10. Dynamics of Infectious Diseases: Epidemic Models and AIDS

10.1 Historical Aside on Epidemics

The history of epidemics is an ever fascinating area; the 14th century Black Death is just the most famous epidemic historically (see Chapter 13, Volume II, which deals with the spatial spread of epidemics, for a brief history of it). In Europe, which had a population of around 85 million at the time, about a third of the population died.

One epidemic which has exercised classical scholars for a very long time is the Plague of Athens (430–428 BC) described in great detail by Thucydides including the symptoms and disease progression. He also gave some exact figures such as that 1050 of 4000 soldiers on an expedition died of the disease. The disease described so minutely by Thucydides, even to the fact that dogs who ate the dead bodies also suffered, has been the source of numerous articles over some hundreds of years with cases being made (with great conviction and defended vehemently) for an incredible range of diseases such as bubonic plague, measles, Malta fever, smallpox, scarlet fever, typhus, typhoid fever and many others. The symptoms described by Thucydides are (i) heat in the head, (ii) inflammation of the eyes, (iii) suffusion with blood of the tongue and throat, (iv) foetid breath, (v) hoarseness with violent coughing, (vi) vomiting of bile, (vii) retching and convulsions, (viii) pustular and ulcerating eruptions of the skin, (ix) total body hyperaesthesia and restlessness, (x) irresistible desire for water to assuage thirst and immersion therein to alleviate body heat, (xi) terminal exhaustion apparently produced by diarrhoea, (xii) loss of toes, fingers and genitalia, (xiii) destruction of eyes and, (xiv) if recovery occurs, amnesia, the latter no doubt a blessing. Based on the symptoms none of the above suggestions seems to fit the Athens disease. Whatever it was it was certainly very nasty. An interesting review article on the Athens plague is given by Poole and Holladay (1979). They conclude that it has either become extinct or has been modified over the millennia. Since then other articles have appeared with yet other possiblities.

One of the interesting aspects of Thucydides' account is that there is no mention of person-to-person contagion which we now accept so freely with diseases. It was only in the 19th century that it was beginning to be discussed. Evil exhalations from the earth, aerial miasmata and so on were generally accepted. The latter explanation for some diseases, or rather illnesses, is not as ridiculous as it might at first appear when you think of the number of people, with the same epidemiclike medical problems, who live on contaminated ground or in regions where the water is iodine-deficient resulting in goitres to mention just two examples. Many South-East Asians can be forgiven for believing

that the smog and smoke belching from the forest fires in Indonesia are responsible for the large upsurge of dengue fever, carried by the mosquito, *Aedes aegypti*. This is a man-made mosquito in effect since it breeds in urban areas in water gathering in plastic, rubber and metallic containers that litter many poor urban areas.

The study of epidemics with its long history has come up with an astonishing number and variety of models and explanations for the spread and cause of epidemic outbreaks. Even today they are often attributed to evil spirits or displeased gods. For example, AIDS (autoimmune deficiency syndrome), the dominant epidemic of the past 20 years and the major one since the 1918[1] influenza pandemic have been ascribed by many as a punishment sent by God. Hippocrates (459–377 BC), in his essay on 'Airs, Waters and Localities' wrote that one's temperament, personal habits and environment were important factors—not unreasonable even today, particularly so in view of the comments in the last paragraph. Somewhat less relevant, but not without its moments of humour, is Alexander Howe's (1865) book in which he sets out his 'Laws of Pestilence' in 31 propositions of which the following, proposition 2, is typical: 'The length of the interval between successive periodic visitations corresponds with the period of a single revolution of the lunar node, and a double revolution of the lunar apse time.'

The first major epidemic in the U.S.A. was the Yellow Fever epidemic in Philadelphia in 1793 in which about 5000 people died out of a population of around 50,000, although estimates suggest that about 20,000 fled the city; see the interesting *Scientific American* article by Foster et al. (1998) and the book by Powell (1993). The epidemic story here is a saga of wild, as well as sensible, theories as to cause and treatment, petty jealousies with disastrous consequencies, genuine humanity and fomented controversies. A leading physician was the strongest advocate of bleeding as the appropriate treatment while others recommended cleanliness, rest, Peruvian bark and wine. This epidemic had a major impact on the subsequent life and politics of the country.

The landmark book by McNeill (1989) is a fascinating story of the relation between disease and people. More recently there have been several books which try to explain various aspects of diseases from the triumphs of medicine (Oldstone 1998) to the socioeconomic (Watts 1998). The latter is written from a very anti-European, western-imperial-colonialists-are-responsible-for-it-all, viewpoint. Europeans are blamed for most of the world's problems with infectious diseases. Leaving aside some of his wilder assertions,[2] the polemics and the emotional outbursts, he has diligently researched historical data and unearthed some dreadful examples of how diseases have been spread by the stupidity of certain colonial western nations with horrifying consequences. Watts'

[1] The influenza epidemic in 1918–1919 is the most deadly pandemic (that is, a world epidemic) per unit time in recorded history and somewhat surprisingly has been to a large extent ignored in historical studies until relatively recently. The Black Death palls in comparison with its severity. The original estimate of the number that died is continually being upgraded. A meeting on the epidemic in 1998 concluded that as many as 100 million people died. Coming towards the end of World War I some people at the time thought it was perhaps germ warfare. If a similar virulent influenza struck in the U.S.A. now, on the order of 1.5 million would die, although current medical treatments could possibly reduce that figure if vaccine could be produced quickly enough. It is about 20 years since the last flu epidemic and many epidemioloigists feel the next is overdue in the cycle of such outbreaks.

[2] For example, Watts asserts that syphilis in the 17th to 19th centuries was a consequence of the Christians' opposition to masturbation.

book is an important contribution to the history and current global relevance of infectious diseases.

Since the end of World War II, public health strategy has focused on the elimination and control of organisms which cause disease. The advent of new antibiotics changed the whole ethos of disease control. Just over 20 years ago, in 1978, the United Nations signed the 'Health for All, 2000' accord which set the ambitious goal of the eradication of disease by the year 2000. AIDS at the time had not yet been discovered, or perhaps recognised is a better word, and in the year before, the last known case of smallpox had been treated. There was certainly cause for optimism albeit short lived. Scientists thought that microbes were biologically stationary targets and hence would not mutate in resistance to drugs and other biological influences.

This comforting image of unchanging microbes started to change shortly after this time with the emergence of microbes that could swim in a pool of bleach, grow on a bar of soap, and ignore doses of penicillin logarithmically larger than those effective in the 1950's (Garrett 1996). The practical reality of bacterial mutation is dramatically seen in New York City with tuberculosis. Control of the W-strain of the disease, which first appeared in the city in 1992, is resistant to every available drug and kills over half its victims, has already cost more than $1 billion. It was only 20 years ago that it was predicted that tuberculosis would be eradicated in the world by 2000.

Another aspect in the current spread of disease is with the modern era of transportation allowing more than a million people a day to cross international borders, the threat of a major outbreak of exotic diseases is very real. The population explosion, especially in underdeveloped countries, is another factor in the microbes' favour. These played key roles in the proliferation of HIV (human immunodeficiency virus) in the 1980's. Recently the World Health Organization (WHO) estimated that over 30 million people worldwide are currently infected with HIV. Information on global and country-specific disease statistics can be found on the Web pages of places such as the WHO (www.who.org) and the Centers for Disease Control (CDC: www.cdc.gov) in Atlanta.

Diseases (including such as heart disease and cancer) cause orders of magnitude more deaths in the world than anything else, even wars and famines. The appearance of new diseases, and resurgence of old ones, makes the case for interdisciplinary involvement ever more pressing. Modelling can play an increasingly significant role. Historians can also play a role. Like the plague of Athens much has been written about the 'sweating sickness' of the late 15th and first half of the 16th centuries in England.[3] The symptoms of the progression of the disease are, among others, high temperatures, body filling with fluid, particularly the lungs, the apparently well-being of a person in the morning and death the same day or within a day or two. The symptoms are so similar to those of the hanta virus in the 1993 outbreak in the Southwest U.S.A. that there is a plausible case they are the same disease but which has been dormant for several hundred years. There is some justification in believing that some of the new diseases are in fact reappearances of old ones.

[3]Henry VIII of England succeeded to the throne because his older brother died of the sweating sickness, and changed the course of history. Henry, for example, dissolved the monasteries, helped usher in the Reformation and developed the British Navy as a professional service which was the basis for the later development of the British Empire.

There are four main disease-causing microrganisms: viruses, bacteria, parasites and fungi. In this chapter, we describe some models for the population dynamics of disease agents and later (in Chapter 13, Volume II) the spatiotemporal spread of infections. Such models have been commonly used to model the spread of viral, bacterial and parasitic infections but considerably less so with fungal infections. We shall discuss several models and then try to exploit the models in the control, or ideally the eradication, of the disease or infection we are considering. The practical use of such models must rely heavily on the realism put into the models. As usual, this does not mean the inclusion of all possible effects, but rather the incorporation in the model mechanisms, in as simple a way as possible, of what appear to be the major components. Like most models they generally go through several versions before qualitative phenomena can be explained or predicted with any degree of confidence. Great care must be exercised before practical use is made of any epidemic models. However, even simple models should, and frequently do, pose important questions with regard to the underlying process and possible means of control of the disease or epidemic. One such case study, which went through various hypothetical scenarios, is the model proposed by Capasso and Paveri-Fontana (1979) for the 1973 cholera epidemic in the port city of Bari in southern Italy.[4]

An interesting early mathematical model, involving a nonlinear ordinary differential equation, by Bernoulli (1760), considered the effect of cow-pox inoculation on the spread of smallpox. The article has some interesting data on child mortality at the time. It is probably the first time that a mathematical model was used to assess the practical advantages of a vaccination control programme. Thucydides mentions immunity in connection with the Athens plague and there is evidence of an even more ancient Chinese custom where children were made to inhale powders made from the crusts of skin lesions of people recovering from smallpox.

Models can also be extremely useful in giving reasoned estimates for the level of vaccination for the control of directly transmitted infectious diseases. We discuss one case study later in the chapter when modelling bovine tuberculosis; see, for example, Anderson and May (1982, 1985, 1991), and Herbert et al. (1994). The recent paper by Schuette and Hethcote (1999) discusses vaccination protocols in connection with chickenpox and shingles and highlights certain dangers of extensive vaccination. Among other things, they evaluate with their models the effects of different vaccination programmes. The classical theoretical papers on epidemic models by Kermack and McKendrick (1927, 1932, 1933) have had a major influence in the development of mathematical models and are still relevant in a suprising number of epidemic situations; we

[4]In the epidemic, cases of cholera were most common in the poorer areas near the port. At the time raw sewage from the hospital that treated the cholera patients went directly into the sea. One suggestion was that the bacteria infected local people bathing in the area. On investigation this did not seem to be borne out. Another thought was that the water in the stand pipes, commonly in use in these districts, was contaminated. Again this was found not to be the case. Yet another thought was that the cholera entered the mussel population which was caught in the shore areas near the port and which was sold and eaten at the local stalls and shops by the local inhabitants as a delicacy, thus passing it on to humans. However, after a few hours away from direct bacterial contact mussels actually kill the cholera bacteria so this was also discarded since several hours elapsed between catching and selling. The solution was finally found to be indeed in the infected sea water. The stall holders kept a bucket of (contaminated) sea water with which they regularly doused the displayed mussels to make them look fresh and succulent. It was the bacteria in the 'fresh' sea water sprayed on the shells which caused the cholera infection.

describe some of these in this chapter. The modelling literature is now extensive and growing very quickly. Although now quite old, a good introduction to the variety of problems and models for the spread and control of infectious diseases is the book by Bailey (1975). The article by Hethcote (1994) reviews three basic epidemiological models. The book by Diekmann and Heesterbeek (2000) is a good introduction to the field. For example, they discuss how to use biological assumptions in constructing models and present applications; they cover both deterministic and stochastic modelling. Other sources are to be found in the above references and in the papers referred to in the rest of this chapter. Particularly useful sources for the latest information on specific diseases, either globally or for a specific country, are the WHO (http://www.who.org/) and the CDC (http://www.cdc.gov/); their search and information features are very efficient.

In this chapter we discuss several quite different models for very different diseases which incorporate some general aspects of epidemiological modelling of disease transmission, time evolution of epidemics, acquired resistance to infection, vaccination strategies and so on. The use of mathematical modelling in immunology and virology is also growing very quickly. We discuss in some detail models for the dynamics of HIV infections and relate them to patient data. We also discuss a bacterial infection and one involving parasites. In Chapter 13, Volume II we consider the geographic spread of infectious diseases and describe in detail a practical model for the spatial spread of rabies, a possible means of its control and the effect of including immunity. The modelling of infectious diseases involves the concepts of population dynamics which we have dicussed in earlier chapters. Although the detailed forms of the equations are different the essential elements and analysis are very similar.

At the basic level we consider two types of models. In one the total population is taken to be approximately constant with, for example, the population divided into susceptible, infected and immune groups: other groupings are also possible, depending on the disease. We first discuss models in this category. In the other, the population size is affected by the disease via the birth rate, mortality and so on. Host–parasite interacting populations often come into this category. We only discuss deterministic models which are deficient in certain situations—eradication of a disease is one, since here the probability that the last few infected individuals will infect another susceptible is not deterministic. Nevertheless it is perhaps surprising how useful, and quantitatively predictive, deterministic models can often be; the examples below are only a very few examples where this has proven to be the case.

10.2 Simple Epidemic Models and Practical Applications

In the classical (but still highly relevant) models we consider here the total population is taken to be constant. If a small group of infected individuals is introduced into a large population, a basic problem is to describe the spread of the infection within the population as a function of time. Of course this depends on a variety of circumstances, including the actual disease involved, but as a first attempt at modelling directly transmitted diseases we make some not unreasonable general assumptions.

Consider a disease which, after recovery, confers immunity which, if lethal, includes deaths: dead individuals are still counted. Suppose the disease is such that the

population can be divided into three distinct classes: the susceptibles, S, who can catch the disease; the infectives, I, who have the disease and can transmit it; and the removed class, R, namely, those who have either had the disease, or are recovered, immune or isolated until recovered. The progress of individuals is schematically represented by

$$S \longrightarrow I \longrightarrow R.$$

Such models are often called *SIR* models. The number of classes depends on the disease. *SI* models, for example, have only susceptible and infected classes while *SEIR* models have a suceptible class, S, a class in which the disease is latent, E, an infectious class, I, and a recovered or dead class, R.

The assumptions made about the transmission of the infection and incubation period are crucial in any model; these are reflected in the terms in the equations and the parameters. With $S(t)$, $I(t)$ and $R(t)$ as the number of individuals in each class we assume here that: (i) The gain in the infective class is at a rate proportional to the number of infectives and susceptibles, that is, rSI, where $r > 0$ is a constant parameter. The susceptibles are lost at the same rate. (ii) The rate of removal of infectives to the removed class is proportional to the number of infectives, that is, aI where $a > 0$ is a constant; $1/a$ is a measure of the time spent in the infectious state. (iii) The incubation period is short enough to be negligible; that is, a susceptible who contracts the disease is infective right away.

We now consider the various classes as uniformly mixed; that is, every pair of individuals has equal probability of coming into contact with one another. This is a major assumption and in many situations does not hold as in most sexually transmitted diseases (STD's). The model mechanism based on the above assumptions is then

$$\frac{dS}{dt} = -rSI, \tag{10.1}$$

$$\frac{dI}{dt} = rSI - aI, \tag{10.2}$$

$$\frac{dR}{dt} = aI, \tag{10.3}$$

where $r > 0$ is the infection rate and $a > 0$ the removal rate of infectives. This is the classic Kermack–McKendrick (1927) model. We are, of course, only interested in non-negative solutions for S, I and R. This is a basic model but, even so, we can make some highly relevant general comments about epidemics and, in fact, adequately describe some specific epidemics with such a model.

The constant population size is built into the system (10.1)–(10.3) since, on adding the equations,

$$\frac{dS}{dt} + \frac{dI}{dt} + \frac{dR}{dt} = 0 \quad \Rightarrow \quad S(t) + I(t) + R(t) = N, \tag{10.4}$$

where N is the total size of the population. Thus, S, I and R are all bounded above by N. The mathematical formulation of the epidemic problem is completed given initial

conditions such as

$$S(0) = S_0 > 0, \quad I(0) = I_0 > 0, \quad R(0) = 0. \tag{10.5}$$

A key question in any epidemic situation is, given r, a, S_0 and the initial number of infectives I_0, whether the infection will spread or not, and if it does how it develops with time, and crucially when it will start to decline. From (10.2),

$$\left[\frac{dI}{dt}\right]_{t=0} = I_0(rS_0 - a) \quad \begin{cases} > 0 \\ < 0 \end{cases} \quad \text{if} \quad S_0 \quad \begin{cases} > \rho \\ < \rho \end{cases}, \quad \rho = \frac{a}{r}. \tag{10.6}$$

Since, from (10.1), $dS/dt \leq 0$, $S \leq S_0$ we have, if $S_0 < a/r$,

$$\frac{dI}{dt} = I(rS - a) \leq 0 \quad \text{for all} \quad t \geq 0, \tag{10.7}$$

in which case $I_0 > I(t) \to 0$ as $t \to \infty$ and so the infection dies out; that is, no epidemic can occur. On the other hand if $S_0 > a/r$ then $I(t)$ initially increases and we have an epidemic. The term 'epidemic' means that $I(t) > I_0$ for some $t > 0$; see Figure 10.1. We thus have a *threshold phenomenon*. If $S_0 > S_c = a/r$ there is an epidemic while if $S_0 < S_c$ there is not. The critical parameter $\rho = a/r$ is sometimes called the *relative removal rate* and its reciprocal $\sigma(= r/a)$ the infection's *contact rate*.

We write

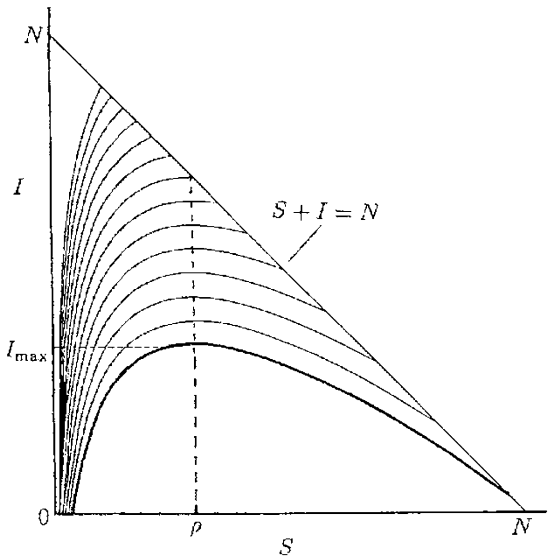

Figure 10.1. Phase trajectories in the susceptibles (S)-infectives (I) phase plane for the *SIR* model epidemic system (10.1)–(10.3). The curves are determined by the initial conditions $I(0) = I_0$ and $S(0) = S_0$. With $R(0) = 0$, all trajectories start on the line $S + I = N$ and remain within the triangle since $0 < S + I < N$ for all time. An epidemic situation formally exists if $I(t) > I_0$ for any time $t > 0$; this always occurs if $S_0 > \rho(= a/r)$ and $I_0 > 0$.

$$R_0 = \frac{rS_0}{a},$$

where R_0 is the basic *reproduction rate* of the infection, that is, the number of secondary infections produced by one primary infection in a wholly susceptible population. Here $1/a$ is the average infectious period. If more than one secondary infection is produced from one primary infection, that is, $R_0 > 1$, clearly an epidemic ensues. The whole question of thresholds in epidemics is obviously important. The definition and derivation or computation of the basic reproduction rate is crucial and can be quite complicated. One such example is if the population is heterogeneous (Diekman et al. 1990).

The basic reproduction rate is a crucial parameter grouping for dealing with an epidemic or simply a disease which is currently under control with vaccination, for example. Although the following arguments are based on R_0 they are quite general. Clearly one way to reduce the reproduction rate is to reduce the number of sucepti-bles, S_0. Vaccination is the common method of doing this and it has been successful in eradicating smallpox. In the U.S.A. it reduced the incidence of measles from 894,134 reported cases in 1941 to 135 in 1997 and for polio from 21,269 in 1952 to the last indigenously acquired case of wild-virus polio reported in 1979 (the Western hempisphere was officially certified polio-free in 1994) with similar reductions in other childhood diseases. Mass vaccination is the cheapest and most effective means of disease control. However, although vaccines are generally extremely safe, no medicine is totally risk-free, however small the risk may be. (There have, however, been a few cases of instant death from diptheria and tetanus vaccines and there is currently much controversy about the vaccine for Anthrax for the military.) As people in the West forget the ravages of polio, measles, diptheria, rubella and so on, many will become less keen to have their children vaccinated because of the risk even if very small. Vaccination not only provides protection for the individual it also provides it for the community at large since it keeps the effective reproduction rate below the level which would allow an epidemic to start. This is the so-called 'herd immunity.' The point is that once the threshold herd immunity level of R_0 has been reached and memory of former diseases fades there is the possibility that people will not have their children vaccinated but have a free ride instead; the unvaccinated have effectively the same immunity. In this situation the best, but unethical, strategy for parents is to urge all other parents to have their children vaccinated but free ride with their own. The important point to keep in mind, however, is that an epidemic can start and rise very quickly if the reproduction rate increases beyond the critical value for an epidemic so in the end free-riding is not without its own risks. (This happened with the Conquistadors in Mexico.)

We can derive some other useful analytical results from this simple model. From (10.1) and (10.2)

$$\frac{dI}{dS} = -\frac{(rS - a)I}{rSI} = -1 + \frac{\rho}{S}, \quad \rho = \frac{a}{r}, \quad (I \neq 0).$$

The singularities all lie on the $I = 0$ axis. Integrating the last equation gives the (I, S) phase plane trajectories as

$$I + S - \rho \ln S = \text{constant} = I_0 + S_0 - \rho \ln S_0, \tag{10.8}$$

where we have used the initial conditions (10.5). The phase trajectories are sketched in Figure 10.1. Note that with (10.5), all initial values S_0 and I_0 satisfy $I_0 + S_0 = N$ since $R(0) = 0$ and so for $t > 0$, $0 \leq S + I < N$.

If an epidemic exists we would like to know how severe it will be. From (10.7) the maximum I, $I_{\max}$, occurs at $S = \rho$ where $dI/dt = 0$. From (10.8), with $S = \rho$,

$$\begin{aligned} I_{\max} &= \rho \ln \rho - \rho + I_0 + S_0 - \rho \ln S_0 \\ &= I_0 + (S_0 - \rho) + \rho \ln \left(\frac{\rho}{S_0} \right) \\ &= N - \rho + \rho \ln \left(\frac{\rho}{S_0} \right). \end{aligned} \tag{10.9}$$

For any initial values I_0 and $S_0 > \rho$, the phase trajectory starts with $S > \rho$ and we see that I increases from I_0 and hence an epidemic ensues. It may not necessarily be a severe epidemic as is the case if I_0 is close to $I_{\max}$. It is also clear from Figure 10.1 that if $S_0 < \rho$ then I decreases from I_0 and no epidemic occurs.

Since the axis $I = 0$ is a line of singularities, on all trajectories $I \to 0$ as $t \to \infty$. From (10.1), S decreases since $dS/dt < 0$ for $S \neq 0$, $I \neq 0$. From (10.1) and (10.3),

$$\begin{aligned} &\frac{dS}{dR} = -\frac{S}{\rho} \\ &\Rightarrow \quad S = S_0 e^{-R/\rho} \geq S_0 e^{-N/\rho} > 0 \\ &\Rightarrow \quad 0 < S(\infty) \leq N. \end{aligned} \tag{10.10}$$

In fact from Figure 10.1, $0 < S(\infty) < \rho$. Since $I(\infty) = 0$, (10.4) implies that $R(\infty) = N - S(\infty)$. Thus, from (10.10),

$$S(\infty) = S_0 \exp\left[-\frac{R(\infty)}{\rho} \right] = S_0 \exp\left[-\frac{N - S(\infty)}{\rho} \right]$$

and so $S(\infty)$ is the positive root $0 < z < \rho$ of the transcendental equation

$$S_0 \exp\left[-\frac{N - z}{\rho} \right] = z. \tag{10.11}$$

We then get the total number of susceptibles who catch the disease in the course of the epidemic as

$$I_{\text{total}} = I_0 + S_0 - S(\infty), \tag{10.12}$$

where $S(\infty)$ is the positive solution z of (10.11). An important implication of this analysis, namely, that $I(t) \to 0$ and $S(t) \to S(\infty) > 0$, is that the disease dies out from a lack of infectives and *not* from a lack of susceptibles.

The threshold result for an epidemic is directly related to the relative removal rate, ρ: if $S_0 > \rho$ an epidemic ensues whereas it does not if $S_0 < \rho$. For a given disease, the relative removal rate varies with the community and hence determines whether an epidemic may occur in one community and not in another. The number of susceptibles

S_0 also plays a major role, of course. For example, if the density of susceptibles is high and the removal rate, a, of infectives is low (through ignorance, lack of medical care, inadequate isolation and so on) then an epidemic is likely to occur. Expression (10.9) gives the maximum number of infectives while (10.12) gives the total number who get the infection in terms of $\rho(=a/r)$, I_0, S_0 and N.

In most epidemics it is difficult to determine how many new infectives there are each day since only those that are removed, for medical aid or whatever, can be counted. Public Health records generally give the number of infectives per day, week or month. So, to apply the model to actual epidemic situations, in general we need to know the number removed per unit time, namely, dR/dt, as a function of time.

From (10.10), (10.4) and (10.3) we get an equation for R alone; namely,

$$\frac{dR}{dt} = aI = a(N - R - S) = a\left(N - R - S_0 e^{-R/\rho}\right], \quad R(0) = 0, \tag{10.13}$$

which can only be solved analytically in a parametric way: the solution in this form however is not particularly convenient. Of course, if we know a, r, S_0 and N it is a simple matter to compute the solution numerically. Usually we do not know all the parameters and so we have to carry out a best fit procedure assuming, of course, the epidemic is reasonably described by such a model. In practice, however, it is often the case that if the epidemic is not large, R/ρ is small—at least $R/\rho < 1$. Following Kermack and McKendrick (1927) we can then approximate (10.13) by

$$\frac{dR}{dt} = a\left[N - S_0 + \left(\frac{S_0}{\rho} - 1\right)R - \frac{S_0 R^2}{2\rho^2}\right].$$

Factoring the right-hand side quadratic in R, we can integrate this equation to get, after some elementary but tedious algebra, the solution

$$\begin{aligned} R(t) &= \frac{\rho^2}{S_0}\left[\left(\frac{S_0}{\rho} - 1\right) + \alpha \tanh\left(\frac{\alpha a t}{2} - \phi\right)\right] \\ \alpha &= \left[\left(\frac{S_0}{\rho} - 1\right)^2 + \frac{2S_0(N - S_0)}{\rho^2}\right]^{1/2}, \quad \phi = \tanh^{-1}\frac{1}{\alpha}\left(\frac{S_0}{\rho} - 1\right) \end{aligned} \tag{10.14}$$

The removal rate is then given by

$$\frac{dR}{dt} = \frac{a\alpha^2\rho^2}{2S_0}\,\mathrm{sech}^2\left(\frac{\alpha a t}{2} - \phi\right), \tag{10.15}$$

which involves only 3 parameters, namely, $a\alpha^2\rho^2/(2S_0)$, αa and ϕ. With epidemics which are not large, it is this function of time which we should fit to the public health records. On the other hand, if the disease is such that we know the actual number of the removed class then it is $R(t)$ in (10.14) we should use. If R/ρ is not small, however, we must use the differential equation (10.13) to determine $R(t)$.

We now apply the model to two very different epidemic situations.

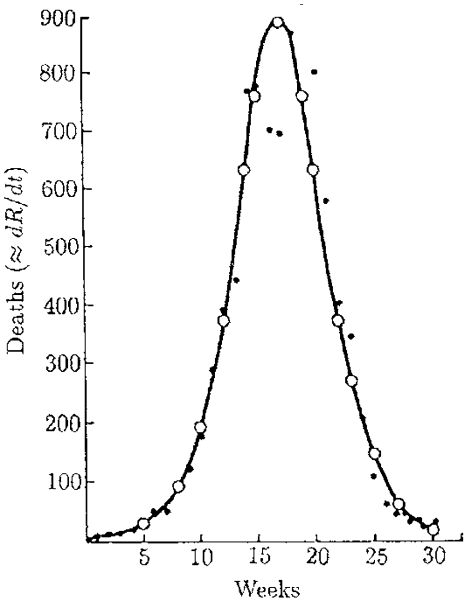

Figure 10.2. Bombay plague epidemic of 1905–1906. Comparison between the data (•) and theory (○) from the (small) epidemic model and where the number of deaths is approximately dR/dt given by (10.16). (After Kermack and McKendrick 1927)

Bombay Plague Epidemic 1905–1906

This plague epidemic lasted for almost a year. Since most of the victims who got the disease died, the number removed per week, that is, dR/dt, was approximately equal to the number of deaths per week. On the basis that the epidemic was not severe (relative to the population size), Kermack and McKendrick (1927) compared the actual data with (10.15) and determined the best fit for the three parameters which resulted in

$$\frac{dR}{dt} = 890\,\mathrm{sech}^2\,(0.2t - 3.4). \tag{10.16}$$

This is illustrated in Figure 10.2 together with the actual epidemic data.

Influenza Epidemic in an English Boarding School 1978

In 1978 in the British medical journal, *The Lancet*, there was a report with detailed statistics of a flu epidemic in a boys' boarding school with a total of 763 boys. Of these 512 were confined to bed during the epidemic, which lasted from 22nd January to 4th February 1978. It seems that one infected boy initiated the epidemic. This situation has many of the requirements assumed in the above model derivation. Here, however, the epidemic was severe and the full system has to be used. Also, when a boy was infected he was put to bed and so we have $I(t)$ directly from the data. Since in this case we have no analytical solution for comparison with the data, a best fit numerical technique was used directly on the equations (10.1)–(10.3) for comparison of the data. Figure 10.3 illustrates the resulting time evolution for the infectives, $I(t)$, together with the epidemic statistics. The R-equation (10.3) is uncoupled; the solution for $R(t)$ is simply proportional to the area under the $I(t)$ curve.

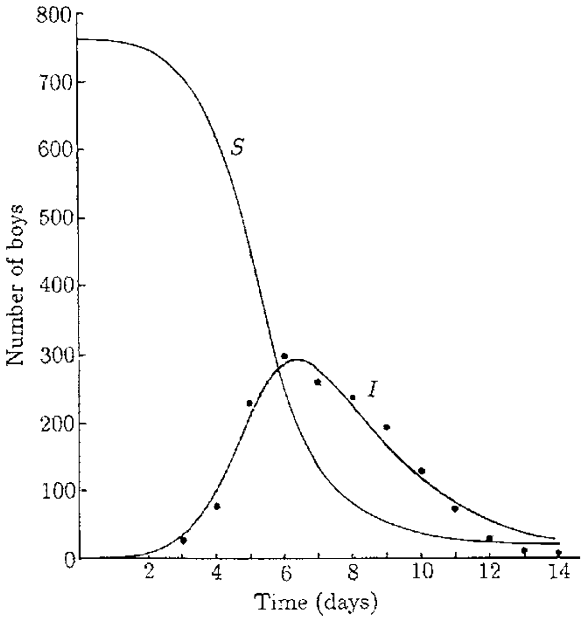

Figure 10.3. Influenza epidemic data (•) for a boys' boarding school as reported in the British medical journal, *The Lancet*, 4th March 1978. The continuous curves for the infectives (I) and susceptibles (S) were obtained from a best fit numerical solution of the *SIR* system (10.1)–(10.3): parameter values $N = 763$, $S_0 = 762$, $I = 1$, $\rho = 202$, $r = 2.18 \times 10^{-3}$/day. The conditions for an epidemic to occur, namely, $S_0 > \rho$, are clearly satisfied and the epidemic is severe since R/ρ is not small.

Plague in Eyam, England 1665–1666

There was an outbreak of plague in the village of Eyam in England from 1665 to 1666. In this remarkable altruistic incident, the village sealed itself off when plague was discovered, so as to prevent it spreading to the neighbouring villages, and it was successful. By the end of the epidemic only 83 of the original population of 350 survived. Raggett (1982) applied the *SIR* model (10.1)–(10.3) to this outbreak. Here, $S(\infty) = 83$ out of an initial $S_0 = 350$. This is another example, like the school flu epidemic, where the epidemic was severe. Raggett (1982) shows how to determine the parameters from the available data and knowledge of the etiology of the disease. He reiterates the view that although the initial form was probably bubonic plague, the pneumonic form most likely became prevalent; the latter form can be transmitted from the cough of a victim (see Chapter 13, Volume II for a brief description of the plague and its history). The comparison between the solutions from the deterministic model and the Eyam data is very good. The comparison is much better than that obtained from the corresponding stochastic model, which Raggett (1982) also considered. We discuss a model for the spatial spread of plague in Chapter 13, Volume II.

If a disease is *not* of short duration then (10.1), the equation for the susceptibles, should include birth and death terms. Mortality due to natural causes should also be included in equation (10.2) for the infectives and in (10.3) for the removed class. The

resulting models can be analysed in a similar way to that used here and in Chapter 3 on interacting populations: they are still systems of ordinary differential equations. It is not surprising, therefore, that oscillatory behaviour in disease epidemics is common; these are often referred to as epidemic waves. Here they are *temporal* waves. *Spatial* epidemic waves appear as an epidemic spreads geographically. The latter are also common and we consider them in detail in Chapter 13, Volume II.

Many diseases have a latent or incubation period when a susceptible has become infected but is not yet infectious. Measles, for example, has an 8- to 13-day latent period. The incubation time for AIDS, on the other hand, is anything from a few months to years after the patient has been shown to have antibodies to the human immunodeficiency virus (HIV). We can, for example, incorporate this as a delay effect, or by introducing a new class, $E(t)$ say, in which the susceptible remains for a given length of time before moving into the infective class. Such models give rise to integral equation formulations and they can exhibit oscillatory behaviour as might be expected from the inclusion of delays. Some of these are described by Hoppensteadt (1975, see also 1982). Nonlinear oscillations in such models have been studied by Hethcote et al. (1981); see also Hethcote (1994). Alternative approaches recently used in modelling AIDS are discussed below. Finally age, a, is often a crucial factor in disease susceptibility and infectiousness. The models then become partial differential equations with independent variables (t, a); we consider one such model later in this chapter.

There are many modifications and extensions which can and often must be incorporated in epidemic models; these depend critically on the disease and location. In the following sections we discuss a few more general models to illustrate different but important points. The books and references already cited describe numerous models and go into them in considerable detail.

10.3 Modelling Venereal Diseases

The incidence of sexually transmitted diseases (STDs), such as gonorrhea (*Neisseria gonorrhoeae*), chlamydia, syphilis and, of course, AIDS, is a major health problem in both developed and developing countries. In the U.S.A., for example, as reported by the Centers for Disease Control (www.cdc.gov), in 1996 there were over 300,000 cases of gonorrhea reported and over 11,000 cases of syphilis and nearly 500,000 cases of chlamydia. Whereas the rate has been decreasing for gonorrhea and syphilis it is growing for chlamydia. We give some of the numbers for HIV incidence in the AIDS sections below.

STDs have certain characteristics which are different from other infections, such as measles or rubella (German measles). One difference is that they are mainly restricted to the sexually active community so the assumption of uniform mixing in the whole population is not really justified. Another is that often the carrier is asymptomatic (that is, the carrier shows no overt symptoms) until quite late on in the development of the infection. A third crucial difference is that STDs induce little or no acquired immunity following an infection. Equally important in virus infections is the lack of present knowledge of some of the parameters which characterise the transmission dynamics.

Although gonorrhea, syphilis and AIDS are well known, with the latter growing alarmingly, one of the STDs which has far outstripped gonorrhea is the less well-known *Chlamydia trachomatis*, which in 1996 struck more than gonorrhea and syphilis put together and is on the increase. It can produce sterility in women without their ever showing any overt symptoms. Diagnostic techniques are now sufficiently refined to make diagnosis more accurate and less expensive and could account in part for the increase in reported cases.[5] The asymptomatic character of this disease among women is serious. Untreated, it causes pelvic inflammatory disorders (PID) which are often accompanied by chronic pain, fever and sterility. With pregnancy, PID, among other complications, can often cause premature delivery and ectopic pregnancies (that is, the fertilised egg is implanted outside the womb) which are life threatening. Untreated gonorrhea, for example, can also cause blindness, PID, heart failure and ultimately death. STDs are a major cause of sterility in women. The consequences of untreated STDs in general are very unpleasant. The vertical transmission of STDs from mother to newborn children is another of the threats and tragedies of many STDs. Another problem is the appearance of new strains: in connection with AIDS, HIV-1 is the common virus but a relatively new one, HIV-2 has now been found. With gonorrhea the relatively new strain, *Neisseria gonorrhoeae*, which was discovered in the 1970's proved resistant to penicillin.

In this section we present a simple classical epidemic model which incorporates some of the basic elements in the heterosexual spread of venereal diseases. We have in mind such diseases as gonorrhea; AIDS we discuss separately later in the chapter. The monograph by Hethcote and Yorke (1984) is still a good survey of models used for the spread and control of gonorrhea. They show how models and data can be used to advantage; the conclusions they arrived at are specifically aimed at public health workers.

For the model here we assume there is uniformly promiscuous behaviour in the population we are considering. As a simplification we consider only heterosexual encounters. The population consists of two interacting classes, males and females, and infection is passed from a member of one class to the other. It is a criss-cross type of disease in which each class is the disease host for the other. In all of the models we have assumed homogeneous mixing between certain population subgroups. Dietz and Hadeler (1988), for example, considered epidemic models for STDs in which there is heterogeneous mixing. More complex models can include the pairing of two susceptibles, which confers temporary immunity, several subgroups and so on. We discuss a multi-group example later in this section.

Criss-cross infection is similar in many ways to what goes on in malaria[6] and bilharzia, for example, where two criss-cross infections occur. In bilharzia it is between

[5] One U.S. Public Health official when asked some years ago about the high incidence of chlamydia and what doctors were doing about it, is said to have remarked 'Doing about it? Most of them can't even spell it.'

[6] A very interesting, exciting and potentially important new and cheap treatment for malaria, which kills around 2.7 million people a year, has been discovered by Dr. Henry Lai, and his colleagues in Bioengineering in the University of Washington. They found that the malarial parasite *Plasmodium falciparum* (the deadliest of the four malarial parasites) can lose vigour and die when subjected to small oscillating magnetic fields (of the order of the earth's field). They suggest it may be due to the movement caused in the very small iron particles inside the parasite which damages the parasites by disrupting their feeding process which involves the haemoglobin in the red blood cells of the host. They found that exposed samples of the parasite ended up with 33–70% fewer parasites as compared to unexposed samples.