

# Bubonic plague: a metapopulation model of a zoonosis

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Bubonic plague (*Yersinia pestis*) is generally thought of as a historical disease; however, it is still responsible for around 1000–3000 deaths each year worldwide. This paper expands the analysis of a model for bubonic plague that encompasses the disease dynamics in rat, flea and human populations. Some key variables of the deterministic model, including the force of infection to humans, are shown to be robust to changes in the basic parameters, although variation in the flea searching efficiency, and the movement rates of rats and fleas will be considered throughout the paper. The stochastic behaviour of the corresponding metapopulation model is discussed, with attention focused on the dynamics of rats and the force of infection at the local spatial scale. Short-lived local epidemics in rats govern the invasion of the disease and produce an irregular pattern of human cases similar to those observed. However, the endemic behaviour in a few rat subpopulations allows the disease to persist for many years. This spatial stochastic model is also used to identify the criteria for the spread to human populations in terms of the rat density. Finally, the full stochastic model is reduced to the form of a probabilistic cellular automaton, which allows the analysis of a large number of replicated epidemics in large populations. This simplified model enables us to analyse the spatial properties of rat epidemics and the effects of movement rates, and also to test whether the emergent metapopulation behaviour is a property of the local dynamics rather than the precise details of the model.

**Keywords:** Black Death; epidemic; stochasticity; persistence; spatial model; animal diseases

## 1. INTRODUCTION

Bubonic plague (caused by the bacterium *Yersinia pestis*), also known as the Black Death, devastated populations in Europe from the 14th–16th centuries, killing between one-third and one-half of the entire population (Langer 1970). Not surprisingly, there has been a vast amount of research into the disease from a historical perspective, cataloguing the panic and social changes that it caused (Shrewsbury 1970; Appleby 1980; McEvedy 1988; Risse 1992; Scott *et al.* 1996). However, bubonic plague is far from being confined to history; the pandemic in the early 1900s killed many millions (Commission for the Investigation of Plague in India 1906; Hirst 1938; Sharif 1951; Curson & McCracken 1990; Risse 1992) and even today the World Health Organization reports 1000–3000 cases of plague every year. Recent surveys indicate that bubonic plague is widespread throughout the wild rodent population in the United States, southern Asia, southern Africa and South America; thus, even in areas which have suffered few human cases there may still be the potential for a large-scale human epidemic.

Two factors add extra importance to the study of this disease: its recent re-emergence in India and Africa, and the evolution of multi-drug-resistant strains of the bacterium. Over the last decade there has been a significant increase in the number of reported cases of bubonic plague, with prolonged human epidemics arising in three main areas: Surat, Mozambique and Madagascar (Kumar 1995; Barreto *et al.* 1994; Boisier *et al.* 1997). In 1997 it was reported that a drug-resistant strain of the bacterium had evolved in Madagascar (Galimand *et al.* 1997). These two aspects have led many to speculate

that this historical disease may re-emerge to become an important public health problem (Pinner 1996; McCormick 1998; Gratz 1999).

In a previous paper (Keeling & Gilligan 2000), we introduced a stochastic metapopulation model for bubonic plague. Here we consider the full deterministic dynamics and stochastic behaviour in more detail. In particular, we concentrate on the rat dynamics at the local spatial scale, showing that the invasions are controlled by short-lived epidemics, whereas the persistence of the disease is governed by a few endemic subpopulations. The sensitivity of key model output variables to changes in parameters is discussed, with attention throughout the paper focusing on the role of flea searching efficiency and movement of rats and fleas, and their effects on the potential for human cases.

We first characterize the epidemic patterns observed in the historical data at three time-scales ranging from one to 60 years. The full deterministic model is formulated, linking rat, flea and human populations and describing the spread of the disease from rats to humans. The sensitivity of this model to parameter values is discussed in some detail. In §5 more biological complexity is introduced, making the model both stochastic and spatial, and obtaining irregular human epidemics characteristic of the historical data sets. Using this model we postulate that bubonic plague persists even in quite small rodent populations and therefore the observed historical dynamics are caused by fluctuations in the number of rat cases rather than random imports of infection. In §6 we focus attention on the potential risk to humans, and by examining the occurrence of bubonic plague in other wild rodents we are able to estimate lower bounds for the flea searching efficiency and hence the threshold for human cases. Finally, to test the robustness of our complex

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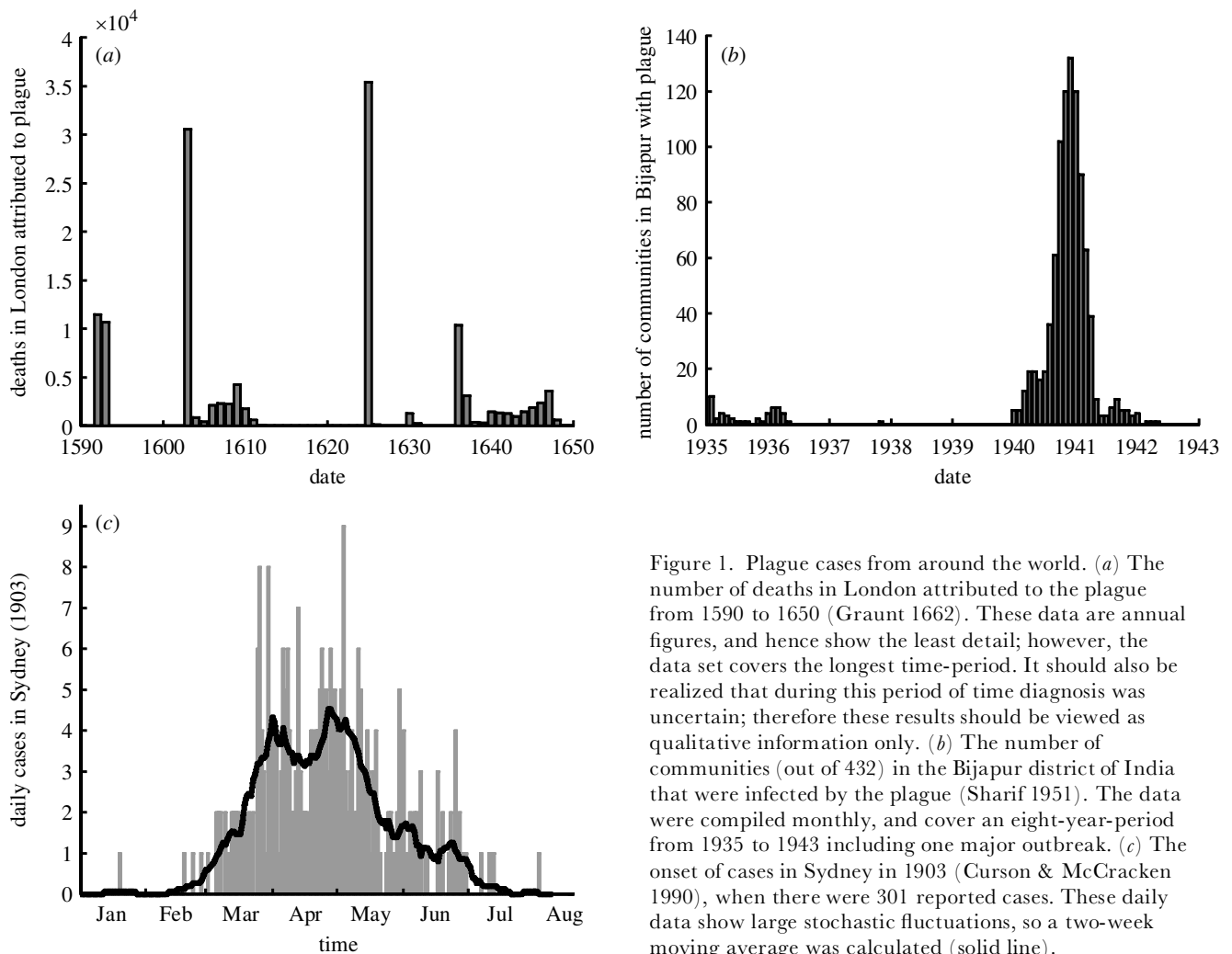


Figure 1. Plague cases from around the world. (a) The number of deaths in London attributed to the plague from 1590 to 1650 (Graunt 1662). These data are annual figures, and hence show the least detail; however, the data set covers the longest time-period. It should also be realized that during this period of time diagnosis was uncertain; therefore these results should be viewed as qualitative information only. (b) The number of communities (out of 432) in the Bijapur district of India that were infected by the plague (Sharif 1951). The data were compiled monthly, and cover an eight-year-period from 1935 to 1943 including one major outbreak. (c) The onset of cases in Sydney in 1903 (Curson & McCracken 1990), when there were 301 reported cases. These daily data show large stochastic fluctuations, so a two-week moving average was calculated (solid line).

stochastic model, a cellular automaton is developed in § 7. This displays all characteristics of the full stochastic model, but enables us to assess larger scale spatial patterns.

## 2. HISTORICAL DATA

Figure 1 shows the dynamics of bubonic plague in three very different locations (London in the middle ages, and Bijapur, India, and Sydney, Australia, in the 20th century) and over three very different time-scales. All three graphs show similar properties. Human epidemics occur sporadically and for a limited period, with long disease-free periods between epidemics (figure 1*a,b*). Also, the highly stochastic nature of this system is apparent (figure 1*c*), with variable duration and intensity and no clear evidence of a regular deterministic pattern (figure 1*a*).

## 3. THE MODEL

Before Keeling & Gilligan (2000), all models of bubonic plague concentrated on the human aspects of the disease, attempting to model the number of cases by an SIR-type framework (Nobel 1974; Raggett 1982; Scott *et al.* 1996), classifying humans as either susceptible, infectious or recovered. Using the notation of Nobel (1974), the

number of susceptible ( $S_H$ ) and infectious ( $I_H$ ) individuals is given by

$$\begin{aligned} \frac{dS_H}{dt} &= -\beta_H S_H I_H, \\ \frac{dI_H}{dt} &= \beta_H S_H I_H - m_H I_H, \end{aligned} \quad (1)$$

where the subscript H shows that we are considering the human population,  $\beta_H$  is the contact rate and  $m_H$  is the mortality rate. In this model the disease is considered fatal to humans, so there is no recovered class. Although the pneumonic form of the disease is highly contagious and is transmitted readily between humans, historical evidence shows that by far the greatest proportion of cases have been caused by transmission from rats to humans via fleas (Appleby 1980; Busvine 1993). Bubonic plague is therefore termed a zoonosis, being a disease of animals that can be passed on to humans (zoonoses include other publicly feared diseases such as rabies, ebola, Lyme disease, and hantavirus). Full understanding and prediction of the number of bubonic plague cases requires a model of the entire transmission route, with equations for the rat, flea and human populations (Keeling & Gilligan 2000). This leads to an SIR-type model for the rat population in a similar manner to

equations (1), describing the number of susceptible, infectious and resistant rats:

$$\begin{aligned} \frac{dS_R}{dt} &= r_R S_R \left(1 - \frac{T_R}{K_R}\right) + r_R R_R (1 - p) - d_R S_R \\ &\quad - \beta_R \frac{S_R}{T_R} F [1 - \exp(-aT_R)], \\ \frac{dI_R}{dt} &= \beta_R \frac{S_R}{T_R} F [1 - \exp(-aT_R)] - (d_R + m_R) I_R, \\ \frac{dR_R}{dt} &= r_R R_R \left(p - \frac{T_R}{K_R}\right) + m_R g_R I_R - d_R R_R, \end{aligned} \tag{2}$$

where  $T_R = S_R + I_R + R_R$  (the total rat population size). Both susceptible ( $S_R$ ) and resistant ( $R_R$ ) rats breed with a net reproductive rate of  $r_R$  and a carrying capacity  $K_R$ ; however, a proportion  $p$  of the offspring inherit resistance to the disease from their parents. All rats have a natural death rate of  $d_R$ . Transmission of infection is via infected fleas, of which there are  $F$ . The precise form of the infection term corresponds to infected fleas randomly searching for a new rat host, for some given time-period (cf. Nicholson & Bailey 1935). If they find a host and it is susceptible, then with a given probability the rat becomes infected. Therefore  $\beta_R$  is the transmission rate to rats and  $a$  is a measure of the searching efficiency of the fleas. Finally, rats leave the infected class at a rate  $m_R$  and a fraction  $g_R$  of these survive to become resistant; the remainder die and release their infected fleas back into the environment.

The dynamics of the flea population are modelled by  $N$ , the average number of fleas living on a rat (called the flea index), and  $F$ , the number of free infectious fleas that are searching for a host:

$$\begin{aligned} \frac{dN}{dt} &= r_F N \left(1 - \frac{N}{K_F}\right) + \frac{d_F}{T_R} F [1 - \exp(-aT_R)], \\ \frac{dF}{dt} &= (d_R + m_R (1 - g_R)) I_R N - d_F F. \end{aligned} \tag{3}$$

In the absence of bubonic plague, the flea index  $N$  obeys a logistic growth model, with carrying capacity  $K_F$ . The other term in the differential equation for  $N$  is due to free fleas finding a new rat host and therefore increasing the average flea index. Free infected fleas are released into the environment every time an infected rat dies, and on average this should release  $N$  fleas. Free fleas are assumed to die from starvation at a rate  $d_F$ .

The final section of the model is the human population. Ignoring density dependence in the birth and death rates we obtain

$$\begin{aligned} \frac{dS_H}{dt} &= r_H (S_H + R_H) - d_H S_H - \beta_H S_H F \exp(-aT_R), \\ \frac{dI_H}{dt} &= \beta_H S_H F \exp(-aT_R) - (d_H + m_H) I_H, \\ \frac{dR_H}{dt} &= m_H g_H I_H - d_H R_H. \end{aligned} \tag{4}$$

Although this is again an SIR-type model, the infection term in equations (4) is proportional to the number of fleas that do not find a new rat host. It is important to realize that the human dynamics do not affect the disease behaviour; the human cases are merely a by-product of

Table 1. Parameters used in the epizootic model for bubonic plague

(Those parameters marked with an asterisk have been estimated from either laboratory experiments or field observations: 1, Buckle & Smith (1994); 2, Hirst (1938); 3, Wheeler & Douglas (1945); 4, Macchiavello (1954); 5, Hinnebusch *et al.* (1998); 6, Bacot (1915). The carrying capacity for rats and the fleas searching efficiency ( $\dagger$ ) are fundamental parameters of the model, and sensitivity to these is discussed in §6. The remaining parameters have been chosen within biologically realistic bounds, and the model dynamics have little sensitivity to the precise values used. It should be noted that the human parameters are not used in the calculation of the potential force of infection  $\lambda_H$ . All rates are measured per year.)

parameter	value	meaning
$r_R^*$	5	rat's reproductive rate
$p^{*2}$	0.975	probability of inherited resistance
$K_R \dagger$	2500	rat's carrying capacity
$d_R^*$	0.2	death rate of rats
$\beta_R^{*3-5}$	4.7	transmission rate
$m_R$	20	(infectious period) <sup>-1</sup>
$g_R^{*2}$	0.02	probability of recovery
$\mu_R$	0.03	movement rate of rats
$a \dagger$	$4 \times 10^{-3}$	flea searching efficiency
$r_F$	20	flea's reproductive rate
$d_F^{*6}$	10	death rate of fleas
$K_F^{*2}$	3.29 $\rightarrow$ 11.17, mean 6.57	flea's carrying capacity per rat
$\mu_F$	0.008	movement rate of fleas
$r_H$	0.045	reproductive rate of humans
$d_H$	0.04	death rate of humans
$\beta_H$	0.01	transmission rate to humans
$m_H$	26	(infectious period) <sup>-1</sup>
$g_H$	0.1	probability of recovery

the progression of the disease in the rodent community. Therefore, for simplicity, we can just model the number of fleas that fail to find a host,  $\lambda_H$  (Keeling & Gilligan 2000), where

$$\lambda_H = F \exp(-aT_R). \tag{5}$$

Hence,  $\lambda_H$  is the number of infected fleas which could feed on and infect a human host; we call  $\lambda_H$  the potential force of infection to humans. Note that the true force of infection for humans should be proportional to (but less than)  $\lambda_H$ , because not all the available fleas will successfully find and infect a human. As the human demographic parameters are dependent upon the particular community being modelled, throughout the rest of this paper we concentrate on the behaviour of  $\lambda_H$  and do not explicitly model the human population, thus giving our results greater generality. The parameter values used in the model are derived wherever possible from experiments or field observations (table 1). Other parameters are set within biologically realistic bounds and are checked for sensitivity with respect to the disease dynamics.

#### 4. DETERMINISTIC RESULTS

Figure 2a shows how  $\lambda_H$  varies with the number of free fleas,  $F$ , and the total rat population  $T_R$ . It is clear that

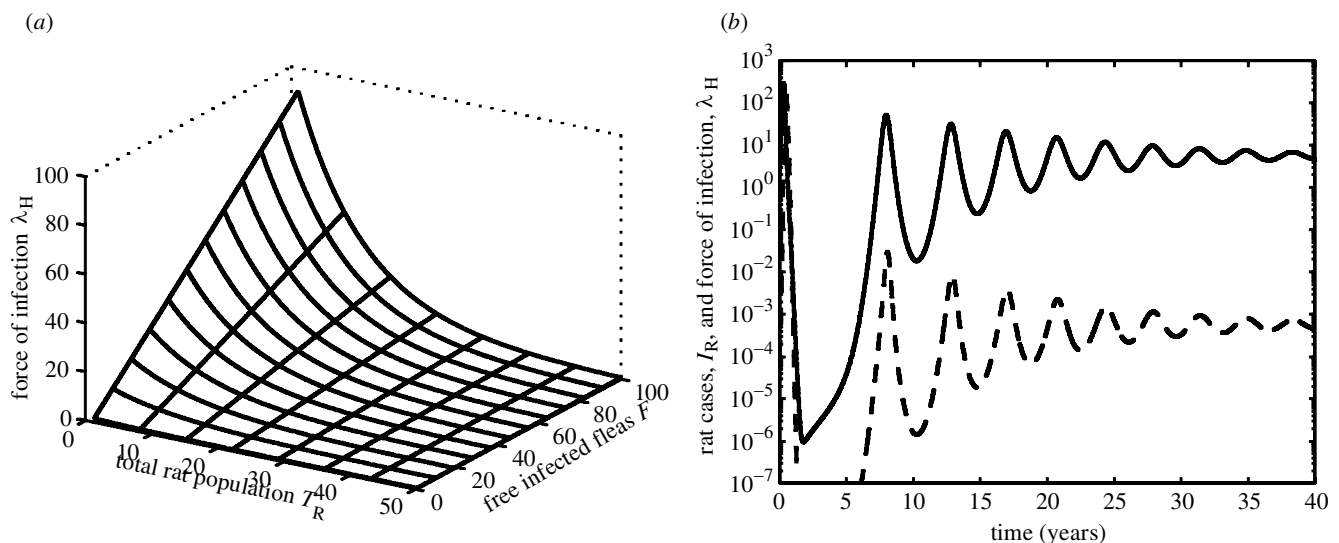


Figure 2. Results from the deterministic model for bubonic plague. (a) The potential force of infection to humans,  $\lambda_H$ , given  $F$  free-living infected fleas and a total rat population of  $T_R$ .  $\lambda_H$  increases linearly with the number of fleas, but decreases exponentially with the number of rats. (b) The number of infectious rats (solid line) and the potential force of infection to humans  $\lambda_H$  (dashed line) for the deterministic model, starting with a totally susceptible rat population. Note that after the first epidemic outbreak, which lasts about one year, the value of  $\lambda_H$  never exceeds unity, suggesting that human cases would be very rare. Parameter values are given in table 1.

the real danger to humans occurs when there are many infected fleas, such that there is a large reservoir of infection, but few rat hosts, so that fleas are forced to feed on humans. This is the situation after a major epidemic (or more precisely, an epizootic) in the rat population. From this simple observation, one would expect human cases to be maximized by short-lived violent epizootics with high virulence. This should produce many fleas but few surviving rats.

The deterministic behaviour of the disease in rats and the potential force of infection,  $\lambda_H$ , is given in figure 2b, using the parameter values in table 1. From a totally susceptible population, the disease in rats undergoes damped oscillations to a fixed point. The number of cases in humans, which should be proportional to the potential force of infection  $\lambda_H$ , lags behind the rat cases by about four weeks (this corresponds well with historical data; Curson & McCracken 1990). It should also be noticed that the size of each human epidemic is damped faster than the epizootic in rats. This means only large outbreaks in the rodent population, far from equilibrium, can cause a substantial number of cases in humans.

#### (a) Sensitivity to parameter values

Almost all the model parameters have been taken from the literature, and have been determined by either experiment or observation (table 1); however, understanding the sensitivity of the model to each parameter enables us to understand the roles of geographical or temporal heterogeneity in parameter values. Figure 3 shows the sensitivity of the deterministic model to 11 parameters that characterize the behaviour of rats and fleas; the parameters controlling the human population can be ignored by simply considering the potential force of infection,  $\lambda_H$ , rather than modelling the human dynamics explicitly. Three model outputs are examined: the equilibrium number of rat cases, the period of the first epizootic cycle, and the potential force of infection during this cycle.

For each output variable  $V$  of the model and any parameter  $P$  we define the sensitivity  $S$  conventionally as follows:

$$S = \lim_{P \rightarrow P_0} \frac{\log \left( \frac{V(P)}{V(P_0)} \right)}{\log \left( \frac{P}{P_0} \right)} = \frac{P_0}{V(P_0)} \frac{\partial V}{\partial P}, \quad (6)$$

where  $P_0$  is the default value of the parameter and the partial derivative is evaluated at this point. From this definition we see that the sensitivity measures the proportional change in the output variable,  $V$ , for a small proportional change in the parameter  $P$ . When  $V$  is proportional to the parameter  $P$ , the sensitivity  $S$  is equal to unity.

We can reverse the definition (6) and examine the relative change to any output variable as we alter the parameters:

$$V(P) \approx V(P_0) \left( \frac{P}{P_0} \right)^S.$$

It is clear that large values of the sensitivity  $S$  lead to faster than linear changes in  $V$  as the parameter alters, and this is undesirable.

From multiple simulations, we note that even when parameters are changed by a factor of two the essential pattern of sensitivity remains, showing that  $S$  is a robust measure of the effects of parameter change. Only  $K_F$ , the carrying capacity of fleas per rat, has any effect that is much stronger than linear, although  $r_R$ ,  $1-p$ ,  $K_R$  and  $a$  all have effects on the number of rat or human cases that are close to linear (figure 3). Out of these five most sensitive parameters, only  $a$  and  $K_R$  have not been determined by experiment or observation (see table 1). While the rat carrying capacity,  $K_R$ , is clearly going to vary between

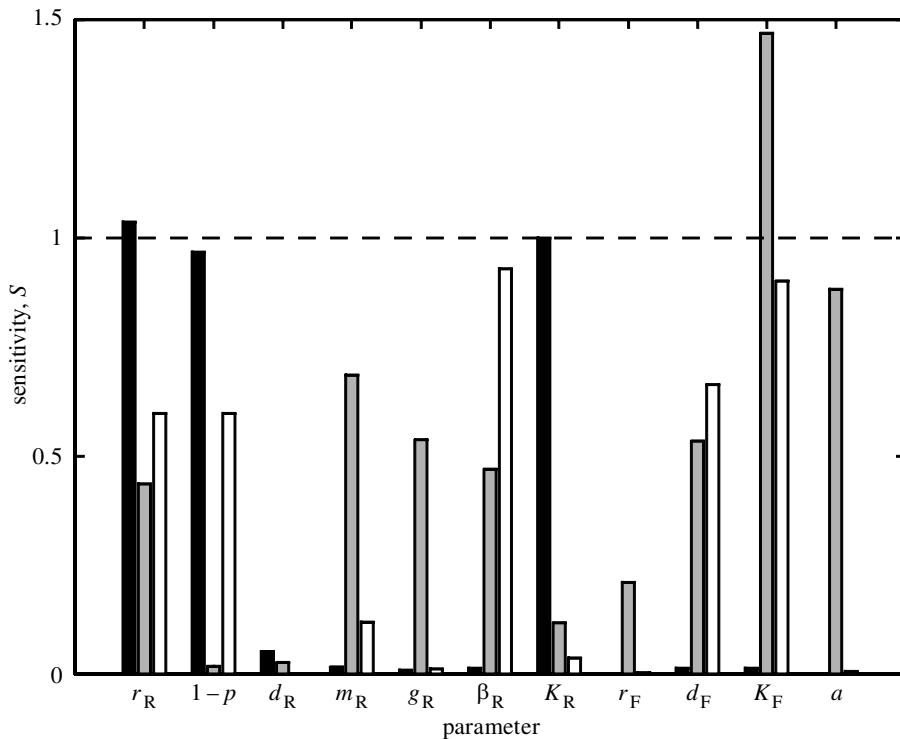


Figure 3. Sensitivity of the deterministic model to the rat and flea parameters. Three properties of the model are measured: the number of rat cases at equilibrium,  $I_R/m_R$  (closed bars), the potential force of infection to humans over the first epizootic wave (grey bars), and the period of the first epizootic wave (open bars).

populations, it is probable that the flea searching efficiency,  $a$ , will be universal. Therefore, in §§ 5–8, we shall always consider whether our results are robust to changes in the parameter  $a$ .

**5. GREATER BIOLOGICAL REALISM**

Although the deterministic model possesses many of the short-term dynamics characteristic of bubonic plague, with biologically reasonable parameters only fixed-point behaviour is observed; this is contrary to the historical data. Greater biological realism is included in the model by introducing temporal forcing, individuality and spatially distinct subpopulations. These three forms of heterogeneity lead to more realistic patterns of human cases, and long-term global persistence of the disease in the rodents.

The flea index is known to vary seasonally throughout the year (Hirst 1938); this is modelled by seasonally forcing the flea carrying capacity:

$$K_F = k_F(1 + \kappa_F)^{\sin(2\pi\text{season})},$$

where  $0 \leq \text{season} < 1$  measures the time of year. This seasonality invariably leads to annual cycles in the deterministic model, although these cycles are not sufficient (nor even necessary) to produce the violent epidemics observed (figure 1a). The seasonality in temperature or humidity, and hence flea activity, is considered to be responsible for the decrease in the number of cases during the winter months in Britain (Raggett 1982; Scott *et al.* 1996) and during the dry season in India (Hirst 1938). We have therefore included seasonality for the sake of completeness, although extensive exploratory simulations

(not given here) show that its influence on the dynamics is only observed at the short time-scale. At time-scales of one year or more, the effects of the seasonal fluctuations are averaged out.

The dynamics are now made stochastic, such that each event happens at random but with rates determined by the underlying differential equations (2)–(4). In this formulation we no longer see fixed-point behaviour, but stochastically driven large-scale epidemics arise (see Bartlett 1956; Renshaw 1991). Stochastic models allow us to examine the question of disease persistence (Bartlett 1957; Grenfell 1992; Keeling 1997), but the unrealistic complete mixing of infected fleas and susceptible rats leads to rapid extinctions. To prevent this, heterogeneities must be allowed to develop; hence the entire system is spatially discretized into a set of locally coupled subpopulations (see Grenfell *et al.* 1995; Keeling 1997; Grenfell & Harwood 1997). Coupling between adjacent subpopulations is modelled by the slow random movement of rats and free-living fleas at rates  $\mu_R$  and  $\mu_F$ , respectively.

Figure 4 shows two basic statistics at the stochastic subpopulation level starting with various proportions of the rat population being susceptible, for different values of the searching efficiency  $a$ . Figure 4a summarizes the survival times of the disease, starting with a single infectious rat; figure 4b shows the potential number of human cases; the qualitative behaviour of both quantities is fairly robust to quite large changes in the searching efficiency  $a$ . The greatest threat to humans occurs when the rat population is highly susceptible, and in such populations the disease occurs as a short-lived (one- to two-year) epizootic. When the level of susceptibles is lower (25–50%) human cases are rare,

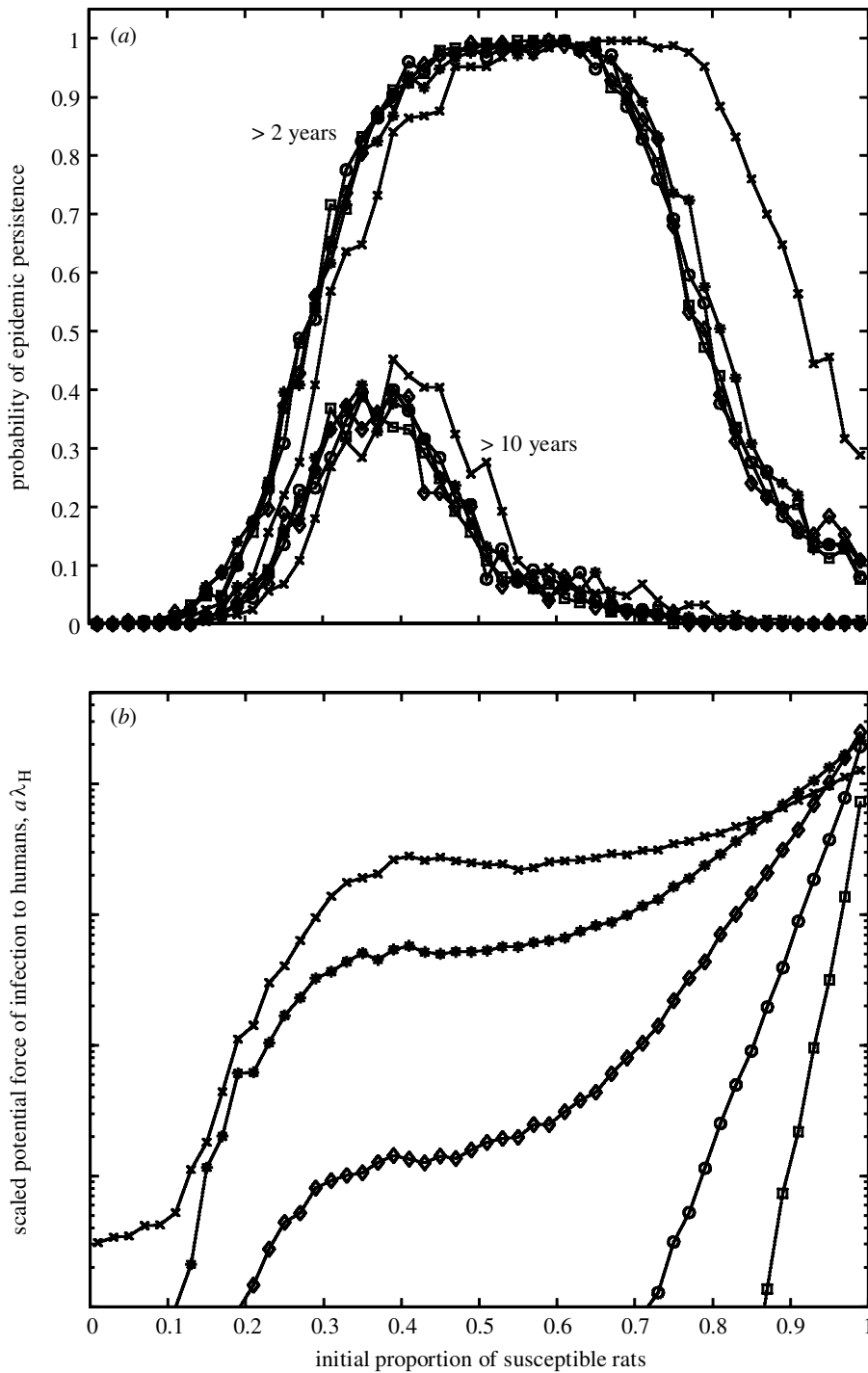


Figure 4. Results from the stochastic model, for a rodent subpopulation with various proportions of susceptible rats. (a) The probability that when the disease is introduced it persists for more than two or ten years, i.e. whether it is a short-lived epidemic ( $< 2$  years) or a persistent endemic ( $> 10$  years). (b) The scaled potential force of infection,  $a\lambda_H$  over the entire duration of the epidemic (note that the y-axis is a logarithmic scaling). The parameter  $a$  is included, because the likelihood of a flea finding a human host should increase in proportion to its searching efficiency. (crosses,  $a = 0.001$ ; asterisks,  $a = 0.002$ ; diamonds,  $a = 0.004$ ; open circles,  $a = 0.008$ ; open squares,  $a = 0.016$ .)

but the disease frequently enters an endemic, highly persistent phase, surviving for about ten years. As expected, if the level of susceptibles is very low the disease fails to invade because the effective reproductive ratio is less than unity. These three simple observations, which are robust to parameter changes, are the key to the success of the stochastic spatial model and allow us later to form a simple cellular automaton approximation for the spatial dynamics.

These stochastic dynamics, when placed in a metapopulation framework, demonstrate a high level of persistence and realistic global behaviour (Keeling & Gilligan 2000). A population of 60 000 rats (typical of a medium-sized town) is divided into  $5 \times 5$  subpopulations with nearest-neighbour coupling governed by the rats and flea movement rates of  $\mu_R = 0.03$  per year and  $\mu_F = 0.008$  per year, respectively (figure 5). At a few of the sites the disease persists at low levels for long periods of time, and from

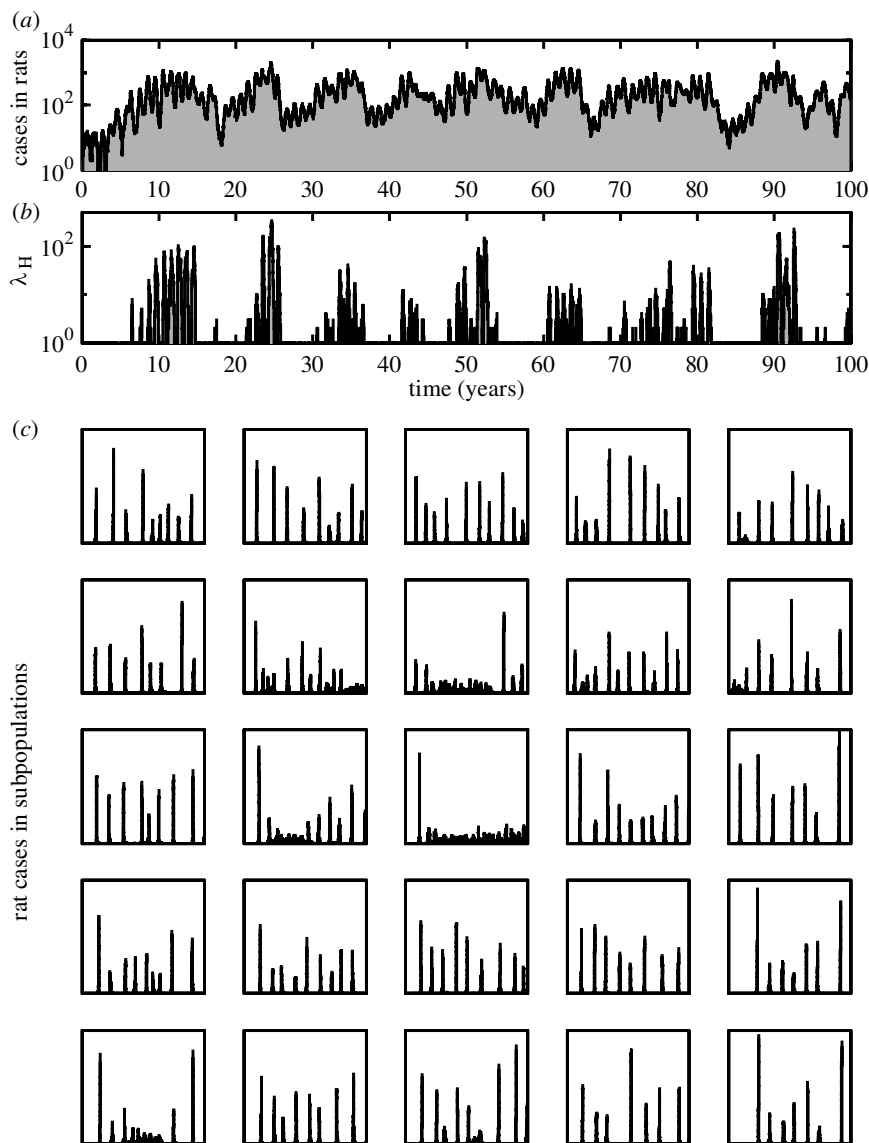


Figure 5. Time-series results from the stochastic metapopulation model, comprising 25 subpopulations in a  $5 \times 5$  grid; nearest-neighbour coupling is controlled by the rat and flea movement rates  $\mu_R$  and  $\mu_F$ . All graphs are from a single simulation of 100 years; the results are typical and are not particularly sensitive to the exact parameter values. (a) The number of infectious rats,  $I_R$ , on a log-scale; the initial low number of cases is due to transient dynamics. (b) The value of  $\lambda_H$  (the force of infection to humans), again on a log-scale. It is clear that while infectious rats are always present, the force of infection to humans is much more erratic. The bottom set of 25 graphs (c) shows the number of infectious rats in each of the subpopulations over 100 years; many subpopulations show long periods of endemicity, which is in stark contrast to the epidemic behaviour.

these sources it spreads to other subpopulations creating waves of short-lived epidemics. In this population of 60 000 rats, bubonic plague easily persists in the rodent population for over 100 years without the need for external imports of new cases. However, the potential force of infection,  $\lambda_H$ , suggests that occasional large-scale human outbreaks should be observed about once every ten years. Such dynamics present a new interpretation on historical data.

By far the vast majority of historical information on the spread of bubonic plague is concerned with the number of human cases, and these outbreaks tend to be short lived, even in large communities (Sharif 1951; Shrewsbury 1970; Twigg 1993). Until now the standard assumption has been that each human outbreak was triggered by some external source, for example, infected rats arriving by ship (Appleby 1980; Slack 1980). While this is undoubtedly true for many small populations, the model developed

here offers an alternative explanation. In large towns and cities it is likely that the plague was endemic in some sections of the rat population and this could trigger sporadic epidemics in other areas; such a pattern of behaviour was speculated for bubonic plague in India during the early 20th century (Sharif 1951). This persistence in the rat population may explain why human epidemics were still experienced, even in cities such as Venice, when stringent quarantine measures were in effect (Appleby 1980). To date, much of the historical interpretation has concentrated on human cases, ignoring the true epizootic in rodents, and therefore neglecting the full dynamics.

## 6. POTENTIAL FOR MODERN HUMAN EPIDEMICS

Estimates of the current mortality from bubonic plague are in the range of 1000–3000 deaths per year, with

sustained human cases in many urban areas, e.g. Mozambique (Barreto *et al.* 1994), Madagascar (Boisier *et al.* 1997; Chanteau 1998) and Surat (Kumar 1995; Saxena & Verghese 1996)). According to World Health Organization reports, although human cases are rare in many areas, bubonic plague is actually widespread throughout the wild rodent community. Examples of this situation are southern Africa, the Middle East and the United States (Kimsey *et al.* 1985; Rosser 1987; Craven *et al.* 1993). However, due to the large number of urban rodents, the potential exists for much larger outbreaks within towns or cities; hence is it important to consider the risk of spread to the human population.

In §§4 and 5, which were concerned with historical cases, we were interested in the persistence of the disease in communities already infected with the plague. Here, in contrast, we wish to model the invasion into a disease-free modern urban population. Large-scale infection of humans depends on two distinct factors: the disease spreading from the wild rural rodent population to rodents in the cities, and then the chance of an outbreak in urban rodents causing cases in humans. The first stage of this process is difficult to predict and will depend on a variety of external factors. In particular, the mixing between urban and rural rodents will be influenced by weather, food availability and the habitat surrounding the town or city. For the second stage, the stochastic model already developed can be used to estimate the total potential force of infection over the entire rodent epizootic ( $\Lambda_H = \int \lambda_H dt$ ) once the disease has entered the urban rat population.

As with all metapopulation models, there is some arbitrariness in the area of each subpopulation. Clearly the carrying capacity ( $K_R$ ) of each subpopulation should increase with the area. However, the rate at which free fleas find a rodent host should be proportional to the density of rats and not the absolute number. Therefore, changing the area of a subpopulation should increase the carrying capacity and decrease the searching rate such that the product  $aK_R$  remains constant. This behaviour is clear from simulations (figure 6); it can also be seen that a large human outbreak is possible whenever  $0.5 < aK_R < 20$ . These limits correspond to the situation where  $\Lambda_H \approx K_R$ . This form was chosen so that  $\Lambda_H$  scales linearly with the area of a subpopulation and each rat produces one infected flea which fails to find a suitable rodent host and therefore may bite humans. Because the behaviour is solely dependent upon the product  $aK_R$  and not their individual values, it is clear that the model we have developed is not dependent upon the scale of the subpopulations. The upper limit ( $aK_R = 20$ ) can only be achieved by very high densities of rodents, so although above this limit  $\Lambda_H$  is less than  $K_R$ , the potential for many human cases is still high; we can therefore concentrate exclusively on the lower bound.

We note that  $aK_R$  can be related to the basic reproductive ratio of the disease,  $R_0$ :

$$R_0 = \frac{\beta_R K_F}{d_F} [1 - \exp(-aK_R)].$$

From standard theory, rat epizootics can occur whenever  $R_0 > 1$ , which corresponds to  $aK_R > 0.39$ . This means

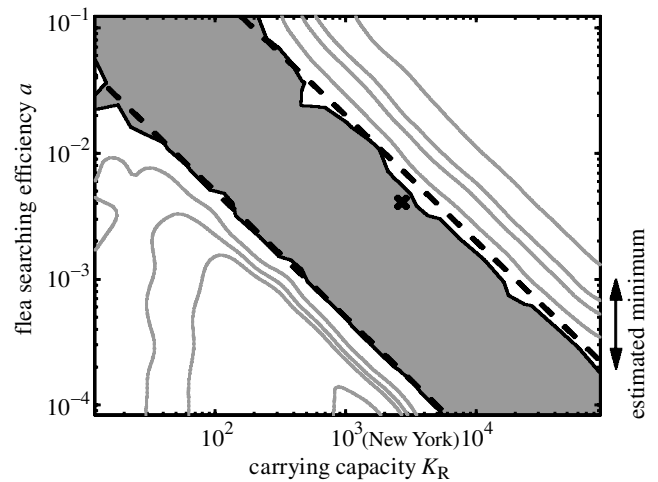


Figure 6. Contour plot of the potential force of infection to humans relative to the number of rats ( $\Lambda_H/K_R$ ) against the rat carrying capacity ( $K_R$ ) and the flea searching efficiency ( $a$ ). The region where  $\Lambda_H > K_R$  is shaded grey, and is bounded by thin black contours. The grey contours are when  $\Lambda_H K_R = 0.01, 0.1, 0.2$  and  $0.5$ , and show the steepness of the transition. The dashed lines correspond to  $aK_R = 0.5$  and  $aK_R = 20$ , which correspond closely with the  $\Lambda_H = K_R$  contour. The cross indicates the set of parameters used in the previous simulations. On the  $x$ - and  $y$ -axes are given the estimated rodent density in New York, and the plausible lower bound on the searching efficiency  $a$  at a scale of  $1 \text{ km}^2$ .

that there is only a very small parameter regime ( $0.39 < aK_R < 0.5$ ) in which the disease can invade the rodent population, but the chance of getting human cases is rare. If bubonic plague enters an urban rat population there is a strong potential for human infection.

The invasion threshold for the disease ( $R_0 > 1 \Rightarrow aK_R > 0.39$ ) allows us to estimate the crucial parameter  $a$ , by examining the incidence of sylvatic plague (bubonic plague in wild populations). Epidemics of bubonic plague have been recorded in a variety of wild rodent populations, including chipmunks, prairie dogs, ground squirrels and mice (Barnes 1982; Menkens & Anderson 1991; Davis 1999). By definition, these outbreaks can only occur when  $R_0 > 1$ ; therefore, by looking at the density of populations which sustained a large outbreak, we can estimate a lower bound on  $a$ , although the true value is probably much higher. Table 2 gives the estimated densities and the calculated minimum value of  $a$  for several rodent species in North America that have suffered plague outbreaks.

Even with the lowest values of  $a$  calculated, there is still the potential for an outbreak in modern urban cities. It is widely believed that in large cities, such as New York, there is at least one rat for every human being; which puts the rodent density at around  $4500 \text{ km}^{-2}$ . With such high densities of rodents, the arrival of the disease is likely to trigger a large epizootic with obvious problems for human health.

## 7. A CELLULAR AUTOMATON APPROXIMATION

To further test the robustness of our results, we introduce a cellular automaton approximation (Durrett & Levin 1994; Keeling 1999), which is derived from the

Table 2. Estimates of population density (from Walker & Nowak 1999) for four species of wild rodent that experience outbreaks of bubonic plague

(By assuming that at these densities  $R_0 \geq 1$  a lower bound on the searching efficiency,  $a$ , can be calculated.)

species	density (km <sup>-2</sup> )	calculated minimum $a$
eastern American chipmunk	500–1000	$3.91 \times 10^{-4}$ to $7.82 \times 10^{-4}$
western American chipmunk	around 1500	$2.61 \times 10^{-4}$
black-tailed prairie dog	640–1560	$2.51 \times 10^{-4}$ to $6.11 \times 10^{-4}$
ground squirrels	400–2000	$1.96 \times 10^{-4}$ to $9.78 \times 10^{-4}$

local dynamics of the fully stochastic spatial model. In keeping with the approach of Hassell *et al.* (1991), we suggest that if this much-reduced model can produce qualitatively similar dynamics, then these dynamics must be attributable to the underlying behaviour and not specifics of the modelling approach. The greater computational speed of this cellular automaton model also allows us to address questions of spatial clustering and the effects of movement rates in more detail.

As previously stated, four factors contribute to the stochastic dynamics of the disease within the spatial rodent metapopulation:

- (i) in the absence of the disease, the proportion of susceptible rats increases;
- (ii) epidemics and endemics can infect neighbouring susceptible populations;
- (iii) highly susceptible subpopulations give rise to short-lived epidemics;
- (iv) moderately susceptible subpopulations can often lead to endemic persistence.

We let each site in the two-dimensional cellular automaton be in one of three basic states, short-lived epidemic ( $E$ ), persistent endemic ( $P$ ) and uninfected or susceptible ( $S$ ). The susceptible state is further divided into  $\mathcal{N}$  substates; in the absence of infection each site moves sequentially through the susceptible substates, from  $S_0$  to  $S_{\mathcal{N}-1}$ , where  $S_{\mathcal{N}-1}$  corresponds to a fully susceptible population. Other transition rates are given in table 3 and can all be estimated from the stochastic behaviour of a subpopulation.

The greater computational speed of the cellular automaton model allows analysis of replicated epidemics over long times. Like the full stochastic metapopulation model, the cellular automaton also shows regions of endemic behaviour (black sites) which give rise to sporadic waves of epidemics (dark grey sites) (figure 7a). It is clear from this snapshot that both endemic and epidemic sites show a high degree of clustering. The presence of endemic regions greatly increases the probability of global persistence of the disease; without endemic regions ( $Q_i = 0$ ) we observe a single wave spreading through the population which rapidly extinguishes itself.

Measuring the mean–variance relationship for a variety of sampling windows allows a rigorous study of the spatial data from the cellular automaton model. When the observed variance against the mean on a log–log scale, a power-law relationship is expected (Taylor 1961; Keeling *et al.* 1997; Keeling & Grenfell 1999). It is clear that for all window sizes the power is greater than unity

Table 3. Transition probabilities used in the cellular automaton

( $T$  is the probability of an epizootic triggering cases in the neighbouring subpopulations, and  $Q$  is the probability that these triggered cases give rise to a persistent endemic. Finally, due to the reduced cases in the endemic phase, the probability of this triggering neighbouring cases is reduced by a factor  $q$ .)

transition	probability	
$S_i \rightarrow S_{i+1}$	1	for all $i < \mathcal{N}$
$E \rightarrow S_0$	1	
$P \rightarrow S_m$	$d$	
$S_i \rightarrow E$	$T_i(1 - Q_i)$	if $E$ in neighbourhood
$S_i \rightarrow E$	$qT_i(1 - Q_i)$	if $P$ in neighbourhood
$S_i \rightarrow P$	$T_iQ_i$	if $E$ in neighbourhood
$S_i \rightarrow P$	$qT_iQ_i$	if $P$ in neighbourhood

(figure 7b), suggesting that epidemics are clustered at a variety of scales, and outbreaks are correlated across large distances (up to 1000 lattice sites). In fact, for windows larger than  $300 \times 300$  the power-law asymptotes to two, which would imply synchrony of epidemics at this scale.

Finally, we can use this cellular automaton model to consider the effects of coupling between neighbouring cells  $T_i$ . The transmission probabilities  $T_i$  are increasing functions of the parameters  $\mu_R$  and  $\mu_F$  which control the spatial spread in the full model. As shown in figure 7c, there is clearly a threshold level of coupling (at *ca.*  $T_{\mathcal{N}-1} = 0.375$ ) below which the disease fails to spread. As the coupling increases we find that there is a monotonic increase in the number of endemic sites, although the number of epidemic sites reaches a maximum when the coupling is around  $T_{\mathcal{N}-1} = 0.55$ . It would therefore appear that drastically reducing the spatial spread of the rats and fleas may be an effective means of controlling the disease.

## 8. CONCLUSIONS

Besides being a disease of extreme historical importance, bubonic plague is still prevalent today. Therefore an accurate predictive model has strong public health applications and also helps to explain historical data.

Bubonic plague is amongst a handful of zoonoses (animal-based diseases) that have captured the public's imagination. This may in part be due to the seemingly spontaneous occurrence of these diseases in human populations, and their high mortality rates. Here we have shown that a mathematical understanding of the risks from such diseases requires models for both the human

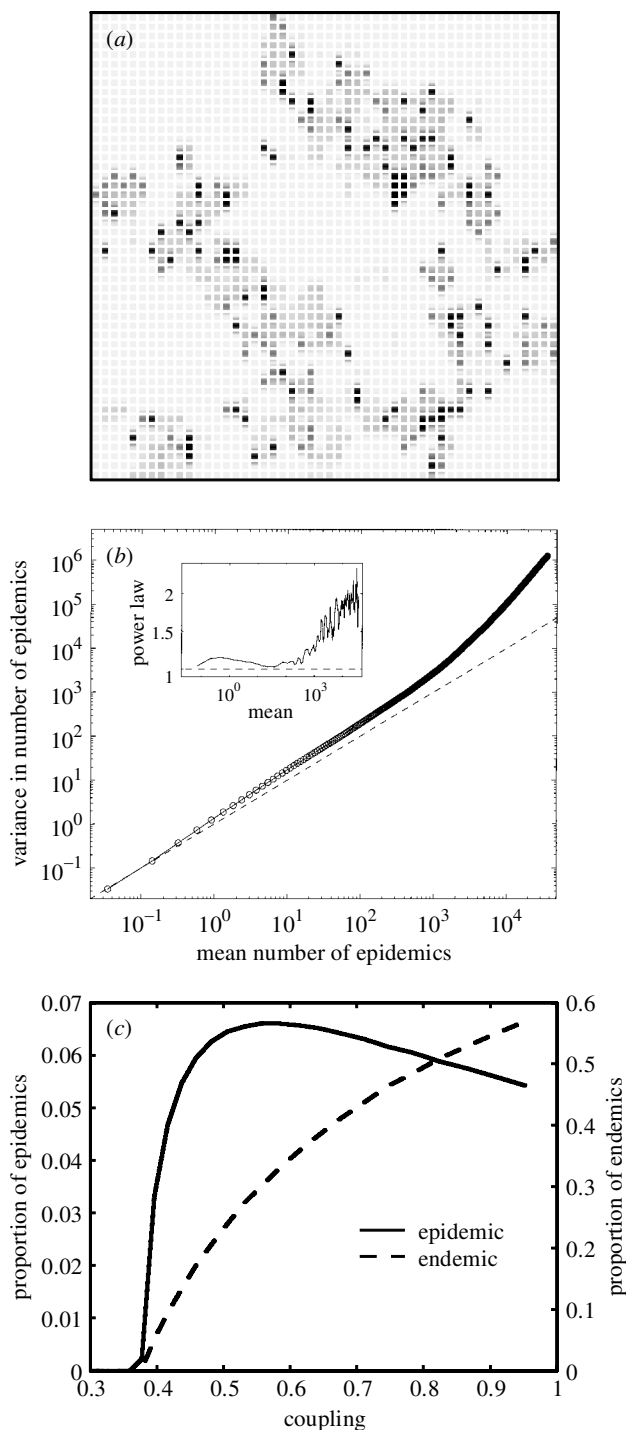


Figure 7. Results from the cellular automaton model. (a) A snapshot from the cellular automaton model for a  $50 \times 50$  grid. Black cells are persistent endemic sites ( $P$ ), dark grey cells are epidemics ( $E$ ) and other shades of grey give the level of susceptibility, with  $S_{N-1}$  being the lightest colour. (b) A Taylor power law log-log plot of mean against variance for the average number of epidemic sites within a square window. Each dot represents the results for one window size (from  $1 \times 1$  up to  $1000 \times 1000$ ) and is averaged over 1 000 000 time-steps. The inset graph gives the local power-law, estimated by the gradient of the log-log plot. (c) The effects of altering the coupling between nearest-neighbour sites. The coupling is measured as the probability that an epidemic triggers an epidemic in an adjacent, fully susceptible site ( $T_{N-1}$ ). All the other transmission probabilities  $T_i$  undergo a similar scaling. The solid line shows the long-term proportion of sites that are epidemic ( $E$ ); the dashed line shows the proportion of sites that are endemic ( $P$ ).

and animal populations. We note, however, that bubonic plague is quite exceptional amongst zoonoses because the risk to humans is not simply maximized by a high number of animal cases, but by a combination of many cases and high mortality. Therefore, although the methodology may be applicable to many other diseases, we believe that the precise results will be highly specific to bubonic plague.

A careful consideration of the biology of bubonic plague has led us to reject the standard SIR model, and develop a more complex set of equations which include the dynamics of the rat, flea and human populations. Although this set of equations contains a large number of parameters, many have already been estimated from laboratory experiments and field observations (Bacot 1915; Hirst 1938; Wheeler & Douglas 1945; Macchiavello 1954; Hinnebusch *et al.* 1998). By considering  $\lambda_H$ , the potential force of infection to humans, the three differential equations and five parameters which relate to human populations can be subsumed into this critical parameter, which considerably simplifies the model. Sensitivity analysis shows that three fundamental model output variables (the equilibrium number of rat cases, the period and the potential force of infection during the first epizootic cycle) are only weakly dependent upon the majority of the parameter values. Numerous simulations of the full stochastic model show that the qualitative behaviour is maintained even when parameter values are changed by a factor of two. The results of the cellular automaton model add extra credence to this argument, showing that it is the general form of the local dynamics rather than the precise details of the model that produces the emergent metapopulation behaviour.

The set of five differential equations that describe the dynamics of the rat and flea populations display damped oscillations tending to a fixed point; this is clearly contrary to observations. To capture the observed dynamics we need to make the model stochastic and spatial. By introducing stochasticity, the fixed point behaviour is destroyed and two contrasting sets of dynamics are observed in the rat population: persistent endemics and short-lived epizootics. The spatial heterogeneities in the rat metapopulation mean that both types of dynamics can be simultaneously present; the short-lived epizootics drive human cases, whereas the endemic populations allow the disease to persist. Our models suggest that relatively small rodent populations can sustain the disease, and hence quarantine measures will only be effective in the smallest communities.

By concentrating on the stochastic dynamics at the subpopulation level, the risk of a severe human outbreak can be estimated and related to  $R_0$ . By examining outbreaks in other rodent species, we have been able to calculate lower bounds on the searching efficiency  $a$ . Although such estimates will be imprecise, the density of urban rats is so much greater than the density of wild rodents that we can be confident that if the disease were to reach an urban population an epizootic would occur. We note that the value of  $a$  used throughout this paper is for some arbitrary subpopulation area; it is the combined value of  $aK_R$  that is dynamically important, and this is independent of the area.

To estimate the risk of a human epidemic would require an accurate parameterization of the chance that an

infected flea (in the absence of a suitable rodent host) can find and infect a human. Such detailed data will be highly dependent upon living conditions, sanitation and building design. We believe that although the risk of the disease moving from rural to urban rodents is probably low, once this step has been made the risk and consequences to humans are sufficiently large to warrant concern.

Given that human cases of bubonic plague are a distinct possibility, it is vital that we consider prevention measures. Surprisingly, implementing rodent control measures soon after human cases have been observed is a very dangerous policy. Human cases only occur when there is a large reservoir of infectious fleas; therefore reducing the number of rats at this time would lead to a larger total force of infection for humans than if the epidemic in rodents were left to run its natural course (Keeling & Gilligan 2000). The only potential methods of preventing human outbreaks of the plague are to reduce the number of rat fleas using insecticides (Maupin *et al.* 1991; Beard *et al.* 1992), vaccinate the rodents or to keep the rat numbers low enough (Buckle & Smith 1994) so that the potential force of infection to humans is negligible.

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