27

CONCEPTS OF INFECTIOUS DISEASE EPIDEMIOLOGY

Chapter contributed by Graham Medley and Ian Dohoo

OBJECTIVES

After reading this chapter, you should be able to:

1. Understand why infectious disease data are fundamentally different from other forms of data previously dealt with in this text.

2. Know the terms used to describe infection and disease processes and understand the basic principles of disease transmission.

3. Understand the principles of modelling infectious disease transmission including SIR and SEIR models.

4. Understand the concepts of effective contact rate and basic reproductive number R_0.

5. Be aware of the variety of possible dynamics demonstrated by infectious disease models.

6. Understand how mathematical models are used to design control strategies.

27.1 INTRODUCTION

In previous chapters, we have examined methods for analysing data in which we assumed the observations were independent (Chapters 14–19), or had some dependency (Chapters 20–26). This dependency could be a function of the observations sharing a common environment, being repeated measures on the same individual, or being spatially related. Infectious diseases are different in that the dependency among individuals is related to the state of other individuals in the population. Individuals are thought of as susceptible or infected, and the probability of transmission depends on the rate of contact among individuals, and the probability of transmission occurring if contact is between a susceptible individual and an infected individual. Consequently, the risk of a susceptible individual becoming infected is dependent on the number of other individuals who are infected. If no individuals are infected, then the risk of infection to those susceptible is zero. This implies that the appropriate level of study for infectious disease is a population—the epidemiology of infectious disease is about the patterns of transmission among connected individuals.

Infectious diseases have a number of other unique characteristics which must be considered when analysing these data.

- Systems of infectious disease are dynamic. The rate at which new infections arise changes over time as the numbers of infectious and susceptible individuals in the population changes. Changes in the present will affect changes in the future. Consequently, the epidemiology of infectious disease has to be viewed over time; longitudinal studies are far more informative than cross-sectional studies.
- The dynamics of the infection process are non-linear. In practical terms, this means that the system does not respond proportionately to changes, whether they are intrinsic to the infection process or are introduced externally. In terms of intrinsic dynamics, epidemics are exponential (the doubling time is constant)—the number of infections increases non-linearly. Vaccination is an example of an external process; vaccinating 50% of a population with an effective vaccine will reduce the incidence of new infections by more than 50%.
- Pathogens must transmit to survive, which means that they require susceptible individuals in a population, *ie* those who can be infected. Immunity reduces the susceptibility of individuals after they have been infected, which provides a negative feedback on the pathogen population. A consequence of this is that infectious disease has a natural balance at the endemic state (*ie* when the incidence and prevalence are constant), which results in the phenomenon termed ‘herd immunity’.
- There is heterogeneity among individuals. However, with infectious disease this heterogeneity is magnified in populations due to non-linear dynamics. Two populations with exactly the same starting conditions (*ie* population structure and environment, number of infectious individuals *etc*) could have different disease outbreaks because transmission of the agent among individuals is a stochastic process, and small differences occurring by chance can result in big differences in the outcome.
- Threshold effects are present. If one infected individual passes the infection to less than one other individual (on average), the infection will die out. The number of new infections arising from one individual in a fully susceptible population is called the basic reproductive number (R_0).

- Infectious agents are continually evolving. For example, pathogenicity of an agent, susceptibility to drugs, *etc* will change over time. Given the relatively short life cycle for many agents, this evolution may take place quite rapidly.
- Interventions targeted at a proportion of a population will have an effect on those individuals not targeted.

The combination of these characteristics means that infectious diseases behave differently than non-infectious diseases. They regularly emerge into human populations causing explosive epidemics (*eg* bubonic plague, HIV, SARS). On the other hand, successful interventions (*eg* vaccination, medication) can have equally dramatic impact on important public health problems in a relatively short period (*eg* smallpox, polio). More recently, it has become evident that there are epidemiological and evolutionary 'tussles' going on between pathogens and interventions, as diseases are controlled but then reemerge (*eg* tuberculosis, *Staphylococcus aureus*), hopefully to be controlled again.

Because infectious disease has one necessary and sufficient cause (but might have other factors involved in causality), it is possible to completely remove the risk of the disease. Infection and disease caused by a pathogen can be (Dowdle and Hopkins 1998):

- **Controlled** so that the incidence and prevalence of disease is reduced from an endemic level through active effort.
- **Eliminated** from a defined population, but intervention is still required because the pathogen exists outside the defined population and might be reintroduced.
- **Eradicated** from all populations. The only human example to date is smallpox.

It is also important to distinguish between **microparasitic** and **macroparasitic** infections. Microparasites are those infectious agents that are too small to count individually, so that modelling the parasite population explicitly is not practically possible. Thus, when modelling such infections, it is necessary to consider the state of the host (*eg* susceptible, infected, immune) leading to **compartmental models**. Macroparasites are those infections for which there is sufficient information and reason to consider modelling the parasite population explicitly using **intensity models** where the principal outcome is a measure of the number of parasites (*eg* parasite burden, tick count).

At a modelling level, the distinction between microparasite and macroparasite is pragmatic. Some infectious agents (*eg* Malaria sp.) may be treated as either, largely depending on the data available and the problem being addressed. This chapter will focus on compartmental models for microparasitic infectious diseases. For information on macroparasitic infections, the reader is referred to Anderson and May (1991) and Cox (1993).

Microparasite infections tend to be associated with the following biological characteristics.

- The agents are generally small and (relatively) antigenically simple (*eg* viruses and bacteria).
- The agents generally multiply rapidly within the host resulting in either death of the host or the production of immunity. Pathogenicity tends to be high. Immunity tends to be strong and long lasting. The duration of infection (*ie* before death or immunity) can be short.
- Sexual reproduction (recombination) is relatively rare and not obligatory; strain variation, for example, in pathogenicity is often considerable.

- If the duration of infection is short, the prevalence of infection is low, and persistence of infection within a population requires continual supply of susceptible hosts (*eg* through births or antigenic change).

In contrast, macroparasitic infections tend to have the following characteristics.

- The agents are large and (relatively) antigenically complex (*eg* nematodes, lice, ticks).
- The agents have complex life cycles involving multiple hosts or free-living stages, and multiply at different rates within the different life-cycle stages.
- The agents have the capacity (and often requirement) for sexual reproduction, and may additionally have asexual multiplication stages.
- Immunity to the agents is often relatively ineffective.
- The agents often have apparent low pathogenicity individually, but the disease impact increases with the numbers (burden) within a host (*eg* gastrointestinal parasites). The burden of infection is key to the impact that these agents have on the host.
- At the population level, macroparasitic infections are characterised by a high prevalence of infections with the number of agents present within the host dependent on external factors that affect the life cycle of the agent (*eg* weather).

These are biological characteristics or general tendencies rather than fixed rules. Examples of archetypal microparasite and macroparasite are measles and *Ascaris*, respectively. Many bacterial and protozoan infections are somewhere between the two. For example, bacteria causing gingivitis may have low pathogenicity (rarely kill the host), generate little immunity in the host, and may be prevalent at quite high levels. Nevertheless, they would be modelled using compartmental models because it is not possible (or necessary) to quantify the number of bacteria present.

27.2 INFECTION VS DISEASE

Infection and **disease** must not be confused. While infection is necessary for disease, not all infected people will become diseased (*ie* develop clinical signs and symptoms). The time courses of infection and disease, sometimes known as the natural history, are shown in Fig. 27.1.

The states of infection are as follows. A **susceptible** individual becomes infected by transmission of the agent from an infectious individual who then enters a **latent period** when the infectious agent is present but the individual is not capable of transmitting the infection. This latent period could be short (*eg* a few days for influenza) or long (*eg* many years for tuberculosis). (**Note** For non-infectious diseases, the term ‘latent period’ refers to the time from the onset of detectable changes, *eg* lesions present or changes in biochemical parameters evident, to the onset of clinical signs. This is also referred to as the subclinical, clinically silent or asymptomatic disease period). The latent period is followed by an **infectious period** during which the host is capable of transmitting the agent. Again, this may be short (*eg* approximately 2 weeks for measles, mumps, and rubella) or long (years for hepatitis B). The lengths of the latent and infectious periods cannot normally be observed directly in humans. However, in a veterinary context experimental infections are very informative (Charleston *et al*, 2011). The infectious period ends when the host is removed from the population or becomes non-infectious through an intervention (*eg* treatment, quarantined), death, or the development of immunity which either eliminates the agent from the host or sufficiently suppresses replication to effectively

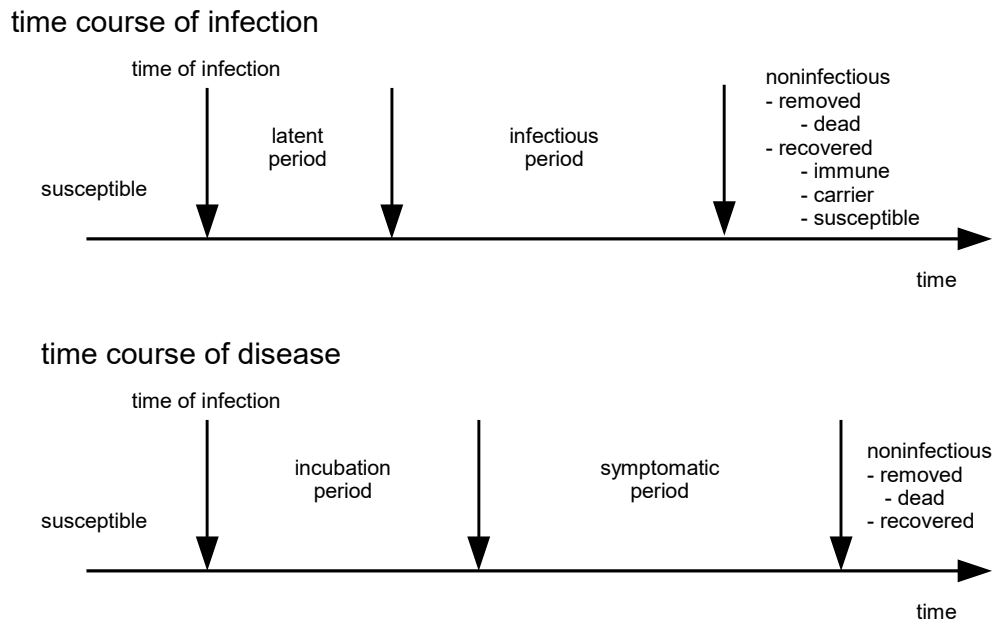

Fig. 27.1 Time courses of infection and disease processes

prevent transmission. For some infections, immunity may be long lasting (*eg* smallpox), while for others the individual may quickly return to a susceptible state (*eg* gonorrhoea).

The states of disease are as follows. On infection, a susceptible individual enters the **incubation period** and remains there until signs of disease develop or immunity develops (in which case the individual may never be symptomatic). The length of the incubation period cannot be observed directly unless the timing of infection is known. The symptomatic period ends when the host recovers (with or without treatment) or dies.

Note that the periods of infection and disease are relatively artificial thresholds in a continuous process, and that there is considerable variation in the time course of infection and disease between individuals. This variation may be related to environmental factors (*eg* nutrition), host genetics, agent genetics (*eg* strain), dose of infection *etc*. Consequently, estimating the duration of these periods is not straightforward. Methods for estimating the incubation period from outbreak data have recently been reviewed (Cowling *et al*, 2007).

The relationship between the **latent period** and the **incubation period** is important from an epidemiological perspective. If the latent period is shorter than the incubation period, there will be asymptomatic individuals who are shedding the agent, which curtails the opportunity to treat or isolate them (*eg* influenza, SARS), and means that disease data lags behind infection (*eg* HIV). This has important implications for implementation of control measures that require diagnosis of infection.

27.3 TRANSMISSION

27.3.1 Routes of transmission

From the viewpoint of the agent, it must transmit in order to survive because no host is immortal. There are a number of routes whereby **transmission** of an agent from an infectious individual to a susceptible person can occur. Again, it is important to remember that these routes are not defined by the agent. It can be useful to distinguish between the route of transmission and the mode of transmission. The route is the epidemiological important aspect, and the mode is important in terms of intervention (Medley and Nokes, 2010). For example, that HIV infection can pass from mother to child is epidemiologically important (regardless of how the transmission is achieved), but whether the mode is transplacental and/or transmammary has important implications in terms of interventions to prevent the transmission. Here we concentrate on the route of transmission.

- **vertical transmission**— from a mother to her offspring (*eg* HIV, hepatitis B)
- **horizontal transmission**
    - **indirect transmission**
        - **vector borne**—often by arthropod vectors (*eg* malaria, *Yersinia pestis* (bubonic plague).
        - **environment**—either environmental contamination (*eg Legionella*) or via other fomite (*eg* transmission of hepatitis B by reused intravenous needles).
    - **direct transmission**
        - **close contact**—transmission requires close contact between 2 individuals (*eg* respiratory syncytial virus).
        - **casual contact**—less intimate contact is required for transmission (*eg* respiratory infections such as influenza and measles).
        - **sexual transmission**—requires sexual contact (*eg* human papilloma virus (HPV) or gonorrhoea).
        - **air/water borne transmission**—can occur over long distances by the agent being carried by wind or water movement (*eg* cholera).

Zoonoses are diseases that are caused by pathogens that primarily (or exclusively) exist in non-human hosts, but which will cause disease if transmitted to humans, *eg* rabies, *Borrelia* spp. Zoonotic diseases can be transmitted by any of the routes listed above. The rest of this chapter will focus primarily on non-zoonotic diseases with direct transmission, particularly those spread through close or casual contact, or sexual transmission.

Transmission depends on **contact** among individuals in the population, and **transmission** given that contact is made. Contact is defined as those encounters between individuals that could (but not necessarily would) result in the transmission of the agent if one individual was infectious and the other susceptible. The **contact rate** (c) is defined as the number of contacts that an individual makes with other people in one time period. The **probability of transmission** (p) is defined as the proportion of contacts which result in transmission if one of the individuals is infectious and the other susceptible. It depends on the characteristics of the agent, the nature of the contact and the degree of infectiousness of the infected person. The product of the contact rate and probability of transmission (cp) is the **effective contact rate**. Table 27.1 presents a list

Table 27.1 Infectious disease parameters

Parameter	Description	Assumption/Calculation
S, I, R, N	the numbers of susceptible, infectious, removed, and total number of people in the population (respectively)	At the start: S=996, I=4, N=1000
c	rate of contacts an individual makes with other people in one time period	10/person/day
p	probability of transmission on contact if one person is infectious and one is susceptible	0.15
cp	rate of 'effective' contacts	1.5/person/day
I/N	proportion of population that is infectious	4/1000=0.004
$\lambda=cp(I/N)$	rate at which susceptible people become infectious - equivalent to our usual definition of I—(incidence rate) (see Section 27.4) - also called the 'force of infection' or 'transmission rate per susceptible'	1.5x0.004=0.006 new inf. per person per day (or 0.006 per person-day)
$i=\lambda S$	incidence=rate at which new infections are occurring in the population - this is the population incidence rate (designated *i* to differentiate it from I (used above and elsewhere in this book)	0.006x996≈6 new inf. per day
d	duration=duration of the infectious period	5 days
cpd	rate of effective contacts per infectious period	1.5x5=7.5/person/period
s=S/N	proportion of the population that is susceptible **Note** In a completely susceptible population $S_0=N$ so $s_0=1$	996/1000≈1
$R_0=cpd$	R_0=basic reproductive number=# of new cases that arise from an infectious individual in a completely susceptible population.	$R_0=1.5x5=7.5$
$R_t=cpds_t$	R_t=effective reproduction number=# of new cases arising from each infectious individual at time t. **Note** $s_t=S_t/N$ **Note** at t=0, s=1, so $R_t=R_0$	

Note The calculations in this table pertain to the first day of the hypothetical outbreak. On the second day, there will be 10 (6+4) infected people so λ becomes 1.5*0.01=0.015 and *i* increases to 0.015*990=14.85.

of parameters and definitions used throughout this chapter, along with a simple set of calculations, based on the first day of a hypothetical outbreak, showing their relationships.

27.3.2 Patterns of transmission

The nature and frequency of contacts is heavily determined by the social structure of the population. Mixing is considered **homogeneous** if everybody has an equal chance of contacting everybody else, and everybody has the same average experience. Mixing is considered

heterogeneous if either a person is more likely to contact others with certain characteristics, for example, age or occupation, or if some individuals have higher contact rates than others. Heterogeneity in contact patterns and contact rates is particularly important as some people are both more likely to be infected and more likely to infect. This group is termed a **core group**. The core group differs depending on the route of transmission and natural history of the disease. So, for example, the core group for gonorrhoea are people with a high rate of change of sexual partners, whereas the core group for measles is children in their first years at school.

For sexually transmitted infections, the highly variable (variance >> mean) distribution of sexual contacts is particularly important (Johnson *et al*, 2012). For transmission through more casual contacts, social (including family) structure is important. In particular, households and schools play pivotal roles for most close contact infections. This is partly because children have a greater frequency of closer contact with other children than adults have with other adults, and partly because children are more susceptible to infection since they are without the immunity generated by previous exposure. For examples of transmission patterns generated by close contacts see Grenfell *et al* (2004); House and Keeling (2009) and Mossong *et al* (2008).

27.4 MATHEMATICAL MODELLING OF INFECTIOUS DISEASE TRANSMISSION

Terminology/Acronyms

Throughout this chapter, I is used to denote the number of infectious individuals in a population. (It does not represent an incidence rate as used elsewhere in the book). The term R is used to denote the number of 'removed' individuals. R is also used for the reproductive number, but in this case it will always have a subscript R_0 or R_t.

Mathematical models are the *lingua franca* of infectious disease epidemiology because of their inherent time dependence and non-linearity (Grassly and Fraser, 2008). Because infectious disease involves at least 2 species (host and pathogen), and frequently involves more (multiple hosts and multiple pathogens), the study of infectious disease epidemiology and population dynamics is embedded in the methodology of population ecology. Parasitism is an ecological process of the same standing as herbivory and predation: influenza viruses use humans as a niche. In this section we outline the basics of these models. For a more in-depth analysis and practical treatment see Anderson and May (1991) and Keeling and Rohani (2007).

Mathematical models can be conceptualised as a collection of assumptions that are combined together to give a quantitative framework describing the numerical changes expected if the assumptions hold. The assumptions are a mixture of explicit and implicit, and the quality of the model is largely determined by the accuracy of the assumptions.

Mathematical models of disease transmission may be developed and used for 3 reasons (Green and Medley, 2002).

- Conceptual models may be used to better understand the effects of interventions in disease control processes. For example, Fraser *et al* (2004) used conceptual models to evaluate the effects of control programs based on active surveillance, and McLean and

Blower (1993) used them to develop a framework for understanding the impact of vaccination.

- Conceptual models may be combined with data derived from experimental research to develop predictive models of disease transmission within populations having set characteristics. These can then be used to estimate the effects of disease control interventions, although this use is more common in veterinary medicine (Charleston *et al*, 2011).
- Conceptual models may be combined with observed data (*eg* from naturally occurring outbreaks) to gain insights into the epidemiology of the disease in those populations, and to estimate parameters such as R_0, for example: Cauchemez *et al*, 2004; Finkenstadt *et al*, 2002.

Generally, disease models may be **deterministic** or **stochastic**. The former produce a single outcome for a given set of parameters. The latter incorporate the chance nature of events (such as transmission) and produce a probability distribution of possible outcomes (Keeling and Rohani, 2007). The mean of the stochastic model is not always the same as the result from a deterministic model, and the former may show that the outcome has a bimodal distribution; for example when a highly infectious individual is introduced into a susceptible population, deterministically the early outcome is an exponentially increasing epidemic, but the stochastic outcome is bimodal with a peak of probability at no epidemic (if the initial invasion happens to fade out by chance) and a peak of probability at an epidemic level. In this case, the mean of the stochastic process is not the same as an estimate derived from the deterministic model.

The simplest model for microparasites is the **Susceptible-Infectious-Recovered** (SIR) model as shown in Fig. 27.2. In an SIR model, the population is divided into three compartments into which every individual fits into one, and only one, of them. Susceptible individuals (S) are assumed to become infected (and immediately infectious) at a defined rate (λ). Infected individuals (I) are assumed to recover (and be immune) at a defined rate (γ). Recovered individuals (R) are assumed to remain in that state for the remainder of their lives. The total population size is $N=S+I+R$.

An SIR model can be used to define the key parameters required for modelling infectious diseases. These are all listed in Table 27.1 along with a simple example of their calculation. This example assumes that an infectious agent is introduced into a closed population of completely susceptible people. The concept of a closed population is common; the assumption is that people neither leave nor enter (*ie* immigration and emigration have zero rates) and there is no contact with any other people. The following specific assumptions complete the model.

- There are 1,000 people and they mix homogeneously ($N=1000$).
- The contact rate among people is 10 contacts per person per day (*ie* each person has 10 contacts with other people on a daily basis) and is homogeneous within the population.
- A new infectious agent is introduced into the population and it initially infects 4 people.
- The probability of transmitting the disease during any one contact is 15% (0.15).

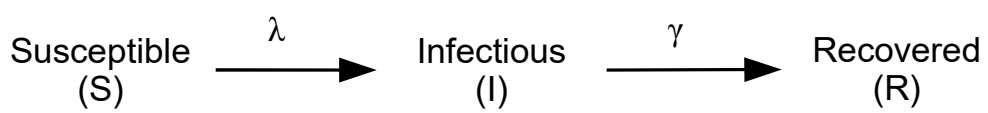

Fig. 27.2 A simple SIR model with two rates: transmission and recovery

- People are infectious for 5 days, at which point they recover and develop sufficient immunity to protect from further infection.

27.4.1 Incidence rates

There are 2 incidence rates presented in Table 27.1. λ corresponds to the usual incidence rate (I) described in Chapter 2. In the example population, there are 1,500 effective contacts happening each day, but only 0.4% of them involve infectious people, so the chance of an individual susceptible person becoming infected on this first day is only 0.006 (equating to 6 people becoming infected on that day). From the perspective of a susceptible person, λ represents their chance of becoming infected in a short time. This is sometimes referred to as the **force of infection**.

As noted, the incidence rate (i) in Table 27.1 is the population incidence rate and represents that rate at which new infections are occurring in the whole population. As the proportion of the population that is susceptible declines, i will fall, even though λ might remain high.

27.4.2 Basic reproductive number

As noted in Table 27.1, the basic reproductive number (R_0) represents the number of new infections which arise, on average, from one infected individual when the entire population is susceptible (*ie* at the beginning of an epidemic) with:

$$R_0 = cpd \qquad \textit{Eq 27.1}$$

R_0 is a product of the rate of effective contacts (cp) and the duration of the infectious period (d). It is a key parameter for understanding infectious diseases. If $R_0 > 1$, then the infection is expected to spread because each infected individual generates, on average, more than one new infection. If $R_0 < 1$, then the infection is expected to die out. However, as noted, transmission is a stochastic process and there is no guarantee that disease will spread if $R_0 > 1$, or that there will not be additional cases with $R_0 < 1$. In addition, R_0 is an average value for a population and there may very well be clusters of individuals (core groups) within a population in which the R_0 could be much higher or lower than the average.

As the infection spreads in the population and some individuals move from susceptible to infectious and then to recovered, the population is no longer completely susceptible. The **effective reproduction number** at time t (R_t) can be computed as:

$$R_t = cpds_t = R_0 s_t \qquad \textit{Eq 27.2}$$

where $s_t = S/N$ (the proportion of the population that is susceptible at time t). This chapter will focus on R_0 as a measure of transmissibility of infection among individuals within a population but it can also be conceptualised in terms of transmission between groups of individuals, *eg* households (Fraser, 2007).

27.4.3 Differential equations

The natural history of infection for the SIR model shown in Fig. 27.2. combined with the assumptions for transmission, can be written as a system of differential equations, which

describe the instantaneous rate of change of the 3 proportions (*S*, *I*, and *R*) in the population (see Table 27.1 for definition of parameters).

$$\dot{S} = -\lambda S = -cp\frac{SI}{N}$$
$$\dot{I} = \lambda S - dI$$
$$\dot{R} = dI$$

Eq 27.3

The differential equations provide rates of change for each compartment (symbolised as *S, I*, and *R* with a dot over each of them), given the state of each compartment. In order to solve them, we require 'initial conditions' or a starting point. Generally it is impossible to derive an analytical solution for such equations, (*ie* equations of the form $S_t=S_0e^{-\lambda t}$) because λ depends on *I* which depends on *S etc*.

This class of problem is known as an 'initial value problem'. Given the model assumptions, parameter values, and initial conditions for *S*, *I*, and *R* at $t=0$, what would be the values of *S*, *I*, and *R* at $t>0$? These equations must be solved numerically. This process follows on from what is presented in Table 27.1—taking a small step in time, one can calculate the new numbers of susceptible, exposed, infected, and recovered people, and then repeat this process. To solve these equations accurately requires a small step size; this is only feasible using computer software, and there are many packages available for solving such systems of ordinary differential equations (*eg* MatLab, Berkeley Madonna, Mathematica, Maple).

27.5 METHODS OF CONTROL OF INFECTIOUS DISEASE

There are 3 ways in which infectious disease can be controlled.

- General or mass reduction in contact rate, *c*, or the probability of transmission on contact, *p*, by changing behaviour. This intervention reduces the basic reproduction number reducing the rate of transmission. Examples include educational interventions to reduce the rate of sexual partner change and advocating the use of condoms (sexually transmitted infections), or compulsory closing of schools to reduce contact between children (influenza). Note that this intervention is not targeted at infected individuals.
- Immunisation of susceptible individuals. Generally immunisation works by changing the immunological state so that individuals are (less) susceptible to infection. Note that this intervention does not change the basic reproduction number: the rate of contact, probability of transmission, and duration of infectiousness are unaltered. Immunisation has been used successfully to control many pathogens (*eg* pertussis), eliminate some (*eg* polio from the Americas) and eradicate one (smallpox).
- Targeted interventions on infected individuals to prevent transmission. This intervention reduces the duration over which an individual is able to infect. Infected individuals that are diagnosed can be treated to remove infection, curtail infectiousness, or reduce their contact with susceptible individuals through quarantine. This has the effect of reducing the duration of infectiousness, *d*, and reduces the basic reproduction number. Note that although quarantine is a reduction in contact, because it is targeted at infected individuals only, it is not the same as a general reduction in contact. This intervention (unlike the others) requires that infected individuals are first identified, for example, through clinical diagnosis and contact tracing of known cases.

27.5.1 Mass reduction in contact

These interventions reduce the effective contact rate, which has a linear impact on R_0 *ie* halving effective contact halves R_0. However, the amount of infection and disease changes non-linearly with R_0 so that reducing R_0 from 10 to 5 has very little impact, but reducing R_0 from 3 to 1.5 will halve the prevalence of infection. The ideal outcome of such an intervention would be to reduce R_0 to below 1, at which point the disease would die out.

Changing contact rates in the general population is popularly seen as the best way of controlling disease: most epidemics are accompanied by exhortations to wash hands, wear condoms, or avoid travel. These messages are important in that they empower susceptible individuals with a means to reduce their risk of infection, but as public health interventions against directly transmitted infection they are largely ineffective; the majority of transmission occurs within the core group (Woolhouse *et al*, 1997). The basic reproduction number in the population outside of the core group might already be less than 1, so changing behaviour of this group does not have a great impact. If such interventions are to be effective, then they need to dramatically change the behaviour of the core group; *ie* stop them being a core group. But this often presents particular problems in terms of compliance and stigmatisation, and the degree of behaviour change required to have impact.

However, such interventions can be highly effective when they are targeted at specific transmission routes. For example, insecticide impregnated bednets have been highly effective at reducing transmission of malaria (Alonso *et al*, 1993; Trape *et al*, 2011).

27.5.2 Immunisation

Vaccines are often used to prevent transmission of infection and/or the development of disease in populations. If a vaccine only prevents the development of disease and has no impact on the spread of the infection (*eg* tetanus toxoid), then it will have no effect on the transmission dynamics of the agent. We will focus on a vaccine having an effect on the transmission of the agent. If a vaccine is 100% effective at preventing infection and is applied to all individuals in the population, then no new infections will occur. However, vaccines are rarely 100% effective, and it is often not possible to vaccinate all individuals in a population.

If a proportion (f) of a population is vaccinated with a vaccine which is fully protective, the effective reproductive number (R_t) is:

$$R_t = R_0(1-f) \qquad \textit{Eq 27.4}$$

R_t will be less than 1 when $f > 1\text{-}1/R_0$, so in this case, the infection will be expected to die out. If you have an estimate of the expected R_0 for an agent in a given population, you can estimate the vaccine coverage that you will need to prevent the spread of infection (sometimes called the **critical percentage** (denoted f_{cp})). For example, if R_0 is 5, then f_{cp}=1-1/5=0.8 or 80% of the population needs to be vaccinated with a 100% effective vaccine to prevent the spread of infection. This is the principle which underlies the concept of **herd immunity**, which states that you do not need to vaccinate every individual in a population in order to prevent an epidemic.

If a vaccine only protects a proportion of individuals (h) (but fully protects those individuals), then $R_f=R_0(1-hf)$ so the proportion of individuals which needs to be vaccinated becomes:

$$f_{cp}=\frac{1-1/R_0}{h} \qquad \textit{Eq 27.5}$$

A vaccine that only changes the immune status of susceptible individuals does not alter the basic reproduction number. However, imagine a vaccine which only reduced the duration of infectiousness by a factor z. If it is given to a fraction f in the of the population, then its impact is to change the basic reproduction number to $cpd(1-f+zf)$. The proportion required to be vaccinated to reduce the new R_0 to 1 is:

$$f_{cp}=1-\frac{1-1/R_0}{1-z} \qquad \textit{Eq 27.6}$$

Vaccine-induced immunity might also have a time limited effect (McLean and Blower, 1993). These concepts are important not only for understanding and modelling the effect of vaccination, but for planning field trials to assess effectiveness of vaccination (see Section 11.10).

27.5.3 Diagnosis and prevention of transmission

The third approach to controlling disease is to intervene directly to prevent its spread from people who are already infected. This requires that infections can be diagnosed and transmission curtailed. Infections can be diagnosed either through clinical signs and symptoms (*ie* when it becomes disease) or laboratory-based assays to detect infection. On detection, infectious cases have to be either cured through chemotherapy (antivirals or antibiotics) or through isolation or quarantine. The effect of such interventions is to curtail the period over which infection is transmitted. As a simple example, suppose that all cases of infection show unmistakable clinical symptoms part way through the infectious period, and that transmission can be stopped at this point. If q is the proportion of the infectious period that remains with this intervention, then the new infectious period can be written dq, so that the basic reproduction number becomes $cpdq$ so that $q < 1/R_0$ if infection is to be eliminated. For example, if R_0 is 5, then in order to eliminate transmission it has to be stopped at or before 20% of the time into the infectious period. Frazer *et al* (2004) used examples of SARS and HIV to point out the importance of the relative length of the time between onset of infectiousness and symptoms to the duration of infectiousness for controlling infections when diagnosis is by clinical means only.

The principal complication of this method of control is that diagnosis and transmission intervention have to be prompt (relative to d). If a diagnostic method requires 3 days to complete (*eg* culturing pathogens from clinical samples), then infected individuals will have 3 days of unstoppable transmission. Additionally, the diagnostic methods are never 100% sensitive, and transmission interventions are never 100% effective. Consequently, for this approach to work, it usually has to be imposed on individuals who are not known to be infected, but for whom there is some level of risk greater than the general population of being infected. Direct contacts of known infections are more likely than the general population to be infected and might be presumed infected, leading to contact-tracing as a means of curtailing the infectious period (ideally to zero). The transmission interventions that can be imposed depend

on public acceptability, economic costs, and health risks, weighed against the size of the presumptive risk. For diseases where there is no vaccine available (which includes all new infections), interruption of transmission is the only method of control available. The most recent examples have been SARS (Lipsitch *et al*, 2003) and influenza (Eames *et al*, 2010).

The combination of two processes (diagnosis and transmission-intervention) poses some problems for management of such interventions, since both have to be sufficiently funded if the whole intervention is going to work (Robotham *et al*, 2007). Cooper *et al* (2004) modelled the role of isolation capacity on methicillin resistant *Staphylococcus aureus* (MRSA) and demonstrated that if the intervention capacity is fixed (*eg* if there are a limited number of beds in an isolation ward), then there is a chance of catastrophic failure, *ie* when the isolation ward is full, control fails.

27.6 ESTIMATING R_0 AND OTHER PARAMETERS

27.6.1 Limitations of R_0

As noted above, if $R_0>1$, the infection is expected to spread in a susceptible population. However, disease transmission is a stochastic process (there is an element of 'chance' as to whether or not transmission will occur). If an infection is introduced into a homogeneous susceptible population, the probability of an outbreak (transmission of the infection past the initial time period) is:

$$p(\text{outbreak}) = 1-(1/R_0)^{I_0} \qquad (\text{assuming } R_0>1) \qquad \textit{Eq 27.7}$$

where I_0 is the number of infectious individuals introduced into the population (at t=0) (Keeling, 2005). Thus, with R_0=7.5 and a single infection introduced, the probability of an outbreak is 87%, but if 4 infections are introduced, this rises to >99%.

However, even if the infection does spread from the initial infectious individuals, the size and timing of the resultant epidemics can vary greatly. Similarly, if $R_0<1$, there is no guarantee that additional cases will not be observed in the population. Fig. 27.3 shows a range of possible epidemic curves for values of R_0 ranging from 0.5 to 2.0. For each value of R_0, 20 outbreaks were simulated and 5 selected to represent the range of possible outcomes. Each outbreak was based on a population of 100 susceptible individuals with one infectious individual being added; duration (d) is 1 day. The solid line represents the expected course of action (deterministic simulation). Even at R_0=0.5, some limited outbreaks occur. At R_0=2.0, some outbreaks die out quite quickly while in others, most of the population becomes infected.

27.6.2 Estimating the probability of transmission

Estimation of the contact rate (c) and the probability of transmission (p) is difficult. In outbreak situations, the **secondary attack rate** (SAR) is a measure of the probability of transmission. (**Note** SAR is actually a risk not a rate.) The SAR is defined as the probability that a susceptible individual will become infected from the first (primary) case in a population. It is the number of secondary cases (infections derived from the primary case) divided by the number of susceptible individuals exposed.

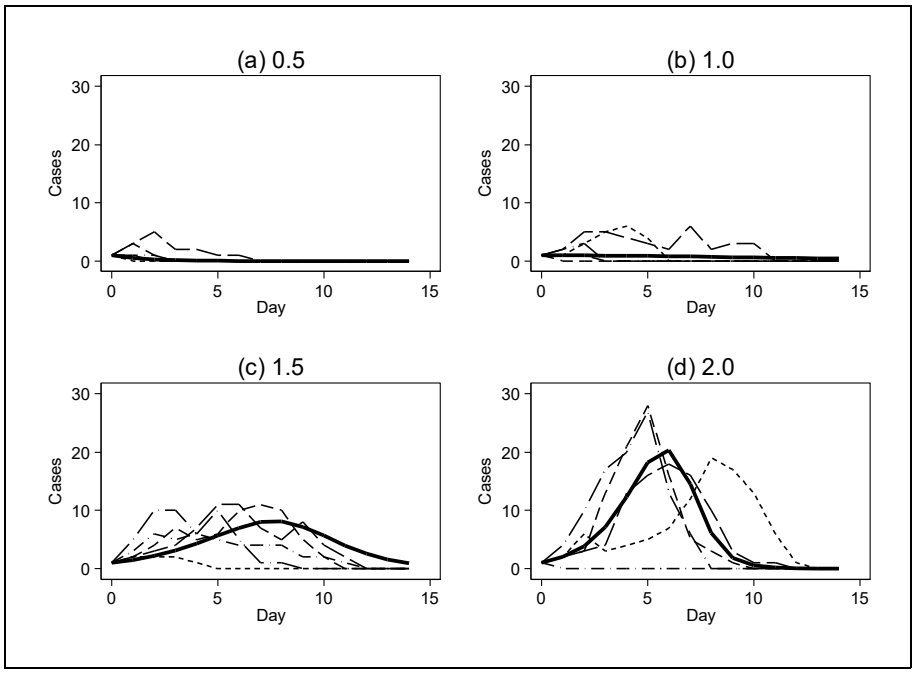

Fig. 27.3 Examples of 6 simulated outbreaks based on R_0 values of 0.5, 1.0, 1.5, and 2.0 in panels (a) to (d), respectively

$$\text{SAR} = \frac{\text{number of secondary cases}}{\text{number of exposed individuals}} \qquad \textit{Eq 27.8}$$

SARs are usually calculated using data from small-scale outbreaks (*eg* an outbreak in a single household) in situations in which it is clear at what time the index case arose. The problem in computing the SAR is deciding which cases are secondary (for an example using tuberculosis, see Brooks-Pollock *et al* (2011)). This requires knowledge about the expected (and minimum and maximum) incubation period of the disease and the latent period of the infection, both of which might be unknown or imprecisely known (Fraser *et al*, 2009). The time of infection of the primary case (t_0) is estimated based on the expected incubation period and the latent period. Secondary cases are defined as those that occur between t_0 plus the minimum incubation period and t_0 plus the maximum incubation period. This is shown graphically in Fig. 27.4. Since data on timing of disease onset is rarely completely accurate, methods that use data on total numbers of cases within a household can be useful.

An alternative approach to estimating p is to use a **binomial model** of disease transmission. Rather than basing the probability of transmission on the number of exposed individuals, a binomial model relates the number of new cases to the total number of contacts with infectious individuals. Consequently, it may be appropriate when susceptible individuals have multiple contacts with potentially infectious individuals. The probability of transmission during any one contact is p so the probability of avoiding transmission is q=(1-p). The probability of avoiding infection from n potentially infectious contacts is q^n so the probability of becoming infected is $1-q^n=1-(1-p)^n$. These models can be extended over time by assuming that the binomial transmission probability is applicable in discrete time units. These are called **chain binomial**

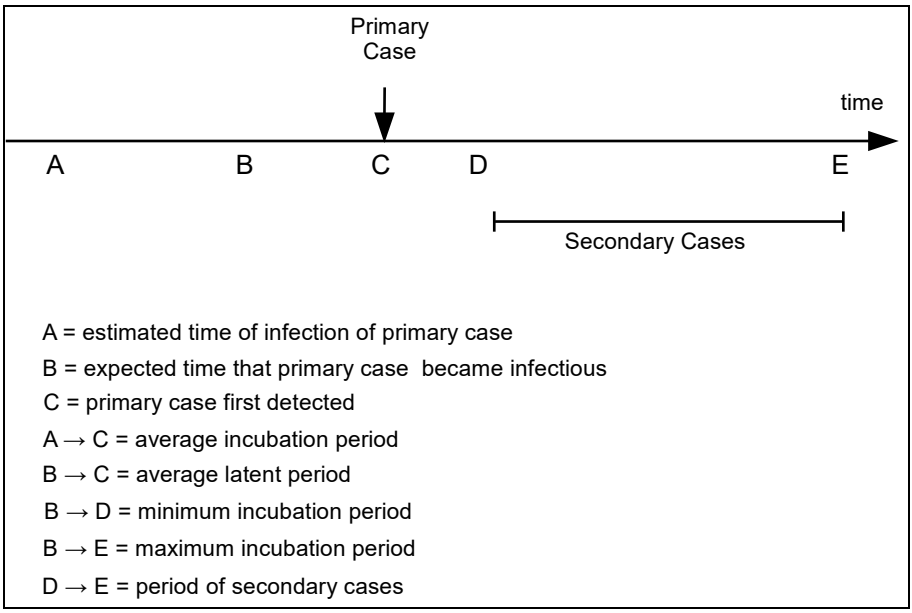

Fig. 27.4 Estimation of a secondary attack rate based on knowledge about expected latent and incubation periods

models and include **Reed-Frost** and **Greenwood** models. The former assumes that exposure to 2 or more infectious individuals in the same time period are independent events, whereas the Greenwood model treats them as a single exposure. Although conceptually appealing for understanding disease transmission, binomial models have largely been superseded by methods that include the possibility of infection from outside of the population under surveillance and other complications (Brooks-Pollock *et al*, 2011; Longini *et al*, 1982).

27.6.3 Estimating R_0 from the exponential phase of an outbreak

During the early stages of an outbreak, the number of new cases occurring is not limited by the availability of susceptible individuals. This phase is referred to as the **exponential phase** and the **doubling time** (t_d=time it takes for the number of new cases to double) is related to R_0 as follows:

$$t_d = (\ln 2)\, d\,/(R_0 - 1) \approx 0.7\, d\,/(R_0 - 1) \qquad \textit{Eq 27.9}$$

where d is the duration of the infectious period. This assumes that the outbreak is growing exponentially, which in turn depends on the number of susceptible individuals not being depleted (Anderson and May, 1991). From this, if an estimate of t_d can be derived from the data and an estimate of d is available from experimental research, then:

$$R_0 = 0.7(d\,/\,t_d) + 1 \qquad \textit{Eq 27.10}$$

One approach to estimating t_d is to fit an exponential regression model, with time as the only predictor, to the data from the exponential phase of an outbreak and:

$$t_d = \ln 2/\beta \quad \text{and} \quad R_0 = (\beta_d) + 1 \qquad \textit{Eq 27.11}$$

where β is the slope from the regression. If the infection process involves both latent and infectious periods, d is replaced by the **generation interval** which is the sum of the infectious and latent periods. Estimates of t_d (or R_0) using this approach are sensitive to the choice of distribution for the duration of the generation interval (Wallinga and Lipsitch, 2007).

At the peak of an outbreak, where the epidemic curve switches from increasing to decreasing (*ie* the number of new infections in a time period switches from rising to declining) then R_t=1 (*ie* one new infection per existing infection. Because R_t=R_0 *s_t=1, then:

$$R_0 = 1/s_t \qquad \textit{Eq 27.12}$$

where s_t is the proportion of the population susceptible at the time of the peak (called the **critical proportion susceptible**). However, given the variability in the form of outbreaks (see Fig. 27.3), this approach is not used.

27.6.4 Estimating R_0 from time series

As noted above, R_0 is specific for a given agent in a specified population at a point in time. Nevertheless, estimates of R_0 from some populations can provide some insight into what to expect in new situations. However, given the range of possible outbreaks scenarios that are consistent with a single value of R_0, estimation of R_0 from a single outbreak will be of limited value.

The methods outlined above are limited by rather strict assumptions. These assumptions are needed to overcome the complication that exact data on all relevant events and timing of events are not available, and are generally unknowable. If the date of infection and onset of infectiousness was known for all individuals, then estimation of R_0 and all attendant parameters would be relatively straightforward. Modern computational resources mean that methods have become feasible which test different values for missing observations to see how they affect the estimates of R_0. A detailed discussion of these techniques, mostly based on the Markov Chain Monte Carlo (MCMC) approach, is beyond the scope of this chapter, but the interested reader is referred to the following papers as an introduction to the literature: Auranen (2000); Cauchemez *et al* (2004); Cooper *et al* (2008); Gibson and Renshaw (1998); and Jewell *et al* (2009).

27.6.5 Estimating R_0 for endemic diseases

So far, we have considered the situation where an infection is introduced into a population and gives rise to an outbreak or epidemic. These instances attract the most political and public attention. However, most infections are endemic (*ie* they survive continuously in a population). Even if there are fluctuations in the incidence over time, the continual existence of the infection means that each infection produces, on a long-term average, one other infection (*ie* R_t=1 and therefore s_t=1/R_0). Note that this is the same situation as at the peak of an epidemic. For a disease to remain endemic, there must be a supply of susceptible individuals—the reason that epidemics (c) and (d) in Fig. 27.3 became extinct was that there were no susceptible individuals left in the population.

The two principal sources of susceptible people are birth and loss of immunity. The endemic state is at a dynamic equilibrium created by the tension between supply and loss (through

infection) of susceptible individuals. A simple numerical example illustrates this. Imagine a population in which 10 susceptible individuals arise every day. If there are more than 10 infections every day, then the total susceptible population will fall, which will mean that eventually the amount of infection will reduce. If there are less than 10 infections every day, then the number of susceptible individuals is increasing, and eventually the amount of infection will increase. Because the change in the number of infections is positively correlated with the number of susceptible individuals, there is an equilibrium rate of infection (in this example 10 per day), at which the numbers of susceptibles and infections exactly balance. The proportion of the population susceptible at this steady state is termed the critical proportion susceptible, and denoted s^*. From Eq. 27.12, it is easy to see that:

$$s^* = 1/R_0 \qquad \textit{Eq 27.13}$$

Although it is theoretically possible to use this relationship to estimate R_0 for an endemic infection, in practice it requires knowledge about risk behaviour and the core group, which is usually lacking (for an exception see Johnson *et al* (2012)). However, for childhood viral infections such as measles, mumps, and rubella (MMR), the core group is defined by age, and this approach is naturally used to estimate R_0. At endemic equilibrium, the average age at which individuals become infected (A) and the average lifespan of individuals (L) can be used to estimate λ (the incidence rate of new infections), as well as R_0 and s^*:

$$\lambda = 1/A \qquad R_0 = L/A \qquad s^* = A/L \qquad \textit{Eq 27.14}$$

This approach only works when L is a threshold (*ie* everybody survives to age L and then dies) and the total population size is constant, which is approximately true for people in developed countries, but not for developing countries (Anderson and May, 1991). The estimate of R_0 is an overall estimate representing an average level of transmission within and between different groups. Knowledge about contact rates is required to come up with estimates of group-specific estimates of R_0.

If data about the age-serologic profile of an infection within a population are available, it is possible to derive an estimate of λ (population incidence rate). The proportion remaining susceptible at age=a (denoted s_a) can be determined from a survival curve plot (*eg* Fig. 27.5). The slope of this curve at age=a is related to the incidence rate of infections (λ) according to the following relationship:

$$\text{slope}(a) = ds/da = -\lambda s_a \qquad \textit{Eq 27.15}$$

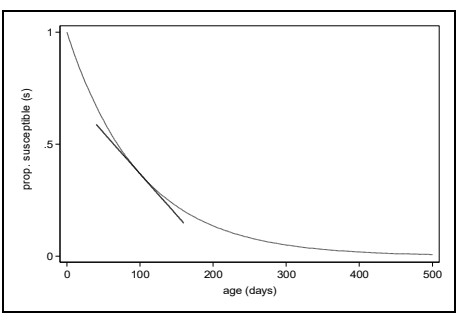

Fig 27.5 The slope of a survival curve can be used to estimate λ at any particular age

The approach avoids the assumption that the incidence rate of new infections is constant with age and λ can be estimated for different age groups.

Note If only a single age profile at one point is available, then time-dependent and age-dependent changes in λ are indistinguishable. See Vynnycky & White (2010) for more details of estimation from age-serological profiles.

Mathematical modelling was first used to predict the impact of immunisation on MMR (Anderson and May, 1991). One of the more surprising impacts is that those individuals who are not immunised will be older if and when they become infected, simply because the infection is made rarer by the immunisation. If the risk of disease increases with age at infection, then immunisation can increase disease. Unfortunately, this has been observed for rubella in Greece (Panagiotopoulos *et al*, 1999). The lesson here is that models are not just theoretically interesting: infectious disease transmission dynamics really are non-linear and complex.

27.7 Developing more complex models

27.7.1 More complex natural histories

A very simple SIR model was presented in Fig. 27.2. More complex models can account for more complex interactions between an agent and a host. For example, (as in Fig. 27.1) a newly infected individual will go through a latent period before becoming infectious. This gives rise to an SEIR (Susceptible—Exposed—Infectious—Recovered) model. Similarly, individuals may either die or recover (with immunity) after the infectious period, giving rise to the model shown in Fig. 27.6. In this model, there are only 3 rate parameters (λ γ δ) but there is an additional probability (probability of death) which needs to be estimated. Much more complex models can be found in the literature, but are beyond the scope of this text. For example, some infections develop an infectious carrier state (Medley *et al*, 2001) or periodic recrudescence of infectiousness (Brisson *et al*, 2000; Schiffer *et al*, 2010).

Note that the (implicit) assumption in the models in Figs. 27.2 and 27.6 is that the rate of progress through the E and I compartments is constant. This is equivalent to a constant hazard rate in survival analysis. In Table 27.1 the assumed duration of stay in the I class is exponentially distributed with mean 5 days. Other factors such as age effects on susceptibility and reproductive status on transmission can be incorporated into complex models. In practice, the complexity is limited by the availability of data and sufficient human and computational resources. It is not the case that more complex models are better; indeed, additional complexity can make models harder to understand and use, and can mask underlying principle results

27.7.2 Transmission heterogeneities

The simple SIR model assumes that each individual has the same average contact experience, and that each individual has the same chance of contacting all other individuals: the transmission term *pcSI/N*. In this section, we consider two approaches to capturing the fact that individuals do not contact each other at random. First, we consider sexually transmitted

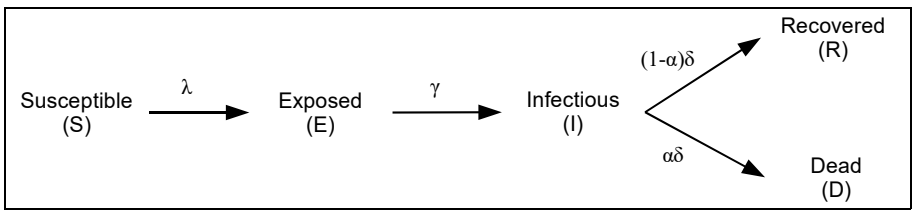

Fig. 27.6 SEIR model that allows for individuals to either recover or die

diseases in a heterosexual context, *ie* where there are two types of individual (male and female), these identities are fixed, and infection is only passed between them. Second, we briefly consider network approaches.

Separate populations: sex

For simple sexually transmitted infections, the population has to be divided between male and female, so that males become infected at a rate $p_M c_M S_M I_F$ (where the subscripts denote gender) and females become infected at rate $p_F c_F S_F I_M$. R_0 no longer depends on a single contact and transmission probability, but is an average of the male-to-female and female-to-male transmission rates. Generally, calculation of R_0 for multiple populations and transmission routes is not straightforward, and depends on the matrix of possible transmissions. For this two population model (male and female), the matrix of rates of infection is:

$$\begin{bmatrix} 0 & p_M c_M \dfrac{I_F}{N_F} \\ p_F c_F \dfrac{I_M}{N_M} & 0 \end{bmatrix}$$

where the zeros indicate that the infection cannot be passed between individuals of the same sex (non-zero entries here would indicate that transmission is possible between individuals of the same sex (*eg* male-to-male transmission of HIV)). In this case, assuming that the infectious period is the same for the two genders, the appropriate measure for R_0 is:

$$R_0 = d\sqrt{p_M p_F c_M c_F} \qquad \textit{Eq 27.16}$$

For a more complete discussion of multiple population diseases see (Deikmann and Heesterbeek, 2000). However, the principal complication for sexually transmitted disease models is that individuals vary greatly in their rates of sexual partner change, creating a very strong core group effect (Johnson, 2012).

Networks

The above approach to modelling transmission assumes that individuals contact other individuals at some rate, which is modified by the connectance between the groups that individuals occupy. In other words, there is a mean rate of contact, but 'who contacts who' is random. However, individuals tend to contact the same individuals repeatedly: *ie* individual have a network of contacts comprising family, friends and work/school colleagues. The 2 principal ways of modelling non-random interaction between individuals are household models, where individuals interact strongly within small cliques (Ross *et al*, 2012), and network models where links between individuals are explicitly stated (Keeling and Eames, 2005). However, although mathematically interesting, and of great potential, the challenge of such models is how to construct and parameterise them.

27.7.3 Reinfection threshold—diversity and variability

Infection with most pathogens does not create a solid immunity: MMR are the exception in this respect. Generally, immunity is either partial (*ie* it reduces the probability of infection on exposure) or wanes with time since infection (*ie* individuals start fully immune but eventually become fully susceptible to reinfection) (Gomes *et al*, 2004a). Observed immunity is a

relationship between host responses and pathogen diversity and pathogen variability. Diversity refers to the heterogeneity in pathogens at a point in time, and variability refers to the dynamic changes in the pathogen population. For example, if the antigens (those parts of the pathogen recognised by immunity) in a pathogen population change completely, then all individuals become susceptible again, and it appears that immunity has waned, although immunity might still be solid to pathogens expressing the previous antigens. Clearly, those pathogens that do change their antigens and are able to reinfect have an evolutionary advantage to pathogen types that retain the same antigens: pathogens are competing with each other for hosts and host susceptibility. Influenza is the prime example of this mode of reinfection. This gives rise to the concept of phylodynamics—the combination of epidemiological, immunological, and genetic processes that creates the diversity and variability in pathogen populations (Grenfell *et al*, 2001; Smith *et al*, 2004).

Pathogen diversity and variability have important implications for immunisation since they determine what proportion of infections can be prevented, and how long the immunisation is effective. The majority of vaccines are still made from preparations of pathogens, particularly killed pathogens, and live attenuated forms of the pathogen, and consequently vaccine inspired immunity generally has the same effect as immunity derived from natural infection. For pathogens in which natural immunity is solid (and births are the only source of susceptible individuals), vaccines work exceptionally well, and can eliminate infection. However, for pathogens in which reinfection is the norm, such vaccines might have no impact on the transmission dynamics of infection (although they might impact on disease). The proportion of infections that are reinfections is determined by the value of the basic reproduction number, so that a vaccine will have different apparent efficacies dependent on the value of R_0. There is a threshold, the reinfection threshold, above which immunity and vaccination have very little effect on transmission dynamics (Gomes et al, 2004b). Suppose that the proportion of infections that are prevented by natural immunity is 75%. If $R0<1/(1-0.75)$ or equivalently $R_0<4$, then immunity constrains the incidence of infection. However, if $R_0>4$, then the infection can survive in a population composed of people who have already been infected. This is the reinfection threshold: the value of R_0 below which completely susceptible people (from births usually) are required for the infection to invade and persist, and above which the infection can invade and persist in a population composed of people who have been previously infected. If a vaccine that provides the same degree of protection as natural immunity is used below the reinfection threshold, then it will appear to be effective to some degree. But if the same vaccine is used when R_0 is above the reinfection threshold, then it will appear to be completely ineffective, *ie* it will prevent no infections (Gomes *et al*, 2004b).

27.8 USING MODELS

In this section we discuss some of the ways in which models can be used in the real world, and the complications of such applications. Any model is essentially a collection of assumptions. Additionally, mathematical models are quantitative, and use the language of mathematics to describe the assumptions. As with any model, in order to be valid, it has to be internally consistent, and reasonable in terms of the mechanisms that it includes to realise its assumptions. For example, a model of a vector-borne disease has to have within it (explicitly or implicitly) the size of the vector population and rate at which the vectors feed on people. Once a model is 'right' in this sense, it has to be fitted to the real world, and validated before it can inform policy.

27.8.1 Fitting models

Most mathematical models consist of parameters that represent the rates of events, and the values of the parameters have to be chosen carefully. This is usually done by reference to literature (*eg* Mossong *et al* (2008) for age-related contact rates), or by fitting sub-models to observed or experimental data.

In other cases, the whole model must be fitted to observed data. The most straightforward is to use non-linear regression to find the values of parameters that minimise the sum of squared differences between the model and the data (lines and points). However, as shown in Fig. 27.3, epidemics are stochastic by nature: an individual outbreak rarely conforms to the expected average. Thus, the *cp* estimated from a single outbreak will not capture the possible values of *cp* that might have created these data. If data from multiple outbreaks are available, the range of estimates will provide more insight into the dynamics of the infectious process. An alternative is to use stochastic models which provide insight into the range of possible values for parameters such as R_0 which are compatible with the single outbreak data. These are generally beyond the scope of this book, but examples include Bjørnstad *et al* (2002); Ferrari *et al* (2005) as well as the MCMC papers referenced in section 27.6.4.

27.8.2 Validation and sensitivity analyses

In most models, there are a small number of parameters for which direct estimates are unobtainable, and where there are insufficient observed data to enable model-fitting. This is often the case for models which aim to forecast the outcome of an epidemic of a threatening, but unknown, pathogen. Sensitivity analysis (and the related uncertainty analysis) allows the influence of such parameters on model outcomes to be quantified. Such analyses might indicate that the parameter has little influence on the relevant outcomes, or that it is critically important, and more data and information are required before any reliable outcomes can be gained. All the references in section 27.8.3 contain sensitivity analyses.

If a model's predictions are to be believed as a basis for policy decisions, then it has to have been tested to at least demonstrate that it 'predicts' the current situation. Any model of non-trivial complexity cannot be formally proven to be correct; all models operate within a context so that they can be considered correct for some situations and not others. For example, a model of hepatitis B virus built for the UK (where the majority of transmission occurs in adults with high-risk behaviour) is highly unlikely to be relevant for Taiwan (where the majority of transmission was between children before the advent of immunisation).

Although the use of sensitivity analysis and formal model validation can provide evidence about the potential usefulness of a model, the ultimate test is one of common sense. Models frequently reveal outcomes and dynamic properties that are not necessarily obvious, but which are logically explicable once recognised.

27.8.3 Models in policy

Once a model has been created and validated for a particular context, it can be used to inform policy, which essentially consists of decisions about interventions. Such decisions include many dimensions, most of which are not included in any model, so models can only inform a process

rather than drive it. Increasingly models are being combined with economic analyses, to inform the likely cost effectiveness of an intervention, especially in publicly funded health systems (Walker *et al*, 2010). Such analyses have played a significant role in decisions to introduce vaccination (*eg* HPV—Marra *et al* (2009), pneumococcus—Melegaro *et al* (2010)), or not (*eg* chicken pox—van Hoek *et al* (2011), rotavirus—Mangen *et al* (2010)).

27.9 SUMMARY

This chapter has provided a summary of mathematical modelling of infectious disease transmission dynamics, with pointers into the literature. However, there are many aspects that we have not addressed, such as explicit dependence on time or geographical space (particularly important for vector-borne infections), or pathogen evolution (and the development of drug resistance). These and other aspects are introduced in various textbooks already cited (Anderson and May, 1991; Deikmann and Heesterbeek, 2000; Keeling, M. J. and Rohani, 2007; Vynnycky and White, 2012).

REFERENCES

Alonso PL, Lindsay SW, Schellenberg JRMA, Keita K, Gomez P, Shenton FC, et al. A malaria control trial using insecticide-treated bed nets and targeted chemoprophylaxis in a rural area of The Gambia, West Africa: 6. The impact of the interventions on mortality and morbidity from malaria. Trans Royal Soc Tropical Med and Hygiene. 1993;87, Supplement 2(0):37-44.

Anderson RM, May RM. Infectious Diseases of Humans. Dynamics and Control. Oxford: Oxford Univ. Press; 1991.

Auranen K, Arjas E, Leino T, Takala AK. Transmission of pneumococcal carriage in families: A latent Markov process model for binary longitudinal data. J Am Stat Assoc. 2000;95(452):1044-53.

Bjørnstad ON, Finkenstädt BF, Grenfell BT. Dynamics of measles epidemics: Estimating scaling of transmission rates using a Time series SIR model. Ecological Monographs. 2002;72:169-84.

Brisson M, Edmunds WJ, Gay NJ, Law B, De Serres G. Modelling the impact of immunization on the epidemiology of varicella zoster virus. Epidemiol and Inf. 2000;125(03):651-69.

Brooks-Pollock E, Becerra MC, Goldstein E, Cohen T, Murray MB. Epidemiologic inference from the distribution of tuberculosis cases in households in Lima, Peru. J Infect Dis. 2011 Jun 1;203(11):1582-9.

Cauchemez S, Carrat F, Viboud C, Valleron AJ, Boelle PY. A Bayesian MCMC approach to study transmission of influenza: application to household longitudinal data. Stat Med 2004;23(22):3469-87.

Charleston B, Bankowski BM, Gubbins S, Chase-Topping ME, Schley D, Howey R, et al. Relationship Between Clinical Signs and Transmission of an Infectious Disease and the Implications for Control. Science. 2011;332(6030):726-9.

Cooper B, Medley G, Bradley S, Scott G. An augmented data method for the analysis of nosocomial infection data. Am J Epidemiol. 2008;168(5):548-57.

Cooper BS, Medley GF, Stone SP, Kibbler CC, Cookson BD, Roberts JA, et al. Methicillin-resistant Staphylococcus aureus in hospitals and the community: Stealth dynamics and control catastrophes. Proc National Acad Sci. 2004;101(27):10223-8.

Cowling BJ, Muller MP, Wong IOL, Ho LM, Louie M, McGeer A, et al. Alternative methods of estimating an incubation distribution - Examples from severe acute respiratory syndrome. Epidemiology. 2007;18(2):253-9.

Cox FEG. Modern Parasitology: A Textbook of Parasitology. Oxford: Blackwell Science; 1993.

Deikmann O, Heesterbeek JAP. Mathematical Epidemiology of Infectious Diseases: Model Building, Analysis and Interpretation. Chichester (UK): John Wiley & Sons; 2000.

Dowdle WR, Hopkins DR, editors. The eradication of infectious diseases: John Wiley & Sons; 1998.

Eames K, Webb C, Thomas K, Smith J, Salmon R, Temple JM. Assessing the role of contact tracing in a suspected H7N2 influenza A outbreak in humans in Wales. BMC infectious diseases. 2010;10(1):141.

Ferrari MJ, Bjørnstad ON, Dobson AP. Estimation and inference of R0 of an infectious pathogen by a removal method. Math Biosci. 2005;198(1):14-26.

Finkenstadt BF, Bjornstad ON, Grenfell BT. A stochastic model for extinction and recurrence of epidemics: estimation and inference for measles outbreaks. Biostatistics. 2002;3(4):493-510.

Fraser C, Riley S, Anderson RM, Ferguson NM. Factors that make an infectious disease outbreak controllable. Proc National Acad Sci. 2004;101(16):6146-51.

Fraser C. Estimating Individual and Household Reproduction Numbers in an Emerging Epidemic. PLoS ONE. 2007;2(8).

Fraser C, Donnelly CA, Cauchemez S, Hanage WP, Van Kerkhove MD, Hollingsworth TD, et al. Pandemic Potential of a Strain of Influenza A (H1N1): Early Findings. Science. 2009;324(5934):1557-61.

Gibson GJ, Renshaw E. Estimating parameters in stochastic compartmental models using Markov chain methods. J Math Applied in Med and Biol. 1998;15:19-40.

Gomes M, Franco A, Gomes M, al. e. The reinfection threshold promotes variability in tuberculosis epidemiology and vaccine efficacy. Proc Royal Soc London Series B-Biol Sci. 2004a; 271(1539):617-23.

Gomes M, White L, Medley G. Infection, reinfection, and vaccination under suboptimal immune protection: epidemiological perspectives. J Theoretical Biol. 2004b;228(4):539-49.

Grassly NC, Fraser C. Mathematical models of infectious disease transmission. Nat Rev Micro. 2008;6(6):477-87.

Green LE, Medley GF. Mathematical modelling of the foot and mouth disease epidemic of 2001: strengths and weaknesses. Res Vet Sci. 2002;73(3):201-5.

Grenfell BT, Bjornstad ON, Kappey J. Travelling waves and spatial hierarchies in measles epidemics. Nature. 2001;414(6865):716-23.

Grenfell BT, Pybus OG, Gog JR et al. Unifying the epidemiological and evolutionary dynamics of pathogens. Science 2004; 303(5656): 327-332.

House T, Keeling MJ. Household structure and infectious disease transmission. Epidemiol Infect. 2009;137(5):654-61.

Jewell CP, Kypraios T, Neal P, Roberts GO. Bayesian Analysis for Emerging Infectious Diseases. Bayesian Analysis. 2009;4(3):465-96.

Johnson AM, Mercer CH, Beddows S, de Silva N, Desai S, Howell-Jones R, et al. Epidemiology of, and behavioural risk factors for, sexually transmitted human papillomavirus infection in men and women in Britain. Sex Transm Infect. 2012;88(3):212-7.

Keeling M. Models of foot-and-mouth disease. Proc Biol Sci. 2005;272(1569):1195-202.

Keeling MJ, Eames KT. Networks and epidemic models. J R Soc Interface. 2005;2(4):295-307.

Keeling MJ, Rohani P. Modeling Infectious Diseases in Humans and Animals. Princeton (NJ): Princeton University Press; 2007.

Lipsitch M, Cohen T, Cooper B, Robins JM, Ma S, James L, et al. Transmission Dynamics and Control of Severe Acute Respiratory Syndrome. Science. 2003;300(5627):1966-70.

Longini IM, Koopman JS, Monto AS, Fox JP. Estimating household and community transmission parameters for influenza. Am J Epidemiol. 1982;115(5):736-51.

Mangen M-JJ, van Duynhoven YTHP, Vennema H, van Pelt W, Havelaar AH, de Melker HE. Is it cost-effective to introduce rotavirus vaccination in the Dutch national immunization program? Vaccine. 2010;28(14):2624-35.

Marra F, Cloutier K, Oteng B, Marra C, Ogilvie G. Effectiveness and Cost Effectiveness of Human Papillomavirus Vaccine: A Systematic Review. Pharmacoeconomics. 2009;27(2):127-47.

McLean AR, Blower SM. Imperfect vaccines and herd-immunity to HIV. Proc Royal Soc London Series B-Biol Sci. 1993;253(1336):9-13.

Medley G, Lindop N, Edmunds W, al. e. Hepatitis-B virus endemicity: heterogeneity, catastrophic dynamics and control. Nature Medicine. 2001;7(5):619-24.

Medley GF, Nokes DJ. Mathematical Models of Vaccination. Topley & Wilson's Microbiology and Microbial Infections. 10 ed: John Wiley & Sons, Ltd; 2010.

Melegaro A, Choi Y, George R, Edmunds WJ, Miller E, Gay N. Dynamic models of pneumococcal carriage and the impact of the Heptavalent Pneumococcal Conjugate Vaccine on invasive pneumococcal disease. BMC infectious diseases. 2010;10(1):90.

Mossong J, Hens N, Jit M, Beutels P, Auranen K, Mikolajczyk R, et al. Social contacts and mixing patterns relevant to the spread of infectious diseases. Plos Medicine. 2008;5(3):381-91.

Panagiotopoulos T, Antoniadou I, Valassi-Adam E. Increase in congenital rubella occurrence after immunisation in Greece: retrospective survey and systematic review. BMJ. 1999;319(7223):1462-7.

Robotham J, Jenkins D, Medley G. Screening strategies in surveillance and control of methicillin-resistant Staphylococcus aureus (MRSA). Epidemiol and Inf. 2007;135(2):328-42.

Ross JV, House T, Keeling MJ. Calculation of disease dynamics in a population of households. PLoS ONE. 2010;5(3):e9666.

Schiffer JT, Abu-Raddad L, Mark KE, Zhu J, Selke S, Koelle DM, et al. Mucosal host immune response predicts the severity and duration of herpes simplex virus-2 genital tract shedding episodes. Proc National Acad Sci. 2010;107(44):18973-8.

Smith DJ, Lapedes AS, de Jong JC, Bestebroer TM, Rimmelzwaan GF, Osterhaus ADME, et al. Mapping the Antigenic and Genetic Evolution of Influenza Virus. Science. 2004;305(5682):371-6.

Trape J-F, Tall A, Diagne N, Ndiath O, Ly AB, Faye J, et al. Malaria morbidity and pyrethroid resistance after the introduction of insecticide-treated bednets and artemisinin-based combination therapies: a longitudinal study. The Lancet Infectious Diseases. 2011;11(12):925-32.

van Hoek AJ, Melegaro A, Zagheni E, Edmunds WJ, Gay N. Modelling the impact of a combined varicella and zoster vaccination programme on the epidemiology of varicella zoster virus in England. Vaccine. 2011;29(13):2411-20.

Vynnycky E, White R. An Introduction to Infectious Disease Modelling: Google Books; 2012.

Walker DG, Hutubessy R, Beutel SP. WHO Guide for standardisation of economic evaluations of immunization programmes. Vaccine 2010;28:2356-2359.

Wallinga J, Lipsitch M. How generation intervals shape the relationship between growth rates and reproductive numbers. Proc Biol Sci. 2007;274(1609):599-604.

Woolhouse MEJ, Dye C, Etard J-F, Smith T, Charlwood JD, Garnett GP, et al. Heterogeneities in the transmission of infectious agents: Implications for the design of control programs. Proc National Acad Sci. 1997;94(1):338-42.