Biology of Plagues:
Evidence from Historical Populations

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CAMBRIDGE
UNIVERSITY PRESS

PUBLISHED BY THE PRESS SYNDICATE OF THE UNIVERSITY OF CAMBRIDGE
The Pitt Building, Trumpington Street, Cambridge, United Kingdom

CAMBRIDGE UNIVERSITY PRESS
The Edinburgh Building, Cambridge CB2 2RU, UK
40 West 20th Street, New York, NY 10011-4211, USA
10 Stamford Road, Oakleigh, VIC 3166, Australia
Ruiz de Alarcón 13, 28014 Madrid, Spain
Dock House, The Waterfront, Cape Town 8001, South Africa

http://www.cambridge.org

First published 2001

Printed in the United Kingdom at the University Press, Cambridge

Typeface Times 10/13pt *System* Poltype® [VN]

A catalogue record for this book is available from the British Library

Library of Congress Cataloguing in Publication data

Scott, Susan, 1953–
Biology of plagues/Susan Scott and Christopher J. Duncan
p. cm.
Includes bibliograhical references and index.
ISBN 0 521 80150 8
1. Epidemics. 2. Epidemics — Europe – History – 16th century.
3. Epidemics – Europe – History – 17th century. 4. Black death – Europe.
5. Plague. I. Duncan, C. J. (Christoher John) II. Title.
RA650.6.A1 S36 2001
614.4′94 – dc21 00–063066

ISBN 0 521 80150 8 hardback

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Introduction

We first became interested in plagues when studying the demography of northwest England (Duncan *et al*., 1992; Scott & Duncan, 1998), where an epidemic in the town of Penrith in 1597–98 killed some 40% of the population and initiated endogenous oscillations in the annual numbers of births and deaths. In this way, its effects persisted for 150 years. The outbreak spread rapidly, travelling 20 to 30 miles in 2 or 3 days and it was obvious that it was a biological impossibility that this was an outbreak of bubonic plague. We initially thought that this must have been an isolated outbreak of an unknown and unique infectious disease (Scott *et al*., 1996) but further study convinced us that this regional epidemic had many points in common with other outbreaks in England that were believed to be bubonic plague.

In this book, we have attempted an objective (though not exhaustive) study of the plagues that have ravaged humankind for hundreds of years, giving the biological, demographic and epidemiological viewpoints of the available historical evidence. Obviously, the difficulties faced are vastly greater than those of a modern epidemiologist investigating a new outbreak of an unknown disease today. He or she has an array of techniques available from microbiology and molecular biology, can take biopsy and autopsy samples with the back-up of a pathology laboratory, can make on-site investigations of the ecology and epidemiology of the disease, and can discover the clinical features and mode of transmission of the infection. Even so, some features of present-day outbreaks of Ebola, such as the elucidation of the reservoir host, are not yet established with certainty. Where the disease has a complex biology, as in bubonic plague, it took years of painstaking study before all the details were elucidated.

1.1 What is a plague?

The Bible uses the word 'plague' to describe an affliction that was regarded as a sign of divine displeasure or as an affliction of humankind such as the plague of locusts. Nowadays, it is a term used to describe a deadly epidemic or pestilence and *The Wordsworth Encyclopedia of Plague and Pestilence* (Kohn, 1995) lists a seemingly endless catalogue of historical epidemics from all over the world, including smallpox, cholera, typhus and malaria. They were all infectious and potentially lethal, caused high mortality and were serious historic events. The influenza pandemic of 1917–19, with a final death toll worldwide estimated at more than 20 million, is a good example. The incubation period was often less than 2 days so that its worldwide spread was dependent on 20th century means of rapid travel that could move people in bulk, namely steamtrains and steamships of which the troop ships of the First World War are a good example.

However, the basic etiology of these diseases is now usually well understood and, in spite of the terrible death toll, the percentage mortality of the affected populations was not relatively high (Langmuir *et al*., 1985). In this book, we are mainly, but not exclusively, concerned with the Black Death, arguably the most awful epidemic ever to have struck, which raged in Europe from 1347 to 1350, and the unremitting succession of plagues that followed it for 300 years. These reached their peak in continental Europe during 1625–31 and in England in 1665–66, but they then disappeared completely after about 1670. When these plagues struck a naive population, where we have reasonably accurate data available in Italy and England, mortality could reach about 50%; we do not know what was the causative agent in these terrible epidemics.

1.2 Four ages of plague

From whence did the Black Death come? The probable answer to this question is that it originated in the Levant, but Europe had suffered from a series of mysterious plagues for many years before 1347 and it is possible to identify tentatively and arbitrarily four historic ages of plague.

1.2.1 Plague at Athens, 430–427 BC

The epidemic that struck Athens in 430 BC remains one of the great medical mysteries of antiquity and has been discussed by a number of scholars (Morens & Littman, 1972, 1994; Poole & Holladay, 1979;

Longrigg, 1980; Langmuir *et al*., 1985; Kohn, 1995; Olson *et al*., 1996; Retief & Cilliers, 1998), but the first vivid description was given by Thucydides, himself a victim who survived the outbreak (see Page, 1953). It is sometimes termed the Thucydides syndrome because of his evocative narrative.

People were stricken suddenly with severe headaches, inflamed eyes, and bleeding in their mouths and throats. The next symptoms were coughing, sneezing, and chest pains followed by stomach cramps, intensive vomiting and diarrhoea, and unquenchable thirst. The skin was flushed, livid and broken with small blisters and open sores. The patients burned with fever so extreme that they could not tolerate being covered, choosing rather to go naked. Their desire was to cast themselves into cold water, and many of those who were unsupervised did throw themselves into public cisterns, consumed as they were by unceasing thirst. Many became delirious and death usually came on the seventh or eighth day of the illness, although those who survived the first phase often died from the weakness brought on by constant diarrhoea. Many who recovered had lost their eyesight, their memory, or the use of their extremities.

This plague is believed to have originated in Ethiopia and travelled through Egypt and the eastern Mediterranean before reaching Athens. The first cases appeared in Piraeus, the Athenian port and base for many travellers and merchants who probably contracted the disease in their journeys abroad. It spread rapidly to the upper city and whole households were left empty. Mortality among doctors, as among other attendants of the sick, was especially high. Fearful of an attack by the Spartans, the Athenian leader Pericles ordered the inhabitants of the surrounding countryside to move inside the city, where they could be protected by the army and the fortified walls. Many country dwellers, coming to an already overpopulated city, had no place to live except in poorly ventilated shacks and tents. This mass of people, crowded together in the hot summer, created a situation that was ideal for the rapid transmission of the disease. Though there were many dead bodies lying unburied, there was said to be a complete disappearance of birds of prey and dogs. Apparently it was rare to catch the disease twice, or if someone did, the second attack was never fatal. A peak case rate was reached during the Spartan siege, which lasted 40 days, after which the crowded refugees dispersed. The disease remained at a low level through 429 BC (when Pericles died of it) and returned in force in the summer of 428 BC at the time of another Spartan siege. The disease was quiescent, or even absent, from the winter of 428 BC until the summer of 427 BC, but broke out again in the autumn or early winter of

427 BC. This epidemic lasted no less than a year, but there is no further mention of the disease. The total number of Athenians who died is not recorded but, over the 3-year period, of 13 000 enrolled hoplites (soldiers), 4400 died – a mortality rate of 33%. Hagnon took the fleet and sailed to Potidaea carrying the plague there also and this made dreadful havoc among the Athenian troops. Even those who had been there previously and had been in good health caught the infection and so 1050 men out of 4000 were lost in about 40 days.

There have been several identifications of the causative agent of the plague at Athens, including smallpox (Littman & Littman, 1969), scarlet fever, measles and typhus (Shrewsbury, 1950; Page, 1953) but these are all now discredited. Langmuir *et al.* (1985) concluded that the clinical descriptions clearly indicated the involvement of specific organ systems and that there was an obvious inflammatory condition of the eyes and respiratory tract; this acute respiratory infection was severe and probably necrotising; the initiation with vomiting followed by empty retching and later by 'watery diarrhoea' strongly suggested a gastroenteropathy mediated by the central nervous system rather than a local inflammatory process. Langmuir *et al.* (1985) believed that the skin lesions were suggestive of bullous impetigo. They did not suggest that the Thucydides syndrome was identical with the modern toxic shock syndrome but believed that the same basic pathogenic mechanisms were involved, in that there was infection in predisposed hosts by a possibly non-invasive *Staphylococcus* sp. that was capable of producing an exotoxin similar to toxin-1 of the toxic shock syndrome (Rasheed *et al.*, 1985). This toxin may have differed from toxin-1 in that it produced predominantly enterotoxic effects and less profound circulatory collapse, and had only moderate or no erythrogenic potential.

Morens & Littman (1992, 1994) have approached the plague at Athens from a different viewpoint and have arrived at a conclusion that is strongly opposed to that of Langmuir *et al.* (1985). We describe their hypothesis briefly because they use mathematical modelling techniques that we shall also employ to elucidate the epidemiological parameters of later plagues. They have reduced the reliance on clinical symptoms in favour of the epidemiology of the disease because pre-modern descriptions, which lack detailed information on serology and accurate accounts of rashes and other clinical features, always retain a high degree of uncertainty. Use of the Reed and Frost mathematical model (section 2.5) led them to conclude that, under any conditions of crowding that probably prevailed in Athens in 430 BC, an epidemic of influenza would have died out rapidly in a few

weeks. They excluded all common diseases and most respiratory diseases and concluded that the cause of the Athenian epidemic could be limited to either a reservoir disease (zoonotic or vector-borne) or one of the few respiratory diseases that are associated with an unusual means of persistence: either environmental/fomite persistence, or adaptation to indolent transmission among dispersed rural populations. They suggested that the diseases in the first category include typhus, arboviral diseases and bubonic plague and, in the second category, smallpox. Retief & Cilliers (1998) also reviewed the epidemiological evidence and agreed that the only possibilities are epidemic typhus, bubonic plague, arboviral disease and smallpox.

Other workers have suggested that the plague at Athens was an early manifestation of Ebola (sections 1.3 and 13.15). Olson *et al.* (1996) stated that a modern case definition of Ebola virus infection records sudden onset, fever, headache, pharyngitis followed by cough, vomiting, diarrhoea, maculopapular rash, and haemorrhagic diathesis, with a case fatality rate of 50% to 90%, death typically occurring in the second week of the disease. In a review of the 1995 Ebola outbreak in Zaire, the Centre for Disease Control and Prevention reported that the most frequent initial symptoms were fever (94%), diarrhoea (80%), and severe weakness (74%), with dysphagia and clinical signs of bleeding also frequently present. Symptomatic hiccups were also reported in 15% of patients. Olson *et al.* (1996) concluded that the profile of the plague at Athens was remarkably similar to that of the recent outbreaks of Ebola in Sudan and Zaire. Certainly, as we shall see, this devastating epidemic had features in common with later plagues in Europe (section 1.3).

1.2.2 The plague of Justinian

Procopius, the Greek historian, believed that this epidemic (like the plague of Athens) originated near Ethiopia. The pandemic began in Egypt in AD 541 and it then moved through Asia Minor, Africa and Europe, arriving in Constantinople, the capital of the Byzantine Empire, in the late spring and summer of AD 542. Merchant ships and troops then carried it through the known western world and it flared up repeatedly over the next 50 years, causing an enormous mortality, perhaps aided by wars, famines, floods and earthquakes. The plague raged in Constantinople for 4 months in AD 542, with the death toll rising from 5000 to 10 000 per day and even higher during the three most virulent months. The Byzantine emperor Justinian fell ill and recovered, but 300 000 people were said to have died in Constantinople alone in the first year, although Russell (1968) and Twigg

(1984) believed these figures to be greatly exaggerated. The officials were completely overwhelmed by the task of disposing of the dead bodies (Kohn, 1995).

Procopius recorded that people (understandably) were terrified, knowing that they could be struck without warning. The first symptoms were a mild fever which did not seem to be alarming, but bubonic swellings followed within the next few days. Once the swellings appeared, most sufferers either went into a deep coma or became violently delirious, sometimes paranoid and suicidal. It was difficult to feed and care for them properly, although mere contact with the sick did not seem to increase the chances of contracting the disease. Most victims died within a few days, but recovery seemed certain for those whose buboes filled with pus. Black blisters were a sure sign of immediate death; otherwise, doctors often could not predict the course of the disease or the success of various treatments. Autopsies revealed unusual carbuncles inside the swellings and these clinical features led to the conclusion that the Justinian plague was a pandemic of bubonic plague (Kohn, 1995). Shrewsbury (1970) agreed, but suggested that other serious diseases, such as smallpox, diphtheria, cholera and epidemic influenza were also present. It is not possible to be certain from the evidence available, but the rapid spread over great distances, the heavy mortality and other biological features of the pandemic suggest that bubonic plague was not the major component, but that some other infectious disease, spread person-to-person, was responsible.

1.2.3 The Great Age of plagues: the Black Death and thereafter

The Black Death erupted in Sicily in 1347 and the pandemic spread through Europe during the next 3 years, reaching Norway (where two-thirds of the population died; Carmichael, 1997) and Sweden and crossing to England (and thence to mainland Scotland, the Hebrides, Orkney and the Shetland Islands) and to Ireland (Biraben, 1975) and, possibly, to Iceland and Greenland (Kohn, 1995). Its arrival presaged a continuous succession of epidemics in Europe for the next 300 years before it disappeared completely around 1670. The enormous mortality of the Black Death had a major impact on the demography of Europe, and the population of England did not fully recover for 150 years. Events during 1347–50 are described in Chapter 4 and the demographic consequences of a major mortality crisis on a population are discussed further in section 13.17. Were the multiplicity of plagues throughout Europe from 1350 to 1670 all the result of the same causative agent as that responsible for the Black Death,

albeit with some minor mutations during that time? It is not possible to answer this question with certainty, but we believe that the most probable explanation of the etiological and epidemiological details is that it was so.

During the second half of the 14th century, the epidemics in England and continental Europe were less virulent but the infection gradually regained its ferocity, reaching its peak around 1630 in France and 1665–66 in England.

1.2.4 Bubonic plague in the 20th century

The details of the complex biology of bubonic plague were finally unravelled around 1900: it is a bacterial disease of rodents depending on the rat flea for its spread and on a reservoir of resistant rodent species for the maintenance of the disease. Only occasionally does the infection spread to humans when one is bitten by a rat flea but, in the days before antibiotics and modern medicine, this was usually fatal and serious epidemics could be established.

Unfortunately, historians of Europe in the 20th century, almost universally, have concluded that all plagues in the Middle Ages were bubonic, in spite of the fact that the people at that time saw clearly that it spread person-to-person and, even in the 14th century, had already instituted specific quarantine periods. A major objective of this book is to examine the historical facts dispassionately, eschewing any preconceived notions about the behaviour of rats and fleas and to determine the nature of the epidemics of the Middle Ages in Europe. Normally, we refer to these as plagues, but where there is possible confusion with bubonic plague, we designate the former as haemorrhagic plague. To distinguish between haemorrhagic and bubonic plagues we begin in Chapter 3 with a detailed account of the complex biology, etiology and epidemiology of bubonic plague and explain how, in consequence, the spread and maintenance of the disease in rodents and humans is strictly constrained.

Although we have described bubonic plague from 1900 to the present day as the fourth age of plague, the disease has been identified (presumably correctly) and recorded in detail from China since AD 37 (Wu, 1926; Wu *et al*., 1936) and it is likely that it has been present in India and in a gigantic swathe across central Asia for hundreds of years. It probably extended westwards to the Levant and the north African coast and may have erupted sporadically in the warm Mediterranean coastal regions in the 6th century AD (Twigg, 1984) and it was certainly present there in the Middle Ages and continued with occasional epidemics in the 18th century (see Chapter 12).

Where climatic conditions were suitable and reservoir rodent species were present locally, endemic bubonic plague could be established. Where only the climate was suitable, as in the coasts of France, Spain and Italy, epidemics of bubonic plague could potentially break out, having been brought into the ports by sea, but these terminated once the local rats had died. During the third age of plagues, 1347–1670, therefore, Europe probably experienced minor outbreaks of bubonic plague along the Mediterranean coasts of Italy, Spain and France in addition to the major epidemics of haemorrhagic plague.

Finally, endemic bubonic plague erupted in a series of epidemics in India at the very end of the 19th century and spread across southeast Asia, and so began the fourth age of plagues. As we show in Chapter 3, the arrival of steamships then allowed rats and their fleas carrying bubonic plague to be rapidly transported from the grain stores on the docks of China to subtropical regions wherever suitable indigenous rodents occurred.

1.3 The dangers of emerging plagues

From whence did the plague of Athens, the Justinian plague and the Black Death come? How did they emerge with such sudden ferocity? We have seen in the 20th century the emergence of a number of new deadly diseases that are largely resistant to medical science: scientists have identified more than 28 new disease-causing microbes in 1973 (Olshansky *et al.*, 1997). Indeed, it has been suggested that the history of our time will be marked by recurrent eruptions of newly discovered diseases (e.g. Hantavirus in the American West), epidemics of diseases migrating to new areas (e.g. cholera in Latin America), diseases that become important through human technologies (water cooling towers provided an opportunity for legionnaires' disease) and diseases that spring from insects and animals because of human-engendered disruptions in local habitats. Two of the terrors that haunt are the fears that new, unstoppable infectious diseases will emerge and that antibiotics will be rendered powerless. To some extent, these processes have been occurring throughout history. What is new, however, is the increased potential that at least some of these diseases will generate large-scale pandemics, such as a resurgence of the 1918 influenza pandemic; the global epidemic of human immunodeficiency virus (HIV) is the most powerful and recent example. Yet the acquired immune deficiency syndrome (AIDS) does not stand alone; it may well be just the first of the modern, large-scale epidemics of infectious diseases. The world has rapidly become much more vulnerable to the eruption and, most critically, to the

widespread and even global spread of both new and old infectious diseases. This new and heightened vulnerability is not mysterious; the dramatic increases in the worldwide movement of people, goods, and ideas is the driving force behind the globalisation of disease because not only do people travel increasingly, they also travel much more rapidly, and go to many more places than ever before. The lesson is clear: a health problem in any part of the world can rapidly become a widespread health threat (Mann, 1995).

Most emergent viruses are zoonotic, with natural animal reservoirs a more usual source of new viruses than is the spontaneous evolution of a new entity. Human behaviour increases the probability of the transfer of viruses from their endogenous animal hosts to humans. The original source of the AIDS pandemic has been traced back to a subspecies of chimpanzee that has been used for food in West Central Africa, the hunters being exposed to infected blood during the killing and dressing. The virus has probably been living harmlessly in chimpanzees for hundreds of years and may have been transferred to humans throughout history, but the socio-economic changes in Africa provided the particular circumstances leading to the spread of HIV and AIDS.

An outbreak of encephalitis in Malaysia in 1999, which killed 76 people may have been caused by a more deadly version of the Hendra virus, which was first identified in Australia 5 years previously. The difference is that, whereas the virus in the earlier outbreak did not spread easily between animals, the Malaysian version apparently did: all the Malaysian victims were connected with pig rearing. Health officials in Asia now fear that a dangerous new human pathogen has emerged that has spread from fruit bats via pigs and consequently more than 300 000 pigs were slaughtered in southern Malaysia as an initial precautionary measure. The spinal fluid taken from five patients contained a paramyovirus (named 'Nipah') and analysis of the amino acid and RNA sequences confirmed that it is related to the deadly Hendra virus. Why has the virus suddenly begun to kill pigs and people when the bats may have harboured it safety for centuries?

The Ebola virus, a member of the Filoviridae, burst from obscurity with outbreaks of severe haemorrhagic fever. It was first associated with an outbreak of 318 cases and a case fatality rate of 90% in Zaire and caused 150 deaths among 250 cases in Sudan. Smaller outbreaks continue to appear periodically, particularly in East, Central and southern Africa. In 1989, a haemorrhagic disease was recognised among cynomolgus macaques imported into the USA from the Philippines; strains of Ebola virus were isolated and serologic studies indicated that the virus is a

prevalent cause of infection among macaques. Epidemics have resulted from person-to-person transmission, nosocomial spread and laboratory infections but it must be emphasised that the mode of primary infection and the natural ecology of these viruses are unknown. The possible role of the Ebola virus as the causative agent in haemorrhagic plague is discussed in section 13.15.

A mysterious epidemic of Marburg virus (related to Ebola virus) broke out in a remote area of the Democratic Republic of Congo, Central Africa, in December 1998. At least 72 miners suffered from fever, pain, rash and bleeding and 52 had died by May 1999. The victims had spent time in caves and bats are considered to be the leading contender for an animal reservoir of the virus; monkeys die too quickly from the virus for them to be considered for this role.

A virulent influenza pandemic struck from 1917 to 1919, with a final worldwide estimated death toll of more than 20 million lives (Kohn, 1995). It has been termed Spanish influenza (dryly known as 'the Spanish Lady') because this was believed to be the first serious point of attack, with 8 million Spaniards falling ill in 1917–18. It then struck at military bases throughout Europe and death rates mounted ominously in 1918. At the same time (beginning in March 1918) acute respiratory infections were reported at military installations in the USA and by October some US army camps were reporting a death every hour; Britain was then counting 2000 deaths per week, with London at about 300 deaths per week. Country after country felt the ravages of the disease. The weak, the young and the old usually suffer worst in epidemics, but the age group 21 to 29 years proved to be the most vulnerable in this outbreak of Spanish influenza. While manifesting the ordinary symptoms of influenza (headache, severe cold, fever, chills, aching bones and muscles), the Spanish form also generated complications such as severe pneumonia (with purplish lips and ears and a pallid face), purulent bronchitis, mastoid abscess and heart problems. The frightening disease subsided after the end of the First World War and later vanished completely but, by then, it had attacked every country in the world, particularly China, India, Persia, South Africa, Britain, France, Spain, Germany, Mexico, Canada, the USA and Australia.

A radical genetic mutation, called antigenic shift, accounts for the appearance of new viral subtypes capable of engendering influenza pandemics. New viral types originate in ducks, chickens, pigs and other animals, in which reservoirs of influenza viruses change genetically and are then passed into the environment, and to human beings. The strain that caused the 1918 epidemic, H1N1, was found inside pigs and there is always

the fear that this strain may resurface, perhaps in as virulent a form as in 1918. Many pandemics originate in Asia, notably China, where enormous numbers of ducks, pigs, and other virus-producing animals live in close proximity to human beings (Kohn, 1995). Avian influenza A (H5N1) virus has recently been shown to be transmitted from patients to healthcare workers in Hong Kong and this finding may portend 'a novel influenza virus with pandemic potential' (Bridges *et al*., 2000).

Fragments of the virus responsible for Spanish influenza were found in 1998 in the lungs of a woman who died in the 1918 epidemic and whose body was preserved by huge layers of fat and the frost of Alaska and it is hoped that it will be possible soon to map the RNA of the virus to identify the gene that made it so deadly. Preliminary work has produced the complete sequence of one key gene and the existing strain to which the 1918 sequences are most closely related is A/Sw/Iowa/30, the oldest classical swine influenza strain. More recently, influenza 1918 RNA has been found in respiratory tissue and the brains of Spitzbergen coal miners who died in the epidemic and Oxford (2000) suggested that this could be a piece in the jigsaw linking pandemic influenza to the ensuing outbreak of the sleeping disease encephalitis lethargica.

A virulent and drug-resistant form of typhoid caused by the pathogen *Salmonella typhi*, which kills 600 000 people a year, has now emerged in Vietnam. The study of its genome is now almost complete: the nucleus contains three separate pieces of DNA, a massive coil some 4.5 million bases long and two plasmids, smaller loops of genetic data. One of the plasmids contains an array of offensive and defensive genes, which probably explain the potency of this strain of typhoid. It came as a great surprise when it was discovered that the other plasmid contained a sequence of 50–60 genes that are found in *Yersinia pestis*, the bacterium of bubonic plague and thus the Vietnamese microbe appears to be fortified with the genes of other pathogens (Farrar, 2000).

There is a seemingly endless catalogue of lethal infectious diseases that have emerged. Some of these have been described in a very lively manner by Garrett (1995): Lassa fever, Bolivian haemorrhagic fever, Marburg virus, the Brazilian meningitis epidemic and the Hantaviruses. Health officials in New York City reported, in August 1999, an outbreak of what appeared to be St Louis encephalitis, a disease that can spread to humans from birds via mosquitoes. However, it has now been discovered that the infectious agent is West Nile virus, which is normally found in Africa and Asia and is also transmitted by mosquitoes. Helicopters sprayed entire neighbourhoods in Queens, New York, after the disease killed horses,

thousands of birds and several people; there has been a fresh outbreak in New York City in summer 2000 and what really alarms American health officials is the danger of the disease establishing itself permanently in the country. It remains an open question as to how the virus reached the USA (Boyce, 1999). So, it should not surprise us that the classical pandemics of historical times emerged and it is probable that they originated as viral zoonoses. Viruses have a great capacity for mutating and are opportunistic parasites; the worrying thought is (as suggested above) where and when will they next strike?

1.4 Populations and metapopulations

The study of how disease affects groups, or populations, of people is known as epidemiology; the discipline began when doctors wanted to study outbreaks of infectious diseases such as cholera and bubonic plague. Epidemiological studies today gather such data as age, race, sex and even social class, together with the incidence of the disease (the number of new cases appearing in a given time period) and its prevalence (the number of sufferers at any one time). The information can then be used to establish patterns in the disease and thus pinpoint aggravating factors.

Epidemiology can be defined in a number of different ways as, for example, 'the science of the infective diseases – their prime causes, propagation and prevention. More especially it deals with their epidemic manifestations' (LeRiche & Milner, 1971). This definition can then be extended because, if a communicable disease conforms to biological laws, epidemiological processes could be interpreted in terms of medical ecology (Gordon & LeRiche, 1950). Thus what we are studying in this book are the health and diseases of populations and groups and, in contrast to clinical medicine, the unit of study in epidemiology is the population and not the individual (Morris, 1957).

We investigate firstly the epidemiology of plagues in towns, large and small, treating them as circumscribed populations that have an identity but, of course, are not completely closed – infectives will have come into the population and a proportion of the inhabitants may have fled when an epidemic has been recognised. The temporal and spatial spread of the plague within the community (or unit) is governed by the household infection rate and by the ways in which it can spread to other households and thence to other streets and the results may then be compared with other populations. If the spread of the plague is density dependent, the pattern of the epidemic would be expected to be different in communities of

different sizes. The city of London, as we shall see, was a complex population; a very large number of individuals crammed together but with subsets delineated by class and parish, with partial intercourse. The population was freely open, with many immigrants, travellers and merchants arriving daily by land and sea.

The spread of an outbreak of plague may also be studied at a higher population level, i.e. throughout a geographically defined area that might be the size of a country or even part of a continent. Examples are island Britain, and the Iberian peninsula, which was effectively separated from continental Europe by the Pyrenees and, in both, plague epidemics had to enter from the sea via the ports. These may be called metapopulations, a term used by ecologists to describe a population of populations. The study of metapopulation dynamics in biology is normally concerned with the behaviour of a single species over time; there are no static populations and likewise there is no such thing as a static metapopulation. The metapopulation concept in ecology is closely linked with the processes of population turnover, extinction and the establishment of new populations. Ecological metapopulation theory, with one important exception, has not been applied to human populations; indeed, as originally defined, it is not strictly applicable because it deals with extinctions and recolonisations and makes the simplifying assumption that each ecological site is regarded as being in one of two alternative states, either empty or filled at their local carrying capacity, characteristics that were rarely found in England during the age of plagues. The exception concerns studies of spatial heterogeneity and the epidemic spread of infectious diseases through a human metapopulation where individuals can be either infected or uninfected, an example of the interaction between demography and disease.

The spread of epidemics is an important part of modern Geography and we have used such techniques as disease centroids to trace the spatial movements of the plague in a metapopulation where it was endemic (see section 2.12). It becomes evident that the Black Death had a different pattern of spread from subsequent plague epidemics which, in turn, exhibited a range of sharply differing characteristics. The Black Death recognised no boundaries, either natural or human engendered, and spread in a wave-like movement all across Europe and to off-shore islands in about 3 years before disappearing. We can regard its territory for this brief period as a 'supermetapopulation'. Bubonic plague as a disease of rodents, and secondarily of humans, was certainly established as endemic across a huge subtropical area by 1900, from the Levant across to China and Southeast Asia. It has persisted for many years and we can regard this also as a

'supermetapopulation'. Haemorrhagic plague slowly established itself in Europe after the Black Death, with France as its endemic centre. England, Spain and Italy experienced epidemics of differing frequency, being separated from France by various geographical features, but France expanded from a metapopulation into a 'supermetapopulation' in the Middle Ages, which was composed of present-day Germany, the Benelux Countries and France. Here, plague was maintained as endemic, there being a handful of widespread epidemics somewhere maintained by long-distance travelling infectives.

1.5 A cautionary note

It is sometimes difficult to determine whether a marked increase in deaths in a year (a mortality crisis) was really the consequence of a plague epidemic. The health authorities in the city states of northern Italy in the 14th century went to great lengths to distinguish between minor (which they disregarded) and major (which were very serious) 'pests' (as they were called) by examining the victims personally, but historians rarely have such direct evidence on which to base their conclusions. Livi-Bacci (1977) relied on the size of the crisis and wrote

> For several parts of Tuscany between 1340 and 1400 I have calculated that on average a serious mortality crisis – defined as an increase in deaths at least three times the normal – occurred every 11 years; the average increase in deaths was at least sevenfold. In the period 1400–50 these crises occurred on average every 13 years and deaths increased fivefold. In the following half century (1450–1500) the average frequency declined to 37 years and the average increase to fourfold.

Shrewsbury (1970) considered that 'When more than 66% of the total annual burials occurs in the three months of July to September inclusive, the record is almost certainly indicative of an outbreak of bubonic plague' and this led him to conclude, for example, that there were multiple plague epidemics in northwest England in 1623. However, this area was living on the margins of subsistence at this time and mortality was sensitive to a 5- to 6-year cycle in grain prices (Scott & Duncan, 1998) and the constituent communities suffered major mortalities not only in 1623, but in 1587–88 and 1596–97 also. We have shown that in these years the peak of wheat prices coincided with a low in the 12-year cycle of wool prices (Scott & Duncan, 1997, 1998). Those populations that depended on both commodities suffered severely whereas those that depended on only one for their livelihood escaped unscathed. They did not suffer from plague in 1623. It is evident that by the end of the 16th century all towns could recognise plague

when it struck their community and, if an outbreak is not recorded in the parish registers, a rise in mortality should be assumed to be the consequence of a plague epidemic only with extreme caution.

1.6 Pioneers in the study of plagues

We all owe a debt of gratitude to Yersin and his co-workers, to Wu and to the Plague Commission of India for the way in which they slowly and meticulously unravelled the complex biology and epidemiology of bubonic plague. A splendid piece of detective work. However, in this book we also wish to acknowledge the work and writings of a number of people who have influenced us and on whom we have relied heavily:

(i) First, Charles Creighton, 1847–1927, is the doyen of epidemiologists whose *History of Epidemics in Britain* was published in two volumes in 1891 and 1894. He graduated from Aberdeen University MA in 1867 having studied Latin, Greek, Mathematics, English, Logic, Moral Philosophy, Natural Philosophy and Natural History, and as Bachelor of Medicine and Master of Surgery in 1871. His approach in his classic work, which was to provide a chronicle of death and disease in the life and people of England, was that of a professional historian and he worked with great care on his sources (Eversley, 1965). We have relied heavily on his data series in our earlier work on lethal infectious diseases (Duncan *et al*., 1993a,b, 1994a,b, 1996a,b; Scott & Duncan, 1998). He probably knew something about the biology of bubonic plague when he was writing in 1891 because this was being elucidated at the time but he does not seem to assume that this was necessarily related to the plagues in England that he was describing and, consequently, his descriptions are not modified to fit within the life histories of the rat and flea. In later life, he spent 3 months in India at the end of 1904 and reported about rats living in the mud walls of houses and of dead rats being found in a house where the inmates had died of bubonic plague (Underwood, 1965).

(ii) In the preface to the first edition of his book *Infectious Diseases*: *Epidemiology and Clinical Practice*, published in 1969, A. B. Christie wrote 'A good book, it has been said, should be opened with expectation and closed with profit . . .'. His treatise not only lives up to these high standards, but it is read with pleasure: he makes even dull topics interesting, spicing his account with classical allusions, gentle humour and personal anecdotes. He writes authoritatively and clearly on every

infectious disease and this is particularly apparent when he deals with bubonic plague. His clinical experience across continents is revealed when he says that he believes that he had patients in Libya with bubonic plague who were infected by contact with a camel that had been ailing before slaughter and had a swelling in its neck.

(iii) Professor J. F. D. Shrewsbury, a microbiologist, has given us a great work of scholarship in his *A History of Bubonic Plague in the British Isles*, published in 1970, in which 'He has ransacked virtually all published local histories and parish records and he has read very widely in contemporary chronicles and memoirs' (Morris, 1977). Although we have relied heavily on his studies as a data source, we have not attempted to repeat the details of his findings and we suggest that readers who require more information about plagues in England should refer to this basic source book. It is a little dull and confusing in places but is occasionally illuminated by his dry humour:

> 'John Toy ascribed the visitation to God's punitive anger, because He had already twice warned the people of Worcester of their sins by inflicting slighter outbreaks of the disease upon the city; but it apparently never occurred to him that the Almighty would not thus degrade the Infinite to single Worcester out for such irrational punishment, for Worcester was certainly no more sinful than Lincoln, Salisbury, Canterbury, or any other English episcopal centre. It certainly never drew part of its revenue from brothels like the see of Winchester . . .'
>
> '[T]he parish of St Giles, Cripplegate, where a parishioner was summoned in April to appear at the next sessions to answer "for receivinge people into his house sick of the plague brought from other parts to the prejudice of the parish" and for having "at the same tyme another sick of the French pockes [who] liveth incontynently with one Fayth Langley". Was he running the seventeenth-century equivalent of a nursing home?'
>
> 'In 1610 the churchwardens of St Margaret's, Westminster, paid 6*d*. to "Goodwife Wells for salt to destroy the fleas in the churchwardens' pew". Evidently the Anglican worshippers of the seventeenth century were as tormented by this ectoparasite as the monks had been in Salimbene's day. Most of the fleas, which undoubtedly were equally devout and attentive in most English parishes, were the human flea . . .'

As his title suggests, Shrewsbury believed whole-heartedly that bubonic plague was responsible for the majority of the plague epidemics in England and Scotland and yet, as a trained medical microbiologist, he saw that the facts on many occasions, made this a biological impossibility. He was therefore frequently forced to adapt his conclusions. When plague was reported in the months December to February he stated that it must have been a mild winter. When other

facts about an epidemic did not fit bubonic plague he frequently declared it to be an outbreak of typhus, even when plague is recorded in the registers. He invented what he called 'trailer epidemics' to circumvent other difficult events. He was well aware that the mortality levels in many of the epidemics were much higher than would be expected in bubonic plague, particularly in the Black Death, and he reluctantly concluded that the sources from which he had quoted had overestimated the death toll.

Nevertheless, Shrewsbury steadfastly maintained that bubonic plague was the cause of most of the plague epidemics in the British Isles and it is most unfair that he should have twice been attacked, apparently for daring to suggest that there might be weaknesses in the story.

Gottfried (1978) wrote

'Herein lies one of the book's major shortcomings – Shrewsbury's failure to investigate any but printed and easily accessible chronicles and letters. No effort is made to search more obscure printed and manuscript sources: and even when original data are searched, it is done in an extremely uncritical manner. Often, the validity of the records is denied on the basis of uncorroborated value judgements and twentieth century medical information . . . One of his major premises is that epidemic bubonic plague has not changed in character "during the period of recorded history". This is contrary to what other epidemiologists have written. Shrewsbury diminishes the significance of the effects of pneumonic plague in fifteenth century England, saying that it cannot "occur in the absence of the bubonic form". This too seems to run contrary to the evidence . . . Also, interregional travel was far more common in the Middle Ages than Shrewsbury indicates, and was by no means restricted solely to merchants. Thus, both bubonic and pneumonic plague could survive in sparsely populated regions.'

Morris (1977) made a longer and more vigorous attack, particularly because Shrewsbury, who was a medical microbiologist, refused to allow the pneumonic form of bubonic plague to have a role in the epidemics:

'for some reason he has chosen to turn a blind eye to any evidence of pneumonic plague. He does not notice how often the victims are said to have succumbed in three days and if he meets with any reference to plague in cold weather he jumps to the conclusion that the disease must have been something else, preferably typhus . . . But there is much evidence, all of it ignored by Shrewsbury, that the Great Pestilence of 1348–50 contained a high percentage of pneumonic cases and indeed that in many places the plague first appeared in its pneumonic form. This would easily account for the high mortality which Shrewsbury is anxious to whittle down.'

Morris also attacks because of Shrewsbury's statement that bubonic plague has an unvarying relationship with rodent enzootics:

> 'Shrewsbury's main contention is that the country would have had to be constantly re-infected by fresh importations of plague-bearing rats. He has not thought of the possibility that England might well have become an enzootic area in which some rats at any given time are diseased. This is odd since he knows very well that in other parts of the world plague has taken permanent root and produced notorious enzootic or endemic centres. Indeed he argues, mistakenly as it happens, that India has always been one such centre from which Europe has drawn its periodic re-infections . . . Besides, if England became, as obviously it did, a permanently enzootic area in the seventeenth century, why should it not have done so two centuries earlier? That plague was endemic, or at least enzootic in London, needing no imported re-infections, for more than half a century before 1665 is abundantly clear from the annual mortality bills.'

(iv) Biraben (1975, 1976) in his two-volume work *Les hommes et la peste en France et dans les pays européens et mediterranéens* has assembled an impressive set of data on plague epidemics in Europe after the Black Death. He has combed the literature extensively and his bibliography runs to over 225 pages. We have used these data-sets for analysis in Chapters 11 and 12.

(v) Graham Twigg is a zoologist who has specialised in the biology of rodents and who has discussed with Dr D. E. Davis the status of rats in the Middle Ages. In 1984 he wrote *The Black Death*: *A Biological Reappraisal*, in which he carefully develops the evidence that shows that bubonic plague was not the cause of this great pandemic. He summarised his seminal work in the conclusion 'The logistics of the epidemic in England support the hypothesis of an air-borne organism of high infectivity and virulence, having a short incubation period and being spread by respiratory means' (Twigg, 1989). All students of plague should read his work.

1.7 Objectives

An epidemiologist must, by definition, be an historian, even if only in the short term. We present a new analysis of the plagues that scourged Europe from the 14th to the 17th centuries, approaching from biological, ecological and epidemiological viewpoints. We analyse the historical data (hopefully objectively) using modern techniques of theoretical epidemiology, clinical molecular biology, computer-based modelling and the spatial models of epidemic spread that have been developed by geographers.

There is a substantial literature on the Black Death and the Great Plague of London in 1665 but, during the intervening 300 years, Europe suffered from repeated outbreaks of the pestilence and these epidemics have received less attention. Were these epidemics all the result of the same infectious agent? What were its epidemiological characteristics? Were all, some or none the result of bubonic plague? What determines the dynamics of plague epidemics?

To answer these questions we begin by defining epidemiological concepts, such as transmission probability and basic reproductive number, and then explain how the epidemics of some infectious diseases can be modelled with the aid of computer-driven simulations. Once the basic parameters of a disease in historic times have been determined or estimated it is possible to construct models of the epidemics from which the underlying etiology can be suggested.

We have also tried to include the human story of the epidemics in England, showing how each population responded to the outbreak, how the disease spread through the community, how the members responded and how they made their wills. We give detailed case studies of the epidemics at Penrith (Chapter 5) and Eyam (Chapter 10) and have devised a new method of analysing and displaying the spread of the infection in each family group using family reconstitution techniques; this is the only means by which the epidemiological characteristics (e.g. incubation, latent and infectious periods, contact rates and transmission probability) can be determined.

We begin the story of the age of plagues in Chapter 3 with an account of the Black Death and the subsequent outbreaks in the 14th and 15th centuries, but it is not until the 16th century, when parish registers started in England, that firm and detailed information becomes available. The epidemiological characteristics of plague can be deduced therefrom and, the key feature that emerges is the lengthy incubation period of this infectious disease. When one is armed with this information, the reasons for the spread and behaviour of haemorrhagic plague in continental Europe over a period of 300 years (described in Chapter 11) become clear: the key to understanding its epidemiology is the endemic status of the pestilence in France.

Chambers (1972) suggested that long-term demographic trends may have often been caused, not by Malthusian fluctuations in the balance between population levels and food supplies, but by independent biological changes in the virulence of disease and by the rise and fall of the great epidemic scourges, which were not economic in origin. Slack (1977a)

therefore concluded that the epidemiology of plague is a subject that bears on some of the central issues of demographic and social history. Historians have long been puzzled by the paradoxical rapid recovery of the population of England after the undoubted heavy mortality of the Black Death and in section 13.17 we examine some of the demographic consequences of a major mortality crisis in a single population, using the techniques of time-series analysis and computer modelling. We show that, although a population can apparently recover remarkably quickly, subtle demographic consequences could still be detected for over 100 years after the plague had disappeared.