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Local persistence and extinction of plague in a metapopulation of great gerbil burrows, Kazakhstan

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ABSTRACT

Speculation on how the bacterium *Yersinia pestis* re-emerges after years of absence in the Prebalkhash region in Kazakhstan has been ongoing for half a century, but the mechanism is still unclear. One of the theories is that plague persists in its reservoir host (the great gerbil) in so-called hotspots, i.e. small regions in which the conditions remain favourable for plague to persist during times where the conditions in the Prebalkhash region as a whole have become unfavourable for plague persistence. In this paper we use a metapopulation model that describes the dynamics of the great gerbil. With this model we study the minimum size of an individual hotspot and the combined size of multiple hotspots in the Prebalkhash region that would be required for *Y. pestis* to persist through an inter-epizootic period. We show that the combined area of hotspots required for plague persistence is so large that it would be unlikely to have been missed by existing plague surveillance. This suggests that persistence of plague in that region cannot solely be explained by the existence of hotspots, and therefore other hypotheses, such as survival in multiple host species, and persistence in fleas or in the soil should be considered as well.

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Introduction

The persistence and local re-emergence of bubonic plague is poorly understood. Bubonic plague is a flea-borne zoonosis that caused three pandemics in the past millennium (Bertherat et al., 2007; Gage and Kosoy, 2005; Keeling and Gilligan, 2000). Currently, the disease is still present in foci of wildlife rodent populations throughout the Americas, Africa and Asia (Salkeld et al., 2010; Stenseth, 2008). The disease can disappear from foci for long periods of time before re-emerging. An example of this behaviour is the re-emergence of plague in Madagascar in 1991 after an absence of more than 60 years (Duplantier et al., 2005; Neerinckx et al., 2010). However, in the plague foci of Kazakhstan, Central Asia, which have been monitored since 1949, shorter periods of apparent absence are more common, typically lasting about four years (Davis et al., 2007b; Heier et al., 2011).

The etiologic agent of bubonic plague is *Yersinia pestis*, a bacterium able to infect over 200 species of mammals, of which rodents form the largest group (Gage and Kosoy, 2005). The effect of *Y. pestis* on its host varies; epizootics lead to high mortality in prairie dog populations (Biggins et al., 2010; Stapp et al., 2004), while black rats (*Rattus rattus*; Duplantier et al., 2005), and great gerbils (*Rhombomys opimus*), the main host in Kazakhstan, are quite resistant to the disease, although a substantial amount of genetic variation in resistance is alleged to exist within the gerbil population (Gage and Kosoy, 2005; Ergaliyev et al., 1990a).

In this paper we will focus on the great gerbils in Kazakhstan. Speculation on how the bacterium is able to repeatedly re-emerge in Kazakhstan after years of apparent absence has been ongoing for over half a century. A common suggestion on how the bacterium could persist in the region while appearing absent in its main host, is that during these times of absence it resides in alternative hosts or in hibernating fleas (Eisen and Gage, 2008; Gage and Kosoy, 2005; Wimsatt and Biggins, 2009). Another suggestion is that the bacterium continues to be present in the gerbils, but at a prevalence that is too low to be picked up by the existing plague surveillance efforts (Davis et al., 2007b). Alternative hypotheses for plague persistence are survival of the bacterium in the soil (Ayyadurai et al., 2008), in dead hosts (Easterday et al., 2011), or within living hosts during phases of decreased virulence of the bacterium (Wimsatt and Biggins, 2009). Finally, an intriguing possible mechanism for plague persistence is that the bacterium survives during inter-epizootic periods in small sub-regions which retain conditions favourable to its persistence, in so-called hotspots, plague refugia, or microfoci (Fedorov, 1944 as quoted in Davis et al., 2007b; Biggins et al., 2010; Hanson et al., 2006).

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To test whether such hotspots are a viable mechanism through which plague can locally persist, we constructed and studied a spatial model based on the Prebalkhash plague focus in Kazakhstan. The model is a metapopulation model, in which each subpopulation consists of a single great gerbil burrow system (Davis et al., 2007a), with its own infection dynamics. The objective of this study is to determine the minimum size needed for plague to persist in a single hotspot, or in a set of multiple hotspots, for the time of an average inter-epizootic period (±4 years, Davis et al., 2004). In the case where we study the minimum size of a single hotspot, our objective is analogous to determining the Critical Community Size for single homogeneously mixing populations (Diekmann and Heesterbeek, 2000), i.e. the "critical metapopulation size" of the great gerbil burrow system in Kazakhstan that is needed for *Y. pestis* to persist without invoking additional mechanisms.

Background and model

Biology of the gerbils in the Prebalkhash region

The Prebalkhash region is the largest of the 10 plague foci in Kazakhstan (Lowell et al., 2007). A well-studied sub-region (Davis et al., 2007b; Kausrud et al., 2007) of this focus is located south-east of lake Balkhash, and consists of the Bakanas, Akdala and Saryesikotrau plains. These plains together cover ±150 km by 300 km, and form the study area to which our results apply. It experiences an arid continental climate with temperatures frequently falling below −20 °C in winter, and reaching more than 35 °C in summer. Precipitation is less than 200 mm per year (Kausrud et al., 2007), and the vegetation cover is sparse, with a low diversity of plant species (Addink et al., 2010).

The main plague host in the Prebalkhash region is the great gerbil, *R. opimus*, a social burrowing rodent. Great gerbils live in burrows and adjust their daily activity pattern to the season, enabling them to survive in the harsh climate (Kausrud et al., 2007; Prakash and Ghosh, 1975). Burrows are relatively permanent and elaborate features in the landscape, consisting of multiple entrances, food chambers and nesting rooms (Addink et al., 2010; Kausrud et al., 2007; Prakash and Ghosh, 1975). Their density in the Prebalkhash varies between 2 and 7 burrows per hectare (Addink et al., 2010; Davis et al., 2004). As a result of climatic, seasonal and annual changes in population size, the local fraction of burrows that is occupied by a gerbil family fluctuates between almost 0% to nearly 100% (Davis et al., 2004; Samia et al., 2011). Great gerbils live in family groups of typically one adult male, one or more females and their immature offspring (Randall et al., 2005). Adult females produce 1–3 litters each year, between April and September, with 4–7 offspring in each litter. All of the male and approximately half of the female offspring migrate from the nest within 18 months (Randall et al., 2005).

Fleas of all life stages predominantly reside in the burrow detritus, but adult fleas will also reside on gerbils for an hour a day to feed on their blood (Burroughs, 1947; Eisen et al., 2007). The dominant vectors of *Y. pestis* are fleas of the genera *Xenopsylla* and *Coptopsylla* (Rapoport et al., 2010). Adult *Xenopsylla* fleas feed on gerbils predominantly from spring to autumn, except during the hottest months of summer, and hibernate through winter (Bibikova et al., 1963 as quoted in Samia et al., 2007). Adult *Coptopsylla* fleas are active in autumn and winter (Ji-You, 1986). Some of the other flea genera that live within the burrows are active throughout the year, and thus the gerbils are effectively continuously parasitized by fleas. When fleas feed on the blood of a plague-infected gerbil while the latter is undergoing a bacteremic episode (Eisen et al., 2007), the fleas become infected with the plague bacteria themselves, due to the high concentrations of plague bacteria present in the blood of the gerbil during a bacteremia (Perry and Fetherston, 1997; Burdo, 1965). Infected fleas can transmit the infection to other gerbils almost directly (through so-called early-phase transmission; Eisen et al., 2007), or through active regurgitation of the bacteria from the flea foregut into the gerbil (Bacot and Martin, 1914).

There are two possible routes for the transfer of plague between burrows by gerbils and their fleas. The first is through infected juvenile gerbils that migrate to another burrow. Migration is characterized by its low frequency (once or twice in the life of a gerbil; Randall et al., 2005), and its relatively long distance. The second route is through infected fleas that drop off a gerbil after a bout of feeding, while that gerbil is visiting another burrow during their foraging activity, or as part of their social behaviour (Randall et al., 2005; Davis et al., 2007b, 2008). If a large fraction of the burrows in the desert system is occupied by gerbil families, then the transmission of plague between burrows is more efficient, and a local plague outbreak can result in an epizootic period in the whole Prebalkhash region (Davis et al., 2004). Davis et al. (2004) showed that the abundance threshold for plague epizootics can indeed be expressed as the necessary fraction of burrows that needs to be occupied by gerbil families (or more precisely, the product of burrow density and fraction of occupied burrows; Davis et al., 2008). In this regard, the burrow and its possible occupants can be seen as a subpopulation within a larger metapopulation (Davis et al., 2007a), and the spread of plague between the burrows can be characterized mathematically as a percolation phenomenon (Davis et al., 2008). Recent research has shown that besides gerbil occupancy, the flea burden of these gerbils also appears to be an important factor in determining the percolation of plague through the Prebalkhash region (Reijniers et al., 2012).

Model description

The spread of plague is studied in a spatially explicit metapopulation model, whose subpopulations (the burrows) are structured in space on a regular square lattice. Such a lattice is assumed to reflect the over-dispersed distribution and relatively constant density of gerbil burrows in the Prebalkhash region (Addink et al., 2010). The metapopulation model is based on an existing metapopulation model (Jesse et al., 2008), which has been tailored to meet the specifics of gerbil ecology. The model describes a population of great gerbils living in burrows, and within each burrow the gerbils and fleas are assumed to mix homogeneously. The gerbils in the model experience *SIRS*-type infection dynamics, and can thus be in one of the following states: susceptible (S), infectious (I) or recovered/immune (R). Recovered gerbils are only temporarily immune to reinfection by plague, and regain susceptibility after a certain period (Begon et al., 2006; Park et al., 2007).

The model uses a discrete-time approximation of the processes of *birth*, *death*, *recovery*, and *migration of gerbils*, the process of *flea dispersion*, and the process of *gerbil infection by infected fleas*. Each time step, the number of births, etc., per burrow is stochastically determined by discrete probability distributions (see Table 1 for details on the distributions used). The time step is set to five days, which corresponds to the typical incubation time of plague in gerbils (i.e. going from S to I), and the minimal infectious period of gerbils (i.e. going from I to R) (Rivkus et al., 1973; Shmuter et al., 1959), and thus provides an upper limit in the model on how quickly gerbils within the model can move through various stages of infection.

The number of gerbils per epidemiological state in a burrow x at time t is denoted by $S_x(t)$, $I_x(t)$, $R_x(t)$ and the total number of gerbils in a burrow x is given by $N_x(t)$. The different gerbil and flea processes occur within each timestep in the order that they are listed above. The order is artificial, because all these processes are
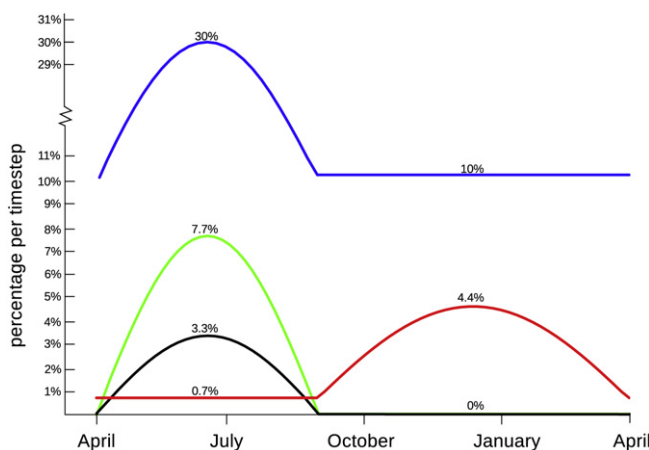
Table 1

All reported rates are per time step, and where a range is indicated, the rate changes according to a sine function (see Fig. 1). I: Randall et al. (2005). II: Korneyev (1968), Rudenchik (1967), Prakash and Ghosh (1975), Randall et al. (2005), and Frigessi et al. (2005). III: Biologically reasonable estimates based on the net growthrates reported in Frigessi et al. (2005). IV: Estimated from plague survival rates of gerbils with different levels of innate resistance in Ergaliyev and Pole (1990) and Ergaliyev et al. (1990b,a). V: Begon et al. (2006) and Park et al. (2007). VI: Erring on the high side of the 6.4% estimated by Eisen et al. (2007).

Parameter	Definition	Values		Sources
		Summer value	Winter value	
m	Migration rate of gerbils	$Bin(S_x + I_x + R_x, p), p \in [0, 0.033]$	0	I
-	Fraction of fleas that disperse from each burrow per timestep	$[0.1, 0.3]$	0.1	II
b	Birth rate of gerbils	$Pois(\lambda), \lambda \in \langle 0, 0.077]$	0	III
d_u	Death rate of uninfected gerbils	$Bin(S_x + R_x, p), p = 0.007$	$Bin(S_x + R_x, p), p \in [0.007, 0.044]$	III

Parameter	Definition	Year-round value	Sources
d_I	Death rate of infected gerbils	$Bin(I_x, p), p = 0.086$	IV
r	Recovery rate of infected gerbils	$Bin(I_x, p), p = 0.52$	IV
g	Rate of loss of immunity in gerbils	$Bin(R_x, p), p = 0.037$	V
h	Transmission chance from flea to gerbil, per infected flea per day	0.1	VI
T	Time step of model	5 days	–

continuous in reality. However, in a discrete model it is necessary to impose an order of events, such that the probabilities of e.g. dying or recovering, are consistently applied to the correct number of individuals, and to ensure that biological constraints such as the minimal incubation time of infected individuals are respected. The model can be written as a set of stochastic difference equations:

$$S_x(t+1) = S_x(t) + bN_x(t) - d_uS_x(t) - \rho S_x(t)$$
$$+ gR_x(t) - mS_x(t) + M_S(x, t), \tag{1}$$

where b is a seasonal per capita birth rate, d_u is the death rate for uninfected gerbils, g the rate at which gerbils lose their immunity, m the per capita migration rate, and $M_S(x, t)$ gives the number of susceptible gerbils migrating into burrow x. The birth, death, and migration rate are seasonal in reality (Frigessi et al., 2005; Randall et al., 2005), and are implemented as discrete probability distributions, whose parameter values vary during the year (see Fig. 1 and Table 1 for details).

Fig. 1. Simplified model implementation of seasonal effects on the gerbil population dynamics. Four gerbil parameters have seasonal effects assigned to them in the model. Gerbil birth rate (green), migration rate (black), and the fraction of fleas that disperse from each burrow per timestep, as a result of gerbil foraging and social activities (blue) have their peak rate during the summer season. The deathrate of uninfected gerbils (red) has it peak rate during the winter season. Further details on the implementation of these seasonal effects are listed in the text and in Table 1. The model assumes a constant annual cycle, consisting of a 5 month summer, starting on the 1st of April, followed by a 7 month winter season. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

The probability ρ that a susceptible gerbil in a burrow becomes infected through fleabites from infected fleas is approximated in the model by the equation

$$\rho = 1 - (1 - h)^{TI_f(x,t)/N_x(t)}, \tag{2}$$

where h is the chance that a single infected flea transfers the infection to the gerbil during its daily feeding bout and $I_f(t)$ is the number of infected fleas in burrow x. The fraction $I_f(x,t)/N_x(t)$ gives the average number of infected fleas foraging on a gerbil at time t. Under the assumption that the infected fleas are uniformly distributed over the available gerbils, the probability ρ can be approximated as 1 minus the chance that a susceptible gerbil does not become infected by any of the infected fleas feeding on it during T consecutive days (where $T = 5$).

The model equations that govern the number of infected and recovered gerbils per burrow are:

$$I_x(t+1) = I_x(t) + \rho S_x(t) - rI_x(t) - d_II_x(t) - mI_x(t) + M_I(x, t),$$
$$R_x(t+1) = R_x(t) + rI_x(t) - gR_x(t) - d_uR_x(t) - mR_x(t) + M_R(x, t), \tag{3}$$

where the per capita recovery rate is denoted by r and the death rate of infected gerbils by d_I. Both parameters are based on observations by Ergaliyev and Pole (1990) and Ergaliyev et al. (1990a,b), and are implemented in the model as binomial probability distributions with a probability p of 0.52 and 0.086, respectively. Because ρ can be a fraction, the number of newly infected gerbils ($\rho \times S_x(t)$) is rounded to a natural number using a Bernoulli distribution. The parameter values, their probability distribution, and their sources are summarized in Table 1. The effects of seasonality are shown in Fig. 1, and discussed in more detail below.

The hot summers and cold winters of the continental climate in the Prebalkhash region have a large impact on the local gerbil ecology (Frigessi et al., 2005; Stenseth et al., 2006; Kausrud et al., 2007). Its seasonal influence on the local gerbil population can be adequately described by a 5 month summer period starting in spring, alternated by a 7 month winter period (Frigessi et al., 2005). Examples of the effect of seasonality on the gerbil population are the birthrate of gerbils, which is larger than zero between spring and autumn, but is zero during the winter months; their death rate, which is limited during the summer months, but kills ±65% of the population during the winter months (Prakash and Ghosh, 1975 as cited in Frigessi et al., 2005). Similarly, migration of juvenile gerbils is predominantly successful if migration occurs between spring and fall, and is otherwise frequently associated with a premature death of the migrating gerbil (Randall et al., 2005). Finally, during the winter season, the gerbils have a shorter (but not well quantified) period of day-time activity (Prakash and Ghosh, 1975; Randall et al., 2005; Frigessi et al., 2005), foraging less outside (instead
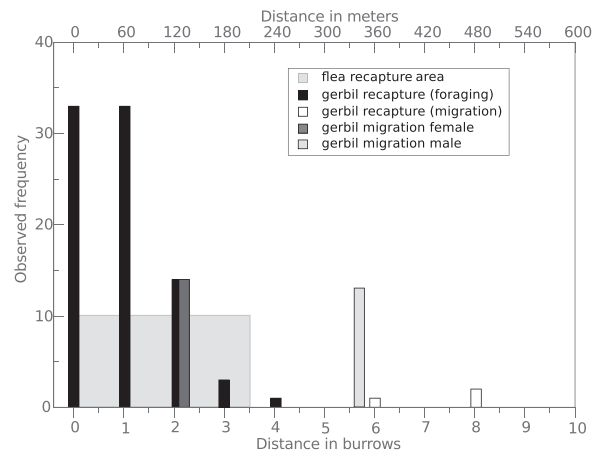
depending more on stored food; Kelt, 2011), and thus interact less with neighbouring burrows. The exact shape of the relationship between seasonality and many of the aspects of gerbil life in the Prebalkhash region is not known, and therefore we have implemented the impact of seasonality in the model by applying a simple seasonal effect on four gerbil parameters that vary between summer and winter, and are important for disease transmission (birthrate, deathrate, migration rate, and foraging rate). The seasonal effect that is applied in the model to these parameters is a constant rate that is appropriate for that season, or a sine function with domain $0 - \pi$ that reaches a maximum halfway through the season before declining again (see Table 1 and Fig. 1 for a specification of the function per parameter). Although the start of the summer season in the Prebalkhash, and the extremity of the seasonality will fluctuate between years with climate fluctuations (Kausrud et al., 2010), the model assumes no variation in the seasonality between years, and always starts the 5 month summer season at the beginning of spring (Frigessi et al., 2005), which we interpreted as the 1st of April.

We assume in this model that the effect of seasonal variation in temperature and humidity on flea ecology can be neglected, because these fleas reside on the warm-blooded gerbils, or in the detritus of the burrow microclimate (Ben Ari et al., 2011), and have a stable source of food (gerbil blood), and are thus at least partially buffered from the effects of seasonality. It has been shown that inter-annual fluctuations in the temperature and humidity to some degree affect flea ecology and the ability of fleas to transmit plague (Stenseth et al., 2006), but the effects on a seasonal timescale are less well-described in the literature. If low temperatures indeed reduce overall flea activity levels (Bibikova et al., 1963 as quoted in Stenseth et al., 2006), then the effect would be that plague persistence within a burrow in winter would become less likely, as gerbils still clear the disease at the same rate, but the infection rate of new gerbils would be lower.

There is no information available that indicates that the recovery rate or the death rate of infected gerbils depends on season, but there is disagreement in the literature on whether the rate of decay of antibodies that confer immunity to plague is seasonal. We have opted to conservatively chose that as with the other within-body processes (recovery rate and death rate of infected gerbils) in the model, the loss of immunity in the model is not seasonal (Begon et al., 2006).

The model describes the population of great gerbils living in burrows spaced 50 m apart, resulting in a density of 4 burrows per ha. This is at the higher end of the Prebalkhash density range of 0.84–4.84 burrows per hectare according to Davis et al. (2008), and is a suitable choice for the burrow density of putative hotspots: areas where the burrow density is high, will more frequently have a *density of occupied burrows* that is above the necessary percolation threshold for plague transmission (Davis et al., 2008; Addink et al., 2010), which facilitates the persistence of plague in the area. The size of the studied lattices range from 3×3 burrows (corresponding to 150 m × 150 m, or 2.25 ha) to 40×40 burrows (corresponding to 2000 m × 2000 m, 400 ha).

We define a hotspot as a small region in which the conditions remain favourable for plague to persist during times where the conditions in the Prebalkhash region as a whole have become unfavourable for plague persistence. We assume that gerbils living within a hotspot during an inter-epizootic period have little incentive to venture outside the hotspot, as there will be few gerbils to interact with, and few foraging opportunities to exploit outside the hotspot. Under these circumstances, a hotspot can be represented in a model system as an independent region, without any interactions with the outside world. We therefore treat the burrows at the boundaries of a modelled hotspot as having no neighbours outside the hotspot: the gerbils in these burrows still migrate and forage

Fig. 2. Available distance and frequency information on foraging and migration in gerbils (Davis et al., 2008; Randall et al., 2005; Begon et al., 2006) and fleas (Korneyev, 1968; Rudenchik, 1967). Capture-recapture data on the daytime travel distance of gerbils, expressed in metres (top *x*-axis) and in the corresponding distance expressed in 'burrow distance' (bottom *x*-axis), based on the average burrow density on the experiment's site.

as much as the gerbils elsewhere in the hotspot, but divide their attention over fewer burrows.

Migration of the great gerbil is typically limited to 100–500 m (Fig. 2), as capture-recapture experiments of *R. opimus* in the Prebalkhash region (Begon et al., 2006), and under similar circumstances in the Kyzylkum desert (Uzbekistan; Randall et al., 2005) show. In the model, migrating gerbils are moved from their original burrow to a randomly chosen burrow (independent of occupancy status) within 1–10 steps on the model grid. Migrating gerbils are assumed to move instantly from one burrow to another and do not visit burrows or change infection status while migrating.

In the model, the flea population size within a burrow is assumed to be in a quasi-steady state with the gerbil population size of that burrow (that is, prior to the flea-dispersal process, where fractions of the flea population are exchanged with neighbouring burrows). As fleas have a short lifespan compared to gerbils, the flea populations within a burrow will generally quickly adjust in size to an equilibrium state that reflect the number of gerbils in that burrow (Frigessi et al., 2005; Krasnov et al., 2002). This assumption might not be valid outside hotspot regions, specifically during periods of explosive growth and catastrophic collapse of the gerbil population. However, within hotspots the conditions for gerbil survival are supposed to be more stable, and thus the number of fleas and gerbils could generally be in this equilibrium state. We further assume a constant number of 100 fleas per gerbil, and thus the number of fleas $N_f(t)$ in a burrow at time t is given by $100N_x(t)$, where $N_x(t)$ is the number of gerbils in burrow x at time t.

The flea population size within a burrow after the process of flea dispersal to neighbouring burrows is modelled as follows: first the processes that influence the number of gerbils per burrow are quantified. Subsequently, the flea population size per burrow is calculated from the number of gerbils in each burrow (see directly above), and the fraction of these fleas that are infected with plague is calculated based on the number of infected gerbils present in each burrow (see below, Eq. (4)). Finally, the flea population of infected and uninfected fleas within each burrow is dispersed to neighbouring burrows, by means of the foraging and social behaviour of gerbils (Randall et al., 2005; Davis et al., 2007b, 2008). The model assumptions are that each burrow distributes a uniform fraction (dependent on season, see Table 1 and Fig. 1) of its fleas to neighbouring burrows within a Manhattan distance of two steps, regardless of the occupancy state or the number of neighbours of the burrow (burrows on the edge of a lattice have fewer

neighbours). Furthermore, twice as many fleas are distributed to burrows at a distance of one step, as are distributed to burrows at a distance of two steps. The resulting flea dispersion of this implementation is similar to observed experimental results (Korneyev, 1968; Rudenchik, 1967 as quoted in Davis et al., 2007a). The number of fleas per burrow after their dispersal is used to calculate per burrow the probability ρ that susceptible gerbils within the burrow become infected by infected fleas (Eq. (2)).

The innate level of plague resistance of *R. opimus* determines the frequency with which gerbils experience episodes of bacteremia during an infection with plague, as well as the duration of the infection (Korneyev, 1968; Rudenchik, 1967; Prakash and Ghosh, 1975). Higher levels of innate plague resistance reduces both the frequency of bacteremia, and the infection duration, and thus lowers the number of fleas that are likely to become infected per infected gerbil. When infected, the rat flea *Xenopsylla cheopis* has a well-documented median survival time of only 2 weeks (Lorange et al., 2005), due to starvation caused by a blockage formed in the foregut of the flea by *Y. pestis*. For the dominant flea species in the Prebalkhash, Bibikova and Klassovskii (1974) report that these either eliminate the plague bacteria in 2–3 weeks, or become blocked by the bacteria and die within 1–12 days. The number of infected fleas is therefore expected to adjusts itself relatively quickly to the number of infected gerbils within each burrow. This relationship has been approximated in the model by
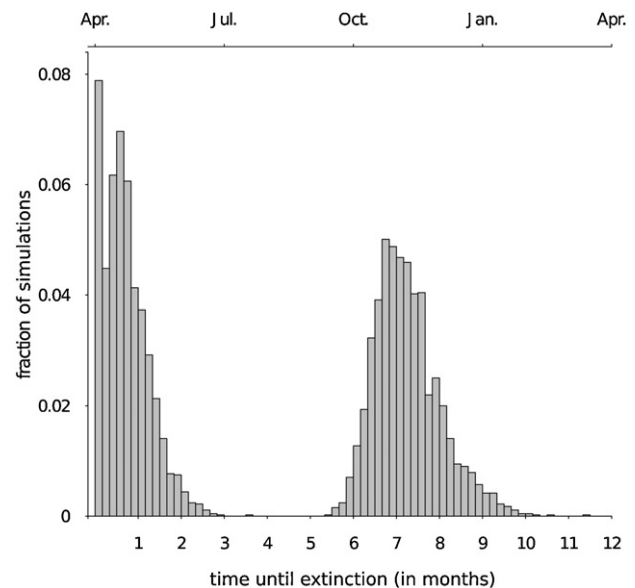
$$I_f(x, t) = 100 a I_x(t)^E, \qquad (4)$$

where $I_f(x,t)$ is the number of infected fleas in burrow x at time t, $I_x(t)$ the number of infected gerbils in burrow x at time t, and E is a phenomenological constant for level of plague resistance. The parameter values $a = 0.11$ and $E = 0.4$ are chosen to tune the number of infected fleas such that the equation fits the observed plague prevalences and plague-related death rate in gerbils (Davis et al., 2004; Ergaliyev and Pole, 1990; Ergaliyev et al., 1990b,a) and fleas (Bibikova and Klassovskii, 1974).

Results

We defined hotspots as small regions in which the conditions remain favourable for plague to persist during times where the conditions in the Prebalkhash region as a whole have become unfavourable for plague persistence. To study how favourable the conditions within a region need to be in order for that region to act as a hotspot, a spatially explicit metapopulation model was constructed. This model was used to repeatedly record the time until plague extinction for different hotspot sizes, gerbil densities, and rates at which recovered gerbils lose their immunity against plague. Initial simulations were conducted for a small area of 100 burrows, with a high average gerbil density of ± 10 gerbils per burrow (which corresponds to 40 gerbils per ha) and an average time of 4.5 months before recovered gerbils lost immunity (Park et al., 2007). Plague was introduced on time $t = 0$, which in the model corresponded to the start of springtime (April 1st). Under these conditions, plague prevalence in gerbils was on average 1–1.15% during the outbreak, and peaked at at most 6%. These prevalence levels are in line with the reported plague prevalence in the field (Davis et al., 2004). In burrows with infected gerbils, plague prevalence in fleas reached 20% in the model, which corresponds to observations on the maximum plague prevalence in fleas in infected burrows in Kazakhstan (Sviridov and Il'inskaya, 1967). In this regard, the model appears to well reflect the prevalence of plague in the Prebalkhash focus.

In roughly half the simulations, the initial introduction of plague in spring fails to establish itself for a longer period of time, and typically dies out within a month after a short epidemic period (Fig. 3), without spreading throughout the entire hotspot. In the

Fig. 3. Histogram of plague extinction time, in a metapopulation of 100 burrows (25 ha), based on 5000 simulations. Plague is introduced on April 1st, in a metapopulation with a gerbil density of on average 10 gerbils per burrow, and a loss of immunity in recovered gerbils of on average 4.5 months.
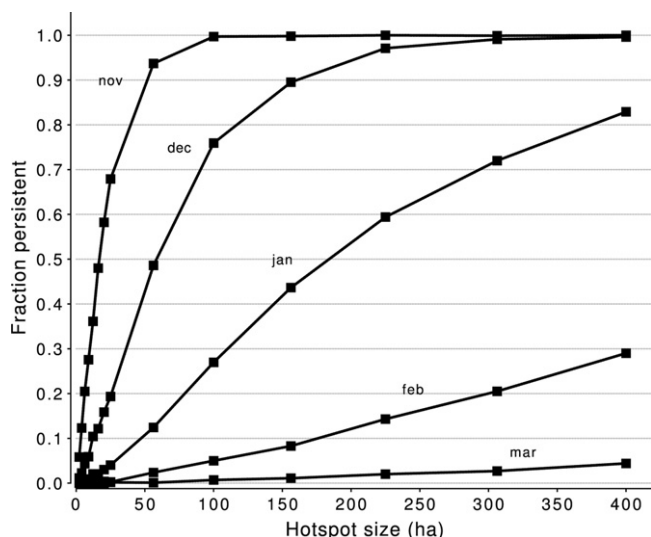
other half of the simulations, plague did establish itself throughout the entire simulated hotspot, but would (under the parameter conditions used) go extinct during the winter months. Since we wish to study the *persistence* of plague between epizootic periods, only simulations where the bacterium manages to establish itself in the metapopulation are analyzed further. Based on Fig. 3, we therefore discard plague outbreaks from the analysis that lasted for less than 4 months. Each datapoint presented in the following results is based on 926–1717 simulations. The variation in the number of simulations per datapoint is due to halting simulations after 1000 simulations were recorded that lasted well beyond the early extinction threshold (>40 timesteps), and an upper limit of 5000 simulations (including those that went extinct early).

Hotspot size

After excluding simulations where plague failed to establish itself (Fig. 3), the relationship between plague persistence and hotspot size becomes apparent: larger field sizes lead to a larger fraction of the simulations in which plague persisted for longer periods (Fig. 4). In about 5% of the hotspots of 40×40 burrows (400 ha), plague persisted until March 1st of the subsequent year. However, for plague to persist within a single hotspot for multiple years, the hotspots would have to be bigger, or the conditions within a hotspot would have to be more favourable then a gerbil density of 10 gerbils per burrow, and a rate of loss of immunity of recovered gerbils of 4.5 months.

Gerbil density and loss of immunity

With an average gerbil density of 10 gerbils per burrow and an average loss of immunity of 4.5 months, the probability was <5% that plague could persist for a year or longer in any area of ≤ 400 ha. At higher gerbil densities, and with a faster loss of protective immunity, multi-year persistence of plague became possible: a gerbil density of 18–24 gerbils per burrow, and a loss of protective immunity within 2–3 months, would lead to a probability of plague persisting for more than 1 year of >1%, even in small areas of just 10×10 burrows (Fig. 5a). However, only at the largest simulated
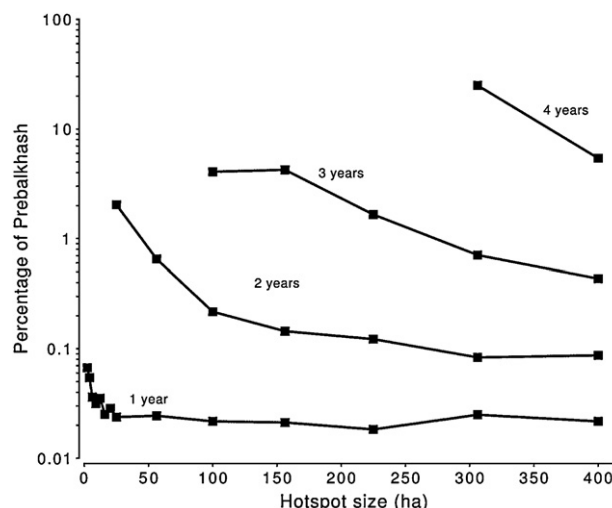
Fig. 4. Plague persistence as a function of field size. Black lines denote the fraction of major plague outbreaks, from the start of the outbreak on April 1st in a given year, that persist until November 1st, December 1st, . . ., to March 1st the subsequent year, for different hotspot sizes. Gerbil density is 10 gerbils per burrow, and recovered gerbils lose their immunity in on average 4.5 months.

Fig. 6. Relative hotspot area in the study region that is necessary for plague persistence. Given the chance that plague persists for Y years in a single hotspot of particular size, the number of hotspots necessary to have a 95% chance that plague persists can be calculated, and the total hotspot area plotted as the percentage of the total area of the Bakanas, Akdala and Saryesikotrau plains. Plotted for hotspot sizes up to 400 ha, under high gerbil densities (23 gerbils/burrow), and a short period of adaptive immunity (2 months).

hotspots (400 ha), and under the most favourable conditions was there a small probability (0.1%–0.5%) that plague would persist for an entire inter-epizootic period (>4 years, Fig. 5b).
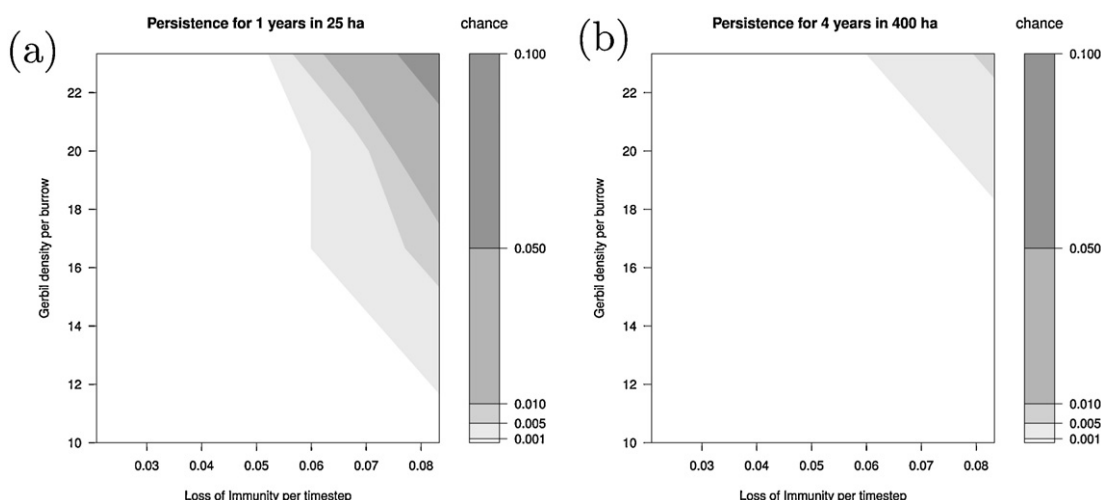
How many hotspots?

For hotspots to be a mechanism of plague persistence in the Prebalkhash region, it is not necessary that a single hotspot is able to maintain plague for four consecutive years. During an epizootic, the bacterium will probably seed multiple hotspots throughout the Prebalkhash, and only one of those hotspots would need to persist for the full duration of the inter-epizootic period for plague to persist in the Prebalkhash region in general. However, although a very large number of hotspots could fit within the Prebalkhash region, the fact that plague was not detected by the surveillance efforts during inter-epizootic periods implies that the combined area of these hotspots (which would contain a much higher density of

gerbils, compared to their surroundings; Frigessi et al., 2005) is small enough to evade detection.

If we assume the most favourable conditions of our tested parameter range (e.g. 23 gerbils per burrow and a loss of immunity in 2 months), the probability that plague persists for Y years in a single area of size S can be transformed into a 95% probability that in at least one of N hotspots of size S, plague persisted for Y years (Fig. 6). Doing so reveals that under these conditions, plague can easily persist for 1 year in hotspots that cover only 0.02% of the combined surface of the Bakanas, Akdala and Saryesikotrau plains (the sub-region of ±3.68 million ha (Davis et al., 2007b) of the Prebalkhash considered in this study). However, for plague to persist in at least 1 hotspot during an inter-epizootic period of 4 years would require a high number of large hotspots (300–400 ha) that together cover between 4.5–25% of these 3 plains (Fig. 6). Although plague might frequently be missed by sampling in a hotspot, the unusual large number of gerbils in these hotspots compared to

Fig. 5. The contour plot in (a) shows the probability of plague persistence for one year in a metapopulation of 10 × 10 burrows (25 ha) and the contour plot in (b) shows the probability of plague persistence for four years in a metapopulation of 40 × 40 burrows (400 ha). The x-axis in both plots shows the rate at which recovered gerbils lose their immunity, where a rate of 0.037 corresponds to an average duration of immunity of 27 time steps, i.e., 4.5 months. On the y-axis the number of gerbils per burrow is shown.

the surrounding terrain would have been noted and documented. Under a more moderate set of parameters (lower gerbil density, longer duration of immunity), the total area of the study area that would have to act as a hotspot would only increase: if we repeat our calculations for a gerbil density of 17 gerbils per burrow, and an immunity that lasts 3 months, a 2-year inter-epizootic period would already require that 32% of the Prebalkhash region consists of plague hotspots.

Discussion

Based on the model simulations (Fig. 6), it has become clear that under normal parameter conditions an unrealistically large fraction (>32%) of the Prebalkhash region would have to act like a hotspot, for hotspots to be the sole mechanism of plague persistence through inter-epizootic periods. Even under very favourable conditions for plague persistence between 4.5% and 25% of the Prebalkhash region would have to act like a hotspot. The high density of gerbils that need to be present for this in such hotspots would undoubtedly have been noticed by the existing surveillance efforts.

The main bottleneck for plague persistence in the model is the winter period (Fig. 3), during which the infection dynamics of plague are largely confined to the within-burrow plague dynamics, as there is no migration and less foraging by gerbils by which infected fleas could spread to other burrows (Prakash and Ghosh, 1975; Randall et al., 2005; Frigessi et al., 2005). Furthermore, no new gerbils are born during winter, and thus the only source of new susceptibles is recovered gerbils that lose their immunity to plague during the winter months. Because of the lower levels of interaction between burrows in winter (which, due to the lack of quantitative data, we assumed to be 3-fold lower than in summer), the increased chance of plague persistence in larger simulated hotspots (Fig. 4) is mostly due to the larger number of burrows with infected gerbils at the start of winter, which makes it more likely that plague will persist until spring in at least one of them.

In the model we assumed that the great gerbil population within hotspots would consist of gerbils with a uniform high level of innate plague resistance, because the prolonged exposure of the gerbil population within a hotspot to plague (both during and between inter-epizootic periods) would have likely selected for a high level of innate plague resistance (Gage and Kosoy, 2005). In future work, this assumption could be tested by combining experimental measurements on plague vulnerability with plague infection dynamic models (Fischer et al., submitted for publication), to elucidate for example the role of older gerbils in maintaining the plague bacteria within otherwise highly resistant gerbil populations. However, whether a larger diversity in innate resistance would be beneficial or detrimental for plague persistence is not clear, and will depend on the balance between its positive effect on between-burrow plague transmission during winter, and its negative effect on the population density of gerbils in general due to a higher mortality rate.

There are several other factors that could also be argued to affect plague persistence by means of hotspots:

- *Dynamic hotspots:* unlike stationary hotspots, the dynamic variant of a hotspot would not be tied to a single location, but would move through the Prebalkhash focus from one favourable area to the next (Fedorov, 1944 as quoted in Davis et al., 2007b; Rohani et al., 1997; Sherratt and Smith, 2008). However, during winter the infection dynamics of plague within a dynamic hotspot would be very similar to that of plague in a stationary hotspot, as the persistence of plague during winter is predominantly determined by within-burrow disease dynamics, as there is no migration and little foraging activity (see Table 1). Therefore, the strong bottleneck

for plague persistence that occurs during the winter season in stationary hotspots would likely apply to dynamic hotspots as well.

- *Slow-down of plague dynamics in winter:* the within-burrow infection dynamics presented in this metapopulation model are formulated as being independent of season. There are however some indications that this might be a too stringent assumption. For gerbils, Park et al. (2007) has reported an up to 5 times faster loss of immunity in gerbils during the winter period than during the summer period, although this finding is still disputed (Begon et al., 2006). For *Xenopsylla* fleas, Gage and Kosoy (2005) reports that these fleas might survive their plague infection in an inactive stage through winter. How frequently infected fleas would survive the winter, and whether these fleas are still infectious after hibernation is unknown. Both an increased loss of immunity in gerbils and an increased chance of survival for infected fleas in winter would have a positive effect on the chance of plague persistence within a burrow through winter.

- *Plague transfer between hotspots:* plague can be transported over long distances via infected fleas carried by predators and birds living in the Prebalkhash region (Aikimbajev et al., 2003; Heier et al., 2011; Wimsatt and Biggins, 2009). This opens up the possibility that during an inter-epizootic period, plague can persist in a relatively small number of hotspots, if these hotspots are frequently re-infected by each other through long-distance transport of infected fleas. Plague transfer between hotspots would in theory reduce the total number of hotspots needed for plague to persist through an inter-epizootic period, as newly infected hotspots compensate for the loss of existing plague-infected hotspots. A similar mechanism has been suggested for plague spread between prairie-dog towns in Colorado (Salkeld et al., 2010).

In conclusion, for plague hotspots to be the primary mechanism of inter-epizootic plague persistence in the Prebalkhash focus, they would have to be so numerous and large that their existence and role would be self-evident from plague surveillance efforts (Fig. 6). Hotspots alone are therefore unlikely to have played a dominant role in plague persistence in the Prebalkhash, and additional mechanisms are needed if *Y. pestis* is to persist in this focus, such as survival in alternative host species, survival in fleas, or in the soil of gerbil burrows. It is an interesting problem for future research to analyze the ability of current surveillance practices in the Prebalkhash region to discover hotspots of the minimal size and frequency that we estimate to be necessary for plague persistence.

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