7.6 Modeling Measles Outbreaks

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7.6.1 Introduction

Epidemiology is one of the areas in biology to which mathematical modeling has been applied most successfully. It was through the mathematical concept of basic reproductive number that Ronald Ross gained the insight that malaria could be controlled if the mosquito population was sufficiently suppressed (Heesterbeek 2002). Later, similar concepts were applied to the eradication of smallpox and the control of many viral diseases through vaccination campaigns (Anderson and May 1991). To date, mathematical models remain an important tool.

Epidemiology studies the distribution of a disease within a host population. Most models used for infectious diseases are based on partitioning the host population into different classes that correspond to the different stages of the infectious process (e.g., susceptible, infectious, and recovered) and the transitions between these classes. Such models work particularly well for diseases caused by microparasites, a class of pathogens that comprises viruses and bacteria and that are characterized by an infection normally accomplished with a single dose that consists of a relatively small number of infective particles (Anderson and May 1991).

Mathematical epidemiology has concentrated on cases for which the disease is endemic or in which large epidemics occur. In this context the reproductive number is an important parameter. It is defined as the average number of secondary infections caused by an infected host over the lifetime of the infection. In a completely susceptible population, this number is known as the basic reproductive number, R_0. If the reproductive number is larger than one, a single infection can lead to a chain reaction of infections and, eventually, to an epidemic or an endemic state. If the reproductive number is smaller than one, large epidemics do not occur and the pathogen is bound to disappear from the population.

If the basic reproductive number is less than one, the numbers of infected individuals hardly ever become truly large and stochastic effects prevail. If this is the case the disease manifests itself in the form of outbreaks that follow the introduction of the disease into the population. The size and duration of an outbreak can vary enormously through chance events. To capture these dynamics a stochastic formalism is needed. In this section we illustrate how the theory of branching processes can be used to describe the epidemiology of pathogens with a reproductive number smaller than one, using the epidemiology of measles as an example. We use this to explain the distribution of disease outbreaks in small island populations, and the effect of a recent decline in vaccination in the UK after a scare about vaccine safety.

7.6.2 The epidemiology of measles

Measles is caused by the measles virus. It is transmitted on close contact via airborne propagules. Infection leads to the development of a typical rash. The

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infectious period is in the order of a week, after which the hosts recover and develop lifelong immunity. Hosts, therefore, are normally infected only once in their lifetime and, if the force of infection is sufficiently large, this happens at a young age, and hence measles is a childhood disease. Although in unvaccinated populations measles is a common disease, infection is not without danger. In developed countries infection with measles leads to complications in one out of seven cases and is fatal in about one in 5000 cases (Ramsay *et al.* 1994; Carabin *et al.* 2002).

The basic reproductive number of measles lies between 10 and 18 (Anderson and May 1991). In large, unvaccinated populations measles is endemic, and a course of measles is a normal part of childhood. Before mass vaccination was introduced, measles used to follow a cyclic pattern, with a period of about 2 years in Europe and North America. Mathematical models have shown that the annual variation in the transmission together with the disease dynamics can result in a 2-year cycle or more complex dynamics (Bolker and Grenfell 1993; Drepper *et al.* 1994). Since mass vaccination was introduced in the UK in the 1970s, measles has lost its periodic character. Over the past decade the vaccine coverage in most parts of Europe was above 90% (de Melker *et al.* 2001) and measles currently only occurs following introduction of the disease.

In small, isolated populations an outbreak of measles can immunize a large part of the population, so the disease disappears even if the reproductive number was larger than one initially. Therefore, measles cannot persist in small populations (Bartlett 1957). In small island populations this is, indeed, the case and measles is not endemic, but comes in the form of outbreaks after importation of the disease (Rhodes and Anderson 1996; Rhodes *et al.* 1997). In a number of small islands these outbreaks have been documented meticulously, which provides an unparalleled record of outbreak patterns.

In the UK, the safety of the combined measles, mumps, and rubella (MMR) vaccine recently became the focus of a heated debate following concerns over the safety of the vaccine (Wakefield *et al.* 1998). None of the claims regarding the safety of the vaccine have been confirmed (Donald and Muhtu 2002; Consumer's Association 2003), but nevertheless this scare resulted in a decreased uptake of the MMR vaccine. As a result, measles outbreaks have increased in size (Ramsay 2003). We use a branching process to describe the epidemiology of measles in a vaccinated population and demonstrate how this model can be used to estimate the reproductive number in the UK population. Such information is of vital importance in public health policy.

7.6.3 A general model for measles

A basic model for the epidemiology of measles outbreaks is founded on a subdivision of the host population into classes. The allocation of individuals to classes is not static: hosts can move from one class to another. Whenever this happens we speak of a transition. Examples of transitions are infection, which moves a host from the susceptible to the infected class, and recovery, which moves a host from the infected to the recovered class.

Table 7.3 Transition rates for the continuous-time epidemic process.

Event	Type of transition	Rate
Infection	$S \to S-1, I \to I+1$	$\beta SI/N$
Recovery	$I \to I-1, R \to R+1$	γI
Death of infected	$I \to I-1, S \to S+1$	μI
Death of recovered	$R \to R-1, S \to S+1$	μR
Vaccination	$S \to S-1, R \to R+1$	νS

We make one important assumption, that the transition rate (i.e., the probability of a host moving from one class to another per unit of time) depends only on the current state of the system and not on the system's history. The state of the system is defined by the numbers of hosts in the different classes (the Markov property discussed in Section 2.3). This assumption is less restrictive than it sounds. It effectively requires us to choose classes in such a way that they contain all the information necessary to predict changes at the current point in time.

We consider three classes: susceptible hosts, infected, and recovered. Susceptible hosts have never been in contact with the virus and have not been vaccinated. The number of susceptible hosts is denoted by S. Upon infection susceptible hosts enter the infected class. The number of infected individuals is given by I. Hosts that acquire immunity to measles, either through exposure to the virus or vaccination, move into the recovered class. The number of recovered hosts is given by R. Models of this type are called SIR models.

The average length of the infectious period for measles is about a week. As this is very short compared to the average lifetime of the human host we assume that the total host population is constant on the timescale of a measles outbreak. The size of the host population is $N = S + I + R$. Susceptible hosts become infected with the virus upon contact with an infected individual. The force of infection (the probability that an individual host acquires the infection per unit of time) is given by $\beta I/N$, where β is the transmission parameter. The force of infection is proportional to the fraction of infected people, I/N, because the number of potential infectious contacts tends to be independent of the population size. The rate at which the number of infected individuals grows is $\beta IS/N$.

An infected host has a probability γ of recovering from the infection per unit of time. The rate at which the number of infected individuals decreases through recovery is thus γI. In addition, birth, death, and vaccination are taken into account. All individuals have a probability μ of dying per time unit. As we wish to keep the population size constant, we replace dead individuals by newborn susceptible individuals. Finally, we model vaccination as a fixed probability per unit of time, ν, of a susceptible host being moved to the recovered class. These transitions are summarized in Table 7.3.

The average duration of infection in this model is $1/\gamma$. The average number of secondary infections is $\frac{\beta S}{\gamma N}$. In a completely susceptible population $S = N$, and hence the basic reproductive number is $R_0 = \frac{\beta}{\gamma}$. In a population in which a

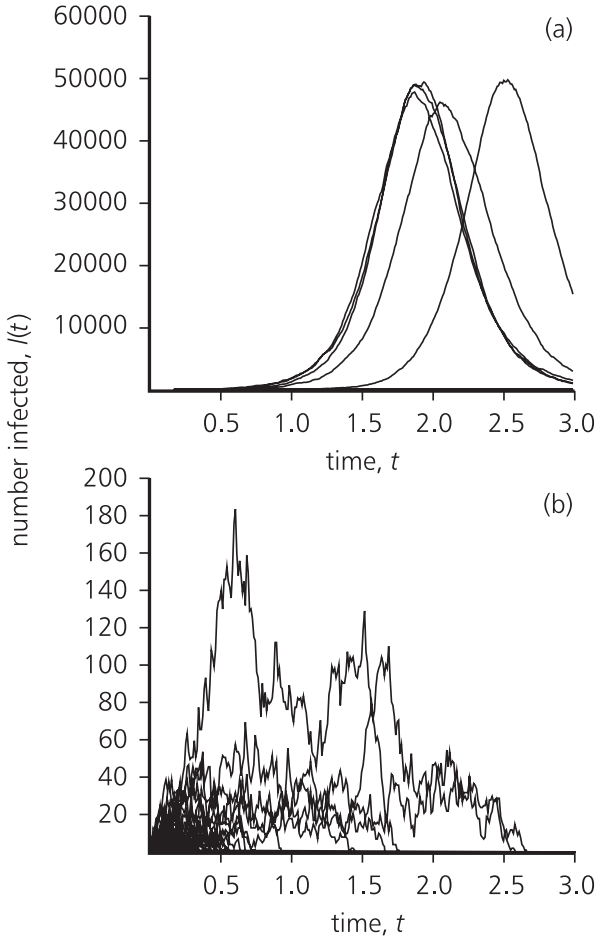

Figure 7.18 Stochastic simulations of the SIR system above and below criticality. For these simulations we used $\beta = 500.1333$, $\mu = 1/75$, and $\gamma = 50$ (corresponding to an average recovery time of about 1 week). (a) For $\nu = 0.108$: if the vaccination dynamics has equilibrated these values correspond to $R_c = 1.099$ and the system is supercritical. After an initial random phase the epidemic looks essentially deterministic (i.e., the graph is smooth) and is well described by the ordinary differential equation system in Section 7.6. In this figure 100 simulations are shown. Most epidemics have faded out and are therefore not visible. (b) For $\nu = 0.1215$: the system has $R_c = 0.989$ after equilibration and the system is subcritical. As can be seen, the outbreaks have a strong stochastic component. In this figure 500 simulations are shown.

fraction c of the individuals is vaccinated and in which the virus is not present the number of susceptible hosts is $S = (1 - c)N$ and the reproductive number is $R_c = \frac{\beta(1-c)}{\gamma} = R_0(1 - c)$.

7.6.4 A deterministic model for endemic measles

If the reproductive number exceeds one an epidemic can start after the introduction of the disease in the population, when it frequently becomes endemic, and affects many people. Once the infection rate has become sufficiently large, stochastic effects play a minor role and changes in the number of hosts in the different classes are largely deterministic (see Figure 7.18a). If this is the case, the dynamics of a

well-mixed population can be described by the differential equations

$$\frac{dS}{dt} = \mu N - \frac{\beta I S}{N} - (\mu + \nu)S \tag{7.80}$$

$$\frac{dI}{dt} = \frac{\beta I S}{N} - (\gamma + \mu)I \tag{7.81}$$

$$\frac{dR}{dt} = \gamma I + \nu S - \mu R \ , \tag{7.82}$$

where the densities S, I, and R are differentiable real-valued functions of time. This is the classic deterministic SIR differential equation model for the dynamics of endemic measles.

Figure 7.18b shows the number of infected individuals over time after introduction into a vaccinated population with a reproductive number smaller than one. These simulations differ from those in Figure 7.18a in that the disease always disappears from the population and that the outbreak size does not become truly large (note the difference in the scales), so that stochastic effects dominate the dynamics. To capture the stochastic nature, we simplify our model further.

7.6.5 A stochastic model for measles outbreaks

For the formulation of a simple stochastic model, we first observe that outbreaks take place on a relatively short timescale, in the order of weeks or months. Demographic processes in humans generally take place at much slower timescales. We can therefore assume that at the timescale of a measles outbreak, birth and death do not have a major impact on the disease dynamics, and we set birth and death rates to zero. Similarly, the process of vaccination only changes the fraction of susceptible hosts relatively slowly and we also set the vaccination rate to zero. Vaccination enters the simplified model through the fraction initially immunized, c.

If the reproductive number is smaller than one the disease disappears from the population and hardly ever infects a substantial part of it. As a further simplification, we assume that the population is very large, and that the presence of the disease does not have an impact on the fraction of susceptible hosts. The fraction of susceptible hosts is constant and remains at $1 - c$ throughout the outbreak. A second consequence of this assumption is that we only need to keep track of the number of infected people. Under these assumptions, the disease dynamics reduces to a linear birth-and-death process (see Table 7.4), as introduced in Section 3.2. Its birth rate is $b = \beta(1 - c) = \gamma R_c$ and the death rate is $d = \gamma$. It follows from Equation (3.10) that

$$\mathbb{E}[I(t)] = M(t) = e^{\gamma(R_c - 1)t} \ , \tag{7.83}$$

if the process started from one single case. This can, of course, also be derived directly from the differential equation for the mean, much as done in Section 3.2.

Table 7.4 Transition rates for the simplified continuous-time Markov process.

Event	Type of transition	Rate
Infection	$I \to I + 1$	$\beta(1 - c)I$
Recovery	$I \to I - 1$	γI

The differential equation argument also applies to the variance of Markov branching processes $V(t) = \mathrm{Var}[I(t)]$. In the present case

$$\frac{dV}{dt} = \gamma(R_c + 1)M - 2\gamma(1 - R_c)V \ , \tag{7.84}$$

which yields exact solutions that, if $R_c < 1$, increase initially, but in the limit of large t decrease as $e^{-2\gamma(1-R_c)t}$, grow linearly in the critical case $R_c = 1$, and, if $R_c > 1$, in the limit of large t increase as $e^{\gamma(R_c-1)t}$. This is in analogy with the asymptotic formulas for more general branching processes in Section 3.2, and exactly as in the discrete Markov (i.e., Galton–Watson) case (Section 2.2). We see that only in the subcritical situations does the variance vanish with time and, indeed, if the reproductive number is close to one, realizations are not at all close to the mean (Figure 7.19). To investigate the behavior near criticality we derive the distribution of outbreak sizes.

7.6.6 The size distribution of outbreaks

In the subepidemic case, outbreaks are sparked by the introduction of the disease into the population. To derive the distribution of their size, we apply the branching process interpretation used to generate the realizations in Figures 7.18 and 7.19. In stochastic simulations the system remains unchanged most of the time and only changes because of transitions: jumps in which the numbers in the model classes change by one. The probability of change per unit time is constant between jumps and therefore the times between successive jumps are distributed exponentially, with a mean equal to the reciprocal of the total rate of leaving the state the system is in. For our simulations the time to the next jump is drawn from an exponential distribution. The probability of leaving the initial state and ending in a particular state is given by the rate that corresponds to this transition, divided by the total rate of leaving the initial state. This procedure, which follows directly from the probabilistic structure of the process, is known as the Gillespie algorithm (Gillespie 1976, 1978; Feistel 1977). It is a computationally efficient way to generate realizations of continuous-time Markov processes.

Let us apply this procedure to the system if it has I infected individuals. The rate of leaving that state is given by $(b + d)I = \gamma(R_c + 1)I$, as previously introduced, and the average waiting time is $1/(\gamma(R_c + 1)I)$. Upon leaving this state the system can either go to the state $I + 1$ if the most recent event was an infection or to the state $I - 1$ if it was a recovery. The next event is an infection with probability $\frac{b}{b+d} = \frac{R_c}{R_c+1}$ and a recovery with probability $\frac{d}{b+d} = \frac{1}{R_c+1}$ (Table 7.5). Note that these probabilities do not depend on the number of infected individuals.

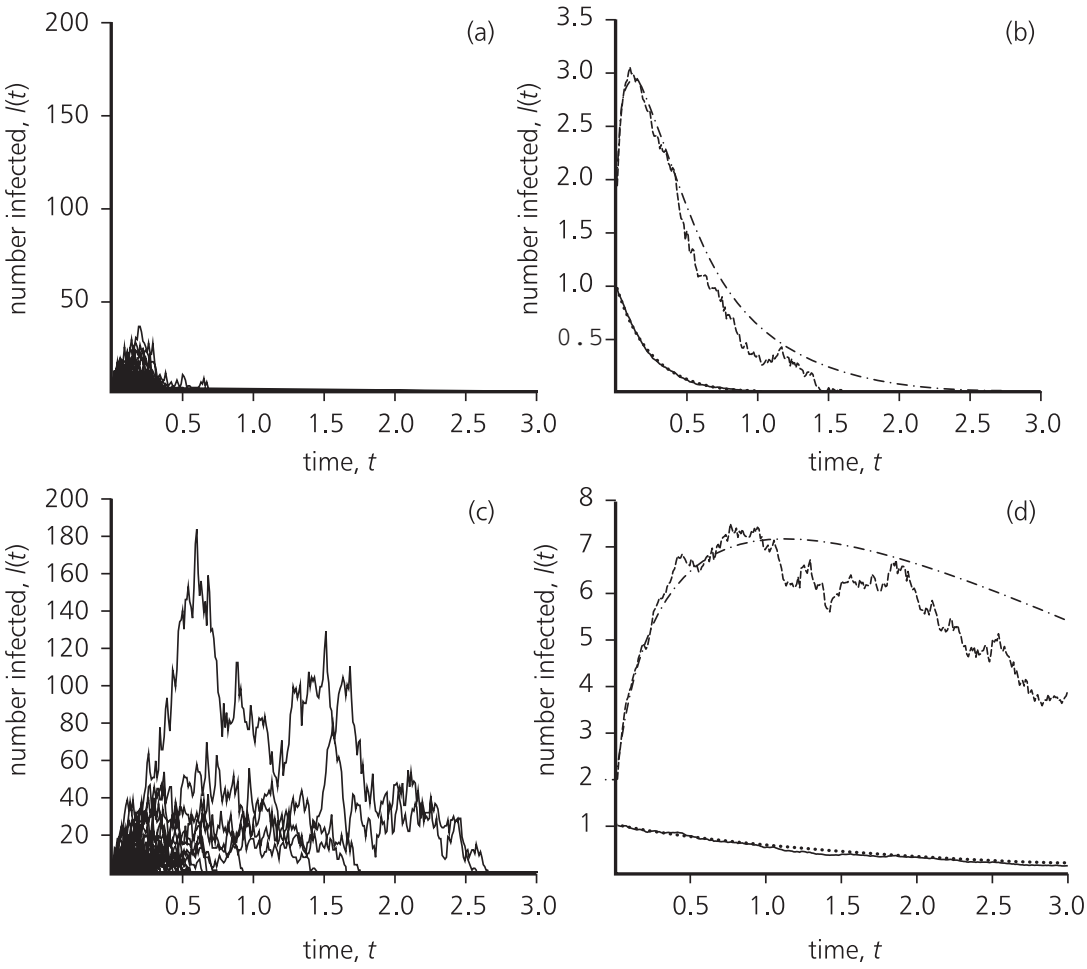

Figure 7.19 The left panels show the different realizations and the right panels show the observed ensemble mean (continuous) and variances (dotted) and predicted ensemble mean (dashed and dotted) and predicted ensemble variance (dashed). For (a) and (b) 10 000 simulations were used, for (c) and (d) 500 simulations. The lower curves almost coincide, which indicates a good approximation. Parameters: (a, b) $\nu = 0.132$, (b, c) $\nu = 0.1215$.

Table 7.5 Transition rates for the simplified event based discrete-time Markov process.

Event	Type of transition	Probability
Infection	$I \to I + 1$	$\frac{R_c}{R_c+1}$
Recovery	$I \to I - 1$	$\frac{1}{R_c+1}$

To calculate the distribution of the number of cases that result from a single introduction we need not know when these cases occurred. We therefore discard the part of the algorithm in which the waiting time is computed, and follow the process from event to event, events being infection or recovery. This transforms the continuous-time branching process into a discrete-time branching process with constant transition probabilities, a simple random walk.

The number of events that have passed is indicated by the variable T. Let $p(I, T)$ be the probability that there are I infected individuals after T events. The algorithm outlined gives the transition probabilities from event to event. If $I > 1$, this probability satisfies the recursion

$$p(I, T+1) = \frac{R_c}{R_c+1} p(I-1, T) + \frac{1}{R_c+1} p(I+1, T) \,, \tag{7.85}$$

and otherwise

$$p(1, T+1) = \frac{1}{R_c+1} p(2, T) \tag{7.86}$$

and

$$p(0, T+1) = p(0, T) + \frac{1}{R_c+1} p(1, T) \,; \tag{7.87}$$

at $T = 0$ all probabilities are 0 except $p(1, 0) = 1$.

By transforming to a discrete branching process we have lost some information (when events happen), but we gain a tremendous simplification in that the transition probabilities have become constants. The recursion above has the solution

$$p(I, T) = T! I \frac{(R_c+1)^{-T} R_c^{\frac{1}{2}(T+I-1)}}{(\frac{1}{2}(T+I+1))!(\frac{1}{2}(T-I+1))!} \tag{7.88}$$

if $T - I - 1 > 0$ and if $T - I - 1$ is even, and $p(I, T) = 0$ otherwise. It is easy to check that this solution is correct by substituting it into Equations (7.85)–(7.87).

We use this to find the probability that an outbreak with a total of x cases occurs. Suppose that the outbreak stops after T events, when the individual infected last recovers. Therefore, at $T - 1$ the number of infected individuals has to be one and $(T-1)/2$ of the past events must have been infections (otherwise the process cannot have returned to $I = 1$). The total number of cases in the outbreak is $x = 1 + (T-1)/2$ (half of the events must have been infections, one infection is added to account for the infected individual present at $T = 0$), from which follows $T = 2x - 1$. Let $q(x)$ be the probability that the final size of the outbreak is x. For the outbreak to stop after $2x - 1$ events the last event has to be a recovery and hence this probability is

$$q(x) = \frac{1}{R_c+1} p(1, 2x-2) = \frac{{R_c}^{x-1}}{(R_c+1)^{2x-1}} \frac{(2x-2)!}{x!(x-1)!} \,. \tag{7.89}$$

Alternatively, the moment generating function of the outbreak size distribution of the embedded Galton–Watson process could be derived, as described in Section 3.1 (see Section 7.6.9). Although this method is systematic it has the disadvantage that the probability distribution is found in terms of a series that is not easy to interpret. We therefore prefer the method given above, as it leads directly to the probability distribution. In case the moments rather than the distribution are of interest, the generating function procedure is readily applicable.

Often the probability of a certain outbreak size or larger is of practical use. This probability is given by $\sum_{x=n}^{\infty} q(x)$. Before deriving an expression for this quantity we first observe that if the reproductive number is smaller than one the disease always disappears from the population and hence $\sum_{x=1}^{\infty} q(x) = 1$. However, if $R_c > 1$, the disease can disappear by chance from the population. This happens with probability $\sum_{x=1}^{\infty} q(x) = 1/R_c$. In our model the disease goes to infinity with probability $1 - 1/R_c$, which corresponds to an outbreak that affects a large fraction of the population in a large finite population. Using this we find that the probability of an outbreak of a certain size or larger is given by

$$\sum_{x=n}^{\infty} q(x) = \max\left(0, 1 - \frac{1}{R_c}\right) + \frac{(4R_c)^{n-1}}{(1+R_c)^{2n-1}} \frac{\Gamma(n-\frac{1}{2})}{\sqrt{\pi} n!} \, {}_2F_1\left(1, n-\frac{1}{2}, n+1, \frac{4R_c}{(1+R_c)^2}\right) \quad (7.90)$$

where ${}_2F_1$ is the hypergeometric function (Abramowitz and Stegun 1964).

7.6.7 Measles outbreaks in small islands

Historical records of measles outbreaks in small islands show tremendous variation in outbreak size: most are small, but sometimes a substantial part of the island population becomes infected. It has been shown that the size distribution of the outbreaks can be described by a power law (Rhodes and Anderson 1996). Power laws are fingerprints of critical systems (Stanley 1971; Jensen 1998), and it has been suggested that the dynamic behavior of measles in small islands is an example of criticality (Rhodes *et al.* 1997). This has been supported by individual-based models in which this behavior was replicated (Rhodes and Anderson 1996; Rhodes *et al.* 1997).

Another characteristic property of critical systems is the divergence of the variance (Stanley 1971; Yeomans 1992). This phenomenon is shown in Figure 7.19 for reproductive numbers close to one. In the critical case the frequency distribution of events can be described by a power law. Figure 7.20a illustrates how the distribution of outbreak sizes approaches a straight line in a log–log plot if the reproductive number goes to one. Indeed, in the limit of the reproductive number tending to one, we find

$$\lim_{R_c \to 1} q(x) = 2^{1-2x} \frac{(2x-2)!}{x!(x-1)!} \approx \frac{x^{-3/2}}{2\sqrt{\pi}} , \quad (7.91)$$

and the probability to find an outbreak of size n or larger tends to

$$\lim_{R_c \to 1} \sum_{x=n}^{\infty} q(x) = 2^{2-2n} \frac{(2n-2)!}{((n-1)!)^2} \approx \frac{n^{-1/2}}{\sqrt{\pi}} , \quad (7.92)$$

where we used Stirling's formula for the approximation and hence it holds for large n (Stollenwerk and Jansen 2003). We have thus found that our branching process model predicts a power law in the frequency of outbreaks with an exponent of

$-3/2$, and the frequency of an outbreak of a particular minimum size with exponent $-1/2$. This is close to the value found in the data for the Faeroe Islands, which was -0.27 ± 0.014 (95% confidence interval; Rhodes *et al.* 1997). For whooping cough (pertussis) and mumps similar exponents were found. This suggests that the reproductive number in these small island populations for all these diseases is close to one. In these populations the number of susceptible hosts builds up between outbreaks, which increases the reproductive number. Every outbreak immunizes a part of the population and thus reduces the reproductive number. This process keeps the reproductive number, on average, at unity. The deviation in the exponent from $-1/2$ in the Faeroe data could result from additional effects, such as spatial structure (Jensen 1998).

The occurrence of power laws in the outbreaks of measles has been explained previously by the spatial structure in the population. Here we show that power laws arise in a simple branching process without any spatial structure. This fact has long been known (see, e.g., Harris 1963; Jensen 1998), but previously has received little attention in the biological literature. Simple branching processes provide a simple and parsimonious explanation for the occurrence of power laws in epidemiological data.

7.6.8 The basic reproductive number following the MMR scare

The reduced vaccine uptake in the UK after the MMR scare has coincided with a large number of measles outbreaks. These outbreaks can be reconstructed from epidemiological data by grouping all the cases that have had epidemiological contact. This requires a detailed investigation and the resultant clusters are, to an extent, subjective. The distribution of the outbreak sizes can be used to infer important epidemiological information, in particular it can be used to estimate the reproductive number (De Serres *et al.* 2000; Farrington *et al.* 2003). We use data on outbreak size to show how the reproductive number in the UK population has changed in response to the MMR scare.

Using the outbreak size distribution derived in this chapter, a maximum likelihood estimate can be found. The rationale behind likelihood estimates is that one tries to identify the most likely estimate for R_c given a set of observed outbreak sizes. To do so, consider a set of n observed outbreaks of size $(x_1, \ldots, x_n)$. The likelihood of the data (i.e., the probability of observing these data given that the reproductive number is R_c) is proportional to

$$\prod_{i=1}^{n} q(x_i) = \frac{{R_c}^{mn-n}}{(R_c+1)^{2mn-n}} \prod_{i=1}^{n} \frac{(2x_i-2)!}{x_i!(x_i-1)!} , \tag{7.93}$$

where we use $m = \frac{1}{n}\sum_{i=1}^{n} x_i$ to denote the mean outbreak size. We want to know for what value of R_c the likelihood is maximized. By differentiation with respect to R_c we find that the maximum likelihood is found for

$$(m-1)\frac{1}{\hat{R}_c} - (2m-1)\frac{1}{\hat{R}_c+1} = 0 , \tag{7.94}$$

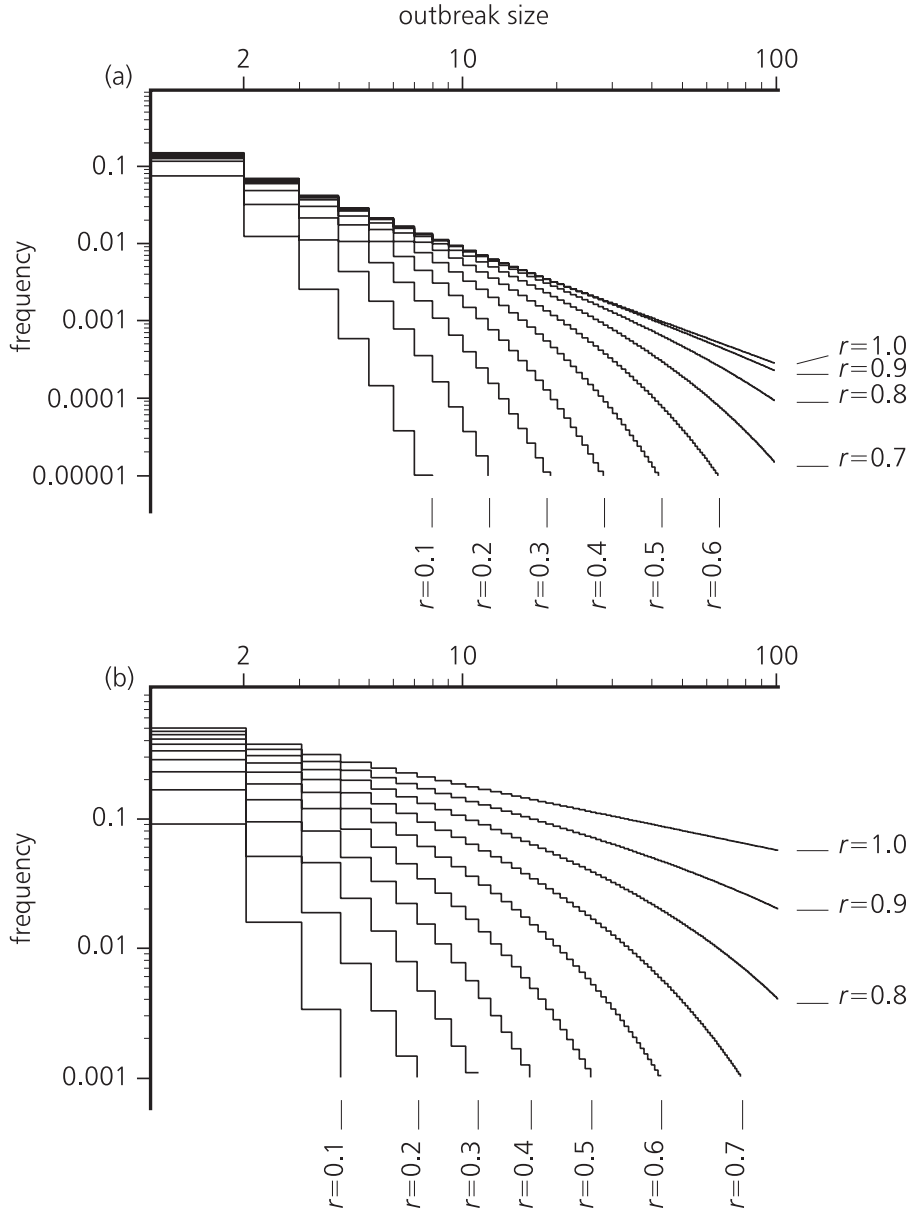

Figure 7.20 (a) The distribution of outbreak sizes. The distribution approaches a straight line with a gradient of $-3/2$ in a log–log plot if the reproductive number goes to one. (b) The distribution of the probability of an outbreak of a certain size or larger $[P(x \geq n)]$. This distribution approaches a straight line with a gradient of $-1/2$ in a log–log plot if the reproductive number goes to one.

and hence for $\hat{R}_c = 1 - 1/m$. Note that the predicted mean outbreak size is given by

$$\sum_{x=1}^{\infty} xq(x) = \frac{1}{1 - R_c} \text{ if } R_c < 1 \, . \tag{7.95}$$

The resultant estimates for the UK were $\hat{R}_c = 0.35$ for the period 1995–1998 and $\hat{R}_c = 0.70$ for 1999–2002, which indicates a clear increase.

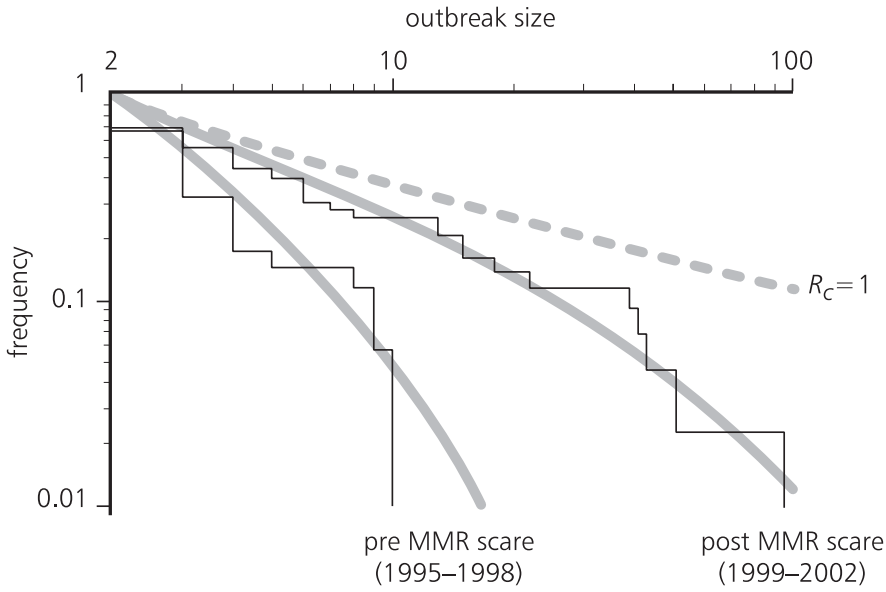

Figure 7.21 The frequency of an outbreak of measles of a particular size or larger in the UK in the years 1995–1998 and 1999–2002. Isolated cases and Steiner outbreaks are excluded. The continuous lines are the expected distributions. The dashed line is the distribution for $R_c = 1$. Modified from Jansen *et al.* (2003).

So far we have used all the reported cases of measles in the UK in the years 1995–2002, grouped over outbreaks. In such data sets isolated cases tend to be misrepresented for several reasons. First, one can expect that the introducing individuals would normally spend less than their entire infectious period in the country they are importing the infection into. This results in an under-representation of isolated cases. A more serious source of error is that sometimes epidemiological analysis fails to connect infections to the outbreak they are part of. This tends to over-represent isolated cases. Indeed, for the data 1999–2002 the model that used all data points can be rejected through a Kolmogorov–Smirnov test.

A more reliable estimate of the reproductive number is found by excluding isolated cases. This can be done as follows. The probability of an isolated case is $q(1) = \frac{1}{R_c+1}$. The distribution of outbreaks of size $x \geq 2$ is given by $q(x)/(1 - q(1))$. We now find the maximum likelihood estimator to be $\hat{R}_c = 1 - 2/m$. The resultant estimates are 0.47 for the period 1995–1998 and 0.82 for 1999–2002. These agree well with observed data (Figure 7.21). The conclusion that the reproductive number has increased was further corroborated by a bootstrap argument in Jansen *et al.* (2003).

Clearly, the reproductive number increased after the reduction in vaccine uptake decreased following the MMR scare (Jansen *et al.* 2003). Vaccine uptake has reached the lowest point for 10 years. The consequence of this is a further accrual of unvaccinated individuals and, inevitably, a further increase in the reproductive number. If the vaccine uptake does not increase, this will eventually lead to a re-emergence of measles as an endemic disease in the UK. An indication that the measles epidemiology in the UK is approaching the critical point at which the reproductive number equals one is provided by the distribution of outbreak sizes.

By comparing the distribution of outbreak sizes before 1999 with the distribution for the years 1999–2002 a progression toward criticality can be seen (Figure 7.21).

Currently, about 200 cases of measles are reported in the UK per year. The risk of a child actually suffering measles complications is negligible because of the low incidence. If the reproductive number increases above unity, this situation will change and unvaccinated individuals will have a substantial chance of contracting the disease. Although the risk of serious complications is small, this risk certainly outweighs the risk associated with vaccination (Carabin *et al.* 2002). To put this risk in context, before mass vaccination was introduced measles caused about 100 deaths per year in the UK (Gay *et al.* 1995). The decision not to vaccinate one's child so as to avoid a perceived risk can have the ironical consequence that the child is exposed to a much larger risk if this behavior is taken up by the population at large.

7.6.9 The moment generating function of the embedded process

Consider the embedded Galton–Watson process of Section 3.1, which defines the outbreak initiator as the ancestor and all those directly infected by the initiator as its direct offspring, which thus constitute the first generation. Those infected by members of the latter make up the second generation, and so forth. If we write Z_n for the number of members of the nth generation thus defined and $Z_0 = 1$ (i.e., one initiator) this constitutes a Galton–Watson process, whose reproduction distribution is easily seen to be geometric with the parameter $R_c/(R_c + 1)$. Since an infection occurs with probability $\frac{R_c}{R_c+1}$, the probability of infecting k or more individuals during the individual's period of infection is

$$\mathbb{P}(\xi \geq k) = \left(\frac{R_c}{R_c + 1}\right)^k . \tag{7.96}$$

The mean number of individuals directly infected by any single person is thus $\mathbb{E}[\xi] = R_c$, and the size of the outbreak is the accumulated total size of the embedded Galton–Watson process,

$$Y = \sum_{k=0}^{\infty} Z_k . \tag{7.97}$$

We note immediately that Y is finite if $R_c \leq 1$, the expected total size of the outbreak being

$$\mathbb{E}[Y] = \begin{cases} \sum_{k=0}^{\infty} R_c^k = 1/(1 - R_c), & \text{if } R_c < 1 , \\ \infty, & \text{if } R_c = 1 . \end{cases} \tag{7.98}$$

If $R_c > 1$, Y is finite if and only if the embedded Galton–Watson process dies out. Since the reproduction generating function is

$$f(s) = \frac{1}{1 + R_c(1 - s)} , \tag{7.99}$$

the probability Q of this, being as always the smallest non-negative root of $Q = f(Q)$, is $1/R_c$ for $R_c > 1$ (see Section 5.3).

To find the distribution of the outbreak size, note that $Y_n = Z_0 + Z_1 + \cdots + Z_n$, starting from one individual, has a generating function, $h_n(s) = \mathbb{E}[s^{Y_n}]$, that satisfies the recursive relation

$$h_{n+1}(s) = \mathbb{E}[s\mathbb{E}[s^{Z_1+\cdots+Z_{n+1}}|Z_1]] = \mathbb{E}[s\mathbb{E}[s^{1+\cdots+Z_n}]^{Z_1}] = sf(h_n(s)) \; . \quad (7.100)$$

Passage to the limit $n \to \infty$ yields a functional equation, $h(s) = sf(h(s))$, which can be solved in the present case, since it reduces to a second-degree equation.

The generating function then yields the probability distribution after an inverse transformation as a series. See, e.g., Jagers 1975, pp. 39 ff; this and other textbooks also contain the intriguing consequence of the so-called Ballot theorem, that the total size of a branching process or, in this case, an infection outbreak satisfies

$$\mathbb{P}(Y = k) = \mathbb{P}(Z_1 = k - 1|Z_0 = k)/k \; , \quad (7.101)$$

from which the form of the outbreak size probability distributions, in theory, can be found (Jagers 1975, p. 42).

For a detailed description of the use of branching processes in epidemiology see Farrington *et al.* (2003).

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7.7 Metapopulations

M. Gyllenberg

7.7.1 Introduction

Most population models, both deterministic and stochastic, assume that all individuals of the population live in the same habitat and interact homogeneously with each other. Models of this type have been used successfully to describe, explain, and predict the local dynamics of one or several interacting species.

Natural populations of most species have a spatial structure, with several geographically distributed habitat patches that can support local populations. Such a population of populations is called a *metapopulation*. Local populations in a metapopulation are connected by migration. A local population may become extinct while the metapopulation persists. An empty patch may be colonized by migrants from other patches. Extinction and recolonization are the essential features of metapopulation dynamics. Hanski and Gilpin (1991) even characterized the study of metapopulation dynamics as the study of conditions under which these two processes are in balance and the consequences of this balance to associated processes.

Many important questions in ecology, genetics, and evolution require the metapopulation concept to be analyzed appropriately. For instance, conservation biology is an important area in which metapopulation dynamics plays a prominent

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References in the book in which this section is published are integrated in a single list, which appears on pp. 295–305. For the purpose of this reprint, references cited in the section have been assembled below.

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