evolution (see Chapter 13). In practice, co-infections are characterized by one parasite strain arriving first, and another strain second. Hence, the immune response against the primary infection and the cross-reactions by the immune system to the secondary infection (by another strain or parasite) are important. The combination of responses will determine the final outcome, i.e. the transmission success of a second infection after the immune system has been exposed to a previous infection (Table 11.3). This suggests that transmission rate, $\beta$, one of the most important parameters for the population dynamics of host and parasite, is affected by the immune response, for example, in co-infections. Such effects also introduce heterogeneity in the population, as some hosts may be co-infected whilst others harbour single infections.

11.6.2 Effects of acquired immunity on epidemiological patterns

An important pattern in epidemiology is the age-specific infection curve, e.g. the parasite intensity in hosts of different age classes. An often observed pattern is a ‘peak shift’, that is, higher maximum infection intensity in younger age classes when transmission intensity, or the force of infection, is high. Such a pattern is indeed observed in experimental infections of mice (Figure 11.10), as well as for infections by Schistosoma in humans (Woolhouse 1998; Woolhouse and Hagan 1999). Numerous theoretical studies have addressed how this pattern is affected by acquired immunity, i.e. by previous exposure to the same or similar strains, and the building up of herd immunity in certain age classes (Figure 11.10).

Theory also suggests that the expected effects on the age-specific parasite load are rather complex. Explicit models of host–parasite dynamics as, for example, used in the study of macroparasites (Box 11.7), can incorporate different modes of mixing of parasites and hosts, such as

Table 11.3 Expected effects on transmission of the secondary infection (parasite success) from immune protection against the primary infection, and as cross-response to a secondary infection. Parasites can also suppress the host immune system. The actual outcomes depend on the relative strengths of these factors (after Graham et al. 2007).

<table>
<thead>
<tr>
<th>Does primary infection generate suppression of immune system?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is secondary infection controlled by same mechanism as primary?</td>
<td>Transmission decreases slightly</td>
<td>Transmission decreases</td>
</tr>
<tr>
<td>Yes</td>
<td>Same mechanism reduces success</td>
<td>Same mechanism reduces success.</td>
</tr>
<tr>
<td>No</td>
<td>Transmission increases</td>
<td>Transmission increases slightly</td>
</tr>
<tr>
<td></td>
<td>Wrong mechanism combined with suppression increases success.</td>
<td>Wrong mechanism increases success.</td>
</tr>
</tbody>
</table>
Figure 11.10 Peak shifts. (a) The predicted prevalence of infection as a function of age, \( a \), and the force of infection, \( \lambda \). The profile results from transient immunization of recovered hosts in a standard SIR-model, such that with the notations of Box 11.4, age-dependent prevalence is
\[
P(a) = \frac{\lambda}{(\lambda + v)} [e^{-\lambda a} - e^{-\lambda v}].
\]
(b) Peak shifts in mice experimentally infected by different doses of cercariae (10 to 300 cercaria per groups of mice) of the trematode *Schistosoma mansoni*. Maximum infection shifts towards younger age classes under high infection doses. Redrawn from Woolhouse (1998) with permission from Elsevier.
homogeneous and heterogeneous mixing in space. Under some of these circumstances, the models predict no shifts. Furthermore, strain-specific immunity, in combination with a general priming against infections, such as in the case with malaria parasites, can considerably complicate the effects of immune protection on the age-specific curve of parasite infection intensity (Gupta and Day 1994). It is therefore important to confirm observed peak shifts in separate studies or by measurements on the levels of immune defences in combination with epidemiological observations (Woolhouse 1993, 1998) (Figure 11.10).

11.6.3 Effects of immunity on population dynamics

Selection resulting from host–parasite interactions changes the genetic composition of host and parasite populations, and is affected by the individual variation in immune responses and protection. The understanding of such processes can be approached from different angles; for example, by studying the effect of investment into immune defence that might come at the cost of another fitness component, such as reduced fecundity (Koella and Boete 2003). In this case, the host–parasite dynamics may change depending on how costly immune defence is, and, therefore, how much host fecundity is reduced. Models assuming fecundity reductions show that, at high costs, and with increasing transmission rates, the population dynamics changes into cycling populations. At low costs, or when transmission is weak, host and parasite populations may reach stable equilibria instead. At the equilibrium, there are evolutionary stable levels of investment into defence (hosts) or infectiousness (parasite).

If a parasite strain is already present endemically in its host population, immune protection and cross-reactivity towards a novel, second strain might seriously affect the chances that the novel strain can spread and cause an epidemic. Not astonishingly perhaps, theory (using the SIR-model, Box 11.4) indeed shows that cross-immune responses to different parasite strains have important implications for the dynamics of this interaction. However, additional factors are crucial to mediate this effect (Restif and Grenfell 2006). For example, when both strains have an equal epidemiological capacity (i.e. the same value of $R_0$), the novel strain will quickly spread because—by virtue of imperfect cross-immunity—it can infect more frequently, as individuals lose protection against the novel strain more quickly than against the (initially more frequent) endemic strain. However, as the epidemic runs its course, both strains will run out of susceptible hosts and will eventually settle to co-existence at equilibrium values. Should, however, a novel strain differ in its basic reproductive number ($R_0$), cross-immune response to the novel strain may lead to the extinction of the strain (endemic, or novel) with the lower $R_0$. Including stochastic effects, one of the two or both strains might become extinct after an initial period of seemingly standard host-parasite dynamics (Restif and Grenfell 2006). Regardless of the details of these processes, at least in theory, immune responses can, therefore, significantly alter the host–parasite dynamics (and leave traces in the genetic structure of parasite populations; Lythgoe 2002). To understand these changes, and to show them happening in real field situations, remains a challenging task, however.

11.7 Epidemiology with evolutionary change

The time scale of epidemiological processes is given by the infection dynamics and the recruitment of new susceptible hosts into the population. Often, this time scale is very short relative to the time scale of evolutionary change. However, parasite populations can adapt very fast to selective pressures as is, for example, shown by the rapid emergence of antibiotic resistance. In such cases, models such as the SIR-equation (Box 11.4), where neither hosts nor parasites change their biological characteristics, might not be appropriate. Rather, the analysis must take into account evolutionary changes unfolding on a similar time scale as the ecological processes governing the epidemiological interactions. We here look at the effects of evolutionary change by considering the micro-phylogeny of parasites, i.e. how different parasite variants propagate through ecological-evolutionary time. The other major aspect of how parasite virulence changes as a result of host-parasite co-evolution will be discussed in the next chapter.
The distributions of parasite strains and their phylogenetic dependencies are shaped by mutation, selection, genetic drift, and gene flow among neighbouring populations. By studying the evolutionary history of phylogenetic lineages of parasite variants, the 'phylodynamics', specific hypotheses about the underlying epidemiological processes can be formulated. Such analyses are most appropriate when parasites have a high mutation rate generating a large amount of variation on which selection (by the host's defences) can act, whilst the hosts evolve slowly, and where numerous and long genetic sequences are available (Drummond et al. 2003). Conditions such as these are met in viruses, especially RNA viruses, which have generally high mutation rates.

Evolutionary processes can be aligned with epidemiological processes by considering how an infecting population produces new variants, which are then differentially eliminated by natural selection as imposed by the host's immune system, followed by an episode of transmission. For one thing, new variants can emerge through mutations, or by exchange and recombination among co-infecting strains. In RNA viruses, such as HIV, one virion can contain two different RNA-strands. As the viral genome is replicated in an infected host cell, the responsible enzyme will first start reading the genetic information from one strand but then jump to read onwards from the other strand, and back again to the first strand. Although this mechanism is different from meiotic recombination by chromosome cross-overs in eukaryotes, the result is the same—a new recombinant genetic sequence emerges. When the parasite population persists and replicates within the host, the new variants become exposed to selection by the host's immune system. After some time, the infecting population will have accumulated a number of new variants, depending on the strength and specificity of the immune response. Eventually, a subset of the variants will be transmitted to a new host, i.e. the parasite population undergoes a bottleneck. If the bottleneck is dominated by random processes, the population changes according to the laws of genetic drift. Alternatively, if the successfully transmitted sub-sample is itself a result of selection, the process will bear the respective signatures of natural selection. Such selection pressure could result from the competition among parasite variants to reach a vector. Furthermore, the parasite's transmission stages might have to endure a period of adverse conditions in the environment (e.g. spores waiting in the soil), which selects for variants that are more resistant to such conditions.

Regardless, the laws of epidemiology become important at the stage of transmission, whereas host immune defences exert selection inside the host. This interplay of factors can generate a wide variety of tree shapes for the phylogeny of parasite variants (Figure 11.11). For example, when immune pressure is weak and cross-immunity among strains is low, large population sizes of the infecting parasite are to be expected. At the same time, the diversity of parasite variants is high; the evolution of the parasite is unlikely to be dominated by immune selection but rather by epidemiological processes. On the other hand, when immune pressure is strong, most parasites will be eliminated or persist in small populations, which limits the absolute number of possible new variants that can emerge. At an intermediate level of selection by the host's immune defences, the number of new variants is at its maximum, since selection is sufficiently strong but also parasite population size is reasonably large (Grenfell et al. 2004) (Figure 11.11).

The phylogenetic diversification of measles, or of influenza virus, over time shows two different patterns. Measles virus has a tree with several groups separated by deep branches, which is indicative of an evolutionary process driven by (global) epidemiological dynamics in space. In this case, relatively short infections and long immune protection drive pronounced epidemiological cycles, because susceptible hosts are quickly exhausted, but a large variety of strains is maintained overall (Figure 11.12a). For influenza virus, the diversity of parasite variants is limited at any one time, but the phylogenetic trace rapidly moves along some major direction, reflecting strong selection by the host's immune system and antigenic shifts by the virus population. In particular, transient cross-immunity limits strain diversity within hosts and favours the continuous establishment of novel strains against which the hosts are not yet protected (Ferguson et al. 2003b) (Figure 11.12b).

The study of epidemic trees not only suggests possible major processes that affect the host-parasite inter-
action, but it is also useful to devise control measures. For example, the outbreak of foot-and-mouth disease in England in 2001 was effectively stopped by using the laws of epidemiology, rather than by sophisticated molecular techniques. Using such epidemiological data, even post-event, provides important lessons for what branches of an epidemiological tree need to be pruned for the most effective control method (Haydon et al. 2002). Phylogenetic analyses and the explicit consideration of evolutionary processes are also important elements to understand and predict the emergence of new diseases, i.e. the invasion of a parasite into a new host population.

11.8 Within-host epidemiology

The dynamics of parasites within a host and their interactions with the immune cells of the host, especially when several strains co-infect, is an important extension of modern epidemiology. Such studies have often focused on how escape variants of a parasite emerge (Bonhoeffer and Nowak 1994b; Sasaki 1994; Nowak and May 2000), what determines the diversity of the infecting population (Nowak et al. 1990; Bonhoeffer and Nowak 1994a), or how within-host epidemiology affects the evolution of parasite virulence. Here, we will consider a viral infection as an example of how to study the within-host epidemiology.
11.8.1 Within-host dynamics of parasites

The analysis of within-host dynamics of parasites can use the same approach as the one adopted for the populations of host individuals and their parasites (Box 11.4). Instead of host individuals, some other variables can be used. For example, for modelling a virus infection, the focus is on the target cells that the virus usually infects. These can be the cells of a specific organ, or the cells of the immune system itself, as in the case of HIV.

Once infected, the cells produce new virus that enter the population of freely circulating virus in the host. Note that no transmission to other hosts is included in these models to start with. Such a scenario might be appropriate for long-lasting, chronic infections, where transmission events are infrequent or very late in the infection process. Again, HIV is a case that comes close to these assumptions. When transmission to new hosts is added, a model combining within- and between-host dynamics is appropriate, a so-called ‘nested model’ (Mideo et al.}

Figure 11.12 Phylogenetics of viruses. Shown are the shapes of the phylogenetic trees for viral types. Each tip of a branch indicates a different virus type (as given by the genetic sequence). (a) Measles in England before vaccination, based on the nucleocapsid gene (63 sequences). Redrawn from Grenfell et al. (2004) with permission from AAAS. (b) Influenza virus A, subtype H1, between the years 1977 to 2000 shows the phenomenon of antigenic shift (104 sequences). The bar indicates number of nucleotide substitutions. Redrawn from Ferguson et al. (2003b) with permission from Macmillan Publishers Ltd.
In some cases, parasites and the cells of the immune system can be thought of as a prey–predator (or parasitoid) system. Consider a viral infection, where a number of free viruses ($V$) circulate in the host that can infect their target cells ($T$), which are thereby turned into infected cells ($I$) (Figure 1). A helpful approximation is that the number of free virus is proportional to the number of infected cells, $V \mu I$, (a quasi-steady state), which yields the basic model of viral dynamics inside a host (Nowak and May 2000):

$$\frac{dT}{dt} = b - \mu T - \beta TI$$
$$\frac{dI}{dt} = \beta TI - \delta I = I(\beta T - \delta)$$

(1)

where $b$ is the constant proliferation (‘birth’) of new target cells, $\mu$ the background death rate of target cells, $\beta$ is the transmission rate from infected to target cells, assuming the mass-action principle. Infected cells are removed at death rate, $\delta$, which includes the effect of the virus as well as the removal by the host’s immune system (e.g. by cytotoxic lymphocytes).

Similar to the SIR-dynamics, we can look at the basic multiplication rate of infected cells when the virus enters the hosts, with all cells being susceptible target cells initially ($I \approx 0$). In this case, $T^* = b/\mu$, is the equilibrium number of susceptible target cells when no virus is yet present. Interpreting the growth rate of the infected cells from eqn 1, as the basic replication number of the viral infection, we have:

$$R_0 = \frac{b}{\mu}$$

(2)

If $R_0 > 1$ the infection spreads, i.e. the number of infected cells increases and, eventually, will level out at an equilibrium given by:

$$T = \frac{\delta}{\beta}$$
$$I = \frac{b}{\delta} = \frac{b}{\beta} \left( 1 - \frac{1}{R_0} \right)$$

(3)

Analogous to the study of population epidemiology an infection will produce a higher endemic equilibrium and control of the process will be more difficult with an increase in $R_0$. This is because the equilibrium number of infected cells increases very steeply with the value of $R_0$. A viral drug treatment might operate so as to reduce the rate of new infection

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**Box 11.8 Within-host dynamics**

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$$\frac{dI}{dt} = \beta TI - \delta I = I(\beta T - \delta)$$

(1)

where $b$ is the constant proliferation (‘birth’) of new target cells, $\mu$ the background death rate of target cells, $\beta$ is the transmission rate from infected to target cells, assuming the mass-action principle. Infected cells are removed at death rate, $\delta$, which includes the effect of the virus as well as the removal by the host’s immune system (e.g. by cytotoxic lymphocytes).

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

(3)

Analogous to the study of population epidemiology an infection will produce a higher endemic equilibrium and control of the process will be more difficult with an increase in $R_0$. This is because the equilibrium number of infected cells increases very steeply with the value of $R_0$. A viral drug treatment might operate so as to reduce the rate of new infection

(Continued)
of cells, $\beta$, or facilitate the shedding of cells, including infected ones, i.e. increases death rate, $\delta$. A reduction of $\beta$ leads to an increase in the number of target cells, $T$, which in turn paradoxically increases the number of newly infected cells by virtue of eqn 3. Hence, any treatment that reduces this transmission rate must be very effective to actually suppress the number of infected cells below a given threshold.

$\frac{dI}{dt} = bI - \delta I - \mu T$

Competition in malaria is also suggested by the observation that genotype turnover is high where also transmission is more frequent (Daubersies et al. 1996). Similarly, clinically noticeable cases of malaria are associated with fewer and, presumably, more rapidly replicating clones of the parasite, than those found in asymptomatic patients (Mercereau-Puijalon 1996; Smith et al. 1999b).

Competition between co-infecting parasite strains has been shown in experimental studies (Read and Taylor 2001). Experimental tests with malaria have suggested that the outcome of the competition depends on a number of factors (de Roode et al. 2003, 2005a), such as the dose in the inoculum, with the more common clone in the dose usually becoming dominant afterwards. However, the case is more complex, as the relative

Figure 1 Within-host dynamics. Viruses infect their target cells ($T$) that become infected cells ($I$) at rate $\beta$ (transmission rate). The infected cells die at rate, $\delta$, by the effect of the virus or when removed by the host’s immune system. Target cells are proliferating at rate, $b$, and die at rate $\mu$. In the simplest case, it is assumed that the number of circulating free virus ($V$) is proportional to the number of infected cells. After Nowak and May (2000).

<table>
<thead>
<tr>
<th>Model Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$b$</td>
<td>Proliferation of target cells</td>
</tr>
<tr>
<td>$\beta$</td>
<td>Transmission rate</td>
</tr>
<tr>
<td>$\mu$</td>
<td>Death rate of target cells</td>
</tr>
<tr>
<td>$\delta$</td>
<td>Death rate of infected cells</td>
</tr>
</tbody>
</table>

Box 11.8 Continued
proportion of strains in the infection transmitted to the mosquitoes does not favour the majority strain at the time of infection, or even the majority strain among those circulating in the vertebrate host (Taylor et al. 1997). Similar to the effect by the host’s immune response, success in competition might also depend on the differential effects of drugs. A generally important effect, however, seems to be the order of infection, which typically gives an earlier strain an intrinsic advantage over a strain arriving later (de Roode et al. 2005a).

• Epidemiology, in the sense used here, is the study of the population dynamics of host–parasite systems. Mathematical modelling started with Daniel Bernoulli in the eighteenth century. The classical Nicholson–Bailey model is an example that analyses host–parasitoid systems.
• SIR-models analyse the epidemiology of hosts and their microparasites. An important variable from these models is the reproductive number, $R_0$, which is the number of secondary infections resulting from a primary infection in a fully susceptible host population. The standard SIR-models assumes the mass action principle, where hosts and parasites encounter each other randomly and in proportion to their numbers. Deviations from such homogeneous mixing are biologically more realistic.
• Analysing how $R_0$ is determined can be used to formulate vaccination strategies that lead to parasite eradication (where $R_0 < 1$). The standard SIR-models can also be extended in other ways to include age structure of the host population, latency periods, or sexually transmitted parasites.
• Stochastic processes can affect the spread of a parasite, such that an epidemic can die out even when $R_0 > 1$. Furthermore, spatial effects introduce variance in transmission and strongly affect the value of $R_0$.
• When an epidemic has eventually settled to equilibrium numbers of hosts and parasites, infections can be maintained, usually at a low level, in an endemic state. Periodic outbreaks can occur from the endemic state, driven by seasonal effects, time lags, or stochastic events. Time-series analysis of infection numbers can reveal what periodic processes might underlay the outbreaks.
• The epidemiology of vectored microparasites, such as malaria, can similarly be analysed with modified SIR-models, e.g. the classical Ross–Macdonald model. The epidemiology of macroparasites follows similar principles by taking into account the free-living stages of a parasite. The distribution of macroparasites across hosts is of special interest. It is usually aggregated, and the degree of aggregation strongly affects the epidemiology.
• The immune defences by the host, especially protective immunity (memory) and cross-reactivity for different parasite strains, can affect the distribution of infections among age classes (peak shift), and influences the epidemiological dynamics, too. Immuno-epidemiology is a field of study that analyses these processes.
• With short-lived parasites and selection by the host, evolution can happen on the same time scale as the ecological dynamics unfolds during the course of an epidemic. One way to study these questions is by phylodynamics because different evolutionary-ecological processes produce different phylogenetic trees.
• The dynamics of an infection with the host can likewise be scrutinized as an epidemiological process where, for example, viruses and their target cells represent the parasite–host system. How immune protection and cross-reactivity affect the dynamics of multiple infections is of special interest.