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Metapopulation dynamics of bubonic plague

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Bubonic plague is widely regarded as a disease of mainly historical importance; however, with increasing reports of incidence[1–3] and the discovery of antibiotic-resistant strains of the plague bacterium *Yersinia pestis*[4], it is re-emerging as a significant health concern[5,6]. Here we bypass the conventional human-disease models, and propose that bubonic plague is driven by the dynamics of the disease in the rat population. Using a stochastic, spatial metapopulation model, we show that bubonic plague can persist in relatively small rodent populations from which occasional human epidemics arise, without the need for external imports. This explains why historically the plague persisted despite long disease-free periods, and how the disease re-occurred in cities with tight quarantine control. In a contemporary setting, we show that human vaccination cannot eradicate the plague, and that culling of rats may prevent or exacerbate human epidemics, depending on the timing of the cull. The existence of plague reservoirs in wild rodent populations has important public-health implications for the transmission to urban rats and the subsequent risk of human outbreaks.

Large-scale human epidemics of bubonic plague have been recorded throughout history, from Roman times to the pandemic in the early 1900s. This disease has had a major social and demographic effect[7–10]; its arrival in Europe in 1348 led to the death of around one-third of the human population, and even today bubonic plague kills people in many areas of the world[1–3]. Historical data, from a variety of locations, show occasional large outbreaks of plague separated by long disease-free periods, and yet the disease clearly persists[7–9]. Understanding persistence is a common problem in general epidemic modelling[11–13], and for bubonic plague it is a central historical question. Previous models of bubonic plague have been highly anthropocentric, modelling the disease as if it were transmitted solely within human populations[10,14,15]. But consideration of the biology shows that bubonic plague is primarily a disease of rodents that is spread by fleas and only occasionally infects humans; such a disease is termed a zoonosis. From this perspective, we formulate an epizootic (animal-based disease) model for the rat and flea populations, and by coupling this with a standard epidemic (human disease) model, we identify epidemic patterns and the circumstances in which the disease causes a large number of human cases.

The life cycle of the plague can be partitioned into four stages. (1) Fleas feeding on an infected rat ingest the bacteria causing bubonic plague, and soon become infectious. (2) When an infected rat dies, its fleas leave to search for a new host. (3) The fleas usually find other rats, infect them, and so spread the disease through the rodent community. (4) Only when the density of rats is low are the fleas

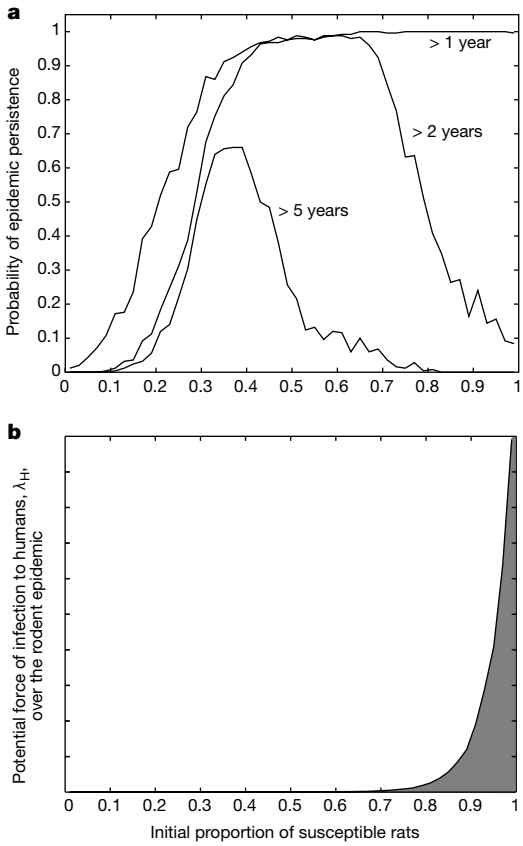

Figure 1 Results from 250 simulations of the stochastic epizootic model of bubonic plague with a rat population of 2,500. **a**, The probability that an infectious import generates an epidemic/endemic that lasts for more than 1, 2 or 5 years in the rat population. If the disease persists for more than 5 years it is likely to be in the endemic state. **b**, The potential force of infection for humans over the entire outbreak in rats ($\int_0^\infty \lambda_H(t)dt$), measured as the total number of infectious fleas that fail to find a suitable rodent host and may therefore bite and infect humans.

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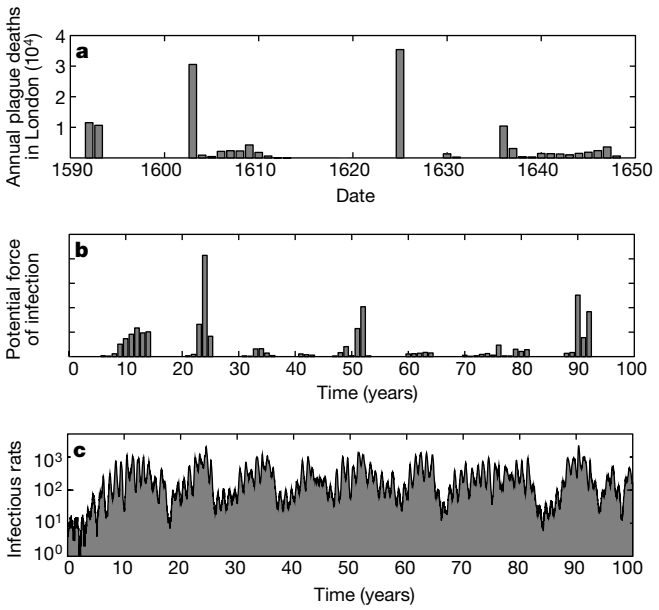

Figure 2 Comparison between historical data and the results from the metapopulation model. **a**, The annual deaths attributed to bubonic plague in London (1592–1661)[20]. **b** and **c**, Results from a stochastic simulation of 100 years, with a rodent population of 60,000 distributed over 25 subpopulations (see Methods). **b**, Potential force of infection for humans showing erratic epidemics; for comparison with the historical data, yearly aggregates are shown. **c**, Number of infectious rats from the same simulation, showing how plague can persist in an isolated but spatially heterogeneous metapopulation.

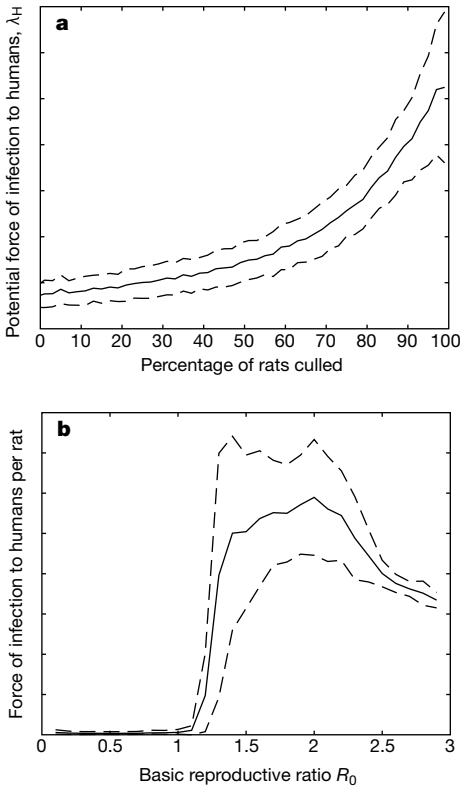

Figure 3 Results from the stochastic model for a single rat subpopulation. Solid lines, means; dashed lines, 95% confidence intervals. **a**, The effect of culling the rats once human cases have been detected. **b**, The potential force of infection to humans per rat over the entire outbreak shows clear threshold behaviour. The basic reproductive ratio R_0 is defined as $R_0 = \beta_R K_F / d_F [1 - \exp(-aK_R)]$. Different values of R_0 were obtained by varying the flea-searching efficiency, **a**, and the rat carrying capacity, $\mathbf{K}_R$.

forced to feed on alternative hosts such as humans, and a human epidemic occurs. (Although the pneumonic form of the disease can be passed directly from human to human, historical evidence suggests that this is rare[8,16], and is only triggered as a consequence of many rat-related cases.) This informal set of rules can be made precise via a set of differential equations, given in the Methods. We identify the potential force of infection for humans, λ_H, which allows us to assess the expected number of human cases. Owing to the slow localized spread of plague in rodents[8,9], the dynamics and persistence of the disease in both humans and rats is appropriately considered using a spatially structured version of this model with stochastic dynamics.

Using a metapopulation framework[17,18], the community is divided into a set of subpopulations, each of which has its own stochastic dynamics[19] (see Methods). Two phenomena at the local subpopulation scale control the global dynamics of the model (Fig. 1). When the proportion of susceptible rats is low (between 25% and 50%), an import of bubonic plague can often lead to highly persistent endemic behaviour in rats and a very low force of infection to humans. In contrast, when the proportion of susceptible rats is high (greater than 80%) the arrival of infection is followed by a short-lived rat epizootic and a large force of infection to humans (Fig. 1). The global persistence of the disease within the metapopulation depends on a small number of rat subpopulations which are in the endemic state and do not cause human cases; these endemic populations occasionally trigger large but short-lived outbreaks in neighbouring rat subpopulations which in turn lead to major human epidemics.

The potential force of infection for humans, λ_H, from the stochastic metapopulation model can be compared with historical data for mortality in London[20] (Fig. 2a and b). Although the predicted number of human cases is erratic with long inter-epidemic periods, plague persists in the rat population (Fig. 2c). In fact, relatively small rodent metapopulations (50,000 individuals) allow the disease to persist globally for many years, although localized extinctions are common. This is attributable to the spatial heterogeneity that develops[21] and the nonlinear density-dependent behaviour of the disease in rats. The persistence of the disease within the rodent population presents a new perspective on the historical data, as a sudden outbreak of bubonic plague in humans does not have to coincide with fresh imports of the disease from an external source. This resolves a controversy in the historical records for some European cities during the fifteenth and sixteenth centuries, when despite very tight quarantine controls frequent human epidemics still occurred[8,22].

Contemporary control or eradication of the plague can be considered using two main approaches, vaccination or culling. However, both methods have associated complications. Because bubonic plague is a zoonosis, primarily passed from rats (via fleas) to humans, there is no 'herd immunity' effect[23,24] associated with vaccinating humans. For most contagious diseases, once the vaccination coverage has exceeded the vaccination threshold (70–80% for smallpox, 90–95% for measles and 99% for malaria) the disease cannot persist in the population[23]. For bubonic plague, only those individuals vaccinated are protected, and vaccination of humans cannot provide a means of eradication because the disease is driven by the rat population. An alternative approach is to reduce the rodent population; but our model predicts that there may be difficulties with the timing of any cull. If the rats are kept at a permanently low level, then the risk of a large outbreak in rodents—and therefore the risk of human cases—is reduced. But if the cull is only brought into effect after the first human cases have been reported, then this action can create a far larger force of infection for humans (Fig. 3a). By the time human cases arise, there is already a large reservoir of infection in the rodent population; a cull therefore releases many infected fleas, which may bite humans in

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Table 1 Parameter values

Parameter	Value	Meaning	Reference
r_R	5	Rat reproductive rate	25
p	0.975	Probability of inherited resistance	27
K_R	2,500	Rat carrying capacity	*
d_R	0.2	Natural rat death rate	25
β_R	4.7	Contact rate	28
m_R	20	(Infectious period)$^{-1}$	–
g_R	0.02	Probability of recovery	27
a	0.004	Flea searching efficiency	*
r_F	20	Flea reproductive rate	–
d_F	10	Natural flea death rate	29
K_F	6.57	Flea carrying capacity per rat	27

Details of the model are given in Methods.
* The parameters a and K_R together control the basic reproductive ratio, R_0, of the disease. The effect of changes in these parameters is therefore described more fully in the text and Fig. 3b. The parameters m_R and r_F have been chosen to be within biologically realistic bounds. Extensive simulation over a range of parameter values shows that the qualitative dynamics of the model have little sensitivity to the precise values used[30].

the absence of a suitable rodent host. This highlights the importance of considering bubonic plague as an epizootic infection and explicitly modelling the rat dynamics.

Given the difficulties in control, it is important to calculate the conditions under which a large human outbreak is likely. The recent discovery of antibiotic-resistant strains[4] increases the importance of the prevention of human cases in the absence of a reliable cure. For many cities in both developing and developed countries, rats are still a serious problem[25] and in many of these areas, including the United States, southern Africa, southern Asia and South America, there are large reservoirs of plague in wild rural rodents[26]. Hence there exists the potential for the disease to enter the highly susceptible urban rat population, with clear public-health consequences.

From the metapopulation model, the potential number of human cases associated with an outbreak is found to depend primarily on the basic reproductive ratio of the disease in rats, R_0 (Fig. 3b), with human cases much more likely above some threshold value. Consideration of the disease in other wild rodent species allows us to place bounds on the flea searching efficiency a, which in turn means that the R_0 threshold corresponds to a rat density of about 3,000 km^{-2}. Many urban populations exceed this critical density, and identifying those communities at high risk is of obvious public-health importance. □

Methods

Deterministic model

The natural history of the epizootic infection leads to five differential equations describing the dynamics of rats and fleas,

$$\frac{dS_R}{dt} = r_R S_R(1 - T_R/K_R) + r_R R_R(1 - p) - d_R S_R - \beta_R S_R F[1 - \exp(-aT_R)]/T_R$$

$$\frac{dI_R}{dt} = \beta_R S_R F[1 - \exp(-aT_R)]/T_R - (d_R + m_R)I_R$$

$$\frac{dR_R}{dt} = r_R R_R(p - T_R/K_R) + m_R g_R I_R - d_R R_R$$

$$\frac{dN}{dt} = r_F N(1 - N/K_F) + d_F F[1 - \exp(-aT_R)]/T_R$$

$$\frac{dF}{dt} = (d_R + m_R[1 - g_R])I_R N - d_F F$$

$$\lambda_H = F\exp(-aT_R)$$

Here S_R is the number of susceptible rats, I_R is the number of infectious rats, R_R is the number of resistant rats and $T_R = S_R + I_R + R_R$ is the total rat population. In the absence of plague, the rat population experiences logistic growth, with slowly waning resistance to the disease at the population level governed by the parameter f. N gives the average number of fleas on a rat (the flea index), and F is the total number of infected fleas currently searching for a host. N is again modelled by logistic growth, although it is increased whenever a searching flea finds a new host. Given that fleas search randomly for a new rat host in a limited area, the probability of success is given by $1 - \exp(-aT_R)$, where a is a measure of searching efficiency.

λ_H is the potential force of infection to humans, and as such gives a measure of the number of expected human cases. In fact λ_H is calculated as the number of infected fleas that fail to find a rat host, and therefore is proportional to (but greater than) the rate at which human cases occur. This set of differential equations always shows oscillatory convergence to an equilibrium point with a very low λ_H.

Parameter values

See Table 1.

Stochastic metapopulation

Stochastic spatial dynamics are becoming an increasingly common form of epidemiological modelling. We move from a deterministic framework to a stochastic (or Monte Carlo) simulation, by allowing each possible event (for example, birth, death, infection) to occur randomly but at a rate given by the differential equations[19]. To introduce spatial structure, the entire rodent and flea population is discretized into 25 smaller subpopulations in a square lattice arrangement. Each subpopulation has its own stochastic dynamics derived from the differential equations, and adjacent subpopulations are coupled by the random movement of rats and fleas at rates $\mu_R = 0.03$ and $\mu_F = 0.008$, respectively. These movement rates are consistent with the observed slow spread of the disease through communities[8,9].

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Involuntary orienting to sound improves visual perception

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To perceive real-world objects and events, we need to integrate several stimulus features belonging to different sensory modalities. Although the neural mechanisms and behavioural consequences of intersensory integration have been extensively studied[1–4], the processes that enable us to pay attention to multimodal objects are still poorly understood. An important question is whether a stimulus in one sensory modality automatically attracts attention to spatially coincident stimuli that appear subsequently in other modalities, thereby enhancing their perceptual salience. The occurrence of an irrelevant sound does facilitate motor responses to a subsequent light appearing nearby[5–7]. However, because participants in previous studies made speeded responses rather than psychophysical judgements, it remains unclear whether involuntary auditory attention actually affects the perceptibility of visual stimuli as opposed to postperceptual decision and response processes. Here we provide psychophysical evidence that a sudden sound improves the detectability of a subsequent flash appearing at the same location. These data show that the involuntary orienting of attention to sound enhances early perceptual processing of visual stimuli.

The influence of involuntary auditory attention on speeded motor responses to visual stimuli has been examined in experiments wherein an auditory cue, such as a sudden burst of noise, was presented to the left or right side of a participant who looked at a central spot[5–11]. A visual target was then presented unpredictably either on the same side as the cue or on the opposite side, and participants had to respond as quickly as possible to the target. Studies involving location-based go/no-go judgements[5] or elevation discriminations[6,7] have shown that motor responses were typically faster for targets appearing on the same side as the cue than for targets appearing on the opposite side when the delay between the cue and target was brief (< 300 ms between cue and target onsets). On the basis of these findings, some investigators have proposed that involuntary orienting of attention to a sudden sound enhances perceptual processing of subsequent visual stimuli, as if the sensory responses to those stimuli in the brain were being amplified[12,13]. However, speeded motor responses cannot be taken as definitive evidence for improvements in perceptual processing because response times are also influenced by a number of postperceptual factors. In particular, the appearance of a spatial cue can modify an observer's willingness to respond[14] and can reduce the uncertainty of an observer's decision[15]. The spatial relationship between cue and target can also give rise to stimulus–response compatibility effects and surprise-related disruptions that can affect motor reaction times[16].

Here we used signal detection measures to investigate whether involuntary orienting of attention to a sudden sound influences the perceptual or postperceptual processing of a subsequent visual stimulus appearing nearby. Unlike reaction times, signal detection measures allow for the separation of perceptual and decision-level effects of attention. In the framework of signal detection theory, the d' parameter reflects an observer's ability to discern a sensory event from its background[17]. Thus, if the involuntary orienting of attention to a sound's location facilitated visual perceptual processes, d' should be larger for flashes appearing in proximity to a previous sound than for flashes appearing farther away. Conversely, if the involuntary orienting of attention to a sound's location affected only postperceptual decision processes, then observers might simply require less visual information to decide whether a target is present when it appears closer to the sound source. Such a change in decision would be reflected by a reduction of the decision criterion parameter, β.

We tested these predictions in two cross-modal spatial cueing experiments. The methods were adapted from those recently used to study the effects of visuo-spatial attention on visual detection performance[18,19]. As shown in Fig. 1, a spatially nonpredictive auditory cue appeared to the left or right side of fixation. This was followed after a brief interval by a visual mask either at the same location (valid trials) or at the opposite location (invalid trials). On half of the trials, a faint visual target was presented at the masked location immediately before the onset of the masking stimulus. On the other half of the trials, the target was absent from the display. Target-present and target-absent trials were randomly intermixed. Participants were informed that the auditory stimulus provided no information about the location of the visual stimuli or whether the target would be present or absent. The task was to press a button to indicate that the target was present, and to refrain from pressing the

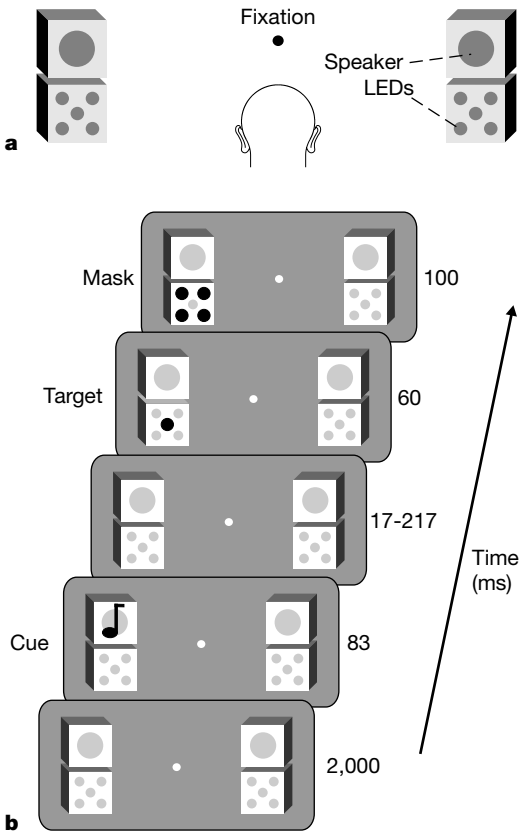

Figure 1 Experimental set-up. **a**, Schematic illustration of the audiovisual apparatus (not drawn to scale). **b**, Illustration of the events occurring on a valid, target-present trial. The cue–target stimulus onset asynchrony is obtained by adding the cue duration and the variable time interval that follows.

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